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Diseases of the Aorta

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To my wonderful wife who has been patient and supportive through all my training and pursuits,

My children who bring a smile to my face every day,

My parents and family who taught me to always strive to do my best,

To God who makes it all possible.

Robert S. Dieter

Foreword

As the largest artery of the body, the aorta is susceptible to many types of problems, including congenital anomalies, occlusion, thrombosis, infection, dissection, connective tissue disorders, fistula formation, and tumors. However, the most frequent form of aortic disease is aneurysm formation, which usually results from weakening of the aortic wall. With time, the stress imposed by pulsation and by the aortic contents may cause the wall to balloon outward, leading to a potentially fatal rupture. Currently, there is much interest in preventing or managing these lesions through lifestyle changes, such as regulation of blood pressure and diet, promotion of exercise, and cessation of cigarette smoking. Once an aneurysm enlarges or begins to cause symptoms, however, repair is usually necessary.

Aneurysm surgery has long been a special interest of mine. As a young surgeon, in the early 1950s, I helped develop some of the first techniques for treating aneurysms of the aorta and major arteries. Since then, many new surgical options have become available, but the outcomes have not always been successful. Today, endovascular repair, including the use of expandable stent grafts, is becoming increasingly widespread, especially in elderly patients or those at high risk for open surgery; another recent option is hybrid repair, which combines open and endovascular techniques.

Successful treatment of aortic disease depends on highly trained specialists who are thoroughly familiar with this constantly evolving field. The current volume, edited by my colleague and friend Ray Dieter, Jr., and his sons Ray Dieter III and Robert Dieter, provides an outstanding, in-depth look at the entire spectrum of aortic disease and its treatment. Having known the Dieters for many years, I have followed their careers with interest. I applaud the growing series of textbooks they have published concerning all aspects of the circulatory system. This volume, like its predecessors, should be of special value to vascular surgeons, interventional cardiologists, and other healthcare professionals involved with the prevention and treatment of aortic diseases. It also should be enlightening to general practitioners, family care physicians, and laypersons interested in this field.

Denton A. Cooley
Founder and President Emeritus
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Preface

This is our fifth vascular textbook, sixth medical textbook (non vascular textbook on Thoracoscopy) and is unique in that it focuses on the aorta rather than vascular diseases by body region. Not unique, though, is its comprehensive approach to this topic and being a reference textbook.

Diseases of the aorta can occur in the pediatric or adult patient, can be acute or chronic or inherited or acquired, and can be approached in a variety of methods. This textbook systematically reviews all aspects of aortic diseases. Imaging modalities and medical, surgical, and endovascular management are discussed as well as longitudinal surveillance and follow-up.

We are honored that Dr. Denton Cooley was able to write the foreword to this textbook, as he has with our other books. Dr. Cooley was a pioneer in aortic diseases, and prior to his death, we were able to have several conversations regarding his influence and perspective on diseases of the aorta. Drs. Cooley and Ray Dieter, Jr., were contemporaries and both helped shape the understanding of cardiovascular diseases.

As with our other textbooks, we hope that you find this to be readable and a helpful reference in your practice.

IL, USA — Robert S. Dieter
IL, USA — Raymond A. Dieter Jr.
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A Timeline History of Aortic Disease and Therapies, Including Surgery

1

Raymond A. Dieter Jr., Sanjay Singh, Jasvinder Chawla, Daryl A. Drake Jr., John P. Pacanowski Jr., and Robert S. Dieter

Introduction

Aortic disease has long been recognized for its potentially lethal and life-altering effects. Patients have thus presented a therapeutic challenge to physicians for hundreds of years (centuries) as to the treatment options and potential benefits or results. This book presents a large number of aortic disease entities, the patient concerns, the options and the risks for their treatment.

Development of modern aortic disease diagnosis and therapy programs has required not only a great deal of effort but decades of research and therapeutic trials to reach the current level of knowledge and results [1]. The twentieth and twenty-first century advancements and investigations have led to the present level of aortic therapeutics and utilization.

The timeline for delineation of the efforts required to perform modern aortic surgery and the usage of the aorta for non-aortic diagnostic and therapeutic approaches has been slow to develop with many "road blocks" to reach the current level of aortic manipulation, as well as the possible errors in timeline dates and reporting of data or experience. The delineation of various accessory modalities required in the steps over the past centuries (especially the last two) includes such "inventions" as electricity; anesthesia, both general and local; radiology and x-ray techniques; and diagnostic contrast materials demonstrable on radiographic film. All of these considerations and many more, such as cardiopulmonary bypass, and infection control, have been necessary to develop the field of aortic diagnostics and therapeutics. Herein outlined are many of the events which have led to the current ability to diagnose and treat a large number of aortic lesions. Interspersed in the outline, we have added a few of our steps in the chain of aortic "adventures."

This chapter is dedicated to Dr.John Laird for his contribution to education and the treatment of vascular diseases

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Timeline of Aortic Surgery Development

I. *Early Aortic Aneurysm History: 2000 B.C. to 1700s* [2]
   A. The early ancient Egyptian medical text, the *Ebers Papyrus*, one of the earliest known medical writings, describes aneurysms as "tumors of the arteries"—cured only via magic. Peripheral aneurysm treatment should consist of "with a knife and burn it with fire so that it bleeds not too much" and boiling oil treatment [3].
   B. The early Indian text *Sushruta Samhita* noted that aneurysms upon bursting exhibited a rapid flow of hot and red blood and that when situated at any of the vital parts of the body they should be deemed incurable [4].
   C. Ancient Greeks attributed disease to an imbalance of mythological humors—similar to Sushruta [5].
      1. Aristotle's contemporary, Praxagoras, believed epilepsy was due to phlegm accumulation within the aorta.
      2. Hippocrates (460–357 B.C.), a Greek, gave us the "Hippocratic Oath."

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(a) No mention of aneurysms but, ligation of arteries, would stop bleeding
(b) Father of Medicine
3. A.D. 97—Archigenes used ligation in limb amputation.

D. Roman Empire
1. Galen (130–200 A.D.) described aneurysms "as the pulse and beating the arteries make and that the tumor vanishes when the artery is pressed down" [6].
(a) Probably treated aneurysms with bloodletting (venesection) [7].
(b) Noted risks of venesection (VS) is aneurysm development near the incision [8].
(c) Also mentioned VS avoidance near large arteries due to increased risk of fatal aneurysms.
(d) Crucial in the development of anatomy and modern surgery.
2. Praxagoras—influential physician of the "dogmatic" school of medicine [8].
3. Antyllus, "Father of Aneurysm Surgery"—his surgery methods were followed for over a millennium (1000 years) despite unfavorable survival rates [8].
(a) Antyllus method was the first attempt at abdominal aortic aneurysm repair: "ligation of artery above and below the aneurysm followed by incision and emptying the sac"
4. Actius, 200 years later—vague aneurysm classification and postulated improvements in the Antyllus method [9]

E. Medical era (next 8–15 centuries)—little advancement

F. Era of inquiry
1. Astronomy, mathematics, and navigation (with Columbus discovering America in 1492)
2. Lancisi, in 1490, delineated true/false aneurysms, vessel calcification and recognized. Syphilis relationship—prescribed rest, sparse diet, bleeding and herbal palliation [10].
3. Vesalius, in his text in 1543, mapped the definitive course of aneurysm disease [10].
4. René Laennec invented the stethoscope.
5. Dietary treatment/fluid restriction/bed rest advocated for centuries into 1800s [11].

G. Harvey's definition of circulation rather than "to and fro." Statues of early notable physicians, including Harvey, are exhibited in the International Museum of Surgical Science "Hall of Fame" by the International College of Surgeons, Chicago, Illinois, USA

H. Hallowell, in 1762, repaired a brachial artery

I. John Hunter ligated the proximal superficial femoral artery to treat a pulsating popliteal aneurysm in 1785—a new beginning [12]

J. Animal experimentation programs developed

II. *1800s*

A. Better recognition by physicians of aortic disease entities.

B. Anesthetics developed—one wonders "what did they use in the past"—high-quality alcohol or strong men.

C. Electricity "harnessed" and electric lights followed Thomas Edison's work.

D. Increased animal lab usage and facilities.

E. 1817: Cooper (Hunter's student) ligated the aorta proximal to an iliac aneurysm after having ligated a dog aorta in 1809 [13].

F. 1869: Charles Moore successfully inserted 78 feet of thin wire into an ascending aortic aneurysm—unfortunately the patient died of sepsis 5 days later [14].

G. William Halsted at Johns Hopkins designed a progressive metal band aortic occlusion technique—most patients died. Later, Elkin located 25 attempts with five survivals using this treatment [15, 16].

H. In the late 1800s—Medical school education was improving

I. Medical inventions followed the enhancement of the profession
1. Development of hypodermic needles and syringes.
2. Blood clotting of the aneurysms with gelatin therapy—similar techniques were available since early Egypt—received support as did various metallic items and pins [17].
3. Steel watch band insertion.
4. Electricity was added to the wire treatments by others (such as Corrali, an Italian physician, in 1881) as the techniques became more widespread and persisted into the 1970s (Charles Rob) [18].

J. In 1885, Buck summarized "Aneurism Treatment to Date" in his text [18] to include:
1. Rest, blood in good chemical condition, be recumbent, slow to sit, walk slowly after months of treatment, no ire or increased emotions, no valsalva, and bloodletting which could lead to anemia
2. Decreased food intake (8 ounces solid 6 ounces liquid), laxatives/saline purgatives
3. Medications:
(a) Iodide of potassium: to thicken the aneurysm wall and possibly thicken the blood, potash (I_2 of Potassium). If the patient is unable to tolerate KI then sodium iodide (NaI_2) is to be used.
(b) To thicken the blood/slow circulation
1. Ergotine subcutaneous for constriction of the aorta or oral ergot
2. Digitalis

(c) Acetate of lead or tannic acid until deep blue lines developed on the gums
(d) Chloride of Barium
4. Surgery
(a) Ligate vascular branches
(b) Ligate aorta above aneurysm or below
(c) Introduce foreign body to induce clots (fine wine, watch springs, horsehair—unfortunately, they all also caused infection)
(d) Constriction or compression apparatus or by hand/Esmarch elastic bandage
5. Coagulation
(a) Galvanic puncture using battery electricity with one or two needles connected to a positive pole and a negative plate on the abdomen for 20–30 minutes to induce clot formation—repeat 2–3 days or even every 2–3 hours
(b) Coagulating injectables:
1. Medicines
2. Solid items
6. Treatment of pain
(a) Hypodermic morphia
(b) Create small "blisters" over tender part and ice on the chest
(c) Sedatives, narcotics, hydrocyanic H+, ETOH to full dose
(d) Bend knees up
7. Protection
(a) Metal or cloth protector, over aneurysm
(b) Astringents and ergot to decrease bleeding
(c) Quiet [18]

K. 7 October 1896: JB Murphy developed a vascular anastomosis technique and performed the first human vascular anastomosis at Mercy Hospital in Chicago [19]. This was 1 month after the first stab wound of the heart was sutured.

III. *Early 1900s of the 20th Century: Cardiovascular*

A. Early heart procedures
1. 1893: Dr. Daniel Hale Williams explored a right ventricle stab wound; no sutures placed, as bleeding had stopped. Provident Hospital, Chicago [20].
2. 9 September 1896: First successful suture of a stab heart wound performed by Dr. Ludwig Rehn—violating an age-old dictum back to Hippocrates that the heart was off limits to the surgeon [21, 22].

B. 1902: Dr. Hill, with two kerosene lamps and chloroform, successfully treated a 13 year- old at home with a stab wound to the heart on an Alabama kitchen table. The patient died 40 years later, in 1942, of a second stab wound [23].

C. 1910: Alexis Carrel performed a graft from the descending thoracic aorta to the coronary artery after Trendelenburg proposed pulmonary embolectomy with aortic and pulmonary artery cross-clamping in 1908 [24].

D. 1912: Alexis Carrel received the Nobel Prize for vascular suture techniques while working with Charles Guthrie and using aseptic techniques.

E. 1915: Heparin was discovered by a medical student (Jay McLean)—a key to future cardiovascular progress [25].

F. 1923: First successful mitral valvulotomy was performed by Elliott Cutler and Samuel Levine—ahead of the times—after Sir Lauder Brunton proposed elective correction mitral valve stenosis by surgical manipulation in 1902.

G. 1928: Fleming discovers penicillin.

H. 1929: Forssmann performed the first heart and vascular catheterization (on himself) and thus received the Nobel Prize [26].

I. 1938: Lelong reported on pleuroscopic diagnosis of a thoracic aneurysm.

J. Aortic aneurysm external wrapping treatment promulgated, e.g., Albert Einstein's aneurysm was wrapped by R. Nissen in 1948 [27]. (Early in our practice, we used Dacron aneurysm wraps successfully for treatment of both high risk thoracic and abdominal aneurysms.)

K. 1952: Dubost promulgated arterial homografts for utilization on the aorta [28].

L. Antibiotic and asepsis programs became key considerations in vascular surgery success.

M. Gross and Oudot repaired non-aneurysmal aortic lesions in the 1940s and 1950s [29, 30]

N. Many other patch or tube grafts of various materials followed, including the cryopreserved, the cloth, and the Dacron graft sewn by DeBakey on his sewing machine, which when placed within the aneurysm reduced the incidence of aortoenteric fistula development [31].

O. Etiology of aortic aneurysms became primarily arteriosclerotic, while syphilitic aneurysm occurrence was disappearing.

IV. *1940s to Date—Cardiac Surgery—An Integral Part of Vascular Surgery Developmental History*

A. 1952: Hufnagel placed into the descending thoracic aorta a caged ball valve to treat valvular heart disease [32].

B. Congenital cardiovascular surgery
1. In 1913, Tuffier dilated a stenotic aortic valve by aortic wall invagination and the book "Surgery of the Blood Vessels and the Heart" was published regarding experimental cardiovascular surgery [33].
2. 1937: Ductus interruption [34]

3. 1944: Crafoord, in Stockholm, resected an aortic coarctation [35].
4. 1945: Gross repaired a vascular ring of the trachea [36].
5. 1948: Gross performed aortopulmonary (A-P) window closure [37].
6. Cooley: aortopulmonary window repair with cardiopulmonary bypass (CPB) [38].

C. The single organ perfusion pump by DeBakey in 1934, was followed by the tissue perfusion apparatus of Lindbergh [39], of which there is one in the International Museum of Surgical Science (IMSS) in Chicago, of which Raymond Dieter, Jr., M.D. is President.

D. Dodrill performed the first human left-sided heart bypass in 1952 using a General Motors' Mechanical pump [40].

E. In the 1930s and 1940s, before and after WWII, John Gibbon did extensive research using a heart lung machine (CPB), contributing extensively to the field [41]. At a meeting in Europe in the early 1970s, Dr. William E. Neville, Dr. Raymond A. Dieter, Jr., and Dr. Gibbon discussed extensively his decision to progress to the human use of CPB in 1954, despite the less than optimal results in the animal lab, stating he had to make a decision. It was a monumental decision for the benefit of the world's physicians and our patients.

F. 1940s: WWII: Dwight Harkin removed 134 cardiac and mediastinal foreign bodies.

G. Cross-circulation was explored by Lillehei for repair of a VSD.

H. 1946: The Vineberg myocardial ischemic procedure was being developed—"an aortomyocardial shunt"— which we later utilized at the Hines V.A. Hospital, Maywood, Illinois in the late 1960s.

I. 1950s: Dr. Kirklin at the Mayo Clinic utilized CPB for cardiac surgery.

J. Simultaneously, hypothermia, myocardial protection, and cardiac arrest (K+) were under investigation by many investigators, including Clowes and Neville, who were exploring various CPB factors for successful whole body perfusion [42].

K. Transposition of the great vessels was corrected by Senning [43].

L. 1962: Sones and Shirey popularized transaortic coronary catheter angiography [44].

M. 1963: Intra-aortic balloon counterpulsation development was progressing.

N. 23 November 1964: A direct aortocoronary vein bypass was performed (Garrett, Dennis, DeBakey [45]).

O. Oz, Komeya, Neville and Clowes, M.D., continued research using hypothermia and blood volume hemodilution [46].

P. Dieter et al. reported on profound hemodilution, hypothermia, and metabolic aspects of CPB with Ringer's Lactate in 1966 and again in 1970 [47, 48].

Q. 3 December 1967: The first human to human heart transplantation was performed utilizing an aortic segment by Christian Barnard in Capetown, South Africa [49].

R. 1968: Favalaro popularized the saphenous vein aortocoronary bypass at the Cleveland Clinic [50].

S. During this period of time, failing cardiac circulation was treated with the diaphragm wrapped canine heart experiment by Kantrovitz (Cardiomyoplasty) and the Carpentier human aorta wrap with latissimus muscle for aortic counterpulsation [51, 52].

V. *Twentieth and Twenty-First Century: Aortic Surgery Post WWII to Date—Development and Its Progress Entwined with Our Experience*

A. Matas—endoaneurysmectomy and rubber tube stent placement preanticoagulation having previously ligated the aorta proximal to an abdominal aortic aneurysm [53].

B. WWII—traumatic cardiovascular injury (primarily suture) repair was a great impetus to vascular surgery.

C. 1948: Descending thoracic aneurysmectomy with primary aortic reanastomosis (Shumaker) was rapidly followed by Swan, Gross, and the DuBost treatment of aneurysms using aortic homografts [54, 55].

D. 1953: Bahnson reported on six saccular abdominal aortic aneurysms resected, while DeBakey and Cooley resected a 20 cm descending thoracic aortic aneurysm using a homograft replacement [56, 57]. In 1958, Dr. Robert McCray placed an abdominal aortic homograft with the lumbar artery stumps placed anteriorly (Illinois Thoracic Surgery Society 14 April, 1988 minutes describes).

E. During the Korean War—vascular homograft and autogenous vein repair reduced limb amputation rates from 49% to 11% [58].

F. Availability of multiple synthetic grafts followed—including the Dacron (DeBakey) (originally constructed and sewn by him reportedly on a sewing machine), Gore-Tex, and Vinyon-N cloth tubes, and research on permanent shunts by Neville and Clowes to replace aortic segments in 1955 [59, 60]. Others were stimulated to experiment building vascular grafts and medical items in their garages or laboratories.

G. Vascular wards and diagnostic angiograms including the translumbar aortograms (TLA) for renal and iliac disease with 17 gauge 7 1/2 inch needles—of which

we performed hundreds and presented the findings of many to the Hines V.A. vascular conferences, then evolved. Tomograms were later followed by computerized tomographic scans (CTs) aiding greatly in the diagnosis of thoracic and abdominal aneurysms, avoiding right transthoracic aortic aneurysm biopsy, and differentiating such from neoplasms.

H. Aortic therapy—surgical or medical—was promulgated in the 1960s at the Hines V.A. Hospital. The vascular service had grown, under multiple attending physicians (J Canning, R McCray, L. Ganshirt, J Graziano, D. Hutchings), with aneurysm; Leriche Syndrome (occluded aorta) bypass and endarterectomy (aortic, iliac, femoral, carotid) procedures were performed when the author (Raymond A. Dieter, Jr., M.D.) joined the program in 1963.

I. Homograft or Dacron replacement of all segments of the thoracic aorta utilizing cardiopulmonary bypass, including arch replacement and its branches, was initiated by Drs. DeBakey, Cooley, Crawford (who were always available for telephone consultation) and others as an option to replace the "clamp and sew" techniques [61].

J. Metabolic aspects of profound hemodilution, hypothermia, and cardiopulmonary bypass was widely researched and utilized by many, including ourselves, for cardiac, vascular, aortic, tumor resections or trauma repair [62, 63].

K. 1960s–1970s: Open "vascular dilation" procedures were developed and frequently utilized, especially in conjunction with other vascular procedures, by ourselves and others. Currently, this procedure is termed "angioplasty" and performed percutaneously utilizing balloon catheters, which we began performing after Dotter presented the concept. Also, balloon catheters became available—under the direction of Tom Fogarty—for multiple purposes.

L. In 1967–1968, we began to use the Vineberg direct aortocoronary grafts and subclavian coronary grafts for coronary occlusive disease (Dr. William E. Neville, Dr. Roque Pifarre, Dr. Raymond A. Dieter, Jr., Dr. Bernie Leinenger and others at the Hines V.A. and Loyola University Hospitals).

M. Beginning in the late 1960s, Raymond Dieter, Jr., personally performed repair of hundreds of ruptured aortas or "leaking" aneurysms in community hospitals (on occasion performing 3 or 4 aortic repairs in a 24-hour period in 3 or 4 different hospitals), along with his associates Drs. Robert McCray, Glen Asselmeier, George Kuzycz, Farouk Hamouda, Robert Wilson, and Robert Maganini.

N. By 1968–1969, CPB was utilized by ourselves for shock syndromes, such as after a perforated peptic ulcer with sepsis and profound shock, for resection of renal tumors invading the inferior vena cava and right heart, thoracic aortic disease, huge thoracic tumor resectional surgery, aortic trauma (especially GSW—gunshot wounds) and other noncardiac diagnoses [64, 65].

O. Then, 17 January 1969: we performed the third human heart transplantation in our area—108th in the World—at the Hines V.A. Hospital having performed similar animal (dog, calf, sheep) procedures in the research laboratory and meeting with Christian Barnard. The surgical team included the following surgeons: William Neville, Roque Pifarre, Robert Lynch, Kushroo Patel, Raymond A. Dieter, Jr., and William Cox [66].

P. 1974: Our private group then initiated a Community Hospital diagnostic coronary angiographic (Dr. Neil Agruss), aortocoronary bypass, and valvular heart disease surgical program with no house staff at Central DuPage Hospital (DuPage County, Illinois) after the first coronary angiogram was performed in a patient with a ruptured thoracic aneurysm in preparation for surgery by Raymond A. Dieter, M.D. prior to the availability of CPB. Other early community hospital procedures, such as coarctation of the aorta correction, aortorenal, or aortomesenteric grafts, were already performed along with the closed valvular procedure by Drs. Robert McCray and Salvatore Nigro in the 1960s at Elmhurst Hospital— a community hospital.

Q. 1983: We reported on simultaneous traumatic thoracic aortic rupture repair in the community hospital and renal salvage after the renal artery was torn from the aorta by utilizing a saphenous vein aortorenal bypass and multiple other injuries, including all long bone fractures except one, the ruptured liver, spleen, bladder, diaphragm, etc. [67].

R. Multigenerational genetic or familial vascular/aortic disease with rupture during pregnancy was reported by us [68]. This was the same year (1983) that we reported a tracheal - carinal resection with primary reconstruction for a mucoepidermoid tumor in pregnancy [69].

S. In 1970, we performed our first and poorly accepted thoracoscopy by the medical community. Each year for 20 years, we performed more and more thoracoscopic procedures. In 1990, we developed a series of thoracoscopic (now accepted by MDs) live, 3-day, hands-on animal seminars for cardiothoracic and aortovascular surgeons, which led to the publication of "Thoracoscopy for Surgeons" by Igaku-Shoin (now Williams and Wilkins) [75]. In our Thoracoscopy textbook, we discussed performance of coronary artery surgery with graft intussusception or telescoping of the bypass graft into the coro-

nary vessel as early as the 1960's at the Hines V.A. Research Center. The technique was simple and we did not hesitate to utilize a simple single tacking stitch to avoid possible graft withdrawal.

T. The transfemoral endovascular procedures and grafting (EVAR) were initiated and promulgated worldwide for the aorta, the aortic branch diseases, and the aortic fistulae after Juan Parodi, in 1990, accomplished the first human aortic aneurysm transvascular endograft following the early Cleveland Clinic 1980s EVAR research [70].

U. Similarly, in the 1990s, special diagnostic and therapeutic procedure rooms utilizing transarterial and transvenous catheter angiograms were promulgated, including those devoted primarily to the aorta or transaortic procedures. A huge swing in aortic surgery, from the open to the endograft technique, followed into the 2000s with development of multiple new techniques and prosthetics. Ultrasound techniques progressed and enhanced vascular graft, aneurysm, and potential complication evaluation.

V. We then reported the second endograft placement for an aortoenteric fistula with shock and hemorrhage following multiple nondiagnostic hospital admissions elsewhere [71].

W. Aortic departments, specialists, and clinics have developed, coinciding with the therapy and vascular development programs, as presented by Stephenson in the Cohn and Edmunds text and by Barr in the History of Aortic Aneurysms [1, 2, 72].

X. Various authors of this current text and the enclosed chapters became interested in vascular disease, and promulgated aortic disease therapy, including Raymond A. Dieter, Jr. (1961), Raymond A. Dieter, III (1992), Robert S. Dieter (2003) and Aravinda Nanjundappa (2004) (the latter two under the tutelage of Dr. John Laird at the Washington Hospital Center/Georgetown University). This interest has led to the production of six reference medical textbooks pertaining to the thoracic and vascular fields and the care of 1000s of patients.

Y. More recently, genetic research involving patients with aortic aneurysms continues to develop the concept of molecular and gene therapy to prevent or reduce aortic aneurysms.

Z. Transaortic paraaortic tumor biopsy has been discussed, but few such procedures are accomplished.

Conclusion and Future Directions

The preceding outline and time table has progressed from the early syphilitic aneurysms of 2000 years ago to the current dedicated aortic facilities and staff. More recently, since the late 1990s, endovascular (EVAR) and transaortic valve replacement (TAVR) programs have developed and flourished around the world in both the university and the community setting for the benefit of the patient. This has coincided with the development of insurance, government sponsored healthcare, and Medicaid financial coverage. Vascular and cardiovascular training programs to provide experience for the physician and the staff have been promulgated.

Communication with qualified personnel is now potentially instantaneous and the electronic transmittal of photographs provides the opportunity for urgent worldwide assistive advice or instruction. Similarly, new concepts or device developments are disseminated in a span of months or weeks. Simultaneously, and as a part of this development, was the opportunity for industry and business intervention. With the opportunity to not only recover expenses but to also realize a significant profit in the provision of new technologies, vascular physicians have seen a huge resource input by industry for the successful long term treatment of these critical aortic diseases in our patients.

The book "100,000 Hearts: A Surgeon's Memoir," by Denton Cooley lists 46 personal contributions, 53 surgical inventions and products, and 1400 publications related to Dr. Cooley along with his C-V [73]. The "Giants" in the aortic and cardiovascular field, including Denton Cooley as mentioned above (who provided the foreward for this text) and Michael DeBakey, were followed by individuals such as Edward B. Dietrich (1935–2017), who developed a keen interest in the minimally invasive approach to cardiovascular disease [74]. Various endografts and techniques were developed to meet the anatomic variances for the abdominal or thoracic aorta and its branches. Guidelines for placement of descending thoracic endografts or structure of the perirenal aortic graft neck were devised. Committees formed and widespread input as well as individual entrepreneur concepts were incorporated in this rapidly changing specialty. Patients and their families quickly accepted the new line of minimally invasive aortic treatments.

Diagnosis, presymptomatic, and possible preclinical treatment has been encouraged. Multiple innovative stents, endografts, and insertion techniques (percutaneous or iliofemoral incision) are under close scrutiny as exemplified by the large number of major industrial exhibitors at national or international meetings.

Speakers and researchers submit their cardiovascular concepts, ideas, and results on national platforms for the adult and the tiny infant. The complications of various techniques (open or endo) as well as the long term results continue to be debated and challenged statistically through a large number of comparative patient studies. When should one intervene and whether the open or endo procedure is ideal are continually discussed. What are the risks, especially radiation dose to the patient, physician, or staff and how to reduce such are

of equal concern. Endoleaks or infected fistula, ruptured aneurysms, arch vessels, abdominal branches, follow-up procedures, embolic stroke, and pediatric vascular emergencies will continue to be treated. Where will the future lead us? Who will devise and provide the new era therapies? As early as the mid-1960s, we experimented with sutureless distal anastomosis or intussusception of a distal end of a graft for aortocoronary bypass procedures [75]. This was abandoned for sutured anastomosis but has been utilized more recently for venous outflow in end-stage renal disease by others [76].

It is exciting and challenging to consider the future of aortic disease and its treatment in the era of minimally invasive disease therapy. Balloons, covered grafts, custom fenestrated grafts, genetic modifications, and parallel grafts are only the beginning as demonstrated by Stephenson and Ruggiero in their text of heart surgery classics [72]. These all show a continued improvement from Stone's discussion of syphilitic cardiovascular disease [77]. The dedicated healthcare team—nurses, technicians, manufacturers, physicians, and many more—will continue developing this rapid and changing environment for the benefit of our patients. Dr. Carabello, Professor of Medicine, Chief of Cardiology at East Carolina University stated, in the June 2017 Chest Physician (page 19), "We've spent $2 billion looking for a percutaneous mitral valve replacement and wonders if this makes sense." Huge resources and analytic minds will be applied to the challenges for future disease minimization with the hope for success for such concepts as gene therapy and molecular surgery to reduce or prevent the occurrence of an aortic aneurysm. Will gene editing of DNA become an aortic reality for aortic disease prevention? The future is already here for some diseases with the utilization of the transfemoral intra-aortic blood pump (Procyrion Aortix™) for chronic heart failure patients and lithoplasty for calcified vessels (Disrupt PAD III). These are exciting times.

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Embryology and Anatomy of the Aorta

2

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Embryology

Aorta

Development of the aorta occurs during the third week of gestation. At this time, isolated vascular islands coalesce into plexuses to form the (initially) paired aortae. Each primitive aorta consists of a ventral and dorsal segment. The ventral and dorsal segments of the primitive aorta are continuous through the first aortic arch (Fig. 2.1). The aortic sac is formed from the fusion of the two ventral aortae and the descending aorta by fusion of the dorsal aortae. A six-paired system of aortic arches sequentially develops in cranio-caudal fashion between the ventral and dorsal aortae providing blood flow from the cardiac ventricles to the embryonic circulatory system. In addition, the dorsal aorta gives off several intersegmental arteries (Fig. 2.2).

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Vasculogenesis and Angiogenesis

Vasculogenesis is the de novo formation of endothelial cells from mesodermal precursors in the embryo. The process forms the extraembryonic yolk-sac vasculature, paired aortas, endocardium, and vascular plexus of the embryo, all before the onset of blood circulation. Angiogenesis, the rapid expansion and remodeling of the vasculature, subsequently occurs. This involves endothelial cell sprouting, vessel

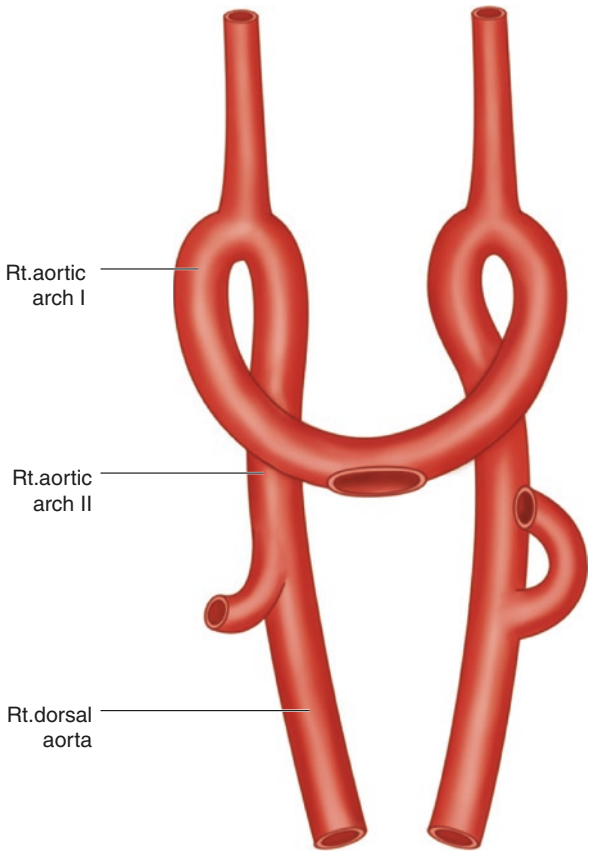

Fig. 2.1 The primitive aorta

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branching, and intussusception from existing blood vessels. This process involves complex regulatory cascades.

Aortic Arch Development

Aortic arch development includes the sequential development and then partial involution of six arch pairs which arise from paired dorsal aortae and fuse distally [1]. The ventral and dorsal segments of the primitive aorta are continuous through the first aortic arch. The second pair of aortic arches makes their appearance in the middle of gestation week 4. They give rise to the stapedial and hyoid arteries (Table 2.1). The first and second pairs of aortic arches regress rapidly and are not seen after day 31. The third pair of vascular arches arise by the end of week 4. Then, the common carotid and

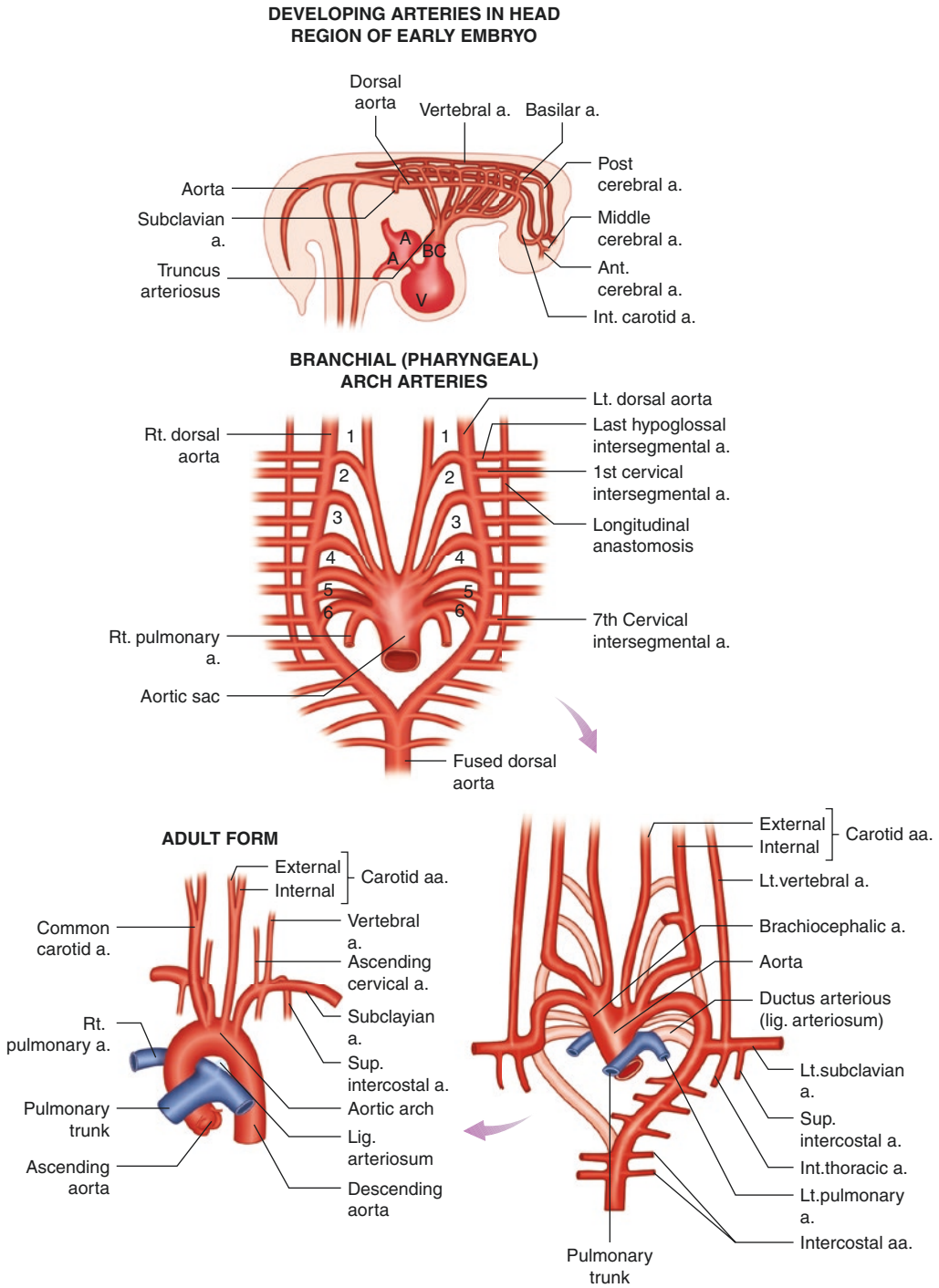

Fig. 2.2 The six-paired system of aortic arches

proximal portions of the internal carotid arteries arise from the third pair of aortic arches. The internal carotid arteries are attached to the cranial portions of the dorsal aortas, which form the remainder of the carotid artery. Next, the fourth pair of arches develops. Interestingly, their development differs depending on the side of the arch discussed. On the right side, the fourth arch forms the proximal portion of the right subclavian artery. The distal portion of the subclavian artery then forms from the right dorsal aorta. The right primitive ventral aorta forms the brachiocephalic arterial trunk and the first portion of the aortic arch. On the left side, the fourth arch becomes the arch of the aorta and is continuous with the primitive left dorsal aorta. The left subclavian artery arises directly from the aorta. Of note, in mammals, the fifth aortic arches are rudimentary and either degenerate or may never even develop. The sixth pair of arches arise by the middle of week 5 and give rise to the left and right pulmonary arteries. Once pulmonary vasculature is established, the communication between the primitive dorsal aorta and the pulmonary arteries regresses. On the right side, the regression is total and complete. On the left side however, the distal portion of the left arch remains in communication with the dorsal aorta until birth, forming the ductus arteriosus. The ductus arteriosus diverts blood from the pulmonary artery to the aorta. In the neonatal period, the functional duct becomes the anatomic ligamentum arteriosum (Table 2.1 and Fig. 2.3).

Aortic Arch Anomalies

Most aortic arch anomalies are secondary to abnormal retention or disappearance of various embryonic vascular segments.

Patent Ductus Arteriosus (Fig. 2.4)

During intrauterine life, the ductus arteriosus allows for blood flow between the pulmonary artery and aorta. In full-term infants, the duct usually closes within the first two days of life. Persistence of the ductus arteriosus postnatally often occurs in premature infants caused by delayed ductal involution [1]. Closure of the ductus involves the prostaglandin cascade as well as mitochondrial oxygen sensing and altered voltage-gated potassium channels. However, the direct pathogenesis of ductal patency has not yet been defined. Ductal patency is two to three times as common in girls as in boys, with most of the cases occurring as isolated defects. However, persistence of a large ductus arteriosus may occur in association with a variety of congenital cardiovascular malformations. Typical concomitant findings are left ventricle hypertrophy and pulmonary artery dilation. A persistent ductus arteriosus may also be associated with coarctation of the aorta, transposition of the great vessels, and ventricular septal defects.

Table 2.1 Correspondence of embryonic aortic arch arteries to their derivative adult counterparts

Embryonic	Adult
Aortic arches	
1	Maxillary artery (portion of)
2	Stapedial artery (portion of) Hyoid artery (portion of)
3	Right and left common carotid arteries (portion of) Right and left internal carotid arteries
4	Right subclavian artery (portion of) Arch of the aorta (portion of)
5	Regresses in humans
6	Right and left pulmonary arteries (portion of) Ductus arteriosus

Coarctation of the Aorta

Coarctation of the aorta is defined as a luminal narrowing of the aortic arch, usually posterior and adjacent to the insertion of the ductus arteriosus. Less frequently, coarctation can occur proximal to the left subclavian artery. The discrete narrowing results in at least a 20 mm Hg gradient across the coarctation and occurs two to five times more frequently in males than females. It is responsible for up to 8% of all cardiovascular congenital defects. Simple coarctation is the most common form. It may be detected de novo in adults and is not associated with other malformations. Complex coarctation is often associated with abnormal aortic valve (AV) morphologies (50–80% of cases of bicuspid AV), abnormal dimensions of the transverse aortic arch (isthmus), and abnormal antegrade left ventricular output in utero. It can also be seen with ventricular septal defects, patent ductus arteriosus, parachute deformity of the mitral valve, and circle of Willis cerebral artery aneurysm (berry aneurysm; 10% of cases).

Aortic pseudocoarctation is a rare congenital anomaly resulting from kinking and buckling of an excessively elongated aorta [2]. Pseudocoarctation is not usually associated with an aortic aneurysm. Aortic atresia, or complete interruption of the aorta, is usually lethal unless it is treated surgically within the first month of life.

The etiology of aortic coarctation is not known. Proposed theories for the development of congenital aortic coarctation include: the flow theory, the reduction of antegrade intrauterine blood flow causing underdevelopment of the aortic arch; the ductal theory, constriction of ductal tissue extending into the thoracic aorta; and simply a primary defect of the aortic wall. Acquired causes include inflammatory processes such as Takayasu arteritis and severe atherosclerosis (Fig. 2.5).

Right Aortic Arch (Fig. 2.6)

In the right aortic arch anomaly, the right rather than the left dorsal aorta is maintained in its entirety. The most common type is the right arch in which there is an aberrant left subcla-

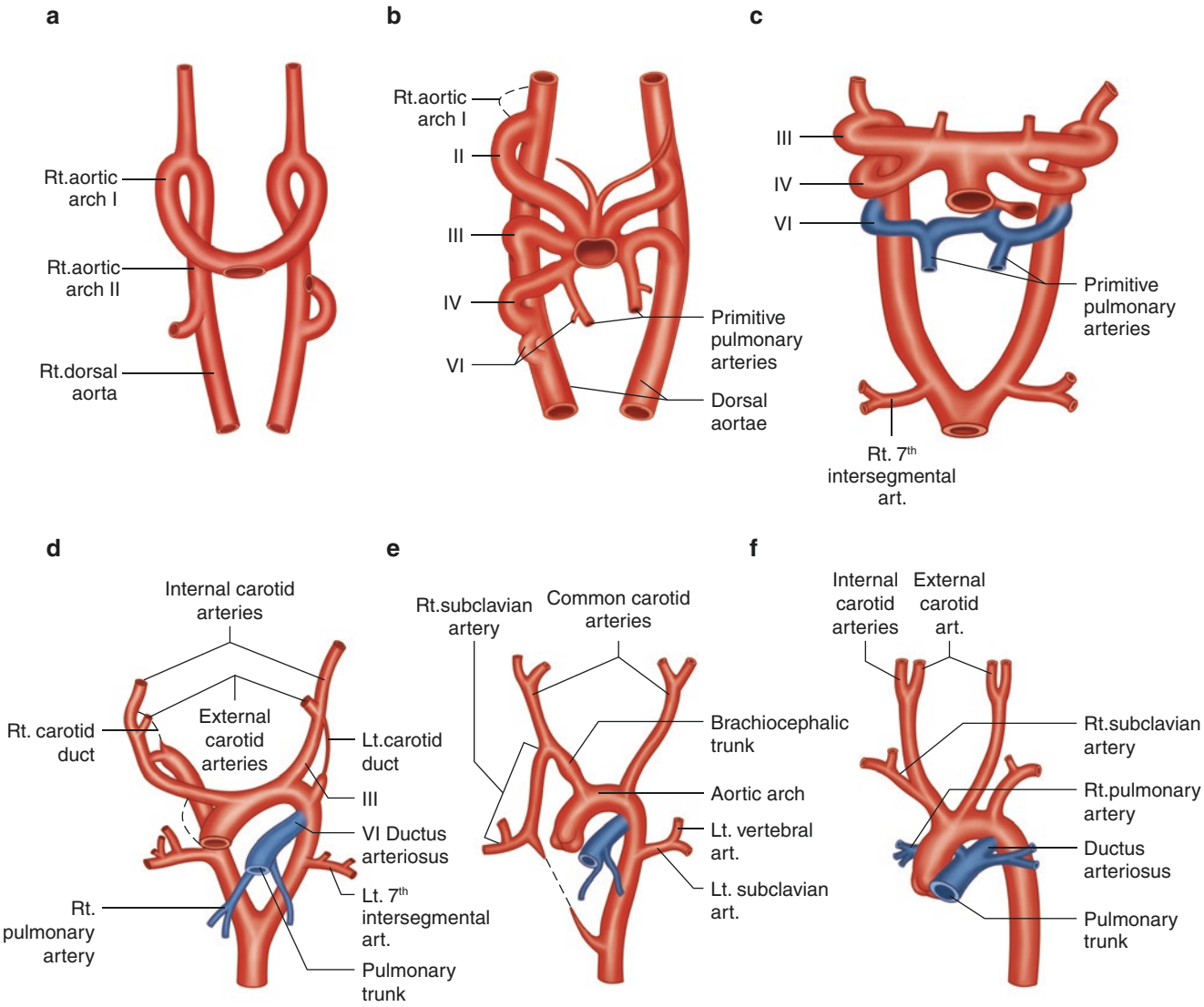

Fig. 2.3 Development of the aortic arch system. Sizes of embryos: (**a**) 3 mm, (**b**). 4 mm, (**c**). 10 mm; the first two aortic arches have regressed; the third, fourth, and sixth are present; and the truncoaortic sac has been divided by the formation of the aortopulmonary septum, so that the sixth arches are now continuous with the PT. (**d**). 14 mm; the dorsal aortas, between the third and fourth arches, have disappeared, and the third arch begins to elongate; the right sixth arch has disappeared, but the left sixth arch persists as the ductus arteriosus. (**e**). 17 mm; the right dorsal aorta has become atrophic between its junction with the left dorsal aorta; the origin of the right seventh intersegmental artery has now become attenuated and later disappears; the remaining components of the right dorsal aorta and right fourth aortic arch form the proximal subclavian artery. (**f**). neonate; the distal part of the left sixth aortic arch, the ductus arteriosus, normally involutes to form the ligamentum arteriosum. Art. artery, Lt. left, Rt. right

vian artery [3]. The vessels originate in the following order: left common carotid, right common carotid, right subclavian, and left subclavian artery. This type is rarely associated with congenital heart disease. Symptoms can result from vascular ring formation. The mirror-image type (branching pattern of the aortic arch is the mirror image of normal – left brachiocephalic trunk, right common carotid, and subclavian arteries) is almost always associated with congenital heart disease, especially cyanotic heart disease. In this case, the arch lies anterior and to the right of the trachea and esophagus.

Double Aortic Arch (Fig. 2.7)

Double aortic arch is the result of persistence and continued patency of the segment of the right dorsal aorta between the origin of the right seventh intersegmental artery and its junction with the left dorsal aorta, allowing for an ascending aorta that divides anterior to the trachea and esophagus, with one arch coursing to the left and one to the right. The arches completely encase the trachea and esophagus and rejoin posteriorly to form the descending thoracic aorta. This encasement can exert a compressive effect and lead to symptoms.

The double aortic arch patient often becomes symptomatic in the first few weeks of life secondary to this constriction, causing airway compression. The most classic sign is nonpositional stridor that is not relieved by bronchodilators. Double aortic arch can also lead to feeding problems, due to compression of the esophagus. Rarely, this can present with other congenital malformations, including ventricular septal defect, atrial septal defect, patent ductus arteriosus, and tetralogy of Fallot. Double aortic arch can be categorized as dominant right, dominant left, or balanced arches.

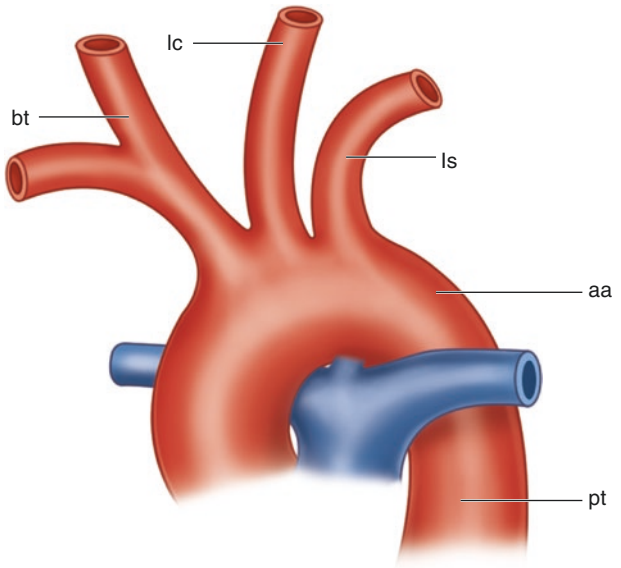

Fig. 2.4 Schematic drawing of a patent ductus arteriosus. Bt brachiocephalic trunk, lc left carotid artery, ls left subclavian artery, aa aortic arch, pt pulmonary trunk, * ductus arteriosus

Interrupted Aortic Arch

Interrupted aortic arch results from a complete interruption or atresia of a segment of the aortic arch [4]. It is classified into three subtypes based on the anatomic location of the atretic segment, known as the Celoria and Patton classification (Fig. 2.8). Type A, the arch interruption occurs distal to the left subclavian artery (1/3 of cases). Type B, the interruption occurs between the left subclavian artery and the left common carotid artery (most common; nearly 2/3 of cases). Type C, interruption occurs proximal to the origin of the left common carotid artery (least common; around 1% of cases). Clinically, the presentation is similar to that of coarctation. Patients remain stable as long as the ductus arteriosus remains patent. This anomaly has been associated with single ventricle, ventricular septal defect, left ventricular outflow tract obstruction, anomalous right subclavian artery, aortopulmonary window, truncus arteriosus, and transposition of the great vessels.

Anomalous Right Subclavian Artery (Fig. 2.9)

The origin of the right subclavian artery is from the right fourth aortic arch, the dorsal portion of the aorta, and the sev-

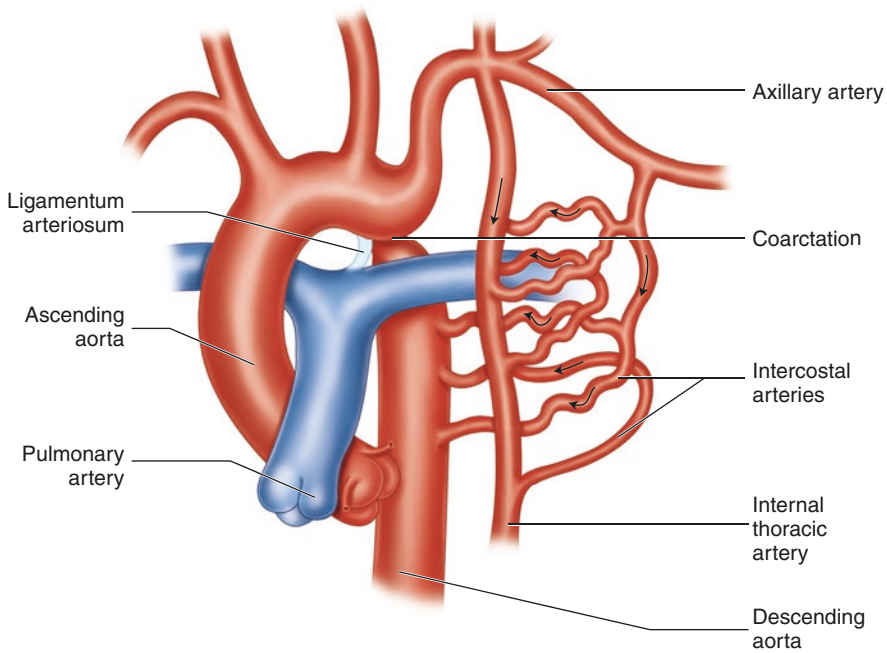

Fig. 2.5 Coarctation causes severe obstruction of blood flow in the descending thoracic aorta. The descending aorta and its branches are perfused by collateral channels from the axillary and internal thoracic arteries through the intercostal arteries (arrows)

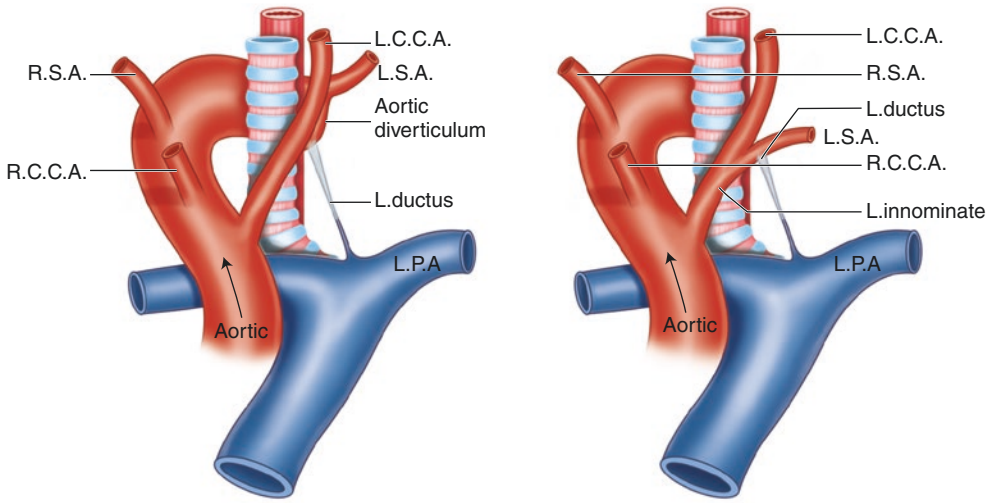

Fig. 2.6 (**a**) Right aortic arch with aberrant left subclavian artery. (**b**) Right aortic arch with mirror-image branching pattern

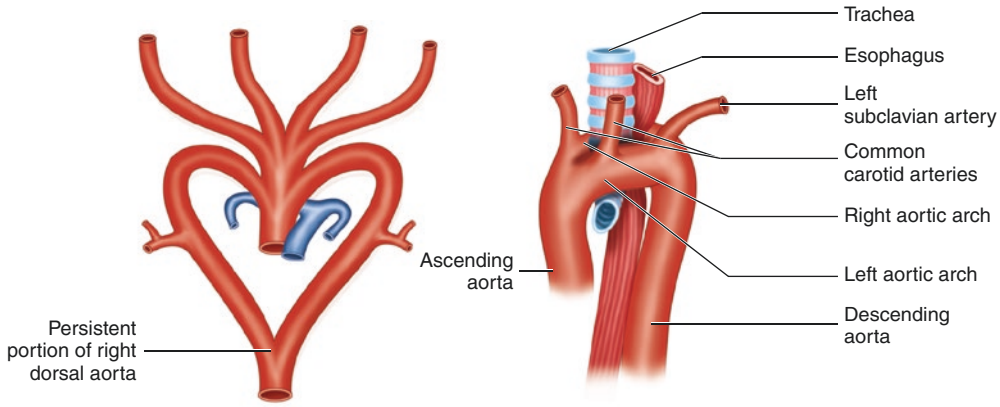

Fig. 2.7 Double aortic arch

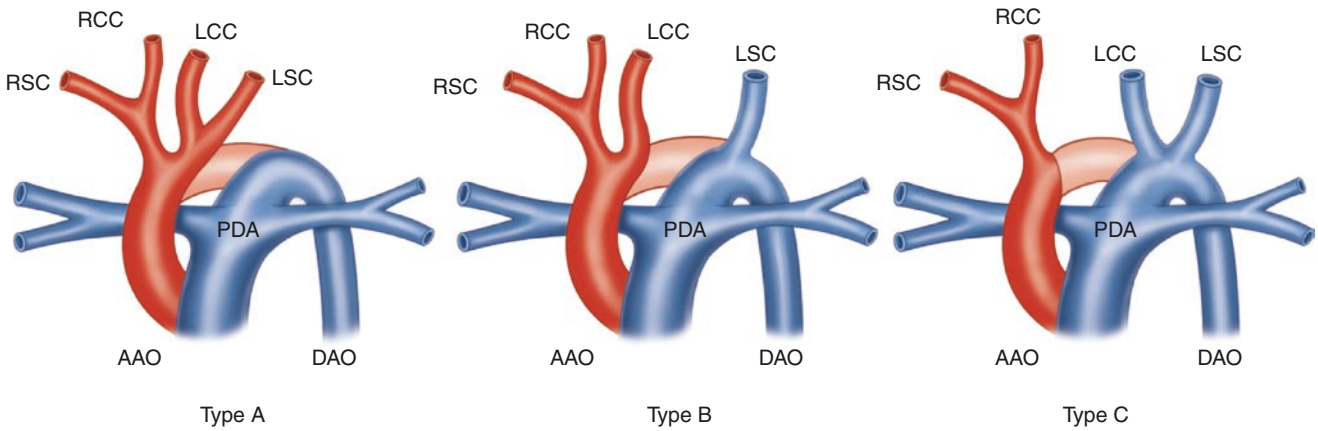

Fig. 2.8 Celoria and Patton classification of interrupted aortic arches

enth intersegmental artery. When this patterned segment is absent, the right subclavian artery can arise from the aortic arch distal to the left subclavian artery [5]. This can only occur if the right dorsal aorta, between the origin of the right seventh intersegmental artery and the junction with the left dorsal aorta, is maintained, so as to form the proximal portion of the right subclavian artery. An anomalous right subclavian artery arising from the proximal portion of the descending thoracic aorta is the most common aortic arch anomaly [6]. However, few patients have clinical symptoms directly attributable to this anomaly. Symptoms that do occur, like airway obstruction and dysphagia, are rare without aneurysmal degeneration of the vessel. Most patients with dysphagia, but without aneurysmal changes, are infants [7].

Absent Left Pulmonary Artery

The left pulmonary artery can be absent when it arises from a left-sided ductus arteriosus (or ligamentum arteriosum), as a result of abnormal disappearance of the proximal left sixth arch.

Absence of one of the pulmonary arteries in itself produces few or no symptoms. If there is no associated cardiac defect, patients may present with slight dyspnea, exercise intolerance, cough, recurrent respiratory infections, pulmonary hypertension in the contralateral lung arteries, or occasional hemoptysis due to the bronchial arterial supply to the affected lung. However, most patients are asymptomatic, and the diagnosis is first suggested by the appearance of the involved lung on a routine chest radiograph. The ipsilateral lung will be smaller than normal, and the contralateral lung will be overinflated and may herniate across the midline [8–10]. When associated with congenital heart disease, it can be seen with right-sided aortic arch, septal defects, truncus arteriosus, and tetralogy of Fallot. Patients who have congenital heart disease and a unilateral absent pulmonary artery usually present with symptoms that are due to their congenital heart lesions.

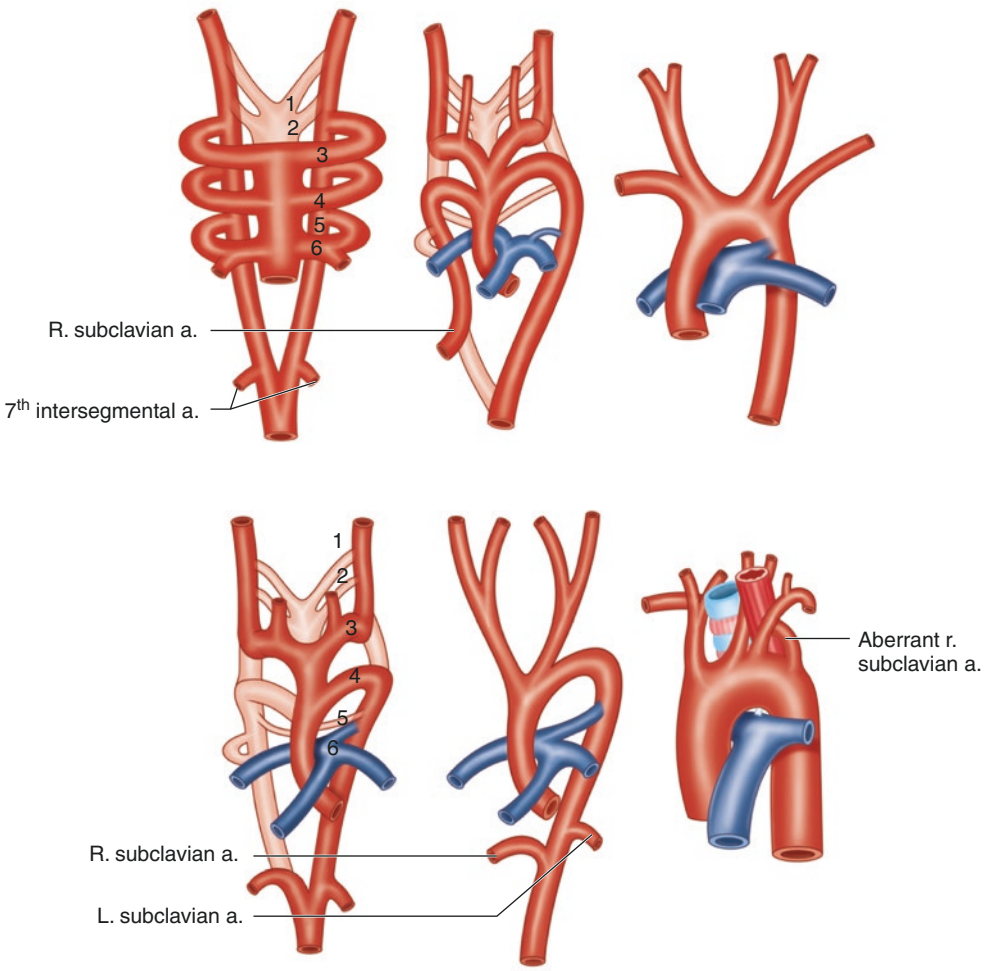

Fig. 2.9 Schematic of aberrant (anomalous) subclavian artery. The shaded arterial segment represents normal right subclavian artery formation in top row and anomalous formation in the bottom row

Normal Aortic Anatomy

The aorta is the largest artery of the human body. Though a continuous structure, for the sake of clinical reference, the aorta is divided logically into the ascending, arch, descending, suprarenal, and infrarenal divisions, and terminates at the iliac bifurcation.

Less than two millimeters (mm) thick in young adults, the aortic wall is, nevertheless, highly resilient [11]. Various modalities (direct observation, ultrasound, CT scan, and MRI) have been used to determine norms for external and internal diameters [12]. In one CT study, mean internal and external aortic diameter for the ascending aorta at end systole in "normal" individuals of both sexes were assessed with findings as follows: external diameter of 35.6, 38.3, and 40 mm for females and 37.8, 40.5, and 42.6 mm for males in age groups 20–40, 41 to 60, and above 60 years, respectively [13], and internal diameter of 38.0, 40.7, and 42.4 mm for females and 40.2, 42.9, and 45.0 mm for males in the same age brackets.

Of course, as volume is carried away by branching muscular arteries arising in its distal course, the volume in the aorta, and hence its diameter, decreases. Age, sex, and size are important covariants as demonstrated in Table 2.2 [14].

A Danish study to establish ultrasonic norms for the abdominal aorta demonstrated a mean suprarenal aortic diameter of 18.4 mm for male vs.16.6 mm for females and for the distal aorta, 16.0 mm vs. 13.7 mm, respectively [15].

The aorta demonstrates the tri-layer pattern seen in all vessels apart from capillaries – tunica intima, tunica media, and tunica externa. The aorta is the prototype "elastic artery" featuring an incredibly thick tunica media rich in smooth muscle and elastic fibers. In fact, the aorta is so thick that it requires its own nutritive capillary network, the vasa vasorum. In dogs, it has been shown that the percent smooth muscle volume varies little across the arterial tree (45–55%), but the aorta has a dramatically greater elastic tissue volume (22.6%) [16].

Ventricular ejection is a very energetic event, and a small but significant portion of the energy is briefly sequestered in the stretching of aortic elastic fibers. This energy is returned an instant later as elastic recoil, sustaining flow to coronary arteries and peripheral vessels beyond systole into diastole (Windkessel effect). This also means that the same flow is delivered at a lower systolic pressure than would be the case for an inelastic tube, so the aorta is not simply a pipe. With aging, the aorta does in fact become more "pipelike," accounting, at least in part, for the higher peak systolic pressures and widening of pulse pressure as years advance [17]. Ultrasound observations of the abdominal aorta confirm a loss of pulsatile expansion with age [15].

Histologically, the aging aorta is characterized by thickening and atherosclerosis of the intima, along with cystic necrosis, elastin fragmentation, fibrosis, and medial necrosis of the media as well as fibrosis in adventitia. These changes of aortic aging decrease aortic elasticity (distensibility) [14].

Thoracic Aorta

The thoracic aorta's greatest relational complexity occurs within the mediastinum. It anchors in the transverse fibrous skeleton of the heart and its ascending segment lies within the pericardium. It ascends from the annulus in intimate rela-

Table 2.2 Gender-specific effects of obesity on regional aortic diameter – data presented as mean with normal range (+/− 2SD)

Aortic diameter (mm)	Normal weight	Overweight	Obese	ANOVA p
		Male		
Aortic valve annulus	24.0 (18.8–29.2)	24.7 (19.5–29.9)	25.7 (20.7–30.7)	<0.05
Sinus of Valsalva	32.2 (24.6–39.8)	32.9 (25.3–40.5)	33.3 (25.3–31.3)	<0.05
Sino-tubular junction	24.9 (18.1–31.7)	25.8 (17.0–34.6)	25.9 (19.1–32.7)	<0.05
Ascending aorta	26.6 (18.2–35.0)	27.8 (18.8–36.8	28.6 (23.2–34.0)	<0.01
Proximal descending aorta	20.4 (14.6–26.2)	21.2 (15.6–26.8)	22.1 (16.5–27.7)	<0.01
Distal descending aorta	17.4 (12.0–22.8)	18.3 (12.7–23.9)	19.0 (14.8–23.2)	<0.01
BMI (kg/m2)	22 +/−1.7	27 +/−1.6	34 +/−4.8	<0.01
BSA (m2)	1.9 (+/−0.1)	2.0 (+/−0.1)	2.3 (+/−0.2)	<0.01
		Female		
Aortic valve annulus	20.2 (17.0–23.4)	21.7 (18.5–23.9)	21.6 (17.6–25.6)	<0.01
Sinus of Valsalva	27.6 (22.0–33.2)	28.6 (21.6–35.6)	27.8 (22.2–33.4)	<0.05
Sino-tubular junction	21.7 (16.7–26.7)	22.5 (16.5–28.5)	22.3 (16.5–28.1)	<0.05
Ascending aorta	24.8 (17.6–32.0)	26.7 (19.3–34.1)	26.9 (19.3–34.5)	<0.01
Proximal descending aorta	18.6 (14.6–22.6)	19.5 (14.9–24.1)	20.1 (15.5–24.7)	<0.01
Distal descending aorta	16.1 (14.1–18.1)	16.9 (14.7–19.1)	17.6 (15.7–19.5)	<0.01
BMI (kg/m2)	22.0 (+/−1.6)	27.0 (+/−1.5)	37.0 (+/−4.8)	<0.01
BSA (m2)	1.7 (+/−0.1)	1.8 (+/−0.1)	2.0 (+/−0.2)	<0.01

tion to the pulmonary artery to the left with the remaining circumference hugged by the right atrium. Its first branches, the coronary arteries, run to the right and left within the atrioventricular sulcus.

As it ascends from the annulus it points just a bit rightward and anterior, in the axis of the heart, and so runs anterior to the posteriorly arching pulmonary trunk to the left and vena cava on the right.

Crossing the left right pulmonary artery, it ascends for approximately five centimeters (cm) where the pericardium fuses with the adventitia as it transitions to the arch. Overlying this pericardial sheet anteriorly is the thymic remnant.

The general orientation of the arch is from right to left and from anterior to posterior. It is a place of significant turbulence as red cells are shouldering one another around the geometric challenge of the arch and the orifices of the brachiocephalic, left carotid, and left subclavian arteries. The resultant microtrauma to the endothelium (tunica intima) contributes to endothelial dysfunction and makes this a site for early (and, often, eventually severe) atherosclerotic transformation [18].

On the lesser curve of the arch, typically just beyond the origin of the left carotid, is a thick, fibrotic tether to the pulmonary trunk bifurcation, the ligamentum arteriosum (LA). Just distal to the LA, the left vagus nerve sends the recurrent laryngeal nerve looping from posterior to anterior around the aorta.

Beyond the left subclavian artery, the arch moves posterior, transitioning to the descending aorta (T4–T5 intervertebral level) which parallels the spine on its downward journey through the diaphragmatic aortic hiatus where it emerges as the abdominal aorta. Throughout the length of the descending thoracic and abdominal aorta, small posterolateral branches emerge to supply various thoracic and abdominal structures (intercostal, subcostal, mediastinal, bronchial, diaphragmatic, esophageal, pericardial, and lumber) (Figs. 2.10 and 2.11).

Before moving on to the abdominal aorta, it is worth noting that congenital variations in the thoracic aorta are not rare. In fact, the most common congenital arterial anomaly is a bicuspid aortic valve, existing in roughly 1% of the population and leading to premature valvular dysfunction. Deviations from the typical brachiocephalic-left common carotid-left subclavian orientation of the great vessels are not rare and, of course, patent ductus arteriosus occurs in 2/1000 term births and 8/1000 premature births [19].

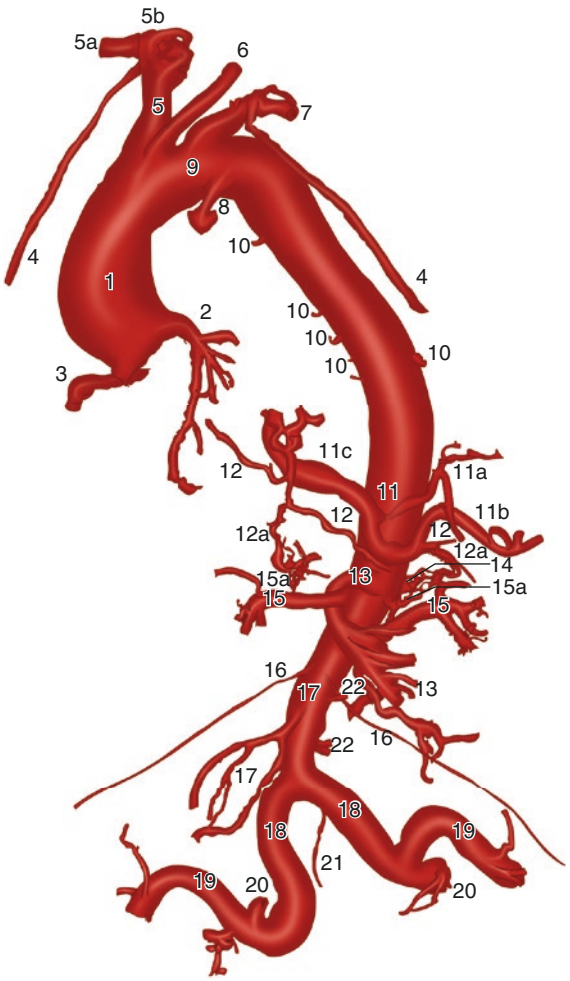

Fig. 2.10 Anterior anatomic dissection of the aorta from aortic valve to aortic bifurcation with labeling of all branches (numbering). 1. Aorta; 2. Left coronary artery; 3. Right coronary artery; 4. Internal thoracic arteries; 5. Brachiocephalic trunk (innominate), (a) Right subclavian artery and (b) Right common carotid artery; 6. Left common carotid artery; 7. Left subclavian artery; 8. Ligamentum arteriosum; 9. Aortic arch; 10. Thoracic intercostal arteries; 11. Celiac trunk, (a) Left gastric artery, (b) Splenic artery, and (c) Hepatic artery; 12. Inferior phrenic arteries, (a) Superior suprarenal arteries; 13. Superior mesenteric artery; 14. Middle suprarenal artery (left only); 15. Renal artery, (a) Inferior suprarenal arteries; 16. Gonadal (testicular or ovarian) arteries; 17. Inferior mesenteric artery; 18. Common iliac arteries; 19. External iliac arteries; 20. Internal iliac arteries; 21. Median sacral artery; and 22. Third and fourth lumbar arteries

Abdominal Aorta

Just beyond the diaphragmatic aortic hiatus, from the anterior aortic wall, the celiac trunk and superior mesenteric artery (SMA) arise in quick succession. Typically, just below the level of the SMA, the left and right renal arteries come off the aorta laterally, though it must be noted that renal arteries not infrequently show significant variation in location and number. Multiple (typically two) renal arteries on one or both sides may exist. Gonadal arteries arise anterolaterally and typically a few centimeters inferior to the renal arteries.

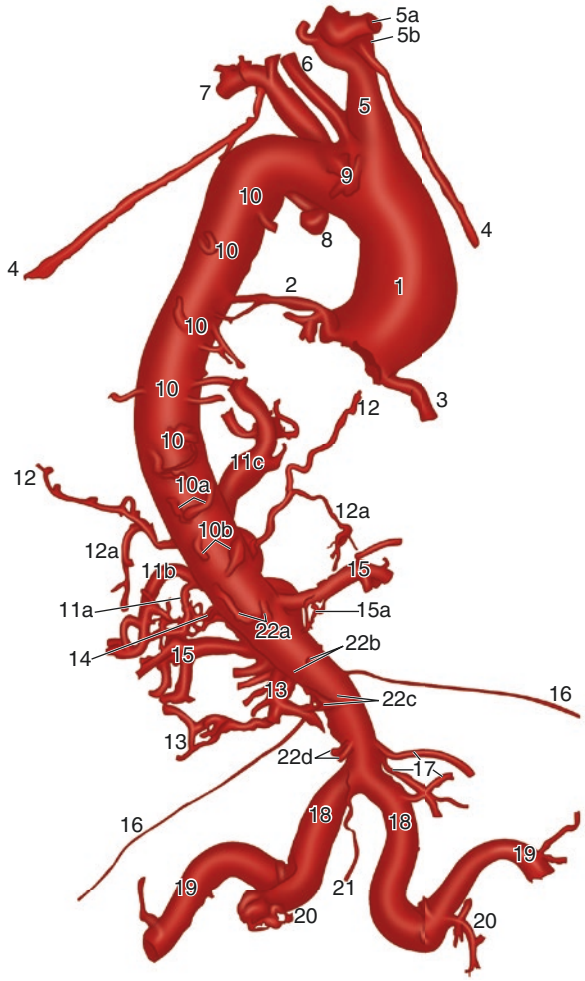

Fig. 2.11 Posterior anatomic dissection of the entire adult aorta from the aortic valve to aortic bifurcation with labeling of all branches. 1. Aorta; 2. Left coronary artery; 3. Right coronary artery; 4. Internal thoracic arteries; 5. Brachiocephalic trunk (innominate), (a) Right subclavian artery and (b) Right common carotid artery; 6. Left common carotid artery; 7. Left subclavian artery; 8. Ligamentum arteriosum; 9. Aortic arch; 10. Thoracic intercostal arteries, (a) T11 and (b) T12. 11; Celiac trunk, (a) Left gastric artery, (b) Splenic artery, and (c) Hepatic artery; 12. Inferior phrenic arteries, (a) Superior suprarenal arteries; 13. Superior mesenteric artery; 14. Middle suprarenal artery (left only); 15. Renal artery, (a) Inferior suprarenal arteries; 16. Gonadal (testicular or ovarian) arteries; 17. Inferior mesenteric artery; 18. Common iliac arteries; 19. External iliac arteries; 20. Internal iliac arteries; 21. Median sacral artery; and 22. Lumbar arteries, (a) L1, (b) L2, (c) L3, and (d) L4

The inferior mesenteric artery (IMA) is the last major branch to arise from the anterior aortic wall and supplies the hind gut just as the celiac trunk supplied the foregut and the SMA the midgut. It arises substantially distal to the renal and gonadal vessels at the level of L3, approximately 5 cm above the iliac bifurcation. It is also very susceptible to atherosclerotic occlusion in the elderly, and in such cases, may be an asymptomatic finding or may be a source for the development of ischemic colitis. Numerous lumbar arteries arise from the aorta. The middle (median) sacral artery is typically the last branch at the level of the aorto-iliac bifurcation.

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Pathophysiology of Ascending Aortic Aneurysm and Dissection

3

Thomas E. Gaines and Lauren Benner Grimsley

Involvement of the ascending aorta is the distinguishing characteristic of type A aortic dissection. Type A dissection remains a highly lethal event with in-hospital mortality rates of 17–26% [1]. Type A dissections occur from childhood to old age with a mean age at presentation of 62 years [1]. Dissections commonly occur in patients with ascending aortic aneurysms but occur unpredictably in patients with minimal or no aortic enlargement. Most dissections occur in the setting of hypertension [2]. Currently prophylactic ascending aortic surgery and control of hypertension are the mainstays of treatment prior to the onset of dissection. Ascending aortic surgery for acute type A dissection remains the preferred approach with better survival than medical treatment even in the very elderly [1]. The intent of this chapter is to provide an overview of the pathophysiology of type A dissection and ascending aortic aneurysms. The following topics are included in the discussion:

- Aortic structural mechanics and function
- Developmental biology
- Micromechanics and microstructure
- Histology and ultrastructural changes in aneurysms and dissections
- Mechanics and prediction models of ascending aneurysms
- Ascending aorta postulates

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Aortic Mechanics and Function

The ascending aorta is a conduit but more than that, part of an essential compliance chamber heavily dependent upon preservation of its elastic elements. Ventricular pulsation delivers a bolus of blood and with it a pulse wave of pressure and flow that repeats with each systole. However, rather than unmitigated pulsatile flow with potentially injurious peak pressures and the associated energy costs to the heart of accelerating the blood mass with each cycle, flow becomes nearly continuous as it reaches peripheral exchange vessels. Much of this amplitude dampening occurs in the proximal aorta and the flow pulse amplitude decreases markedly by the time it reaches the femoral arteries [3]. The compliance chamber of the proximal arterial system expands during systole and then recoils elastically to maintain diastolic blood pressure and flow in the peripheral circulation. A conceptual model relating pressure and flow in the arterial system is termed the *Windkessel* ("air chamber"). The model posits a pump with a compliance chamber connected in parallel with a resistance vessel [4]. The model and constitutive equations have been modified by expanding the original two elements, compliance and resistance, to include impedance and inertial terms and maps well to empirical data [5, 6]. Disturbances in the *Windkessel* properties of the ascending aorta, primarily a loss of elasticity (compliance), occur with disease and aging, resulting in upstream effects on the heart and downstream hypertensive vascular and end organ damage [6, 7].

Elastic properties are characterized by the behavior of the material or structure under conditions of loading. For pure elastic deformations where the material returns to its original state, the relationship between stress or load and strain or deformation is linear and can be expressed by the relationship E = Stress/strain, where E is constant and is termed Young's modulus of elasticity. Young's modulus is an intrinsic material property. The higher the modulus of elasticity, the stiffer is the material. Materials also have a yield point where additional strain results in plastic deformation from which the material does not return to its original state.

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Further strains beyond the yield point lead to a point at which rupture occurs, and this point defines the tensile strength of the material. The elastic behavior of arteries, however, is non-linear, and the stress/strain curves at lower strains show larger deformations relative to load than the values at higher strains [3]. The curve is "J shaped" (Fig. 3.1). That is, the more the strain after a certain threshold is reached, the stiffer the artery wall. This occurs because elastic fibers whose primary structural component is elastin are first tensioned, while collagen fibers that are much stiffer remain slack. Nearer the limit before the tissue ruptures, collagen fibers come under tension, and there is very little strain for large changes in stress. An incremental modulus can be described for a specified level of strain and is termed E_{inc}, represented by the slope of a line tangent to the curve at that strain. The elastic modulus is itself dependent on strain.

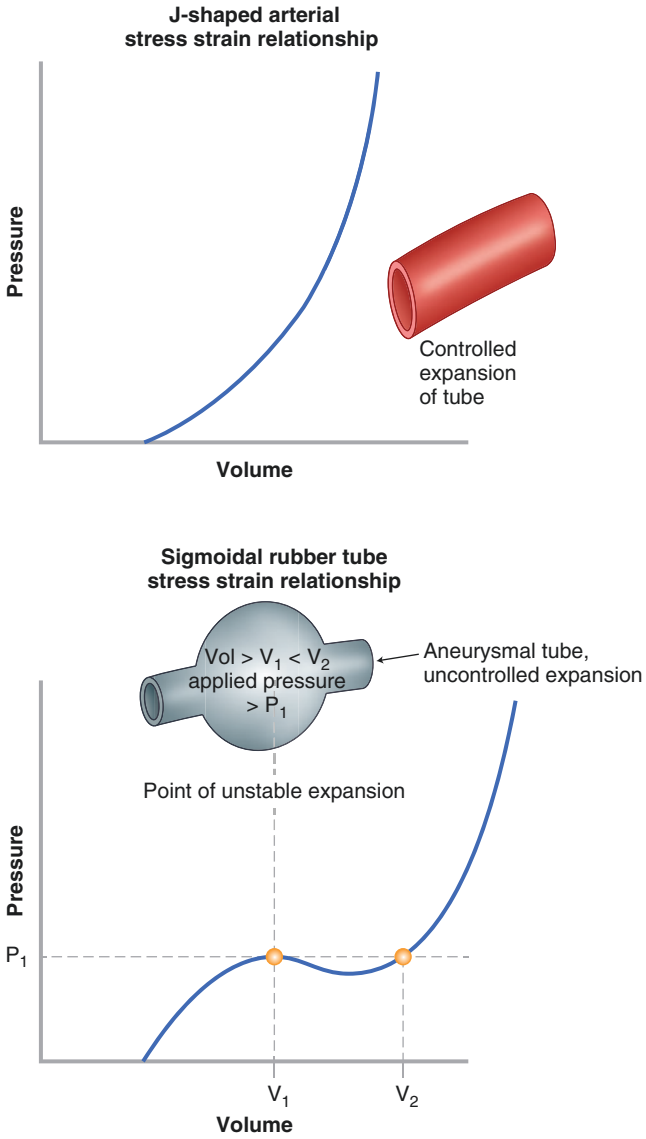

Fig. 3.1 Illustration of the shape of the stress/strain relationship in arteries and in rubber tubes. The elastomeric properties of isolated elastin are similar to those of rubber polymers. Stress is expressed as pressure which is related to wall tension by the law of Laplace as described in the text, and the volume of a cylindrical element is proportional to the square of the radius of that element. The rubber tube is subject to unstable expansion and aneurysm formation when the pressure and volume in the tube exceed a threshold value as one who has ever blown up a balloon or distended a pure rubber hose can attest

Testing of isolated ascending aortic strips from undiseased human aortas gives a tensile strength of 2.18 MPa with strips oriented circumferentially and 1.14 MPa with longitudinal strips. The tensile strength decreases in an older age group (mean age 51 vs. 25) to 1.20 MPa and 0.66 MPa, respectively. The maximum stretch ratio (λ, defined by length at load/length at initial state) observed at tissue failure was about 2.35 for circumferential strips and 2.0 for longitudinal strips in the younger group and about 1.8 and 1.7, respectively, in the older group [8] demonstrating remarkably compliant material and large strains. Based on these results which have been confirmed in animal models [9], the young, healthy aorta is anisotropic, that is, that mechanical properties are dependent upon the direction of loading. Anisotropy, in addition to tensile strength and compliance, diminishes with age, likely as a result of adverse remodeling of the wall structure.

The mechanical shape of the ascending aorta can be approximated by a cylinder of inner radius r_i, outer radius r_o, and thickness t and with internal pressure P. The average circumferential (Kirchhoff) wall tension at an equilibrium condition, τ_θ, can then be expressed by the relation [10]:

$$\tau_\theta = \mathrm{Pr_i}/t\lambda_c^2$$

where λ_c is the circumferential stretch ratio. This is the familiar "law of Laplace" implying that the wall tension in an aneurysm is proportional to the product of the radius and the blood pressure.

The cylinder is also subject to longitudinal (or axial) stress τ_z, given by the relation:

$$\tau_z = \frac{\mathrm{Pr_i}}{t\left(r_i + r_o\right)\lambda_z^2} + F\left(l\right)$$

where $F(l)$ is the sum of longitudinal forces in addition to P as described below, and λ_z is the longitudinal stretch ratio.

In the simple case of a thin-walled, closed cylinder, with small deformations and no force other than internal pressure, the stretch ratios are close to 1, the inner and outer radiuses are almost equal, and the longitudinal stress would be about half the circumferential stress.

Wall shear stress τ_w is a function of blood flow Q and viscosity μ [11].

$$\tau_w = \frac{4Q\mu}{\pi r_i^3}$$

Assumptions of this simple model include that the aortic wall is incompressible and that strains are uniform across the thickness of the aortic wall. The former is a reasonable assumption for the aorta and implies that the wall thins as it expands circumferentially and longitudinally. The latter may not be a reasonable assumption since radially oriented stress and strain gradients within the aortic wall may contribute to the formation of dissection planes within the media. A property of the aortic media is that of residual strain and this does tend to normalize the distribution of strain across the thickness. Residual strain (or stress) consists of compression in the inner layers of the wall and tension on the outer layers and is likely caused by differential growth of the layers. This phenomenon can be demonstrated with cylindrical segments of aorta that, when cut open longitudinally, tend to turn inside out. This is quantified by the "opening angle" thus formed [11, 12] (Fig. 3.2). Under physiologic conditions, in vivo, it is estimated that the ascending aorta maintains a longitudinal strain of about 10% increasing to 15–20% at points in the cardiac cycle due to the motion of the heart [11]. Thus arteries are "prestressed" circumferentially and "prestretched" axially apart from the other loading forces of the circulatory system.

At physiologic pressures and in normal arteries, it has been empirically determined that the ratio of internal radius to wall thickness is between 7:1 and 10:1 [13]. Using the equation for circumferential wall tension above, the wall tension is then 7–10 times the blood pressure at the normal size of the artery. If the systolic blood pressure were 120 mmHg, or about 0.015 MPa, the circumferential wall tension in systole would reach about 0.11–0.15 MPa or an order of magnitude lower than the tensile strength of a healthy aorta. If, however, the aortic diameter is doubled from 2.5 to 5 cm, the systolic wall tension would double up to 0.3 MPa (unless the structural thickness also doubled), and while still well below the tensile strength, if hypertension were added by raising the blood pressure to 220 mmHg, the circumferential wall tension rises up to 0.58 MPa, and the longitudinal wall tension would be at least half that or about 0.3 MPa. With a longitudinal tensile strength of 0.66 MPa, the ratio of tensile strength to wall stress has gone from 10:1 to no better than 2:1, and that is even in the absence of thinning and degeneration of the wall.

The composite aortic stress/strain relationship with a more compliant elastin region and increasing stiffness as collagen is tensioned overcomes a difficulty intrinsic to the elasticity of simpler elastic materials that function at large strains. Rubber is such a material and has elastic properties very similar to isolated elastin. This kind of material is sometimes referred to as hyperelastic. For such a material, a plot of wall tension and radius can be generated for the stress/strain relationship. With a rubber tube this results in a sigmoid-shaped curve with a flat midrange portion that corresponds to a very large change in radius for a relatively small increment of wall tension. This is the difficulty: When loaded (or pressurized) to a certain critical point, there is suddenly a very large increase in diameter, much as one sees with the aneurysmal inflation of a balloon or rubber hose [3] (Fig. 3.1). The non-linear, J-shaped stress/strain relationship

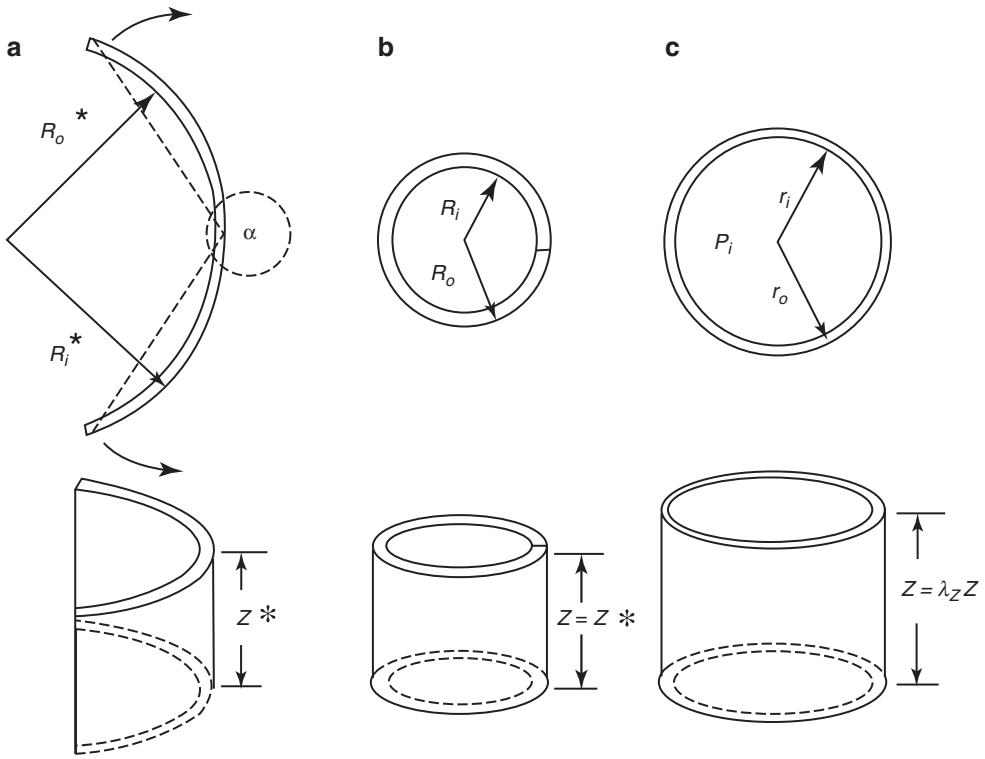

Fig. 3.2 Cylindrical model of aorta. (**a**) represents a segment of aorta opened longitudinally under a condition of no externally applied load. Z^* is the unstressed length of the segment, and R_i^* and R_o^* are the inner and outer radii of the cylinder wall. In this case, with the opening angle alpha greater than 180°, R_i^* is greater than R_o^*. (**b**) is the segment unloaded, and (**c**) is the segment under load. λ_z is the stretch ratio. That is the ratio of the length under load to the length at no load. (From: Okamoto et al. [12]. Reprinted with permission from Elsevier)

both provides the *Windkessel* and is an essential mechanism to avoid arterial aneurysms that might be associated with physiologic range blood pressures.

Longitudinal stress in the aortic wall is more complicated than the longitudinal stress seen in a simple closed cylinder model where it would be about half the circumferential stress. The forces acting to create axial strains include not only intraluminal pressure but the tethering of aortic arch branches and of the aortic root as well as displacement of the heart. On viewing cine aortagrams, a displacement of as much as 14 mm was detected, and a resultant 50% increase in longitudinal wall stress was predicted 2 cm above the sinotubular junction. A similar increase in longitudinal wall stress can be predicted in the absence of aortic root displacement by raising the systolic blood pressure to 180 [14]. The visible and tactile effects of hypertension on the ascending aortic wall are quite dramatic as any cardiac surgeon can attest.

Creep is a material property of importance in sustained and repeated loading of organic materials [15] and therefore of the arterial system, especially with aging. There is very little turnover of elastin and collagen after early growth and development [7] rendering tissues dependent upon these elements subject to repeated micro-injury, and this process likely contributes to the gradual elongation and dilation of aging arteries. Resistance to damage resulting from cyclic loading of aortic tissue is an essential property and a result of the evolutionary background of vascular tissues. Given, however, the low turnover of collagen and elastin, fatigue damage is likely to play a major role in the life history of the aorta. Fracture toughness in pig aortas declines after a million loading cycles [16], and mitral chordae tendineae, another elastic circulatory structure exposed to extreme cyclic loading, exhibit micro-cracks, loose their organized collagen structure, and show an increased creep rate associated with mechanical fatigue [17].

Developmental Biology of the Ascending Aorta

The pathophysiology of ascending aortic aneurysms and dissections begins in perturbations of the complex genetic and microenvironmental processes of the developing aorta. From the earliest stages, there are significant phenotypic differences among cell populations from one region of the aorta to the next. The boundaries of these regions are quite distinct and consistent for both murine and human aortas and in other species that have been studied. The phenotype in each region corresponds to a particular embryonic site of origin [18–21]. These cellular phenotypes manifest differing responses to cellular and intercellular signaling and are associated with differing mechanical properties, structural defects, and responses to injury and aging in different regions of the aorta. Ascending aortic disease primarily involves degenerative aneurysms and dissections that very often have little inflammatory or atherosclerotic component, while the more distal aorta is affected commonly by atherosclerotic lesions with a major inflammatory component.

Patterns of gene expression characteristic of groups of cells at various points in the course of embryonic development can be used to distinguish cells and trace their embryonic lineage. Multiple intra- and extracellular signaling mechanisms can be observed that control gene expression. Studies involving human embryonic stem cells as well as genetically altered zebra fish and mouse embryos have added considerably to an understanding of the cellular mechanisms that underlie differentiation, development, and growth, extending into postnatal life, maintenance, and senescence of the aorta.

Endothelial Origins

Mesodermal outpouchings called blood islands are apparent in the yolk sac of 7-day-old mouse embryos [22] and by 9 days contain angioblasts and erythroblasts, progenitors of both blood and vascular cells. The close association of hematopoietic and endothelial precursors suggests a common progenitor hemangioblast, and the existence of a hemangioblast was documented with the discovery of blast colony-forming cells in gastrulating (the stage at which the three germ layers, endoderm, mesoderm, and ectoderm, are formed) mouse embryos that express the receptor tyrosine kinase Flk-1 (Kdr, VEGFR2) and the mesodermal gene brachyury (T). Flk1 is a receptor for Vegf and seen in the earliest stage of endothelial differentiation. The brachyury gene, a member of the T-box complex, encodes for an embryonic nuclear transcription factor that is identified with hemangioblasts. These cells were found in the highest frequency in the posterior region of the primitive streak [23] prior to the appearance of yolk sac blood islands. The existence of human hemangioblasts was documented with the finding of cells expressing T and KDR (the human equivalent of the mouse genes) and the endothelial marker P1H12 in blast colonies derived from human embryonic stem cells [24]. This common origin for hematopoietic and vascular cell lines is an important feature in the biology of the vascular system and its responses to injury and disease as well as the potential behavior of residual circulating stem cells.

During early vasculogenesis, the aorta is the first artery to develop. Aorta development entails the migration of distinct

populations of arterial progenitor endothelial cells. Differences in sites of origin in the mesodermal germ cell layer between cells that populate the anterior lateral dorsal aorta, the posterior lateral dorsal aorta, and the dorsal aorta (descending aorta homolog) can be detected in zebra fish embryos [25]. Vegf is an important angiogenic signal protein that promotes migration and morphogenesis of vascular structures. Chemokines are small proteins initially identified as immune response mediators that also are important ligands, which along with their corresponding receptors play a major role in vascular development [25]. The chemokine receptor cxcr4a is expressed exclusively in anterior arterial cells derived from anterior lateral but not posterior lateral mesoderm. Embryos with mutant cxcr4a fail to develop normal lateral dorsal aorta connections and demonstrate ectopic migration of arterial endothelial cells as well as inappropriate arteriovenous connections, while dorsal aorta development is unaffected. Development of the dorsal aorta and trunk arteries in this species requires an intact notochord, sonic hedgehog signaling and Vegf for appropriate patterning and morphogenesis, and does not require cxcr4a signaling. Endothelial cell differentiation, starting even before migration and aortic morphogenesis, establishes the appropriate complement of receptors and signaling molecules to locate the cells anatomically as well to provide for programmed responses to local conditions and signals [25].

Notch proteins are large transmembrane receptors that determine cellular differentiation and fate across multiple cell types and species [26]. The Notch signaling pathway involves binding with "jagged" ligands that induces a molecular alteration in the intracellular domain of the Notch transmembrane protein. The intracellular domain of the protein then translocates into the nucleus where it interacts with a DNA-binding protein to form a transactivation complex and induce target gene expression. Early Notch activation of endothelial cells bestows a positional determination that appears to separate parallel populations of endothelial cells destined for a dorsal aortic fate as opposed to a cardinal vein fate. This establishes venous and arterial differentiation at an early phase. This early phase is associated with the dlc ligand and notch 3 receptor activation in zebra fish embryos. The venous endothelial progenitors at this stage lack Notch signaling and remain committed to a venous fate. Subsequent Notch signaling, preserved in arterially committed cells, involves dlc and dll4 ligands and notch 1a and notch1b as well as notch3 receptors. Notch receptors are downregulated in some populations of dorsal aortic cells called sprouting tip cells that then sprout from the dorsal aorta and later lose their connection to the dorsal aorta and form venous connections, developing into intersegmental veins [26].

Media Origins

While the initial pattern of aortic development proceeds from the differentiation, migration, and morphogenesis of endothelial cell progenitors originating from posterior mesoderm near the primitive streak, the media develop from different embryonic origins. As with endothelial cells, smooth muscle cell progenitors have distinct sites of origin depending on their ultimate anatomic location in the aorta [18, 19, 21] (Fig. 3.3). While VEGF promotes endothelial cell differentiation among embryonic stem cells, platelet-derived growth factor BB (PDRF-BB) induces mural cells that come to form the arterial media [27]. During vasculogenesis, endothelial tubes come to be wrapped by layers of cells that differentiate as smooth muscle cells (SMCs). The base of the aorta, just above the aortic valve, is invested with cells originating in the secondary heart field [28, 29]. Cells from the secondary heart field also form the outflow tracts of the left and right ventricles as well as the base of the pulmonary trunk. Within the secondary heart field-derived cardiovascular segment is a junction of myocardial cells making up the outflow tract and smooth muscle cells that make up the media of the aortic root and the pulmonary trunk. The media of the ascending aorta and arch are derived from cardiac neural crest cells and are thus of ectodermal, rather than mesodermal, origin. The descending aorta corresponding to the dorsal aorta of lower vertebrates develops in close proximity to somites and appears to be invested by segmentally derived smooth muscle cells from the sclerotome and myotome of each somite [21]. The transcription factor Pax3 that is important for survival, differentiation, and migration of skeletal muscle myoblasts is expressed in the ventral wall of the descending thoracic aorta in mouse embryos, and mice deficient in Pax3 have thinning of this aortic region. The abdominal aorta originates from splanchnic mesoderm [21].

The migration of cardiac neural crest cells and the role of these cells in the development of the cardiac outflow tracts and ascending aorta were elucidated in a murine model using a technique to activate a reporter gene in neural crest cells and their descendants [19]. Cells expressing the reporter gene can be stained and distinguished throughout the development and life of the animal. At an early stage, when blood flow from the heart is primarily through the second and third pharyngeal arch arteries, neural crest cells can be seen surrounding these arteries, and not the dorsal aorta. As development proceeds with the process of heart looping, the outflow tract comes to originate from the right ventricle, and the second arch artery regresses, while the fourth and sixth arches form connections to the developing aortic sac. Neural crest cells come to completely constitute the subendothelial tissue of the truncus arteriosus and to invade the conal cushions and

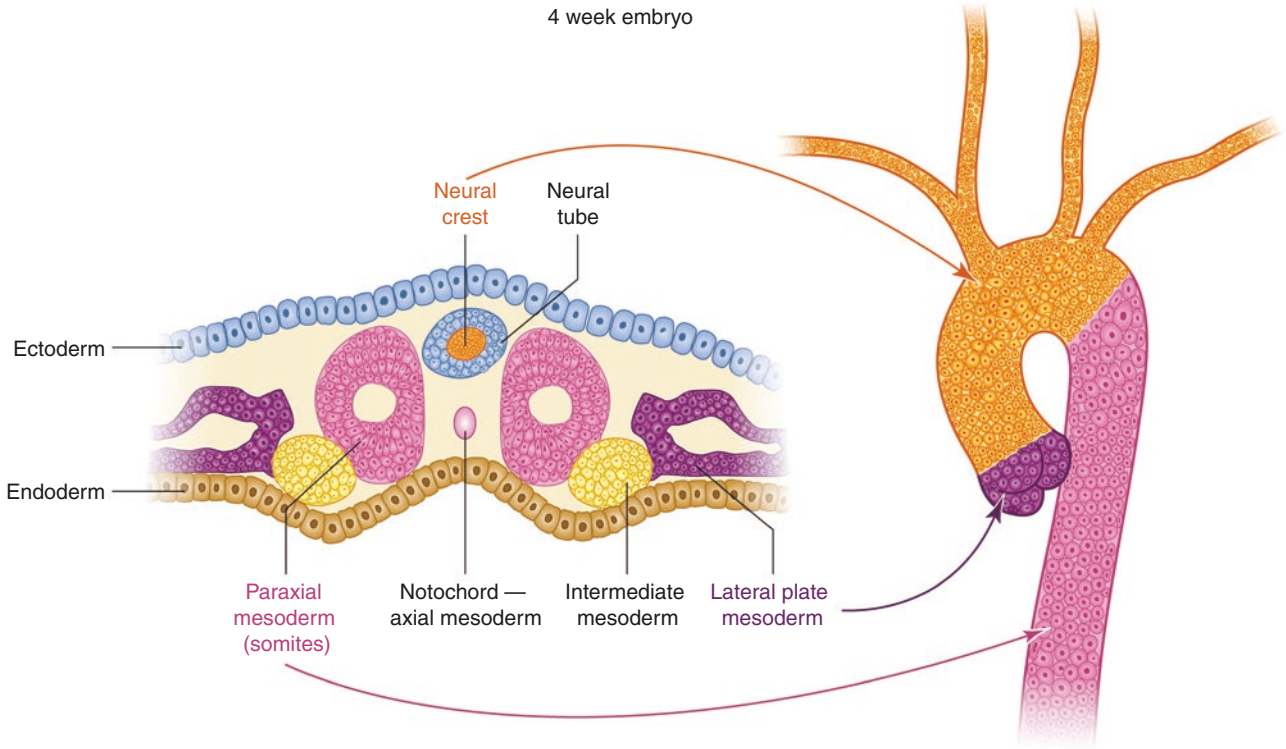

Fig. 3.3 Smooth muscle cells of the aortic root are derived from lateral plate mesoderm called the secondary heart field. The ascending aorta and aortic arch as well as the proximal arch arteries are invested with cells from the neural crest. The descending aortic media is comprised of cells originating in somites of the paraxial mesoderm

thus participate in the septation of the outflow tract. With the asymmetric reorganization of the outflow vessels, labeled cells persist around the left fourth and sixth arches, which come to form the ascending aorta and the ductus arteriosus, respectively.

Notch signaling plays an essential role in the coordination of interactions between secondary heart field progenitors, migrating neural crest cells, and endocardial cushions and promotes an endothelial to mesenchymal transition (EndMT) that has implications in subjects with bicuspid aortic valves (BAV). The association of NOTCH1 mutations and BAV and the role of oscillating VEGF signaling in initiation and termination of EndMTs in this critical junctional region may implicate a deregulation of NOTCH/VEGF pathways in the development of ascending aneurysms associated with BAV [30].

Neural crest cells do not ultimately extend completely to the level of the outflow valves, and this area is derived from the secondary heart field. Neural crest cells are no longer evident in the region of the conotruncal septum after septation of the truncus and outflow tracts but continue to constitute the media of the ascending and arch portions of the aorta as well as the ductus arteriosus, the innominate and right subclavian arteries, and the left and right common carotid arteries. The left subclavian, pulmonary, and distal internal carotid arteries are not of neural crest origin [19].

Migrating neural crest and mesodermal cells that come to constitute the aortic media have smooth muscle cell (SMC) restricted patterns of gene expression that program the formation of the appropriate lamellar structure and mechanical characteristics. Gene expression is controlled by epigenetic modifications of DNA that facilitate targeted expression of specific genes. This process involves changes in chromatin structure that present the specified gene for transcription and is regulated by nuclear proteins that effect histone chemistry, the alkaline proteins around which strands of DNA are wound, including SRF and its many cofactors. Serum response factor (SRF) is a major component of the mechanism that controls SMC restricted gene expression [31]. SRF is, by itself, a weak transcription activator and relies on interactions with coactivators and corepressors. It is a DNA-

binding protein that links DNA at CArG box sites on DNA to MADS box domains on SRF to create docking sites for accessory factors. Myocardin and the myocardin-related transcription factors (MTRF) A and B are cofactors of SRF that play a major role in muscle cell development. Myocardin is expressed in SMCs and cardiac cells only, while MRTF-A and MRTF-B are expressed in a variety of cell types. Myocardin is essential for vascular development, and myocardin-null mouse embryos die with an absence of differentiated SMCs. Mouse embryos homozygous for a MRTF-B loss-of-function mutation die with a range of cardiovascular defects that involve only the subset of SMCs of neural crest origin [32]. This demonstrates not only SMC restricted patterns of gene expression but further restriction specific to subtypes of SMCs derived from different embryologic origins.

Elastin is an early structural matrix protein expressed by SMCs in large elastic vessels. Elastin expression in the avian vascular system begins in the truncus arteriosus near the aorta pulmonary septum and proceeds toward the heart as well as peripherally and is coincident with the condensation of cells around the endothelial tube [11].

TGFβ

Transforming growth factors β1, 2, and 3 (TGFβ) are cytokines with major effects on the aortic media from early development throughout life. TGFβ signaling results in a range of effects in many developmental and homeostatic processes and is highly context dependent [33, 34]. The TGFβ superfamily comprises a group of growth and differentiation factors including the TGFβs, bone morphogenetic proteins (BMPs), activins, inhibins, nodals, and anti-mullerian hormone. The effects of TGFβ family members are mediated through interactions with type 1 and type 2 serine/threonine transmembrane SMC receptors, TGFBR1 and TGFBR2. Seven type 1 and five type 2 receptors have been identified [33]. There are accessory receptors as well that modify access of the signal ligands to receptor sites.

The TGFβ type 2 receptor institutes the signal upon ligand binding by phosphorylating the type 1 receptor, which induces a heterotetrameric complex involving ligand and type 2 and type 1 receptors. In turn the activated type 1 receptor, in the intracellular domain, phosphorylates a receptor-regulated R-Smad. Smads provide the intracellular component of TGFβ signal transduction. The Smad system also has common mediator or Co-Smads and inhibitory or I-Smads. The activated R-Smad forms a heteromeric complex with a Co-Smad (Smad 4) that translocates into the nucleus where gene expression is regulated by this and other inhibitory or activating factors [33]. The Smad system of TGFβ signal transduction comprises the so-called "canonical" pathway. There are multiple additional Smad-independent pathways as well such as the p38, JNK-MAPK, and the phosphoinositide 3-kinase-Akt-mTOR pathways [35]. These are important pathways in many cellular processes including apoptosis, cell morphology, cell migration, and protein synthesis and in many cell lines and impact aging, tumor formation, and metastasis [36].

TGFβ isoforms are secreted as propeptides that are cleaved to form a two-component complex of mature TGFβ peptide and a latency associated peptide (LAP) that maintains the active component in an inactive form. This complex is called the small latent complex (SLC). The SLC is bound by one of the latent TGFβ-binding proteins (LTBPs) to form a large latent complex (LLC). The LTBP has important additional binding sites for ECM components such as fibronectin and integrins as well as for fibrillin. This binding process serves to localize the LLC near an appropriate site for receptor binding as well as to sequester TGFβ ligand. LLCs release the active ligand under the influence of elastases and proteases such as MMP2 [37].

The importance of TGFβ/Smad pathways during embryonic development has been elucidated by mouse knockouts. TGFβ and TGFBRII as well as the ALK5 (equivalent to TGFBR1) receptor knockouts are all fatal during embryogenesis due to vascular abnormalities. Smad knockouts involving Smad4 and Smad2 are lethal. Smad3 knockouts are viable, but most die at 3–8 months with hematopoietic disorders [34]. Smad3 mutations in humans cause the aneurysm-osteoarthritis syndrome classified as Loeys-Dietz syndrome (LDS) type 3, with a virulent, diffuse arteriopathy associated with aortic dissection at small aortic sizes. Smad4 mutations are associated with familial thoracic aneurysm and dissection (FTAAD) as well as associated juvenile polyposis syndrome and hereditary hemorrhagic telangiectasia [38].

TGFβ pathways are clearly an important aspect of syndromic aortopathies especially LDS types and Marfan syndrome (MFS). LDS types 1 and 2 are associated with mutations of the TGFBR1 and 2 genes, respectively, and LDS4 with mutations of TGFB2 that encodes for isoform 2 of TGFβ. LDS type 5 is caused by a mutation in isoform 3 of TGFβ [39]. MFS, which has considerable phenotypic overlap with LDS, is associated with mutations of the FBN1 gene that encodes for fibrillin1 (see below and OMIM 609192, 610168, 613795, 614816, and 154700). It remains unclear how increased or decreased TGFβ signaling contributes to aneurysms and dissections. It seems likely that signaling context is important, especially in view of the multiple ligands in the TGFβ family as well as the many noncanonical signaling pathways potentially activated by TGFβ. Signal modifications and direction associated with specific isoforms of LTBP are important. It has been shown that in the mouse

model of severe MFS that usually die of aortic rupture, the ablation of LTBP3 expression, and therefore the corresponding LLC, results in considerably improved survival and fewer aneurysms [40]. Appropriate canonical TGFβ signaling appears essential for aortic development and stability throughout life. Excessive TGFβ signaling, possibly via noncanonical pathways, may play an important role in provoking ongoing aortic degeneration [41].

An example of the context dependence of TGFβ signaling associated with the ascending aorta and neural crest-derived cells was provided by a study of avian embryos in which tissue culture SMCs derived from neural crest or mesoderm were subjected to various concentrations of TGFβ as well as other peptide growth factors including PDGF-AA, PDGF-BB, basic FGF, EGF, and activin. While all the other growth factors resulted in a similar increase in DNA synthesis, TGFβ consistently increased DNA synthesis in the neural crest-derived cells but resulted in growth inhibition in mesodermal SMCs across a wide range of TGFβ concentrations [42] (Fig. 3.4).

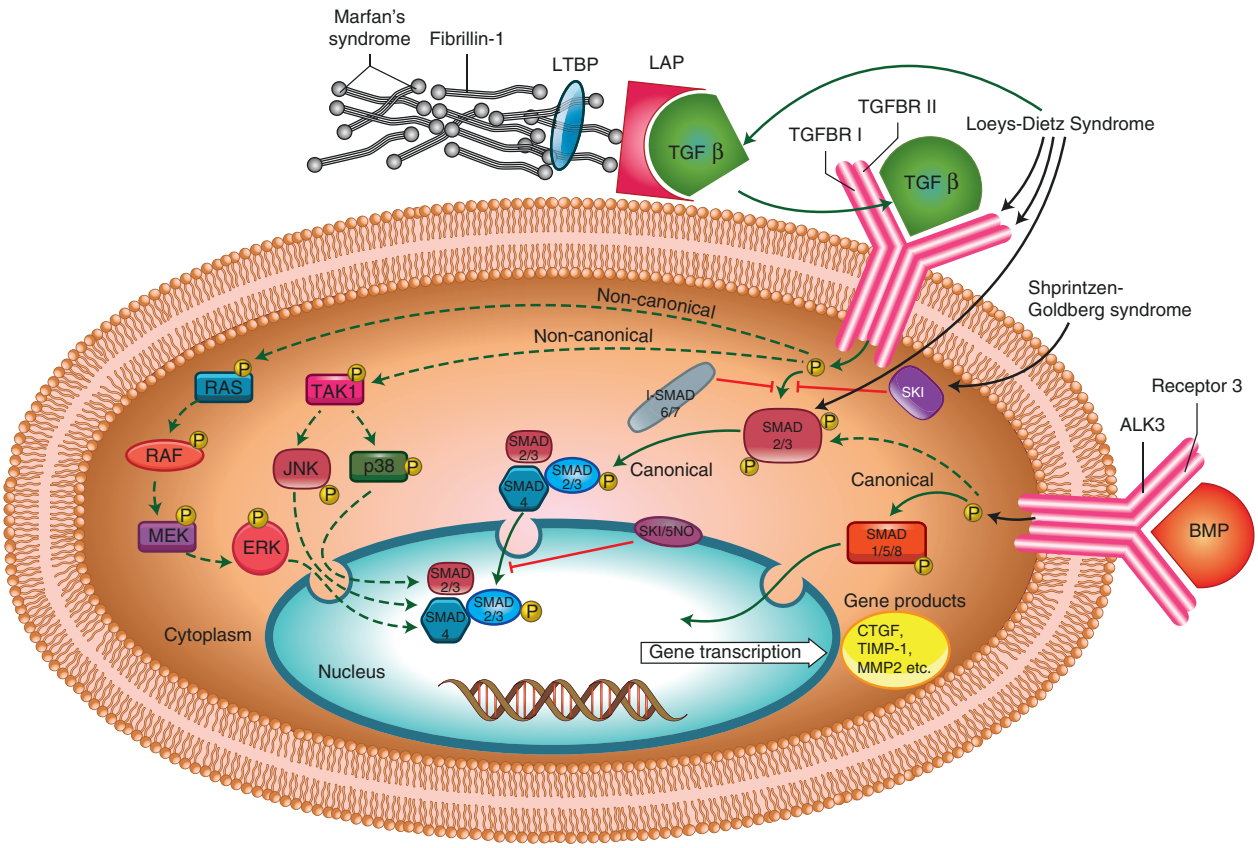

Fig. 3.4 SMC TGFβ pathways: A complicated and vital system. The TGFβ ligands are held in an inactive form by the LAP and positioned by binding to the LTBP which has matrix connections and connections with fibrillin microfibers. The active ligand is released under appropriate circumstances to activate the type 2 receptor that in turn phosphorylates the type 1 receptor and in turn phosphorylates Smad2 and 3 in the canonical pathway. Smad oligomers of Smad 2/3 and Smad 4 form and are translocated into the nucleus where they act as transcription factors inducing gene expression. Noncanonical pathways are activated as well by TGFBR II activation including the ERK, JNK, and p38 cascades. ALK3 (or bone morphogenetic protein receptor1—BMPR1) is an example of an alternative receptor for TGFβ ligands, canonically BMP, and can also result in noncanonical activation of Smad 2. SKI and SNO are important repressors of Smad transcription factor activation. Loss-of-function mutations affecting TGFβ ligands, receptors, or intracellular proteins of the canonical pathway are associated with FTAAD and syndromic phenotypes, possibly as a result of upregulation of TGFβ because of an absence of feedback inhibition. This could paradoxically increase both canonical and noncanonical TGFβ signal reception. The SKI proto-oncoprotein normally induces a negative feedback loop on the phosphorylation of Smads, and a loss-of-function mutation causes an LDS-like phenotype called Shprintzen-Goldberg syndrome. Defects in fibrillin1 may inhibit the appropriate sequestration of TGFβ ligands and result in uncontrolled release. There may be cross talk with the angiotensin II system through the AT1 receptor (not in figure). The result of inappropriate signaling is the upregulation of gene products such as CTGF (connective tissue growth factor), a profibrotic mediator in other contexts, and production of MMPs such as MMP2, in addition to TIMPs. Additional effects include dissolution of cellular junctions and promotion of cell migration and apoptosis as well as matrix dissolution particularly elastolysis

Adventitial Origins

The development of the aortic adventitia is likely strongly related to media development. Formation of the media involves an iterative process whereby successive lamellae are laid down including smooth muscle cells, extracellular matrix, and elastic fibers. There is a pattern among multiple species that normalizes the tangential tension (or circumferential wall stress) per lamellar layer at about 2000 dynes/cm [43]. Smaller species have fewer lamellae than larger species. Therefore, it is likely that the number of lamellae is controlled by signaling processes that respond to pressure and flow. Once the requisite number of lamellae is formed, the adventitia is produced, perhaps by stem cells from the pool of stem cells forming the media. Elastin-deficient mouse embryos provide a clue to this process. Homozygotes develop as expected until the stage at which lamellar development is usually complete and then show unrestrained SMC proliferation with vessel occlusions and exaggerated elongation that is fatal to the embryo. Heterozygotes develop thinner lamellae but continue to add additional layers that appear to derive from the inner adventitia in such a way as to preserve the wall tension per lamella at the usual level, and these mice have a normal life span [44]. The adventitia then comes to contain many different interacting cell types including fibroblasts, adipocytes, microvascular endothelium, nerves, macrophages, lymphocytes, mast cells, and dendritic cells as well as vascular progenitor cells [44].

Micromechanics and Structure

The aortic wall is a composite structure, and its behavior is regionally different with the ascending aorta differing in many ways from the descending and abdominal aortic segments, particularly in the mode of failure, type A dissection, and the tendency to form aneurysms that are not primarily atherosclerotic. The structure of the ascending aorta is characterized by three layers. The intima is a thin layer composed of endothelial cells with tight intercellular connections that control access to the underlying subintimal space and are separated by the internal elastic lamina from the media. The ascending aortic media consists of 53–78 concentric lamellae [45]. Each lamella is made up of a layer of smooth muscle cells with an elastic lamina on each side. Collagen fibers form a concentric network between the layers of smooth muscle cells (SMCs) and elastin [45]. Interlamellar elastic fiber connections form to create an interconnecting network that absorbs and transmits strain energy [11]. The adventitia is the external layer of the aorta, outside the external elastic lamina. This layer has abundant collagen and contains the vasa vasorum that penetrate the outer layers of the media. In it are nerves, lymphatics, and adipose tissue. The adventitia is a niche for stem cells and transmits intercellular signals from surrounding tissue to the media [43, 44, 46].

Media

The mechanical properties of the intact aortic wall are largely determined by the media although in some circumstances, the adventitia, rich in collagen fibers [11], may contain a hematoma resulting from transmural rupture of the media. Elastic fibers, SMCs, and collagen fibers comprise the major mechanical elements. The extracellular matrix (ECM) surrounding the SMCs and mechanical elements is a "viscous interstitial milieu rich in glycoproteins, proteoglycans, glycosaminoglycans, and a complex composition of growth factors, cytokines, chemokines, and proteases" [47]. Fibrillins 1, 2, and 3 and the microfibril-associated glycoproteins MAGP-1 and MAGP-2 are important glycoproteins. There are two classes of proteoglycans in the ECM: the first, a class of large molecule proteoglycans that interact with hyaluronic acid and form an interlacing polymeric network and, the second, a group of small leucine-rich proteoglycans (SLRPs) that bind to other ECM molecules including fibrillin, collagen, and tropoelastin as well as TGFβ [11]. Glycosaminoglycans (GAGs) are large linear disaccharide polymers of variable size including chondroitin sulfate, dermatan sulfate, heparan sulfate, keratan sulfate, and hyaluronan. Proteoglycans consist of a core protein with attached GAG chains. Proteoglycans are likely biologically relevant in matrix assembly [11] and serve as packing material to cushion the effects of compressive loading [47].

Elastic Fibers

Elastic fibers are a composite of elastin and microfibrils. Elastin is the major structural, load-bearing protein that is the core of elastic fibers. Microfibrils are found at the periphery of elastic fibers and provide a scaffold for the deposition of elastin during elastogenesis [48].

Fibrillin

The major constituent of microfibrils is the glycoprotein fibrillin. There are three isoforms, fibrillin-1, fibrillin-2, and fibrillin-3, encoded by separate genes. Fibrillins 2 and 3 are expressed primarily in fetal tissue, and fibrillin-1 is the most important of these for arterial structure and persists throughout life [47]. The fibrillin molecule has multiple domains of several types including calcium-binding epidermal growth factor (EGF) and non-calcium-binding EGF domains, TGFβ-binding protein-like domains, and hybrid domains [48]. The significance of this structure lies in the molecular interactions with multiple associated molecules that regulate SMC behavior and promote or inhibit alterations in the structure of the media. FBN1 is the gene encoding for fibrillin1, and

mutations in this gene cause Marfan syndrome (MFS). There is, however, no single phenotype associated with FBN1 mutations. Some phenotypes exhibit features opposite from those of MFS with brachydactyly and short stature [49] as opposed to the opposite characteristics usually associated. Ascending aneurysm and dissection has been described as a feature of one brachydactyly and short stature phenotype, while most phenotypes of that sort do not have aneurysms [50].

The fibrillin molecule contains within it binding sites for multiple microfibril-associated proteins, including MAGP-1 and MAGP-2, biglycan, decorin, versican, perlican, the fibulins, elastin, and ADAMTS-like proteins [49]. The large latent complex in the TGFβ pathway is targeted and sequestered by fibrillin [49]. Latent TGFβ-binding proteins (LTBPs) have fibrillin binding sites as do bone morphogenetic proteins (BMPs) that belong to the TGFβ superfamily. Binding of these molecules to fibrillin results in conformational changes and calcium binding plays a role in stabilizing a conformation required for recognition of other matrix components. Calcium binding also protects the molecule from proteolysis and restricts the mobility of interdomain regions [48].

Microfibrils are elastic elements, and their elasticity depends on the structural integrity of fibrillin, the organization of fibrillin monomers, and its ability to bind calcium [48]. Theories of elasticity for fibrillin include a pleated model based on domain-domain conformational rearrangements associated with applied mechanical force that would allow the molecule to become more linear. A second model proposes a staggered linear organization of fibrillin microfibrils. Under extension, unfolding of a domain interface results in loss of calcium-binding affinity and release of calcium ions. When the extending force is released, calcium ions are again bound and recoil occurs to the original state [48]. Only certain domains, TB-cbEGF domains, participate in the recoil mechanism, while other domains retain the ability to interact with ECM proteins [48]. Calcium channel blockade is deleterious in a mouse model of MFS. Human clinical data from the GenTAC registry show increased risks of aortic dissection and the need for aneurysm surgery among MFS patients treated with calcium channel blockers for hypertension as compared with those treated with other agents [51].

The production of elastic lamellae with functional load-bearing sheets of elastin is dependent upon the fibrillin scaffold. Fibrillin is also likely to play a major role in sensing mechanical strains and transduction of signals to local SMCs where those signals result in homeostasis or remodeling of the local ECM [49]. It is not clear that fibrillin plays a structural role or modifies the mechanical properties of the aortic media. Young's moduli for isolated fibrillin microfibrils have been measured at 0.56–0.74 MPa and that of elastic fibers at 03–1.5 MPa [52] in one study but were estimated to be two orders of magnitude higher in an earlier work in which it was concluded that microfibrils were "stiff reinforcing fibers" [53].

Elastin

About 90% of the structure of elastic fibers consists of elastin and about 10% is fibrillin, generally located on the periphery of the fiber with strands of it located throughout [47]. Species other than vertebrates do not produce elastin, so that the more basic structural element, which does appear in elastic tissues in invertebrate species, is fibrillin [11]. The *Windkessel* is dependent upon elastin. Elastin is encoded by the ELN gene. Elastin-null mice die of obstructive arterial disease resulting from uncontrolled subendothelial SMC proliferation, and hemizygous mice, like human counterparts with ELN mutations, develop obstructive lesions in large elastic arteries [54, 55]. This demonstrates a fundamental link between elastogenesis and SMC phenotype.

Elastogenesis begins with the cellular synthesis of tropoelastin. This protein is secreted as a monomer by SMCs, and the monomers self-associate through hydrophobic domains in a process called coacervation [47]. Tropoelastin is composed of alternating hydrophobic sequences and lysine-containing cross-linking motifs [11]. Spherical globules of coacervate tropoelastin form at the cell surface during the initial phase of development and retain cellular attachments. The integrin alphavbeta3 mediates the attachment of SMCs to tropoelastin in this process [56]. The droplets are also bound by fibrillin microfibrils and distributed along the microfibrils by the migration of SMCs to form elastin sheets that are cross-linked at the lysine domains by lysyl oxidase [47]. The formation of functional elastic fibers is dependent upon fibulin-4 and fibulin-5. Fibulin-4-null mice do not develop elastic fibers but irregular elastin aggregates, and fibulin-5-null mice develop disorganized and fragmented elastic fibers and have loose skin and lung abnormalities. These fibulins differentially bind fibrillin, lysyl oxidase, and elastin [47]. EMILIN-1 (elastin microfibril interface-located protein) binds both fibulin-5 and tropoelastin and binds to the proTGFβ precursor, inhibiting TGFβ signaling [11].

Elastin is very durable with little turnover in adult life. Elastin synthesis in the ascending aorta occurs at a high level from midgestation and declines after the postnatal rise in blood pressure [11]. The longevity of the protein is dependent upon lysyl oxidase cross-linking that renders the complicated polymers insoluble and stable [11]. Thus aneurysm formation associated with elastin fragmentation and resorption is typically an irreversible process.

While the elasticity of fibrillin microfibrils is comparable to a linear "molecular spring" [48], the elastic mechanism

for the elastin component of elastic fibers is similar to that of rubber [57]. With the large amorphous, three-dimensional elastin polymer, there exist multiple possible conformational molecular states constrained primarily by sites of cross-linking. In any given molecular chain, when points near a cross-link are separated by an extending force, the number of conformational states is reduced, and heat is released. The entropy in the system therefore declines. When the external force is removed, the entropy returns to its maximal state, cooling occurs, and the system recoils to its original state thus creating an entropic spring. Because there is a certain amount of energy lost to heat, the recoiling force at any given strain is less than the force required to create that strain, a phenomenon called hysteresis. Intact elastin demonstrates little hysteresis and a high level of resilience [48]. A method of quantifying the degradation of mechanical properties associated with aneurysmal ascending aortic tissue is to measure hysteresis during tensile testing of strips of aneurysm tissue. Using such an approach, Chung et al. [58] documented a significant increase in energy loss associated with strips from aortas greater than 5.5 cm. However, in aneurysms of the same size demonstrating significant differences in hysteresis, those with preserved elastic lamellae demonstrated much less energy loss.

Collagen

Seventeen different collagen types have been identified in mouse aortas with collagens I, III, IV, V, and VI having the highest levels of expression [11]. Collagen types include fibrillar, FACIT (fibril-associated collagen with interrupted triple helices), transmembrane, network forming, beaded filament, multiplexin, and anchoring [47]. Types 1, 3, and 5 are fibrillar collagens, type 4 is a network-forming collagen, and type 6 is a beaded filament collagen. In human ascending aortas studied by immunoelectron microscopy [45], thick collagen fibers containing collagen types 1, 3, and 5 were found oriented in a roughly circumferential pattern adjacent to elastic lamellae in the media. Adventitial collagen fibers were thickest and those in the intima thinnest. Interlamellar collagen fibers were more random in orientation and thin. Oxytalan fibers extending from SMC surfaces to insert into elastin-associated material were found to contain fibrillin-1 and type 6 collagen as well as traces of elastin. SMCs were surrounded by areas of layered cell-associated material that contained abundant fibronectin. Type 4 collagen was found in amorphous non-layered pericellular areas that also contained proteoglycans, primarily heparan sulfate. Small proteoglycans lined collagen fibrils with the predominant glycosaminoglycan being dermatan sulfate [45].

Mature collagen fibers have a complicated synthetic history. Procollagen is a soluble precursor that is synthesized in the endoplasmic reticulum of SMCs and in plasma membrane infolding recesses that communicate with the extracellular space [47]. Fibrillar procollagen molecules have repeating Gly-X-Y triplets of about 300 nm that are flanked by non-helical, non-Gly-X-Y sequences. The C-terminal end contains recognition sequences and cysteine residues to promote interchain disulfide bonds and initial alignment during synthesis. A triple helix of three alpha chains are produced [47]. Type 3 collagen is homotrimeric [58], that is, it is composed of three identical alpha chains, a feature that is important in the pathogenesis of COL3A1 mutations. Collagens that are heterotrimeric form with differing architecture and mechanical properties [47]. The monomeric unit of collagen fibrils, tropocollagen, is formed by cleavage of the non-helical propeptide ends [47]. Fibrillar collagens assemble by the lateral association of tropocollagen triple helix monomers, first into fibrils of 10–300 nm diameter, then fibers of 1–20 micrometers, and, finally, in some cases, large bundles of up to 500 micrometers. The fibrils assemble in a parallel, staggered alignment and are cross-linked at lysine and hydroxylysine residues to form a semicrystalline, packed structure of high tensile strength [47].

Fibronectin is a glycoprotein with discrete binding sites for collagen, integrins, other matrix proteins, and heparin. It appears to have a role in collagen assembly [47].

In contrast to the amorphous entropic spring of elastin, collagen fibers are highly ordered structures with nearly opposite mechanical features. The elastic modulus of collagen fibers in mammalian tendons is 1.2 GPa or about three orders of magnitude stiffer than that of porcine aortic elastin at 1.02 MPa. The tensile strength of collagen is 100 times greater, at about 120 MPa, but the maximum extensibility is only 13% as opposed to 103% for porcine aortic elastin [47]. Defects affecting elastic fibers result generally in medial degeneration, the formation of aneurysms, and, as a consequence, aortic dissection. In the case of Ehlers-Danlos syndrome type 4 (EDS-IV), a collagen III lesion, there is little medial degeneration. Aortic dissection may occur in about 10% of patients, but aneurysms are much less frequent. Aortic and large vessel tears are the hallmarks of the disease with a 25% risk of a major vascular complication by age 20 [60]. The tensile strength afforded by collagen reinforcement is an essential aortic component.

Heterozygous mutations in the COL3A1A gene cause variable phenotypes. In cases where a glycine substitution occurs in a Gly-X-Y triplet domain or “exon skip mutations” lead to exon splicing errors, equal amounts of abnormal and normal procollagen are produced. However, since type 3 collagen is a homotrimer, the association of trimeric combinations of normal and abnormal procollagens leads to a seven-to-one ratio of normal to abnormal collagen molecules. The result is that only 10–15% of the normal amount of type 3 collagen is produced with the rest being nonfunc-

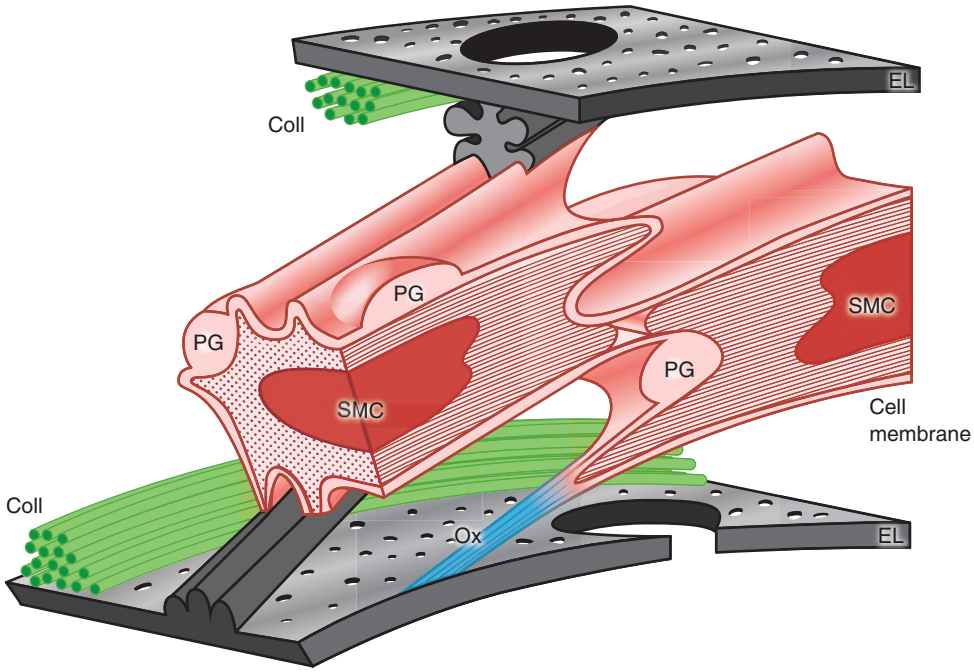

Fig. 3.5 Schematic representation of SMCs and elastic lamellae based on electron micrographs. EL denotes an elastic lamella which is composed of 90% elastin and 10% fibrillin microfibrils. SMC denotes smooth muscle cells. Coll represent thick collagen bundles primarily of type 3 and type 5 collagen. Thinner elastic fiber protrusions extend to the surface of the left SMC from elastic lamellae. Thin oxytalan fibers that contain fibrillin, type 6 collagen, and, near the cell, fibronectin are labeled Ox. Under ordinary conditions of aortic loading, or especially if the tissue were unloaded, the collagen fibers and elastic lamellae would not be straight but wavy and irregular reflecting an ability to stretch and recoil. A basal lamina-like layer containing fibronectin coats much of the cell surface and bridges the gap between cells. Larger deposits in this layer contain type 4 collagen and the proteoglycan heparan sulfate (PG)

tional since all three elements of the trimer must be the same for the fibril to be functional. With nonsense or frameshift mutations, premature terminations are created, and the abnormal mRNA is removed with no protein being produced. Therefore 50% of normal protocollagen is available [59]. Patients with haploinsufficiency as opposed to those with very low levels of type 3 collagen tend to have better surgical outcomes and a higher incidence of aortic involvement. Types A and B dissection do occur, but most aortic pathology involves the abdominal aorta [59] (Fig. 3.5).

Smooth Muscle Cells

Vascular smooth muscle cells are the metabolic hub of the ascending aortic media and contain the machinery that is the target of signaling pathways. These cells carry a precise pattern of differentiation from the migrating neural crest cell progenitors from which they arose and in healthy adults are in a quiescent, synthetic mode finely tuned to the local matrix and signaling environment and responsive to local mechanical forces. SMCs are not terminally differentiated, however. Major changes in phenotype that can affect the stability and mechanical properties of the media may occur in response to many factors including growth factors and inhibitors, cell-to-cell interactions, cell-matrix interactions, inflammatory mediators, and mechanical influences [61]. Mechanosensation and mechanotransduction are key features of differentiated SMC function [49, 61, 62]. This requires a complex system of intracellular and extracellular connections.

The smooth muscle contractile proteins actin and myosin are essential intracellular components of the mechanotransduction system. ACTA2 mutations resulting in a defect in the SMC isoform for alpha actin cause a tendency for ascending aneurysms and for dissection at aortic diameters less than 5 cm. The mutation in some cases results in an SMC proliferative phenotype that is associated with obstructive vascular disease in muscular arteries and in the vasa vasorum of the aorta [63]. Similarly, mutations in MYLK, encoding for myosin light chain kinase, and MYH11, encoding for the myosin heavy chain, cause ascending aneurysms and dissections, and, again in the case of MYLK mutations, dissection may occur with little aortic enlargement [64]. An activating mutation of PRKG1 which encodes for the cGMP-dependent protein kinase PKG-1 that promotes SMC relaxation is also associated with a severe form of FTAAD and dissection at a young age [62].

SMC transmembrane receptor mutations in TGFBR1 and TGFBR2 result in Loeys-Dietz syndrome (LDS) as outlined above and a severe form of aortic disease with early-onset aneurysms and dissection associated with TGFβ signaling distortions [65]. SMC angiotensin II type 1 receptors and receptor blockers may play a role in modifying TGFβ signaling. It has been thought that AT1 receptor blockade attenuates excessive TGFβ signaling. Since excessive signaling has been thought to be a driver of the aortic pathology in both LDS and MFS, AT receptor blockers and neutralization of TGFβ are appealing interventions. Current findings are inconsistent. Enhanced aortic rupture was seen in a mouse model of angiotensin infusion-induced aneurysms where TGFβ antibody neutralization was provided [66]. Despite earlier positive findings in MFS mouse models of aortic root enlargement, in a trial of MFS patients administered with the angiotensin receptor blocker losartan or a beta blocker, there was no difference in the rate of aortic root enlargement [67]. SMCs from the media of ascending aneurysms have been found to have elevated local angiotensin II levels and associated increases in MMP-2, a matrix degradation protein, implicating activation of the AT1 receptor in human aneurysm pathogenesis [68].

Biglycan

Biglycan is an extracellular matrix (ECM) proteoglycan that is a member of the group of small leucine-rich proteoglycans (SLRPs) [69]. Five classes of SLRPs have been distinguished with class I including biglycan and decorin [70]. The biglycan gene (*BGN*) has been mapped to the X chromosome. The protein core contains leucine-rich repeats (LRR) that are bound to one or two glycosaminoglycan side chains that, in turn, interact with multiple components of the ECM. Effects on collagen fibril assembly are structurally significant, with biglycan-deficient mice demonstrating abnormalities of bone and connective tissue, and, when biglycan deficiency is combined with decorin deficiency, a severe Ehlers-Danlos-type phenotype appears [71]. Interactions with biglycan appears to play a role in a number of disease processes including Alzheimer's disease, cancer, diabetes, Duchenne muscular dystrophy, fibrotic liver disease, myocardial infarction, and fibrotic kidney disease. Biglycan signaling appears to upregulate immune responses through interactions with macrophages that involve toll-like receptors TLR4 and TLR2 [69, 70]. There is elevated biglycan expression in fibroblasts from granulation tissue. It acts as well to stimulate osteoblast differentiation and bone formation. Its actions as a signal-modifying protein may require the unsequestered form, and the presence in tissue sections does not correlate with biologic activity. Biglycan interacts with the TGFβ family of receptors and cytokines including TGFβ and TGFBR1 and 2 as well as BMP and BMPR 1 and 2 [69].

BALB/cA mice were bred with *bgn* knockouts and genotyped [72]. 50% of the *bgn* knockout males died suddenly with 82% of these from thoracic aortic rupture and 18% from abdominal aortic rupture. None of the female knockouts and none of the wild-type mice were affected. Aortic ruptures occurred across the intima and media with blood collection between the media and adventitia. This is distinctly different from what is seen in classic Marfan-like ruptures where the dissection plane is in the media, and in addition, there was no sign of "cystic medial necrosis" with fragmentation of elastic fibers and myxoid medial deposits. The pattern seen in these dissections was much like that seen in the Ehlers-Danlos syndrome type 4 model col3a1 knockouts. Mechanical testing of *bgn* knockouts and wild-type aortas showed stepwise failure, with initial failure of the media occurring at about the same strain in both knockouts and wild type and subsequent failure of the adventitia at a lower strain but 50–70% higher load in the wild-type aortas demonstrating much greater maximum stiffness in the wild-type aortas. *bgn* knockout males had the lowest collagen fibril diameter compared with *bgn* knockout females and wild-type males. Wild-type males also had lower fibril diameters than wild-type females [72].

Subsequent to the discovery of the vascular effects of *bgn* knockout mice, five human families were identified with *BGN* mutations with early-onset ascending aortic and root aneurysms and dissection [73]. Aneurysms were observed as early as age 1 and dissections age 15. Males were more severely affected, but aortic root dilation and death related to aortic dissection were observed in females. The phenotype also includes hypertelorism, skeletal abnormalities, striae, and other connective tissue features. Histologic evaluation of aortic tissue from affected individuals showed low to normal collagen content and normal-appearing elastic fibers. Focal expression of decorin, another class I SLRP, in the media was detected and, as in the mouse model, appears to compensate to some degree for the biglycan deficiency. TGFβ signaling as demonstrated by nuclear staining of pSMAD2 was detected with an increasing gradient of staining toward the adventitia [73].

Turner's syndrome provides another example of biglycan deficiency. The 45X karyotype has been shown to have reduced biglycan expression [74]. Turner's patients have a significantly increased risk of aortic dissection as well as ascending aortic aneurysms [75, 76]. In the International Turner Syndrome Aortic Dissection Registry, 20 patients were identified with dissections, 17 of which were type A. All but one of the 20 patients had an associated bicuspid aortic valve. Among nine patients with echocardiographic data preceding their dissection, the aortic size ranged from 2.3 to 5.1 cm with an average size index of 2.7 cm/m^2. The average age at the time of dissections was 31.5 years. These patients therefore tend to have a relatively virulent form of aortic disease and dissect at smaller aortic diameters and at a younger age than the overall population of women with dissections (68 years) [75].

Pathologic Findings in Ascending Aortic Aneurysms and Dissections

A surgical series of 479 patients from the Mayo Clinic with ascending aneurysms and dissections was published in 2006. Two hundred nine of the patients were described as having cystic medial degeneration (CMD). CMD was defined as fragmentation and/or loss of elastic fibers with or without pools of glycoproteins. The pathologic features involved more than 5% of the medial thickness. One hundred patients had laminar medial necrosis (LMN) defined as coagulative necrosis of SMCs, resulting in loss of nuclei and collapse of elastic lamellae. LMN was the sole finding in 2 patients, and 36 also had CMD and 23 aortic dissections (AD). Fourteen patients had giant cell arteritis, CMD, and LMN. CMD was present in half of AD patients. Ninety patients had histologically normal media with ascending aortic diameters ranging from 2.9 to 6.6 cm [77]. This study was undertaken prior to the availability of molecular diagnoses, but only 3 patients with normal aortas were suspected to have an inherited disorder, whereas 57 of 67 thought to have an inherited disorder had CMD. The striking finding in this study is the lack of histological findings in a large proportion of patients with clear aortic pathology.

An ultrastructural analysis of 10 MFS and 6 non-MFS patients with aortic dissection were compared by Dingemans et al. [78] to 77 patients with no aortic disease. Among dissection patients, there were few qualitative differences between those with MFS and those without. MFS patients had more diffuse findings. The findings consisted of multiple, about 20 per dissected aorta, abrupt transverse tears in morphologically normal lamellae that were thick and compact rather than in thin, degenerated lamellae. Interestingly, among the normal non-dissected aortas in individuals over age 35, 40 such tears were found among 59 examined. Most locations in dissected aortas had normal-appearing microfibrils except for focal areas with loss of microfibril extensions to SMCs. The oldest MFS patients had the highest number of absent or reduced elastic lamellar extension bridging to SMCs. There were a higher number of irregularities and interruptions of the layer of extracellular material enveloping most cells in dissected aortas. Patient aortae contained many matrix vesicles, at times being liberated from degenerating SMCs, and there were fibrotic areas from which all cells had disappeared and smooth elastic lamellae often persisted. Inflammatory cells were scarce.

The pathology of ascending aortic aneurysms and dissections suggests an apoptotic mechanism for smooth muscle cell loss and ultrastructural failure at a fibril or molecular level without inflammatory tissue dissolution except in cases of aortitis. The finding of a loss of elastic fiber connections to SMCs, apparently increasing with age in MFS aortas, suggests that loss of mechanosensation and mechanotransduction by SMCs may underlie a tendency for apoptosis and elastolysis. In MFS patients, there would appear to be some ongoing stimulus or signal to degrade previously intact SMC elastic fiber connections. It is striking that the actual medial tears detected in dissected aortas did not occur in degenerated nonelastic lamellae but in more normal lamellae. This would imply that these more degenerated areas have been remodeled to replace elastic tissue with collagen, making focal regions of stiff, probably maximally stretched, tissue that has a higher tensile strength than the more normal surrounding areas. The lack of elastin in these areas produces a marked loss of recoil and permanent extension of the affected areas of the aortic wall leading to dilation and stiffness.

Mechanics of Ascending Aneurysm and Dissection

One of the most important goals in understanding the mechanics of ascending aneurysms is the ability to predict the likelihood of rupture or dissection. It is now possible to image the ascending aorta noninvasively by multiple techniques including computerized tomography (CT), magnetic resonance imaging (MRI), and echocardiography, providing both a means of diagnosis and of making repeated measurements over time. Prophylactic surgical replacement of ascending aneurysms is generally recommended when the diameter of the aneurysm exceeds 5.5 cm except where there are known factors that increase the risk of rupture at a smaller size such as symptoms, a family history of dissection, or a known genetic defect predisposing to dissection. In a series of patients from Yale accrued during the last century, the median diameter at rupture or dissection in a group of operated patients was 5.9 cm [79], and later analysis of the database demonstrated a growth rate of 0.1 cm per year among all patients with enlarged ascending aortas. There was a 6.9% yearly rate of dissection or rupture and an 11.9% yearly death rate for unoperated patients with ascending aortas larger than 6 cm [80]. In a subsequent study by the same group, surgical patients were evaluated by intraoperative epiaortic ultrasound examination [81]. Measurements were made of normal and nonsyndromic aneurysmal ascending aortas including wall thickness and diameter at end systole and end diastole and corresponding blood pressures. For the group of normal aortas, the mean circumferential wall stress at a pressure of 85–100 mmHg was 0.092 MPa, equivalent to the values described above. For aneurysms greater than 6 cm, the mean wall stress increased to 0.377 MPa. The incremental elastic modulus rose from 1.18 MPa in normal aortas to a mean of 6.42 MPa in aneurysms larger than 6 cm demonstrating a major increase in stiffness and loss of compliance as well as dissolution of the ascending aortic contribution to the *Windkessel*. Interestingly, for small aneurysms

less than 4 cm, E_{inc} actually dropped to 0.908 MPa indicating a gain in compliance among the aortas in that group. Aortic thickness was maintained among aortas up to the largest group greater than 6 cm where the mean end diastolic thickness fell to 0.16 cm compared to 0.26 cm in normals. Thus, there is marked deterioration in ascending aortic strength and mechanical properties once the diameter exceeds 6 cm in this group of older adults (mean age 64), and this analysis clearly supports the recommendation for elective repair of ascending aortas larger than 5.5 cm.

Unfortunately, there exists a major difficulty in using the 5.5 cm criterion as a tool to reduce the occurrence of type A dissection. That is the frequent finding of dissection in patients with small aneurysms. Data from the International Registry of Acute Aortic Dissection in 2009 demonstrated that nearly 60% of type A dissections occurred in patients with ascending aortas less than 5.5 cm in diameter and 40% of patients had diameters less than 5 cm [82]. Still, the overall population incidence of dissection at small aortic sizes is quite low given the huge denominator of persons with small aortas. In a population database of subjects with a mean age of 60.7 years, only 0.22% of subjects had an aorta greater than 4.5 cm, but the risk for dissection among this group was 6305 times than that of those who had an aorta less than 3.5 cm [83]. Still, with an incidence of dissection in Western countries of 5–15/100,000 (0.005–0.015%) [2, 83] even at 0.22% of the population, there are likely hundreds of thousands of people in the United States with aortas greater than 4.5 cm who will not suffer an aortic dissection. Thus, while there is clearly a marked deterioration of ascending aortic mechanical properties at 6 cm and prophylactic surgery is definitely warranted to prevent that dimension from being reached, additional strategies are required to identify and manage the majority of patients who now present with type A dissection and who fare much more poorly than those operated prophylactically.

Additional anatomic features apparent on CT images have now been suggested to elevate the risk of type A dissection. Ascending aortic curvature is associated with a calculated tenfold increase in the force acting on the aortic wall as the degree of curvature increases toward a 90° bend [85]. A clinical corollary is that measured ascending aortic elongation has been detected on CT images of patients preceding and simultaneous with type A dissection. On sagittal images, the direct distance between the sinotubular junction and the brachiocephalic trunk was less than 85 mm in 75% of healthy aortas and greater than 91 mm in 75% of dissected aortas [86]. Aortic elongation is asymmetric, with pronounced angulation on the greater curve side, which would increase the aortic curvature. Since most entry tears in dissections are transverse, supporting the concept that it is longitudinal forces that provoke tissue failure [87], an analysis based primarily on the calculation of circumferential stress alone is inadequate, and other features such as elongation and curvature should be considered.

As suggested above, aneurysm geometry plays a very important role in the forces acting to cause deformation and tissue failure. The ascending aorta, even when healthy, has a complicated geometry extending from the aortic root to the aortic arch with a constriction at the sinotubular junction, varying degrees of rotation and curvature, and tethering by the aortoventricular junction, coronary arteries, and arch vessels. To analyze complex elastomeric shapes, a constitutive mathematical model can be created. Several models take the form of the strain energy function, *W*. A Fung-type strain energy function associates the total strain energy in deformation to a series of material constants and small element strains [88]. The material constants can be derived from material testing data, and the elements can be obtained by creating a three-dimensional model of the structure from imaging data and subdividing the model into a mesh of small finite elements. The stress predicted for each finite element can then be computed (on a machine) and is often displayed as a color map with colors corresponding to the stress magnitudes. Using such an approach, Martin et al. have created a more precise analysis of rupture risk for a series of patients who had imaging data and corresponding surgical tissue samples [89]. The mean predicted failure diameter in this group was 51 mm in this series of elective surgical patients with a mean systolic diameter of 51 mm for those with bicuspid valves and 45 mm for those with tricuspid valves. For the highest-risk group, the predicted rupture blood pressure was 234 mmHg. The peak wall stress was often, but not always, on the lesser curve at the level of maximum dilation. The prediction of rupture was not different between bicuspid valve patients and others. The risk of rupture was not associated with overall aortic diameter within this group of aneurysm patients (Fig. 3.6).

A further enhancement of the finite element approach has been made that incorporates the lamellar structure of the aortic media including the mechanical characteristics of elastic lamina and collagen fibers [90]. The fiber arrangement was obtained from multiphoton microscopy images from aneurysmal ascending aortas associated with bicuspid aortic valves. Findings in the model included the expected J-shaped stress/strain relationship and a markedly heterogenous stress distribution in the elastic matrix when the fibers were tensioned at higher applied stretch. A correlation was noted between decreased local fiber density and increased interlaminar matrix stress in that local vicinity raising the potential for delamination in these regions, a finding that would favor aortic dissection. While characteristics of these prediction models are as expected from observed data, such as the size at which dissection would be expected to occur, it is not possible to empirically validate the predictions since tissue

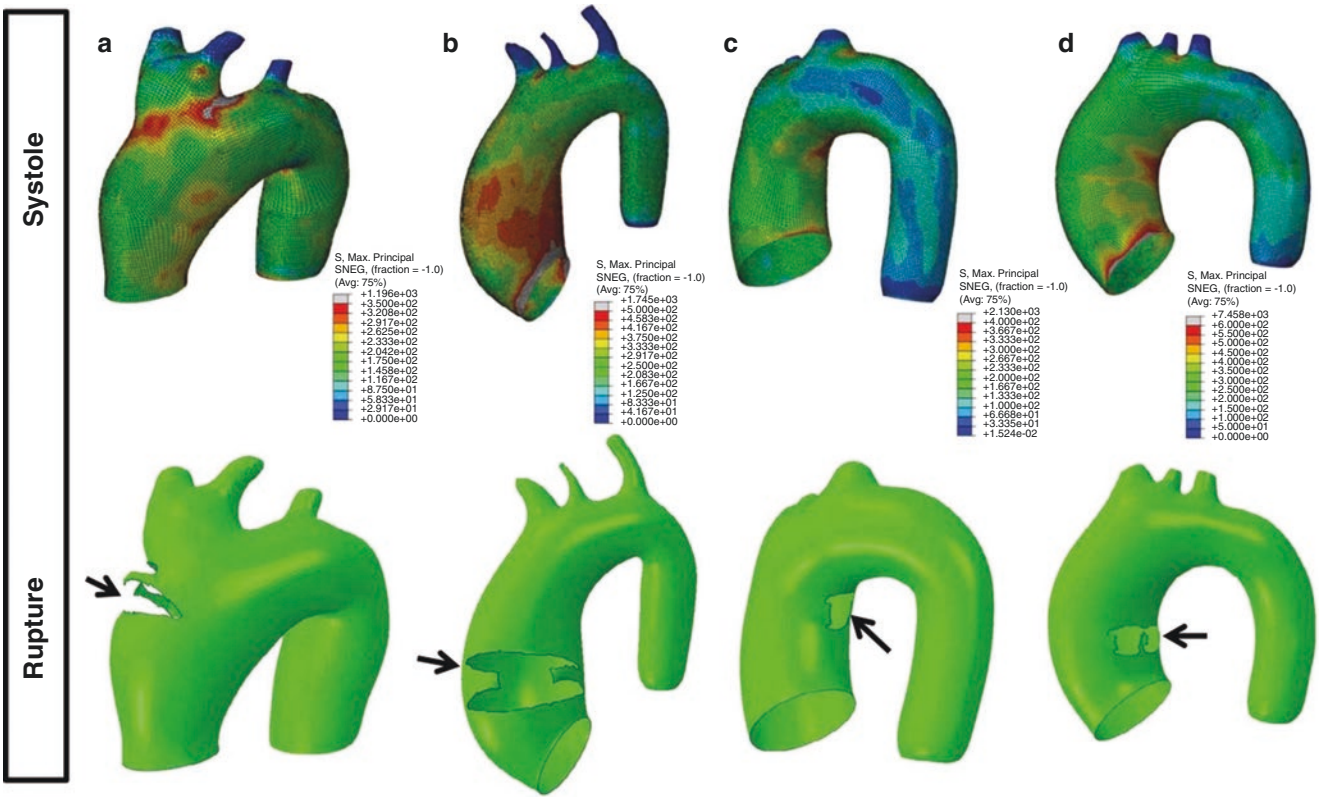

Fig. 3.6 Representative finite element results from Martin et al. In patient A with a bovine aortic arch, the predicted site of rupture is just proximal to the origin of the common trunk on the greater curvature, and the predicted pressure at failure was 14 times the systolic pressure. In patient B who had a bicuspid aortic valve, the predicted rupture site was on the anterior ascending aorta above the sinotubular junction extending around the lesser curve and occurring at six times the systolic pressure. Patient C has a predicted rupture site on the lesser curve at a pressure of three times systolic and therefore appears to have had a moderate risk of rupture. Patient D had a high risk of rupture at a site on the lesser curve above the sinotubular junction at only one times the systolic pressure. From this analysis, it appears that rupture is dependent more on geometry and tissue characteristics than on diameter per se. (From: Martin et al. [89]. Reprinted with permission from The American Physiological Society)

specimens are not prospectively available in unoperated patients and reliable means of predicting material properties noninvasively remain to be developed. Prediction of the point of tissue failure and mechanism based on imaging data remains a work in progress.

Ascending Aorta Postulates

1. Dissection and rupture are associated with mechanical failure due to qualitative or quantitative deficits in collagen fibers. Interlamellar regions are less robustly reinforced radially with collagen than are the lamellae for circumferential and axial stresses allowing for the formation of dissection planes. Dissection is a disease of collagen.
2. Tears that initiate dissection occur in apparently normal areas of the media rather than in areas with degenerated elastic fibers and apoptotic SMCs.
3. Genetic defects with the greatest effect on collagen fiber integrity are likely to be associated with dissections and arterial rupture with lesser degrees of aortic dilation. Type 4 EDS is the prime example of this phenomenon. BGN mutations with abnormalities of the matrix proteoglycan biglycan also provide an example of impaired collagen fibril formation and virulent aortopathy.
4. It is likely that intact SMC contractile proteins are required for appropriate formation of durable collagen and elastic fibers. ACTAII, MYH11, MYLK, and PRKG1 mutations all are associated with dissections at smaller aortic sizes.
5. While associated with elastic fiber defects, mutations involving TGFβ pathways and fibrillin may also affect collagen fiber durability, again manifesting aortic dissection with less aortic dilation, especially in the case of LDS types.
6. Ascending aneurysms are largely a disease of elastic fibers. The formation of ascending aneurysms is associated with elastic fiber degeneration and elastolysis.

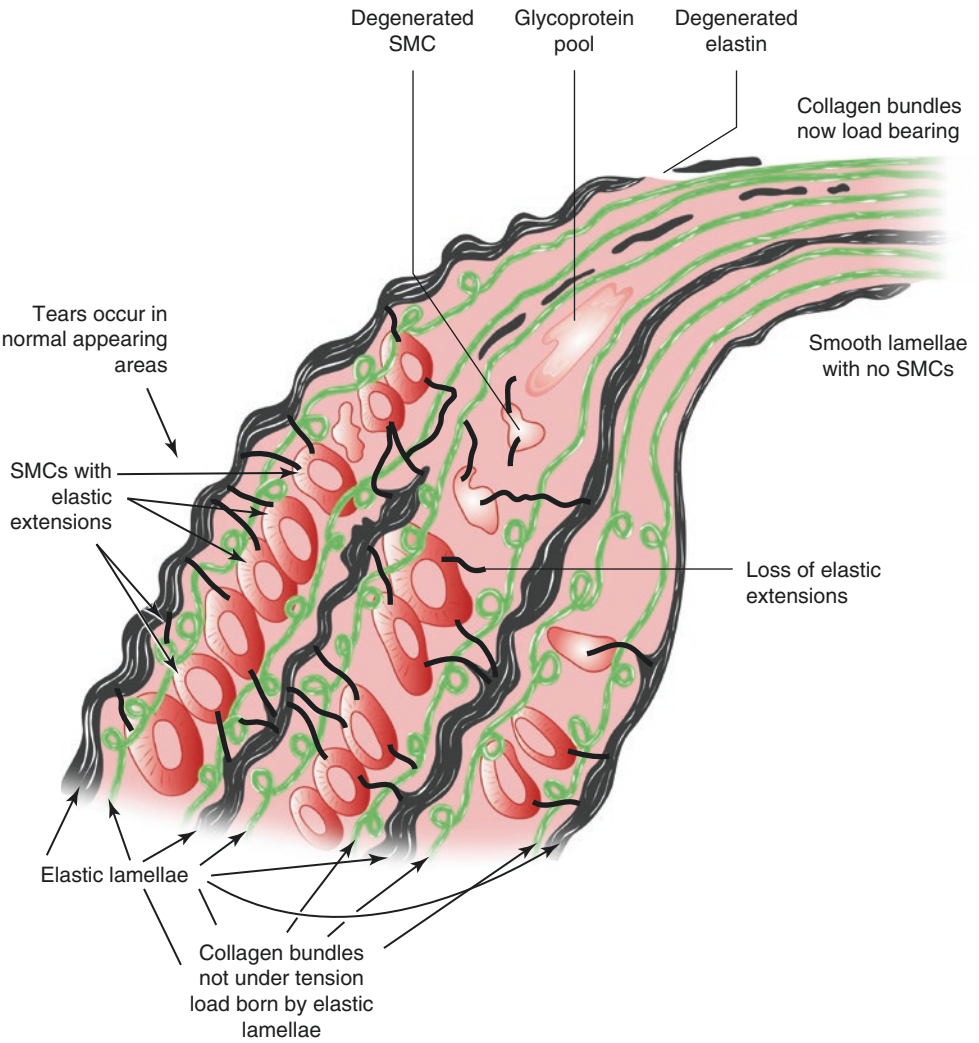

Fig. 3.7 Ascending aneurysm formation. Most aneurysms develop over time and are associated with microstructural changes in the aortic media. In normal elastic lamellae under normal blood pressure conditions, collagen fibers are slack, and elastic fibers carry the load. The normal microstructure includes elastic fiber extensions between the loaded lamellae and SMCs to provide mechanosensation and mechanotransduction. With inappropriate signaling and uncoupling of SMCs, there are matrix degradation, apoptosis of SMCs, and elastolysis. An intermediate stage exists where elastic lamellae may persist without SMCs. The ultimate result is that areas of the media lose functional elastic fibers and have no elastic recoil. Collagen fibers are tensioned, and the aortic diameter necessarily increases, and the wall thins. Tears that may lead to dissection occur in the more normal-appearing areas such as on the lower left

A large proportion of ascending aneurysms have a recognizable genetic defect that promotes this process. Those defects associated with preservation of robust collagen fibers are likely to present later in life with larger aneurysms but remain subject to the mechanical features of the degenerated 6 cm aorta. This group may represent the majority of patients with aneurysms (Fig. 3.7).

7. Impairment in canonical TGFβ signaling is a cause of aneurysms. Upregulation of noncanonical TGFβ signaling, possibly in response to deficient canonical pathways, may be the driving factor.
8. Loss of mechanosensation or mechanotransduction by SMCs with loss of elastic fiber extensions to elastic lamellae likely plays a major role in the pathogenesis of both aneurysm and dissection.
9. The finding of microscopic transverse tears in the media of "normal" aortas may indicate the presence of a subclinical defect but also illustrates the dangers of uncontrolled hypertension where such a tear could provide a nidus for dissection. Aneurysm and dissection are both diseases of hypertension.
10. Accurate prediction of rupture and dissection requires knowledge of the expected micromechanical properties of a patient's aorta as well as a precise morphologic characterization. High-resolution, dynamic imaging combined with genomic testing could result in improved prediction methods.

Syndromic and Nonsyndromic Ascending Aortic Disease

Syndromes of thoracic aneurysms and dissection, known as TAAD, have a strong genetic component and, when inherited by more than one member of a family, are often referred to as familial TAAD (FTAAD). Descending thoracic aortic pathology is associated with hypertension and known risk factors for atherosclerosis. While these risk factors may play some

Table 3.1 Catalog of genetic syndromes involving the ascending aorta

Gene	Locus	Altered protein	Syndrome	Inheritance
ECM proteins				
FBN1	15q21.1	Fibrillin-1	Marfan syndrome	AD
EFEMP2	11q13.1	Fibulin-4	Cutis laxa type IB	AR
ELN	7q11.23	Elastin	Cutis laxa	AD
COL3A1	2q32.2	Collagen 3 alpha-1	Ehlers-Danlos syndrome type 4	AD
COL4A1	13q34	Collagen 4 alpha-1	Hereditary angiopathy with nephropathy, aneurysms, muscle cramps (HANAC)	AD
COL 4A5	Xq22.3	Collagen 4 alpha-5	X-linked Alport syndrome	X-linked
PLOD1	1p36.22	Lysyl hydroxylase 1	Ehlers-Danlos syndrome type 6	AR
PLOD3	7q22	Lysyl hydroxylase 3	Bone fragility, contractures, arterial rupture, deafness	AR
LOX	5q23.1	Lysyl oxidase	FTAAD, (AAT10)	AD
MFAP5	12p13.31	Microfibrillar associated protein 5 (MAGP-2)	FTAAD, (AAT9)	AD
TGFβ pathway proteins				
TGFBR1	9q22.33	Transforming growth factor beta receptor 1	Loeys-Dietz syndrome type 1, (AAT5),	AD
TGFBR2	3q24.1	Transforming growth factor beta receptor 2	Loeys-Dietz syndrome type 2, (AAT3)	AD
TGFB2	1q41	Transforming growth factor beta 2	Loeys-Dietz syndrome type 4	AD
TGFB3	14q24.3	Transforming growth factor beta 3	Loeys-Dietz syndrome type 5	AD
SMAD2	18q21.1	SMAD family 2	Aortic/peripheral arterial aneurysm/dissection	
SMAD3	15q22.33	SMAD family 3	Aneurysms-osteoarthritis syndrome/Loeys-Dietz syndrome type 3	AD
SMAD4	18q21.2	SMAD family 4	Juvenile polyposis/hereditary hemorrhagic telangiectasia	AD
SKI	1p36.33-p36.32	SKI sarcoma oncogene homolog	Shprintzen-Goldberg syndrome	AD
Smooth muscle contractile unit proteins				
ACTA2	10q23.3	Smooth muscle cell alpha actin	FTAAD (AAT6) Moyamoya disease	AD
MYH11	16p13.11	Smooth muscle cell myosin heavy chain	FTAAD (AAT4)	AD
FLNA	Xq28	Filamin A	Periventricular nodular heterotopia	X-linked dominant
MYLK	3q21.1	Myosin light chain kinase	FTAAD (AAT7)	AD
PRKG1	10q11.2	cGMP-dependent protein kinase type 1	FTAAD (AAT8)	AD
Neural crest migration				
NOTCH1	9q34.3	Notch1	Bicuspid aortic valve with aneurysm	AD
Undefined defect				
	11q23.3–24		FTAAD (AAT1)	
	5q13-q14		FTAAD (AAT2)	

Data from: Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). Updated October 19, 2017. World Wide Web URL: https://omim.org/

role in the development of ascending aortic pathology, genetic factors appear to play a larger role. The genetic aspects of ascending aortic pathology can be categorized as syndromic and nonsyndromic. The term syndromic refers to phenotypes of the genetic defect that involve other organ systems as well as the cardiovascular system and occur in recognizable patterns. Nonsyndromic defects appear to be primarily manifested within the aorta or occur as sporadic cases. Syndromic aortic defects are more easily recognizable clinically and include Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), Ehlers-Danlos syndrome type 4 (EDS-IV), Weill-Marchesani syndrome (WMS), aneurysm arthritis syndrome, arterial tortuosity, and cutis laxa [91] (Table 3.1).

Marfan syndrome is an autosomal dominant disorder of connective tissues most commonly due to a mutation in the FBN1 gene encoding for the protein fibrillin 1. Penetrance is 100%, but the phenotype can be variable. The phenotype typically consists of skeletal abnormalities such as pectus excavatum or carinatum, arachnodactyly, scoliosis, increased joint laxity, mitral valve prolapse, ectopia lentis, striae of the skin, and dural ectasia. The most deadly phenotypic manifestation of this disorder is found in the dilation and degenerative changes of the aortic root and ascending aorta, which can lead to dissection and rupture.

Fibrillin mutations also are associated with the Weill-Marchesani syndrome. While fibrillin mutations in MFS

cause tall stature, arachnodactyly, hypermobile joints, and hypomuscularity, the opposite phenotype appears in WMS [49]. WMS patients have short stature, brachydactyly, stiff joints, ectopia lentis, myopia, glaucoma, tight skin, hypermuscularity, and heart defects. WMS can be inherited in an autosomal dominant or recessive fashion. The recessive type has been linked to a gene on chromosome 19. ADAMTS10, a zinc-dependent protease, has been linked to autosomal recessive forms of WMS. The autosomal dominant form has been linked to the FBN1 gene. Cardiovascular defects that affect people with WMS include mitral valve prolapse, aortic and pulmonary valve stenosis, ventricular septal defects, QTc prolongation, and ascending aortic dilation [91, 92].

Loeys-Dietz syndrome is associated primarily with TGFβ signaling pathways. Patients with LDS inherit the phenotype in an autosomal dominant pattern and have chest wall deformities such as pectus carinatum or pectus excavatum, a high arched or cleft palate, pes planus, clubfoot, scoliosis, bifid uvula, hypertelorism, widespread arterial tortuosity, and specifically aortic root aneurysms. They are similar in phenotype to MFS patients, except that the arteriopathy that occurs in LDS seems to be more widespread and occurs in peripheral arteries as well as the aorta. There are five types of Loeys-Dietz syndrome. Type 1 is caused by mutations in the TGFBR1 gene, which encodes for the TGFβ receptor 1. Type 2 is caused by mutations in TGFBR2 [93]. Type 2 patients tend to have joint laxity, easy bruising, velvety skin, diffuse arterial aneurysms and dissections, and near translucent skin [94]. Type 3 mutations are caused by mutations of the SMAD3 gene. Type 4 LDS is caused by a mutation involving the TGFβ 2 ligand [93]. Type 5 LDS is caused by a mutation in the gene encoding for TGFβ 3 ligand. As with MFS, the greatest clinical danger with LDS is the presence of severe cardiovascular defects. LDS is associated with aortic dissection, occasionally with no warning and no apparent dilation. The mean age of first vascular events tends to occur at a younger age, at around 30 years old.

Vascular Ehlers-Danlos syndrome type 4 (EDS-IV) is a connective tissue disorder that affects type 3 collagen. There are more than ten types of EDS, each with a different phenotype. Most phenotypes share similarities in regard to joint hypermobility, cutaneous fragility, and hyperextensibility. Type 4 is generally an autosomal dominant inherited disorder although autosomal recessive forms have also been described. There is significant phenotypic overlap between LDS and EDS-IV. EDS-IV patients are often short and have translucent skin. Their joint hyperextensibility is less pronounced than other EDS types. In addition to frequent arterial rupture, EDS-IV patients are found to have valvular prolapse and frequent spontaneous pneumothorax. Type 3 collagen is deficient in EDS type 4 due to a defect in the COL3A1 gene. This causes markedly increased fragility of connective tissues that may lead to uterine rupture in pregnancy, intestinal perforation, as well as aortic dilation, dissection, and rupture. EDS-IV affects about 6% of EDS patients and is the most lethal form of EDS [95].

Shprintzen-Goldberg syndrome (SGS) is another syndrome with a phenotype similar to LDS and MFS, but the arteriopathy is less severe. SGS phenotypes can include craniosynostosis, arachnodactyly, exophthalmos, hypertelorism, maxillary and mandibular hypoplasia, low set ears, abdominal hernias, pectus deformity, scoliosis, Chiari I malformations, and aortic dilation. Functionally, these individuals suffer from developmental delay, mental retardation, and obstructive sleep apnea. These patients can appear to have a Marfanoid habitus [96]. This syndrome is typically inherited in an autosomal dominant pattern, but there must be a causative event that activates the mutation or some germline mosaicism for the mutation to be expressed. Mutations found in the SKI gene appear to cause aortic dilation that can lead to aneurysmal disease. SKI is a SnoN protein that is normally a TGFβ repressor by inhibiting SMAD. SKI competes with a p300/CBP transcription factor for SMAD binding. When SKI binds, it converts chromatin into a repressive state. SKI binds the MH2 domain of the SMAD2/SMAD3 complex, thereby preventing the transcription of TGFβ. However, when it becomes mutated, there is overexpression of TGFβ. The upregulation of TGFβ causes increased signaling events, but due to the presence of other repressors of the TGFβ pathway, the vascular phenotype is less severe than that of LDS [97].

Turner's syndrome (TS) occurs in roughly 1 in every 2000 live female births. Characterized by short stature, webbed neck, and premature ovarian failure, these women have normal intelligence. The genotype and phenotype are due to complete or partial monosomy of the X chromosome. The most common causes of early fetal demise or later complications are cardiovascular defects. Babies with in utero fetal demise are typically found to have hypoplastic left heart syndrome. Common cardiovascular manifestations of TS include bicuspid aortic valves and aortic coarctation [98]. Some develop ascending aortic dilation, dissection, and rupture that are not always associated with bicuspid aortic valves.

TS is one of the most common causes for aortic dissection in women. Difficulties in diagnosing aortic dilation and predicting rupture may be due in part to the sizing of aortic diameters in short statured women. Adjustment of aortic diameter for height or body surface area indicates significant aortic dilation in up to 1/3 of women with TS [105]. Two-thirds of TS dissections occur in the ascending aorta (see biglycan discussion above).

X-linked Alport syndrome is a familial inherited disorder of collagen that affects the alpha-5 chain of type 4 collagen. Type 4 collagen is an important part of basement membranes. This defect affects the glomeruli of the kidneys leading to

renal fibrosis as well as the cochlea leading to sensorineural hearing loss. Case reports have identified aortic pathology in males with X-linked Alport syndrome. Most of the cases reported involve dissection in young males between the ages of 20 and 30 years. Vascular complications are uncommon in Alport syndrome but arise due to a lack of appropriate procollagen trimers in the type 4 collagen fibers of lamellar basement membranes in the aortic media. This is caused by the absence of alpha-5 chains [100].

Cutis laxa, or elastolysis, comprises a group of connective tissue elastic fiber disorders characterized by loose, redundant skin and may be congenital or acquired. Congenital cutis laxa syndromes present with variable phenotypes and extracutaneous manifestations including ascending aortic aneurysm, genitourinary and gastrointestinal diverticula, diaphragmatic hernia, and emphysema that may lead to cor pulmonale and death in early life. The autosomal dominant form is caused by a defect in *ELN* that encodes for elastin and has less severe involvement of internal organs and vasculature. Autosomal recessive forms present a more virulent phenotype and are associated with mutations in *FBLN4* and *FBLN5*. An X-linked recessive form, now classified with copper deficiency syndromes, is caused by a defect in *ATP7A* [106].

Nonsyndromic FTAADS include a growing number of conditions with identifiable mutations as well as aneurysms associated with bicuspid aortic valves. The MYH11 gene and the ACTA2 gene encode for smooth muscle myosin and actin proteins. Both genes encode muscular elements, and the mutations have been thought to be associated with upregulation of TGFβ signaling. MYH11 encodes a smooth muscle myosin heavy chain isoform. The MYH11 gene mutation is associated with a high penetrance of coexistent persistent patent ductus arteriosus. ACTA2 encodes for smooth muscle alpha actin that is also coincidentally expressed during inflammation and is a transcriptional target of TGFβ signaling [97].

Moyamoya disease is an occlusive vascular disease associated with smooth muscle cell proliferation. This disease has incomplete penetrance and is more common in persons of Asian descent. The proliferative arteriopathy in this disease leads to the formation of abnormal collateral vessels in the brain. These arise to compensate for diminished blood flow in narrowed internal carotid arteries. These collateral vessels eventually occlude due to intimal hyperplasia, despite atrophy of the media layer. There also appear to be defects in the elastic lamellae of the arteries as well; however, this is less well characterized [101]. Moyamoya is associated with FTAADS in individuals with ACTA2 mutations [107].

FTAADs have been primarily found through genome sequencing in families with a history of aneurysmal disease. Sequencing reveals deletions and other probable disease causing mutations, as well as variants of unknown significance. Variants of unknown significance are typically found in coding regions of known genes for fibrillin, TGFβ pathway constituents, and SM. While current surgical indications are primarily based on aortic diameter, the association of specific mutations with phenotypes prone to dissection and aneurysm formation will allow more effective risk stratification. Some patients will benefit from early prophylactic surgery based on their genotype and not size criteria [91].

Bicuspid Aortic Valves

Bicuspid aortic valves (BAV) are the most common congenital cardiac malformation, occurring at a rate of 1–2% [102]. The normal aortic valve consists of three leaflets, and bicuspid valves have two leaflets often with a raphe fusing adjacent, conjoined leaflets. Multiple classification systems exist based on the number of raphes, the position of the cusps/raphes, and the functional status of the valve. One such classification system by Sievers and Schmidtke classified bicuspid valves based on the number of raphe. Type 0 has no raphe, type 1 has one raphe, and type 2 has two raphes. Type 2 bicuspid valves are associated with the highest incidence of ascending aneurysms according to one study of 304 surgical patients [103]. The formation of ascending aneurysms in BAV patients may be caused by the flow dynamics of blood as it passes through a reduced aortic valve opening. Due to the position of the cusps, a high velocity jet is continuously directed toward the convexity of the ascending aorta, eventually causing dilation and dissection or aneurysm [102, 103]. Russo classified bicuspid valves based on where the fusion of the cusps occurred [104]. Type A valves had fusion of the left and right coronary cusps. Type B valves had fusion of the right and noncoronary cusps, and type C valves had fusion of the left coronary and noncoronary cusps. Russo found that type A cusps were the most common. Type A cusps affected a younger subset of patients with a larger mean aortic root diameter. Based on the histopathology of aortic specimens, type A valves and their associated aortas had a higher prevalence of fibrosis, medial necrosis, elastic fragmentation, and inflammation compared to type B valves. This study also found a direct correlation between the degree of aortic wall degeneration and the ascending aortic diameter [104].

Patients with bicuspid aortic valves tend to have increased arterial stiffness due to the degradation of elastin fibers within the aortic wall. There also appears to be abnormal endothelial cell function with downregulation of endothelial nitric oxide synthase (eNOS). Due to the downregulation of eNOS, nitric oxide bioactivity is increased, which subsequently increases MMP2 expression. Increased wall stiffness in the aorta is thought to be mediated by multiple factors and cytokines, but specifically matrix metalloproteinases like MMP2. These aortas are then remodeled leading to dilation of the aortic walls [102].

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4 Pathology of the Aorta: Inflammatory and Noninflammatory Conditions Predisposing to Aneurysm Formation, Dissection, and Rupture

Jessica Gulliver and Erin G. Brooks

Introduction

The aorta is an elastic artery with a caliber that expands with systole and recoils during diastole. In adults, it extends an average of 490 cm in length from thoracic initiation to pelvic bifurcation, and it is anatomically divided into three layers, i.e. the tunica intima, tunica media, and tunica adventitia (Fig. 4.1) [1]. The tunica intima is the layer closest to the aortic lumen and is composed of extracellular matrix proteins and a few multipotent stromal cells [1, 2]. It includes an endothelial cell layer and extends to the internal elastic lamina (IEL). The IEL delimits the tunica intima from tunica media and consists of elastic fibers that form a barrier between large molecules within the circulating blood (e.g. cholesterol) and the underlying layers of the aortic wall. In newborns, the intimal layer is quite thin with the endothelial cells closely approximated to the IEL; with "wear-and-tear" aging, intimal thickness increases due to deposition of extracellular matrix proteins [3]. The tunica media extends to the external elastic lamina (EEL) and is the thickest layer of the aorta. Its components are concentrically arranged into lamellar units with each lamellar unit being composed of a layer of elastic fibers with subjacent smooth muscle cells and some embedded extracellular matrix including collagen fibers and ground substance [1, 2]. In newborns, the number of stacked lamellar units is only about 35; however, by adulthood, this has generally increased to 50–60 lamellar units [3]. The tunica adventitia is the outermost layer of the aortic wall and is composed of connective tissue, adipocytes, lymphatic channels, and the vasa vasorum. Given the width of the aortic wall, a specialized vascular system is needed to supply oxygen and other nutrients to the parts of the aortic wall furthest from the blood flowing within the aortic lumen; thus, the vasa vasorum supplies oxygen and nutrients to the outer third of the tunica media. Disruption to the normal layers of the aortic wall due to a variety of diseases can result in significant morbidity and mortality. Thus, familiarity with clinicopathologic features supportive of particular disease processes is advised.

Overview of Aortic Disease

The recent consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology recommends that aortic diseases detected in surgical pathology specimens be categorized as either inflammatory or noninflammatory processes and offers a standardized approach to the processing of specimens, disease grading, and disease nomenclature [3, 4]. It is anticipated that such standardization will result in enhanced understanding of aortic diseases and improved patient care. Either inflammatory or noninflammatory aortic disease may ultimately result in serious sequelae such as aortic aneurysm formation, acute aortic dissection, or aortic rupture. A brief overview of the pathogenesis and epidemiologic features of aortic aneurysms and aortic dissections is followed by a review of the distinct inflammatory and noninflammatory disease processes that may lead to such phenomena.

Aortic Aneurysm

Pathologically, a true aortic aneurysm is defined as a localized dilatation involving the entire thickness of the wall; it may be congenital or acquired [5]. A false or pseudoaneurysm, in contrast, is defined as a ruptured arterial wall in which blood is confined by surrounding tissues forming an extravascular hematoma [5]. In the United States, true thoracic and abdominal aortic aneurysms represent the 15th leading cause of death in people greater than age 55 and are the 19th overall leading cause of death [6].

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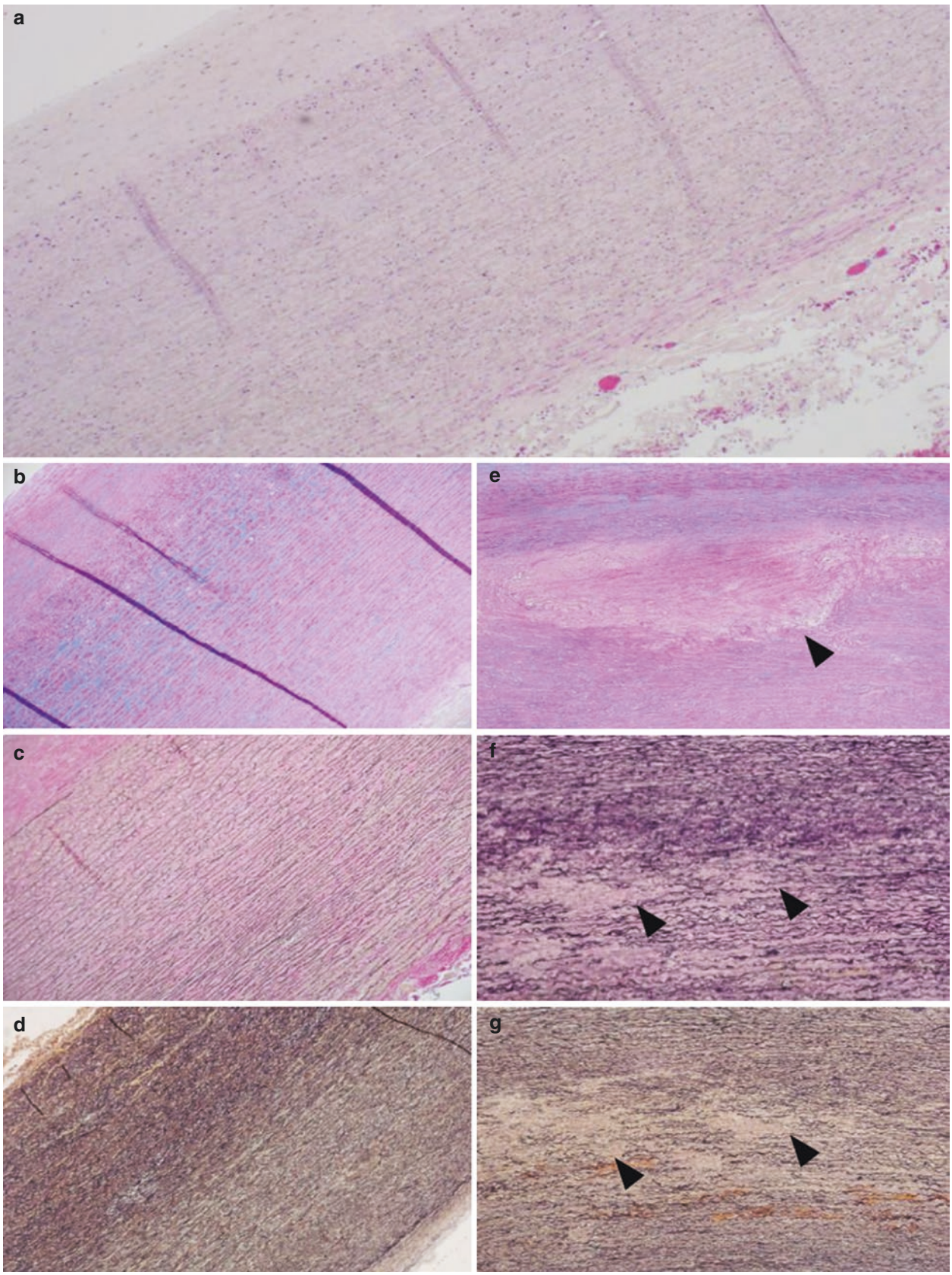

Fig. 4.1 (**a**) Normal layers of the aortic wall with the tunica intima, tunica media, and tunica adventitia. (**b**) There is no medial degeneration present (Alcian Blue/PAS stain). (**c**) The normal aorta contains elastic fibers in an organized pattern (Elastic stain). (**d**) Organized elastic fibers without any degenerative changes (Movat's pentachrome stain). (**e**) Medial degeneration within the aortic wall (arrowhead). (**f**) Elastic fiber fragmentation and loss (arrowheads). (**g**) Increased extracellular matrix material (arrowheads)

Thoracic Aortic Aneurysm

More than 95% of thoracic aortic aneurysms (TAAs) are asymptomatic; the prevalence of clinically silent TAAs is estimated to fall between 0.16% and 0.34% [6]. TAAs are more common in men compared to women [6, 7]. The TAA distribution in 60% occur in the root or ascending aorta, 10% in the arch, 40% in the descending aorta, and 10% in the thoracoabdominal aorta (Fig. 4.2). The incidence of TAAs appears to be increasing [6, 7]. There seems to be a genetic component to TAAs with 21% of patients with a TAA having a family member with some sort of aneurysm. Genetic syndromes such as Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome, and Turner syndrome can have TAAs as part of their clinical manifestations of the genetic abnormality [6]. Other risk factors for development of thoracic aortic aneurysm include aging, systemic hypertension, and bicuspid aortic valve [7].

Histologically, medial degeneration is commonly seen in thoracic aortic aneurysm resections. Medial degeneration leads to a weakened aortic wall which predisposes to dilatation and eventual aneurysm formation. Mucoid extracellular matrix accumulation, loss of smooth muscle cells with disarray, elastic fiber degeneration, and disorderly arrangement are some features of medial degeneration [3, 7]. In patients with Marfan syndrome, mutations in fibrillin-1 are found. Fibrillin-1 is important to the construction of microfibrils in the extracellular matrix. Medial degeneration is often significant in patients with Marfan syndrome [7].

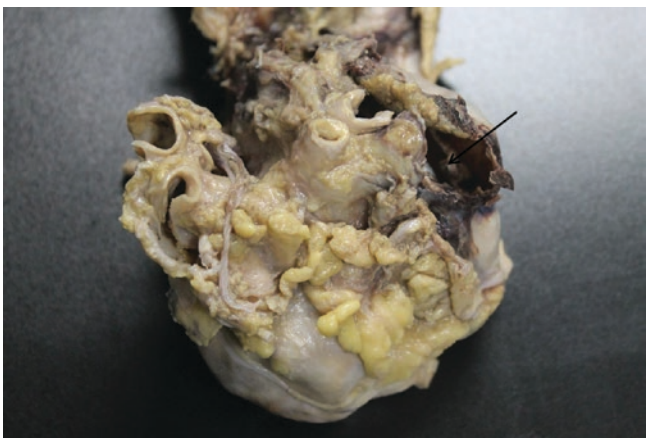

Fig. 4.2 Thoracic Aortic Aneurysm Rupture with hemorrhage (arrow demonstrating aortic arch rupture). Brachiocephalic Artery, Left Common Carotid Artery, and Left Subclavian Artery are adjacent to area of rupture

Abdominal Aortic Aneurysm

Abdominal aortic aneurysms (AAAs) are more common in occurrence when compared to TAAs; up to 80% of aortic aneurysms occur below the renal arteries [7]. Most are due to atherosclerosis, but other causes such as inflammatory aneurysm, tuberculous aneurysm, medial degeneration, or infectious aneurysm are possible [7]. Risk factors for AAAs include smoking, increasing age, greater height, coronary artery disease, atherosclerosis, hypercholesterolemia, and hypertension [7, 8]. Like thoracic aortic aneurysms, genetics also can play a role in AAAs with 12–19% of those patients having an abdominal aneurysm repair being related to a first degree relative with an AAA [8]. In addition, patients with Ehlers-Danlos type IV who have a defect in their type III collagen synthesis are at an increased risk of AAA [8].

Atherosclerotic plaques play a role in development of AAAs. Significant inflammatory infiltrates including numerous macrophages and lymphocytes are common in AAAs which may contribute to extracellular matrix degeneration. Histologically, elastic fiber loss, medial smooth muscle cell degeneration, and fibrosis can be seen. Another common finding is thrombus formation within the aortic lumen associated with the aneurysm. Enzymes such as collagenase and elastase may be upregulated contributing to aneurysmal dilatation [7].

Aortic Dissection

Approximately 3/100, 000 persons/year develop an aortic dissection with a slight male predominance. Risk factors for an aortic dissection include age, inherited genetic connective tissue diseases such as Marfan syndrome and Ehlers-Danlos syndrome, hypertension, aortic valvular disease such as bicuspid aortic valve, trauma, prior aortic operations, and cocaine abuse. The most common symptoms are back, abdominal, or chest pain [9]. An aortic dissection occurs when a tear develops in the intimal layer allowing blood to enter into the tunica media layer creating a true lumen and a false lumen (Figs. 4.3, 4.4, and 4.5). In cases related to an intimal tear, 60% occur in the ascending aorta, 25% in the descending aorta, and 10% in the arch and abdominal aorta [9]. Other causes of aortic dissection could be bleeding from the vasa vasorum in the tunica adventitia into a weakened tunica media layer.

Aortic dissections are often classified into two types: Stanford Type A which occurs in the ascending aorta and Stanford Type B which originates in the descending aorta [9]. Approximately 60% of patients develop Type A dissections with the incidence peaking between 50–60 years of age [9]. In patients with inherited connective tissue diseases, a common histological finding is medial degeneration which is

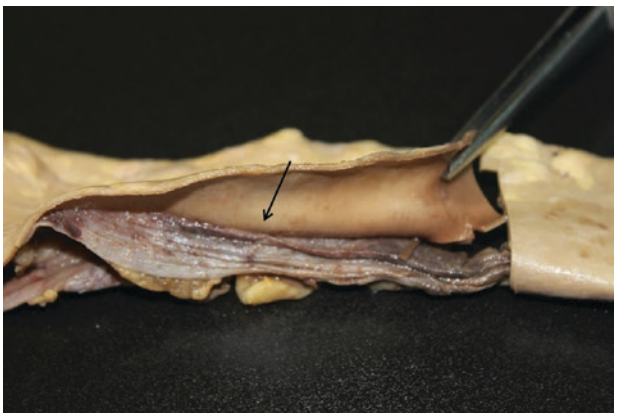

Fig. 4.3 Aortic dissection with true lumen and false lumen (arrow indicating false lumen)

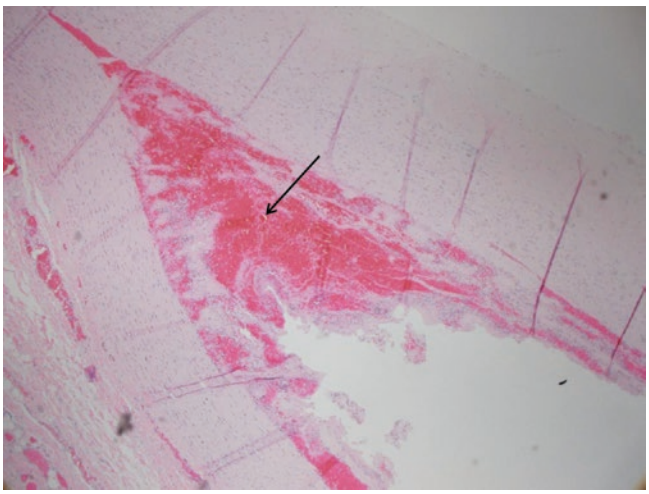

Fig. 4.4 Aortic dissection with hemorrhage (arrow) present within the separating tunica media

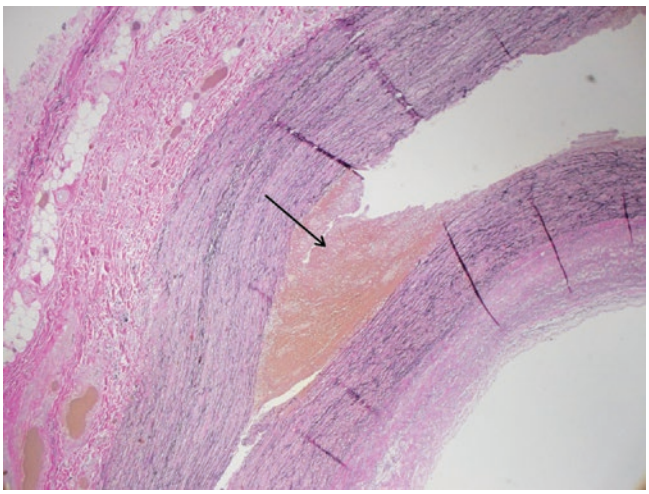

Fig. 4.5 Aortic dissection with elastic fibers stained with an elastic stain showing dividing layers of tunica media as hemorrhage accumulates within the tunica media

characterized by loss of elastic fibers in the tunica media, decrease in smooth muscle cells, and an increase in proteoglycans, glycosylated proteins [3, 9, 10]. In patients without connective tissue diseases, medial degeneration may be milder or less common. Electron microscopy of the layers of the aortic wall has shown in normal aortic walls elastic fibers are organized longitudinally but also with connections between the longitudinal elastic fibers. In patients without a connective tissue disease, it is possible that loss of connection between longitudinal elastic fibers is a mechanism in the pathogenesis of aortic dissection [10].

Noninflammatory Conditions of the Aorta

Degenerative changes of the aortic wall can result from a variety of noninflammatory conditions such as aging, hypertension, genetic syndromes, and congenital anomalies. Histologically, they may show medial degeneration. Medial degeneration includes mucoid extracellular matrix accumulation, elastic fiber fragmentation, thinning, and disorganization, smooth muscle cell nuclei loss and disorganization, laminar medial collapse, and medial fibrosis (Figs. 4.6 and 4.7) [1, 3]. Each of these subcategories are components of medial degeneration and can be graded as mild, moderate, and severe to contribute to the overall grading of medial degeneration as mild, moderate, and severe [3]. Aging, genetic syndromes, congenital diseases, hypertension, cocaine, intense physical exertion, and pregnancy can be associated with degenerative changes within the tunica media [1, 3]. Attempting to streamline the pathologic terminology used to describe abnormalities within the aortic wall may improve understanding of the common histologic appearance of the various causes of aortic pathology [3].

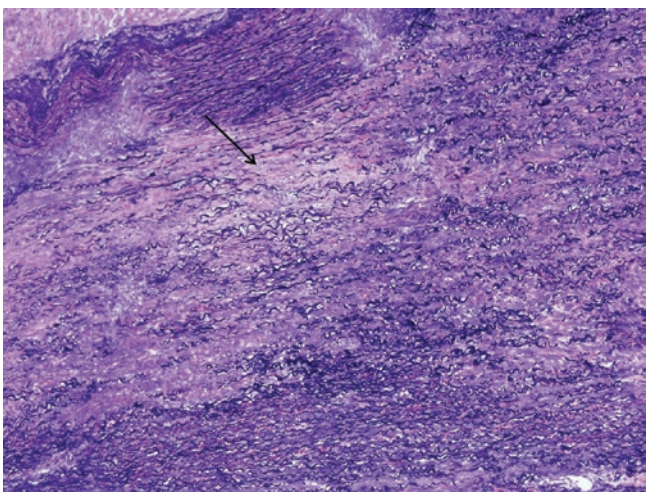

Fig. 4.6 Elastic fiber fragmentation as seen in aging and noninflammatory conditions of the aorta previously described

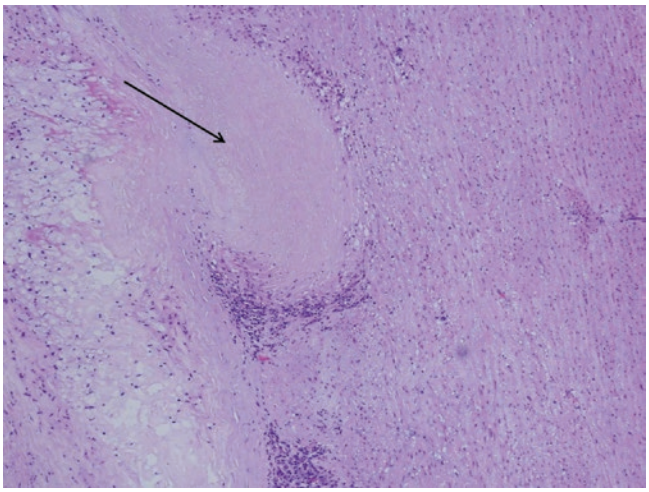

Fig. 4.7 Medial degeneration as previously described in noninflammatory conditions of the aorta

Aortic Disease in the Elderly

As individuals age, the aorta becomes less pliable and enlarges placing them at risk for aneurysm and dissection. Within the thoracic aorta, the diameter changes as people age. However, in the abdominal aorta, the most significant change is an increase in stiffness [1]. Elastin decreases and becomes more fragmented. In addition, there is intimal proliferation and increased disorganized collagen. Smooth muscle cells become less prevalent. Each of these changes presents a challenge for the aorta to repair itself when injury occurs [1].

Aortic Disease in the Young

Genetic syndromes such as Marfan syndrome, Loeys-Dietz syndrome, Turner syndrome, Ehlers-Danlos syndrome, Familial thoracic aortic aneurysm and dissection, Arterial tortuosity syndrome, Shprintzen-Goldberg, and autosomal dominant polycystic kidney disease can demonstrate elastic fiber fragmentation and loss [1, 3]. Marfan syndrome (MFS) results from a genetic abnormality in the fibrillin-1 gene which predisposes 68–80% of individuals to aortic root dilatation by age 19 [11]. Individuals with this syndrome may have pectus excavatum, arachnodactyly, tall stature, lens ectopia, and mitral valve prolapse [1, 11]. At autopsy, annuloaortic ectasia where both the aortic annulus and ascending aorta are enlarged with a flask-like shape may be seen. Histologically, elastic fiber fragmentation and medial degeneration are observed [1, 3, 11].

In Turner syndrome, a sex aneuploidy syndrome where individuals have a single X chromosome, 1.5% of individuals have aortic dilation along with other cardiac abnormalities such as bicuspid aortic valve and coarctation [11]. Other manifestations of Turner syndrome include webbed-neck, short stature, and lymphedema [1]. By contrast, individuals with Ehlers-Danlos syndrome type IV have an abnormality in their collagen, type III, alpha-1 (COL3A) gene which encodes type III 1 collagen found in skin, vessel walls, and hollow organs [11]. Individuals may have thin skin, a thin pinched nose, thin lips, prominent ears, and be prone to bruising [1]. Rupture and dissection tend to be more common than aortic aneurysm formation.

In individuals with autosomal dominant polycystic kidney disease, a mutation found in polycystic kidney disease (PKD) 1 gene, can result in saccular intracranial aneurysms and at times abdominal aortic aneurysm or thoracic aortic aneurysm rupture [1, 11]. Other manifestations include renal cysts and renal failure [11]. Aneurysm rupture could be related to hypertension within these individuals. About 20% of patients being seen for thoracic aneurysm repair have clustering of thoracic aneurysms in their family. Inheritance is usually autosomal dominant and can be caused by a number of different genetic mutations [1, 11].

Loeys-Dietz syndrome, a disorder of connective tissue diseases, shares some features with MFS and vascular type of Ehlers-Danlos syndrome [1, 11]. Individuals may have hypertelorism, changes to their uvula, cleft palate, craniosynostosis, and be at risk for visceral rupture as well as easy bruising [1].

Aortic tortuosity syndrome can occur due to a mutation in solute carrier family 2 member 10 gene which encodes a glucose transporter (GLUT10) [11]. Medial degeneration, specifically, elastic fiber fragmentation may be observed histologically [1].

Congenital

Bicuspid aortic valve affects approximately 2% of the population and is the most common congenital heart abnormality. The cause of bicuspid aortic valve is mostly unknown. About 50% of young men with bicuspid aortic valve have aortic dimensions fitting with an aneurysm and 5% develop an aortic dissection [11]. NOTCH-1 mutations can be seen in those with bicuspid aortic valve [1]. Individuals may develop an aneurysm of the aortic root which is associated with a sixfold increased dissection risk [1]. Medial degeneration within these aortas can range from mild to severe [1]. Other congenital anomalies, such as coarctation of the aorta and narrowing of the aorta distal to the left subclavian artery, can be associated with bicuspid aortic valve and rarely aortic dissection. Histologically, mucoid extracellular matrix accumulation and elastic fiber fragmentation may be observed. Finally, most patients with tetralogy of Fallot undergo repair

but can develop aortic root dilatation as they age. Pathology often demonstrates medial degeneration with lack of lamellar units, elastic fiber fragmentation, mucoid extracellular matrix accumulation, and medial fibrosis [1].

Other Noninflammatory Causes of Aortic Aneurysm and Dissection

Systemic hypertension is one of the most important risk factors for medial degeneration and development of aortic aneurysm and dissection [1, 3]. In a Mayo Clinic study of 513 patients requiring resection of a thoracic aortic aneurysm, 54.4% had a history of hypertension [12]. Hypertension may accelerate the aortic aging process through altered hemodynamic forces which greatly affect the aortic media [1, 12].

Cocaine abuse is associated with multiple cardiovascular abnormalities including aortic dissection. Cocaine causes release of catecholamines which stimulate alpha- and beta-adrenergic receptors which can lead to vasoconstriction and arterial spasm. Chronically, cocaine leads to increased diastolic aortic diameter, loss of aortic elasticity, and increased aortic stiffness [11]. Histologically, resected aortas can demonstrate mucoid extracellular matrix accumulation [1]. When combined with uncontrolled hypertension and smoking, these individuals can be at risk for aortic dissection [11].

Aortic dissection can be seen in weightlifting and severe physical exertion. Typically, patients have preexisting moderately enlarged aortas. The cause of the aortic dissection in this situation could be related to a rapid and extreme elevation in blood pressure during significant exertion against an already dilated aorta [11]. Intense physical exertion can elevate blood pressure over 300 mmHg which increases wall stress [3]. Microscopically, mucoid extracellular matrix accumulation has been seen. The stress on the aortic wall may lead to aortic rupture [3].

Pregnancy can also affect the aortic wall. In women with genetic predisposition to an aortic dissection, such as individuals with MFS, bicuspid aortic valve, an existing aneurysm, or an aortic diameter greater than 4 cm, there is a risk for aortic dissection. The etiology is thought to be from hormonal influences leading to elastic fiber fragmentation and a decrease in aortic wall mucopolysaccharides [3].

Inflammatory Conditions of the Aorta

Inflammatory conditions of the aorta include atherosclerosis, aortitis, and periaortitis [2, 4]. Inflammation of the aorta can result in aneurysm, aortic wall rupture, acute dissection, and obstruction of the aortic lumen [4].

Atherosclerosis

Atherosclerosis is a pathologic process that may cause disease of the cerebral, coronary, mesenteric, and peripheral arteries. Men and women aged 15–34 years of age have been found to have the earliest form of atherosclerosis known as fatty streaks. Risk factors for atherosclerosis include smoking, diabetes mellitus, dyslipidemia, and hypertension. The presence of aortic atherosclerosis indicates systemic atherosclerosis is present.

The pathophysiology of atherosclerosis involves lipid disturbances, platelet activation, thrombosis, endothelial abnormalities, inflammatory responses, oxidative stress, smooth muscle cell proliferation, vascular remodeling, and genetic characteristics.

Classification of degree of severity of atherosclerosis within the aorta appears to differ from classification schemes used in the coronary arteries [4]. Most classification models are based on changes within the tunica intima, but within the aorta the consequences of atherosclerosis are mainly based on changes within the tunica media [4]. Within the aorta, atherosclerosis is categorized as mild, moderate, or severe [4]. No significant atherosclerosis consists of normal or fatty streaks with intimal thickening or hyperplasia and foam cells and lymphocytes seen histologically. Mild atherosclerosis consists grossly of raised plaques and extracellular lipid deposition without fibrosis microscopically. Moderate atherosclerosis consists of raised or confluent plaques which has extracellular lipid deposition and fibrosis as well as destruction of the media up to 1/3 of thickness. Severe atherosclerosis also consists of raised or confluent plaques on gross examination as well as extracellular lipid deposition with fibrosis, but media destruction constitutes more than 1/3 of the thickness. Importantly, pathologists must also comment if plaque disruption, luminal thrombus, or if the plaque is calcified. Noting the presence of thrombus is important for possible embolic events [4].

Atherosclerosis begins as a fatty streak (Fig. 4.8). The fatty streak develops when foam cells (macrophages filled with lipids) accumulate in the intima of an artery. Smooth muscle cells are also present in the intimal layer of arteries and begin to collect. Smooth muscles cells may undergo apoptosis as they increase in the intimal layer which attracts additional macrophages with microvesicles capable of calcifying. This process may facilitate transition of the fatty streak to an atherosclerotic plaque [13].

Once an atherosclerotic plaque develops, there is risk of plaque ulceration or thrombosis (Fig. 4.9). As plaques develop, an extracellular lipid core accumulates covered by a fibrous cap which contains smooth muscle cells and macrophages forming an atheroma (Fig. 4.10) [13, 14]. In plaques with the volume composed predominantly of extracellular lipid and a fibrous cap made largely of macrophages instead

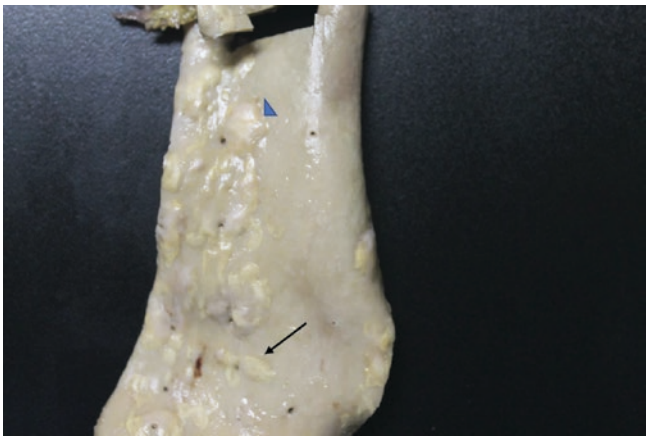

Fig. 4.8 Mild atherosclerosis with both fatty streaks (arrow) and atherosclerotic plaques (arrow head) present

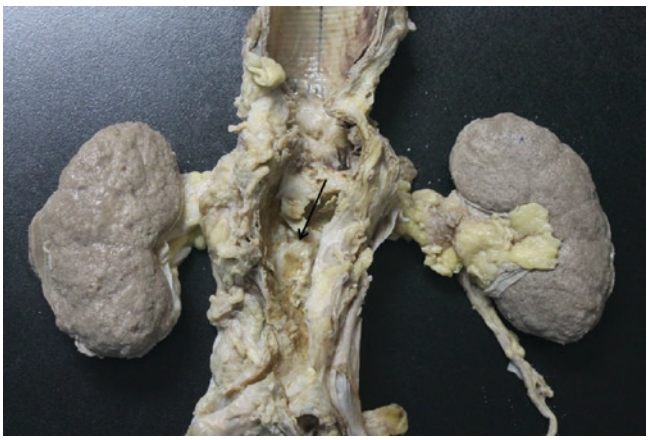

Fig. 4.9 Severe atherosclerosis with ulceration of atherosclerotic plaques (arrow) and shrunken kidneys bilaterally. Graft present superior to area of atherosclerotic plaque ulceration

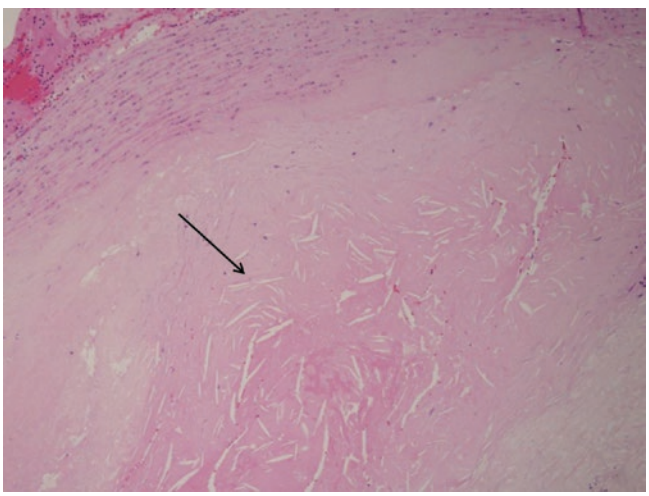

Fig. 4.10 Atheroma within the aortic wall (arrow indicating atheroma and disruption of tunica media)

of smooth muscle cells, thrombosis and ulceration can be seen [14]. Lymphocytes can be observed in the intima, media, and/or adventitia which are mainly CD3+ T-cells, but CD20+ B-cells and plasma cells can also be seen [4]. Disrupted plaques may contain surface thrombus, or if the plaque has existed for a long time, organizing thrombus may be observed. In addition, at the site of disruption, neutrophils can be identified. Cholesterol clefts can cause a giant cell reaction [4].

Some moderate to severe cases of atherosclerosis can have an unusually intense inflammatory infiltrate. Neutrophils can concentrate around the disrupted plaque. Differentiating from bacterial infection can be done by noting absence of necrosis except for in the lipid atherosclerotic core and absence of microorganisms. Gram stain, Grocott-Gomori methenamine silver stain, Steiner, or Warthin-Starry stain may be helpful in identifying infectious causes [4].

Severe atherosclerosis can be associated with an inflammatory atherosclerotic aneurysm especially within the abdominal aorta. Histologically, a lymphocytic, plasma cell, and possibly eosinophilic inflammatory infiltrate is observed within the aortic adventitia along with a severe atherosclerotic lesion. Lack of granulomas, IgG4+ plasma cells, purulent inflammation, or significant necrosis helps distinguish inflammatory atherosclerotic aneurysm from periaortitis.

Aortitis

Ascending aortitis can be a cause of aortic aneurysm. Inflammation of the adventitia and media with giant cells can occur in diseases such as Takayasu arteritis, giant cell arteritis, and isolated arteritis. Takayasu arteritis typically affects individuals between 10 and 30 years of age with a female predominance [2]. Grossly, the aorta appears thickened and rigid due to transmural fibrosis. Areas of narrowing alternating with dilatations can be observed. Histologically, inflammation can be seen in the vasa vasorum initially consisting mainly of T cells. Eventually, inflammation extends to the media and adjacent adventitia. The tunica media can have infiltrates of inflammatory cells including giant cells which lead to elastic fiber and smooth muscle cell loss. When there is destruction of the media, aneurysms can develop. Up to 45% of patients develop aneurysms most commonly in the ascending aorta and aortic arch [11].

Giant Cell Arteritis

Giant cell arteritis is the most common systemic vasculitis to affect the aorta. Patients who develop giant cell aortitis typically lack systemic symptoms usually associated with giant cell arteritis such as unilateral headache, jaw claudication,

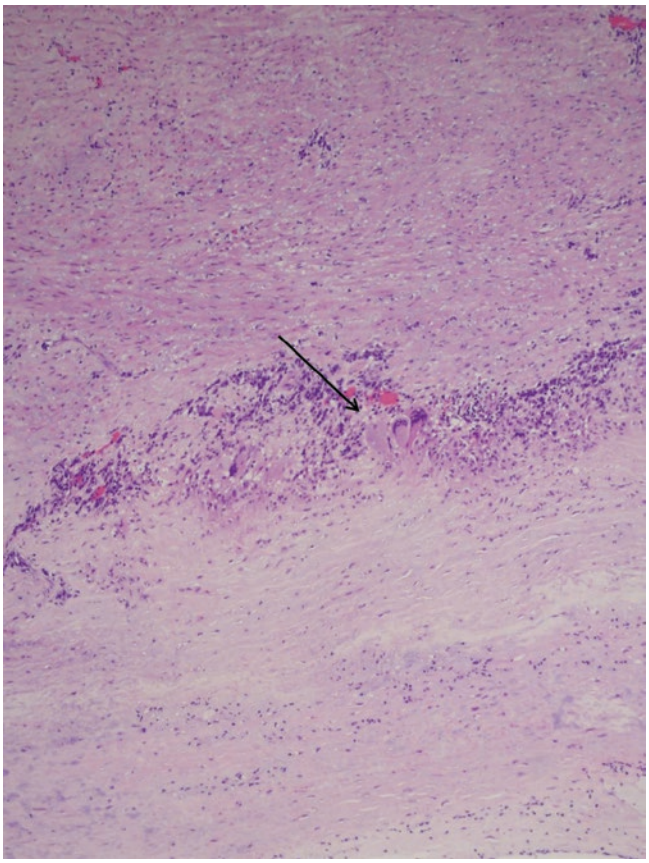

Fig. 4.11 Giant cell aortitis with giant cells and lymphocytic infiltrate (arrow indicating giant cell and surrounding lymphocytic infiltrate within the tunica media of the aorta)

and visual impairment [4]. Aortic intima begins to appear like tree bark due to medial damage, tissue edema, and inherent elastic properties of the vessel itself. Granulomatous inflammatory cells with multinucleated giant cells are seen in the tunica media (Fig. 4.11) [2]. The inner half of the media is predominantly affected [4]. Medial injury results in a moth eaten appearance on elastic stain of the tunica media. When the vasa vasora are involved, the media may infarct and lead to laminar medial necrosis which is seen in both inflammatory and noninflammatory aneurysms [2]. Within the adventitia, a lymphoplasmacytic infiltrate can develop [4]. Those who develop biopsy-proven giant cell arteritis involving temporal or occipital arteries are seventeen times more likely to develop a thoracic aortic aneurysm compared to their healthy age- and sex-matched individuals [2]. In one study, 4% of patients with giant cell arteritis on biopsy developed an aortic dissection.

Takayasu Arteritis

For individuals under the age of 50, particularly adolescent girls and women in their twenties and thirties, Takayasu arteritis is the systemic vasculitis typically affecting the aorta. The disease targets large elastic arteries. Symptoms can be mild such as impalpable pulses or more severe such as subclavian steal syndrome and cerebrovascular events. Geographically, countries such as Japan, Southeast Asia, India, and Mexico have more disease prevalence. Grossly, the aorta may dilate, develop aneurysms, or thrombosis. Inflammatory infiltrates made of granulomas, lymphocytes, plasma cells, and eosinophils can be seen. Medial necrosis with adventitial fibrosis is a common histologic pattern. Giant cell arteritis may appear similarly to Takayasu arteritis. However, Takayasu arteritis typically has a greater aortic wall thickness, and giant cell arteritis usually lacks severe adventitial scarring and inflammation predominantly affects the inner tunica media [4].

Syphilitic Aortitis

Syphilitic aortitis commonly involves the thoracic and ascending aorta with lymphoplasmacytic infiltrates seen in the media and adventitia with obliterative endarteritis in the vasa vasora at times [4]. Warthin-Starry stain can be helpful in identifying the *Treponema pallidum* microorganisms [2]. Aneurysms caused by syphilitic aortitis can erode into nearby tissue whether aortic rupture or dissection is present or not.

Pyogenic Aortitis

Pyogenic aortitis results when bacteria implant on the intimal layer of the aorta which can occur when a patient has bacteremia or endocarditis. Aortic graft placement, spread from an extravascular infection, traumatic inoculation, or embolization of bacteria to the vaso vasora can also result in pyogenic aortitis. Staphylococcus aureus, Streptococcus species, Salmonella species, Gram negative rods, and fungi have been seen in infectious aneurysms. Neutrophils can be seen within the wall of the aorta. Staining for bacteria and fungi can be done, but intraoperative cultures are preferable for diagnosis [2]. If fresh tissue or purulent material was not sent for culture from the operating room, then it is best to send fresh sterile tissue as soon as possible [4]. Additionally, fresh sterile tissue can be used to identify microorganisms by DNA amplification and sequencing. When received, the fresh sterile tissue can be frozen in order to accomplish this [4].

Aneurysm can result from all types of inflammatory aortic disease. Infectious causes usually produce noncircumferential aneurysms that may affect multiple areas of the aorta [2]. Quickly addressing the infection with debridement or an operation could lower the risk of the patient developing a dissection or rupture [2].

Surgical Pathology Processing of the Aorta

When grossing an aortic specimen, it is important when aortic tissue is received to orient, measure, and photograph the specimen. The diameter should be measured and examined for the presence of dissection, intimal tears, presence of atherosclerotic plaques, intimal thickening, evidence of prior operation, and the presence or absence of thrombus material. Decalcification of greatly calcified areas should be done. If Ehlers-Danlos syndrome type IV is suspected, the aortic media should be put in glutaraldehyde for inspection. A minimum of six full thickness sections perpendicular to the lumen should be taken. Evaluation should include a hematoxylin-eosin slide and elastic stain to evaluate the elastic fibers within the aorta. A collagen stain and an Alcian blue periodic acid Schiff stain can be helpful in identifying scarring or accumulation of collagen, proteoglycans, and mucopolysaccharides [11]. If aortitis is suspected, it is recommended to submit at least 1 section of tissue per centimeter or 12 blocks of tissue and to section the specimen perpendicular to the longitudinal axis of the aorta [4].

Conclusion

In summary, it is important for Pathologists and Surgeons to collaborate about the clinical suspicions, findings at the time of operation, identified gross abnormalities, and ultimately the microscopic findings of the aortic pathology. Both noninflammatory conditions and inflammatory conditions of the aorta may lead to aortic aneurysm, aortic dissection, and aortic wall rupture. The most complete understanding of the underlying disease process and etiology of the patient's presentation develops from understanding both the anatomy and histology of the aortic pathology and ultimately using this understanding to guide diagnosis and management of the patient's disease.

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Genetics of Aortic Diseases

5

Arno A. Roscher, Raymond A. Dieter Jr., and Tobias D. Raabe

AbbreviationsAneurysm Types

TAA	Thoracic aortic aneurysm
AAA	Abdominal aortic aneurysm
FTAAD	Familial thoracic aortic aneurysm and dissection
LDS	Loeys–Dietz syndrome
MFS	Marfan syndrome
vEDS	Vascular Ehlers–Danlos syndrome
BAV	Bicuspid aortic valve syndrome
ATS	Arterial tortuosity syndrome

Terms Related to Pathology of the Aortic Wall

ECM	Extracellular matrix
VSMC	Vascular smooth muscle cell
AngII	Angiotensin II
NAD+	Nicotinamide adenine dinucleotide

Terms Related to Heart Disease

MI	Myocardial infarction
CAD	Coronary artery disease

Terms Related to Genetic Analysis

SNP	Single nucleotide polymorphism (the associated rs number unambiguously identifies both the SNP's exact genetic location and specific nucleotide change)
NGS	Next-generation sequencing
GWAS	Genome-wide association study
WES	Whole exome sequencing
Exon	Protein coding DNA sequences of a gene
Intron	Non-protein coding DNA sequences of a gene, usually larger than exons
Promoter	Short DNA sequence located upstream of the transcription start site of a gene that induces production of the mRNA and protein encoded by the gene
Enhancer	Short DNA sequence located up to 100kB away from a gene; interacts with a gene's promoter to enhance protein production of the gene
OMIM	Online Mendelian Inheritance in Man database

Terms Characterizing Genes, RNAs, and Proteins

kB	Kilobases of DNA
kD	Kilodalton of protein
miRNA	microRNA, short ~20 nucleotide long RNA produced by a short gene, it regulates activity of other genes
lncRNA	Long non-coding RNA, a long RNA (produced from a long gene) that cannot be translated into a protein but nevertheless regulates the activity of other genes

Genes Involved in FTAAD and AAA

FBN1	Fibrillin 1
TGFbeta	Transforming growth factor beta

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TGFBR1	Transforming growth factor beta receptor 1
TGFBR2	Transforming growth factor beta receptor 2
TGFB2	Transforming growth factor beta 2
TGFB3	Transforming growth factor beta 3
MYH11	Myosin heavy chain 11
ACTA2	Alpha 2 actin, smooth muscle cell specific
MYLK	Myosin light chain kinase
PRKG1	cGMP-dependent protein kinase 1
MFAP5	Microfibril-associated protein 5
LOX	Lysil oxidase
FOXE3	Forkhead box E3 gene
NOTCH1	NOTCH1 gene
SMAD2	SMAD family member 2 gene
SMAD3	SMAD family member 3 gene
SKI	SKI proto oncogene
LDLR	Low-density lipoprotein receptor
SORT1	sortilin 1
IL6R	Interleukin 6 receptor
MMP9	Metalloproteinase 9
9p21	Chromosome 9 locus 21
ANRIL	Long non-coding RNA ANRIL
SMYD2	SET and MYND Domain containing 2 (protein lysine N methyl transferase)
ERG	ETS-related gene
DAB2IP	DAB2 interacting protein
LINC00540	Long non-coding RNA LINC00540

Introduction

The clinically most important aortic diseases are those that cause aneurysms and dissections in the aortic wall. Aortic aneurysms and/or dissections are sometimes subject to sudden rupture, which often causes sudden death. Currently the biggest problem in addressing sudden rupture is, that early stage aneurysm, which can be successfully treated by surgery, remains usually undetected because it is not associated with clearly detectable symptoms.

Aortic aneurysmal diseases include thoracic aortic aneurysms (TAAs) and abdominal aortic aneurysms (AAAs). TAAs have a strong and well-characterized genetic component. In the western world, TAA occurs with an incidence of about 12 per 100,000 per year in all age groups, shows little gender bias, and does not show strict association with cardiovascular risk factors [1]. In contrast, AAA is generally diagnosed in people over the age of 65, has a prevalence rate of about 8% for men and 1% for women [2] and shows strong association with male gender, smoking and cardiovascular disease. The genetics of TAA is well defined, and more than 20 genes have been found that, when mutated, directly cause TAA in an autosomal dominant Mendelian manner. The genetics of AAA is less well understood, mostly because all genes that have so far been associated with AAA seem to cause a phenotype in concert with environmental factors. In general, the observed prevalence of abdominal aortic aneurysm is likely below its actual occurrence because many cases may go undiagnosed. Combined, all aortic diseases, including inherited and non-inherited, are the 18th most common cause of death and are responsible for 1–2% of all deaths in industrialized nations [3].

At least 20% of all TAA are familial and directly caused by well-characterized mutations which are inherited in an autosomal dominant manner with high penetrance [4–8]. Familial TAAs are abbreviated often as TAAD or FTAAD where F stands for familial and D for dissections.

AAA differs from TAA as it does not usually feature strict Mendelian inheritance due to directly causative mutations. However, in the past several years, it became abundantly clear that AAA is indeed strongly associated with known genetic loci, although in all cases mutations in these loci predispose to AAA and cause AAA only in the context of additional environmental factors [1, 2, 9–11].

With the advent of gene targeting in mice more than 20 years ago that most recently was dramatically facilitated by the new CRISPR technology, it became possible to introduce any type of precise amino acid change into any endogenous gene of the mouse (e.g. [12–14]), and to date, several mutations found in genes of patients with aortic disease have been introduced by gene targeting into the mouse homologues of these genes. This has allowed the generation of experimental mouse models for several genetic types of TAAD and AAA, and these will be discussed below in detail together with the corresponding specific diseases.

The most recent discoveries of genes causing both TAAD and AAA suggest that any patient with TAA or with AAA should undergo genetic screening. If a known aneurysm-associated mutation is found – for TAA, usually a mutation that changes amino acid(s) of a protein coded for by a single gene and for AAA a single nucleotide polymorphism (SNP) usually located in intergenic regions – blood relatives should also be screened for such mutations. Without a doubt this will aid in early detection and therapy of aortic aneurysms and should significantly reduce ruptured TAA and AAA in family members.

Developmental biology has firmly established that the aortic root develops from the secondary heart field, the ascending aorta from the neural crest, and the descending aorta from the paraxial/somitic mesoderm and that the corresponding vascular smooth muscle cells (VSMCs) feature different proliferative and secretory responses to cytokines and produce different types of extra cellular matrix (ECM) in the aortic media [15]. This is consistent with the fact that generation of TAADs and AAAs is mechanistically clearly distinct and, as we describe in the paragraphs below, many of the genes involved in their generation are different. In addition, the cellular pathologies of the dilated aortic wall in TAA and AAA patients are distinct, although they share

some features [16]. A prominent difference is the paucity of atherosclerotic plaques and calcification found in the dilated thoracic aortic wall compared to the undilated and dilated abdominal aortic wall, as well as the distinct Th1-specific immune response for TAA compared to the predominantly observed Th2 immune response for AAA [16]. In addition, intraluminal thrombus is common in AAA but not TAA [17]. On the other hand, for both thoracic and abdominal aortic aneurysms, the aortic media is the predominant location of the causative injury which consists of infiltration of multiple types of inflammatory cells, destruction of the elastic fibers, and loss of VSMC which together lead to structural weakness. The exact proportion of the contribution of inflammatory cells, elastic fiber remodeling, and VSMC metabolism in Mendelian and non-Mendelian forms of TAA as well as AAA is subject of intense research.

Importantly, the knowledge gained from the molecular pathology of inherited aneurysms may also inform how to prevent aneurysms that are not genetically determined, which would be significant as these are the most frequent aneurysms: Indeed several important pathological pathways have already been discovered by genetic linkage analysis and extensively confirmed by animal studies – the TGF-beta pathway was discovered in 2006 to be involved in TAA [18], and this was confirmed extensively [7, 10, 19, 20]. Importantly, this pathway has originally been known to play important roles in the embryonal development of many types of tissues, including the thoracic and abdominal aorta and in the occurrence of many types of cancer – more recently it has been found that it may also be involved in AAA formation [20]. In the past several years, multiple genes regulating the lipid metabolism were found to be involved in AAA [1]. In addition, several genes regulating infiltration of immune cells into the aortic media or affecting extracellular matrix remodeling or proliferation of vascular smooth muscle cells in the media were found to be crucial for development of AAA [1, 21].

The currently known contributions of specific genetic loci to the two main classes of inherited aortic aneurysms, familial thoracic aortic aneurysms and dissections (FTAADs) and abdominal aortic aneurysms (AAAs), are described below.

Familial Thoracic Aortic Aneurysms and Dissections (FTAADs)

The first genetic condition and first familial disease observed to cause TAA is Marfan syndrome, a disease characterized by early TAA-induced cardiac death and characteristically long limbs. Marfan syndrome was also the first familial TAA syndrome shown to be caused by mutations in a specific gene, the fibrillin 1 (FBN1) gene [22]. Later, additional mutations in more than 20 genes causing FTAAD were discovered, and these cause Loeys–Dietz syndrome, vascular Ehlers–Danlos syndrome, Arterial Tortuosity Syndrome, as well as multiple types of non-syndromic familial TAA (FTAAD).

Indeed, familial thoracic aortic diseases are usually classified as either syndromic FTAADs or non-syndromic FTAADs, respectively. Syndromic FTAADs are also referred sometimes simply as syndromic TAADs. Non-syndromic FTAADs are often known simply as FTAADs or even just as TAADs. D for "dissections" is sometimes omitted for brevity. However, if the letter F for "familiar" is not included, the abbreviations can be mixed up with sporadic TAA/TAAD that may lack a genetic cause but indeed comprise the majority (~70+%) of all TAADs. To what degree their molecular pathology is different from that of FTAADs is subject to intense research. For clarity, we will here always include the F for all familial diseases, both syndromic and non-syndromic.

Syndromic FTAADs are characterized by inherited thoracic aortic disease with additional extensive non-aortic-related symptoms, such as long limbs for Marfan disease, while non-syndromic FTAADs have been defined by a lack of additional symptoms. In some cases FTAADs can present as either non-syndromic or syndromic, depending on the age of the patient or the exact position and type of mutation within a given gene, such as for FTAAD caused by mutations in the ACTA2 gene (see below). Each of these inherited aortic diseases is caused by a single mutation in a single different and characteristic genetic locus, and remarkably, at the time of submission of this article, both syndromic and non-syndromic FTAADs are associated with a growing list of genetic mutations in more than 20 different genes. The majority of these mutations are already known to be functionally responsible for FTAAD, based on a combination of family studies and genetic mouse models. Importantly, most of these genetic loci are not involved in AAA, strongly underscoring the functionally distinct pathology of FTAADs.

Among all thoracic aortic aneurysms (inherited plus non-inherited), about 20% are familial and are usually inherited in a classic autosomal dominant manner with high or complete penetrance [4–8]. Due to major recent advances in next-generation DNA sequencing (NGS), new inherited mutations associated with FTAADs are found continuously, and it is likely that the real percentage of FTAADs among all TAAs significantly exceeds 20%. Similar to most forms of AAA, FTAADs typically show distinct and extensive remodeling of the aortic media, characterized by significantly reduced numbers of vascular smooth muscle cells (VSMCs), fragmentation of the elastic fibers in the extracellular matrix (ECM), and inflammatory infiltration of lymphocytes that usually invade from the micro vessels of the adventitia. However, a major difference to AAA is the relative absence of atherosclerotic plaques in the aortic wall of TAA patients [23] (see also Table 5.1).

Since the 1990s, preventative genetic screening of blood relatives of familial syndromic or non-syndromic FTAAD

Table 5.1 Characteristic features of familial TAAD and familial AAA

	FTAAD	Familial AAA
Prevalence of familial disease	At least 20% of all cases	15–20% of all cases
Developmental origin of aortic section	Aortic root: Secondary heart field Ascending aorta: Neural Crest Descending aorta: Somatic mesoderm	Somatic mesoderm
Pathological features as reviewed in [16], for more details on inflammatory cells see [171–174]	Somewhat influenced by non-genetic factors Little or no atherosclerosis Intraluminal thrombus usually absent Extensive fragmentation of elastic fibers in the media - the normal thoracic media is significantly thicker and contains many more elastic lamina than the abdominal media Loss/apoptosis of vascular smooth muscle cells in the media accumulation of proteoglycans, no cyst formation, or overt necrosis (the original diagnosis of cystic medial necrosis is a misnomer) Infiltration of Th-1 inflammatory cells and macrophages through the adventitia into the media. The T-cells have an unusual flattened appearance and thus were not recognized for decades. elevated INFγ, IL2, IL12 and IL18 elevated MMP2 and MMP9	Strongly influenced by non-genetic factors, especially atherosclerosis, smoking and hypertension Frequent/extensive atherosclerosis Intraluminal thrombus is common Fragmentation of elastic fibers in the media Loss/apoptosis of vascular smooth muscle cells in the media Infiltration of Th-2 inflammatory cells through the adventitia into the media as well as NK and NKT cells and macrophages elevated IL4, IL5, IL10, IL12, IL18 and INFγ elevated MMP1, MMP2, MMP3 and MMP9
Types of Syndromic FTAAD all caused by mutations in exons	Caused be mutations in exons of the indicated genes: Marfan syndrome (MFS) FBN1 Loeys-Dietz syndrome (LDS) TGFBR1,TGFBR2,SMAD3,TGFB2, TGFB3 Vascular Ehlers-Danlos Syndrome (vEDS) Col3A1 Bicuspid valve syndrome SMAD6 Arterial tortuosity syndrome (ATS) SLC2A10 Syndromic ACTA2 FTAAD ACTA2	
Types of non-syndromic FTAAD all caused by mutations in exons	Caused by mutations in exons of the indicated genes that affect the: VSMC extracellular matrix FBN1,ELN,FBLN4,MFAP5 VSMC cytoskeleton MYH11, ACTA2 (e.g., Arg39Cys, Arg258 Hi/Cys mutation), MYLK,PRKG1, TGF beta pathway, cell proliferation TGFBR1,TGFBR2,SMAD2, TGFB2, TGFB3, Other pathways LOX, FOXE3, 11q23, 5q13–14	
Types of familial AAA all caused by specific mutations outside of exons but close to the indicated specific genes		Caused by predisposing mutations indirectly affecting expression of the indicated genes involved in: Lipid metabolism LDLR, SORT1 Immune response IL6R VSMC proliferation 9p21/ANRIL, DAB2IP, ERG, SMYD2, LINC00540 Extracellular matrix remodeling MMP9

patients has become routine clinical practice. To date in the USA, most routine genetic tests performed for all individuals with aortic aneurisms assess the presence of mutations in at least 20 separate loci, such as the commercially available Ambry Genetics TAADNext test which assesses 22 loci. This has allowed early treatment of at-risk family members with beta-blockers or blood pressure drugs, regular screening for aneurysms, and/or corrective surgery. A striking example of progress is Marfan syndrome where the average life expectancy has dramatically increased with modern diagnosis, monitoring, and treatment (for details see also section describing MFS below).

Syndromic Familial Thoracic Aneurysms and Dissections (Syndromic FTAADs)

The most well-understood syndromic FTAADs include the dominantly inherited Marfan syndrome (MFS), Loeys–Dietz syndrome (LDS), vascular Ehlers–Danlos syndrome (vEDS), and arterial tortuosity syndrome (ATS) [24]. They are all characterized by acute thoracic aortic dissections and ruptures, which cause sudden cardiac death. In addition they exhibit characteristic features unrelated to the aorta, such as long limbs in the case of MFS and widely spaced eyes for LDS. The first of these syndromic FTAADs was MFS. In 1991, MFS was found to be caused by mutations in the fibrillin 1 gene (FBN1) [22, 25, 26]. Since then, LDS, vEDS, and ATS as well as BAV have been defined by causative mutations in specific genes, and all FTAADs together are now either known or being suspected to be caused by inherited mutations in an increasing number of different genetic loci (currently more than 20), with a few loci being affected most frequently.

Early theories of the causes of human aneurysm mostly focused on inherited or acquired defects in components of the extracellular matrix in the aorta. Although several mutations in the genes encoding extracellular matrix proteins have been recognized, more recent discoveries have also shown important perturbations in cytokine signaling cascades and intracellular components of the smooth muscle contractile apparatus.

There is great utility of genetic diagnostics in the management of syndromic FTAAD, and often essential conclusions for optimal downstream treatment can be drawn since the optimal clinical management of individual FTAADs can be quite distinct. More fundamentally, genetic diagnostics is necessary to diagnose syndromic FTAAD, to exclude syndromic FTAAD and to specify disease types. Combining phenotype with genotype information maximizes the predictability of the course of disease and contributes to a better timing of elective surgery and to a better choice of procedures. Perhaps most importantly, with genetic diagnostics it is possible to predict the birth of children with causative mutations for syndromic FTAAD and to initiate timely drug therapy to prevent the onset of aortic dilatation or to slow down its progression to aortic aneurysm. For all these reasons, it is now standard procedure to apply genetic diagnostics to all new patients with aortic disease.

Marfan Syndrome (MFS)

MFS is a Mendelian disorder of the connective tissue clearly shown to be familial and autosomal dominant in 1931 [27]. MFS is associated with many striking features including long limbs and the presence of dislocated ocular lenses (ectopia lentis). In 1943, it also was shown to be the first Mendelian disorder to cause TAA [28]. In 1991, MFS was shown to be caused by mutations in a specific gene, the fibrillin 1 (FBN1) gene [22]. It is by far the most prevalent Mendelian disease of the aorta and occurs in about 1 of 3000–5000 individuals [29]. The name is a misnomer because the disease originally discovered in 1896 by the French physician Antoine Marfan was almost certainly not MFS but a related disease with similar skeletal malformations, named congenital contractural arachnodactyly (Beals–Hecht syndrome) [30]. MFS is a heritable disorder of fibrous connective tissue and shows highly variable but strongly systemic pathology in the skeletal, ocular, and cardiovascular systems [31, 32]. The current international standard for diagnosis of MFS is documented in the revised Ghent criteria [33]: two of the following four major criteria are needed to diagnose MFS – (1) the presence of dislocated ocular lenses (ectopia lentis), (2) the dilatation or dissection of the aortic root, (3) the presence of a mutation in the FBN1 gene, and (4) the sum of several other features, such as increased height, disproportionately long limbs and digits, anterior chest deformity, mild to moderate joint laxity, and vertebral column deformity (scoliosis and thoracic lordosis) as well as highly arched palate with crowding of the teeth and overbite [34].

In addition to ectopia lentis, myopia, increased axial globe length and corneal flatness are frequent ocular findings [31]. Besides aortic root dilatation and dissection, mitral valve prolapse, mitral regurgitation, and aortic regurgitation are cardiovascular features and together represent the major life-threatening conditions of Marfan patients [31, 35].

Other common manifestations are striae distensae, pulmonary blebs (which predispose to spontaneous pneumothorax), and spinal arachnoid cysts or diverticula [36–38]. By CT scanning, widening of the lumbosacral spinal canal (dural ectasia) was found in 36 of 57 patients with the Marfan syndrome and in none of 57 age- and sex-matched non-Marfan control patients [39]. Severe changes were present in 13 patients, 2 of whom had associated neurologic signs, and included meningoceles or near-total erosion of a pedicle [39].

Due to improved diagnosis, monitoring and treatment, life expectancy for MFS patients has increased from about 44 (men) and 47 years (women) in 1972 to an almost normal life-span as of today as mentioned on website of the Marfan Foundation (https://www.marfan.org/). As a consequence, new MFS features have emerged. These include aortic dilatation beyond the root, type B aortic dissection, aneurysms in arterial branches of the aorta, and cardiomyopathy, as well as cataracts, glaucoma, obstructive sleep apnea, hepatic and renal cysts, degenerative arthritis, osteoporosis, myopathy, and truncal obesity. These new features are an important field of future clinical research.

The fibrillin gene (FBN1) Mutations in the FBN1 gene are the cause of Marfan syndrome, and most FBN1-mutant alleles lead to Marfan syndrome through a dominant negative effect [40, 41]. While the majority of FBN1 mutations cause MFS, a few of the mutations in the FBN1 gene do not cause syndromic disease but asymptomatic FTAAD (OMIM#132900), ectopia lentis (OMIM #129600), or several other very rare conditions. Interestingly, about one-quarter of FBN1 mutations arise spontaneously, but most are inherited from one parent in an autosomal dominant fashion with high penetrance.

The FBN1 gene codes for the extracellular protein fibrillin 1 which is the main and essential component for generation and maintenance of extracellular microfibrils. It is found in connective tissue throughout the body and is a major component of the extracellular matrix (ECM) of the aortic media.

The large size of the FBN1 gene (~200kB) and corresponding fibrillin 1 protein (~350kD) helps explain why more than 1800 different pathogenic mutations, about 1200 of these single nucleotide polymorphisms (SNPs), have been found in the gene, affecting all areas of the corresponding long and repetitive fibrillin 1 protein, according to the current status of the FBN1 Universal Mutation Database that was founded in 2003 [42].

Clearly different functional classes of mutations are seen, although the exact cause and effect relationship is not well understood: 54% of the Marfan patients listed had ectopia lentis, and a higher probability of ectopia lentis was found for patients with a missense mutation substituting or producing a cysteine, when compared with other missense mutations. In addition, patients with a premature termination codon had a more severe skeletal and skin phenotype than did patients with an in-frame mutation. Mutations in exons 24 through 32 were associated with a more severe and complete phenotype, including younger age at diagnosis of type I fibrillinopathy and higher probability of developing ectopia lentis, ascending aortic dilatation, aortic surgery, mitral valve abnormalities, scoliosis, and shorter survival; most of these results were replicated even when cases of neonatal MFS were excluded (FBN1 Universal Mutation Database) [42].

Animal models and molecular pathology of Marfan disease Human MFS affects primarily the aortic root, usually starting with aortic root dilatation.

Indeed, mouse models with mutated FBN1 show overlapping but distinct pathological mechanisms compared to mouse models of AAA. Historically one of the originally most important MFS animal models is the fibrillin 1 mutant mouse used by the Dietz lab to show that either anti TGF-beta neutralizing antibody or angiotensin type 1 receptor blocker losartan reduces aneurysm formation [43]. The potential explanation for this effect was that fibrillin 1 binds to inactive forms of TGF-beta and acts normally as a sump to keep TGF-beta inactive, while mutations in fibrillin 1 protein would set free a pathologically high amount of TGF causing many of the syndromic effects of MFS not only in the aorta but the rest of the body. This finding resulted in the use of losartan (a presumed anti TGF-beta agent) in human subjects of MFS with existing aneurysm (see below). Paradoxically, more recently, using the Angiotensin II-induced mouse model of AAA, TGF-beta inhibition by neutralizing antibodies did not prevent but instead significantly augmented AAA formation mice [44], indicating that perhaps generation and progression of TAA requires different TGF-beta-related stimulation.

Even more intriguing, a more recent mouse model of MFS, the FBN1 C1039G mouse model, altogether questions the original idea that increased TGF-beta levels and thus increased TGF-beta-signaling cause MFS. This is based on the discovery that smooth muscle cell-specific deletion of the TGF-beta receptor TGFBR2 in neonatal FBN1 C1039G mice, which should decrease TGF-beta signaling, actually accelerates, rather than diminishes, aortopathy [45]. In addition, deletion of TGFBR1 (which forms a complex with TGFBR2) in smooth muscle cells of normal adult mice which should diminish TGF-beta signaling causes TAA with 100% penetrance [46]. Losartan, a blocker of the angiotensin receptor, fully rescues this mutation and prevents TAA formation in this mouse model [46], and this is consistent with the fact that the renin angiotensin signaling pathway is upregulated in these mice.

Another twist in the search for novel drug candidates for treatment of TAA was presented by a study in 2016 showing that resveratrol can inhibit specifically TAA progression in the FBN1 C1039G mouse model [47]: resveratrol was administered for 2 months to FBN1 C1039G mice with already existing small TAA, and intriguingly, this completely reversed the TAA to no aneurysm and thus achieved complete cure. Resveratrol promoted extracellular matrix integrity and smooth muscle cell survival and also downregulated the aneurysm-related micro RNA 29b in the aorta [47].

In summary, despite intense efforts using sophisticated genetically engineered mouse models to find new drug targets for MFS, further research will still be necessary. Both

animal models and human genetics of MFS clearly implicate crucial genes of the TGF-beta pathway in TAA formation. While it is clear that in normal mice TGF-beta signaling is necessary for normal early development of arteries including the aorta, it is at present still unclear how the causative FBN1 mutation causes TGF-beta pathway-dependent or -independent development and long-term progression of TAA.

Clinical trials of MFS Multiple clinical trials have been finished, and several are ongoing that are testing angiotensin receptor blockers and/or beta-blockers. Unfortunately, even if a reduction of enlargement of TAA was present due to such treatment, neither beta-blockers nor losartan has so far convincingly changed rates of aortic root surgery, dissection, or death [48]. Several recent trials failed to show a clear positive effect of losartan, the most widely used angiotensin receptor inhibitor, or of any beta-blockers, and careful meta-analysis of all major trials, as well as additional recruitment of patients, may be needed to get a better idea of benefit. Interestingly, the beneficial effect of losartan may depend on the exact nature and location of the causative mutation within the large fibrillin 1 gene as reported for a clinical trial in 2015 [49, 50]. Specifically, losartan alone could very significantly slow down TAA diameter growth in patients with fibrillin 1 mutations that cause haploinsufficiency but no effect at all in patients with dominant negative fibrillin 1 mutations [49, 50]. Indeed, these two types of mutations are functionally distinct as only the dominant negative mutation generates a novel type of fibrillin 1 protein, whose function is not yet well understood, while haplo-insufficient mutations do not change the fibrillin 1 protein but instead cause the fibrillin 1 protein level to fall by about 50% in all tissues.

Additional trials are underway testing more potent versions of angiotensin-receptor blockers [51] such as telmisartan [52]. Truly effective and curative medication for TAA has yet to be discovered, and the multiple recent genetically engineered mouse animal models of TAA will no doubt result in novel candidate drugs to be tested in clinical trials. The recent discovery that resveratrol inhibits TAA expansion in mice is an example of such a new candidate drug [47]. Of note, resveratrol has already shown some positive effects on lipid profiles, body fat, blood pressure, inflammation, and glucose metabolism in some clinical trials [47].

Loeys–Dietz Syndrome (LDS)

LDS was first described in 2005 [53], is exceedingly rare (less than 3 in 100,000 individuals), and is characterized by an aortic pathology similar to Marfan syndrome but lacking a mutation in the FBN1 gene. LDS is an autosomal dominant connective tissue disorder characterized by rapidly progressive thoracic aortic aneurysmal disease, generalized arterial elongation with abnormal twists and turns (vascular tortuosity), increased distance between the eyes (hypertelorism) and bifid/broad uvula or cleft palate [53, 54]. While LDS is similar to MFS in some respects, there are important differences: hypertelorism, cleft palate/bifid uvula, and arterial tortuosity are associated with most forms of LDS but are absent in MFS. Reversely, ectopia lentis (misplacement of the lens) is exclusive to MFS and perhaps directly caused by misfolding or haploinsufficiency of fibrillin 1 which is likely part of the ECM components that hold the lens of the eye in its correct location. Thus ectopia lentis is routinely used to distinguish MFS from LDS and other FTAADs [54].

Based on the most recent genetic studies, mutations in five genes, TGFBR1, TGFBR2, SMAD3, TGFB2 and TGFB3, have been recognized to cause LDS [54, 55] (OMIM database https://www.omim.org/). A single mutation in any one of these genes can be sufficient for full expression of the syndrome. However, not all types of mutations found in these genes cause an "LDS-type" syndrome with the above strong phenotype, and indeed several mutations in these genes have been found that cause only mild symptoms including mild aortic phenotype [56]. This finding highlights the fact that specific mutations in the same gene can have different phenotypes and can cause indeed different diseases. Interestingly, all of the above five genes are involved in the TGF beta pathway that regulates multiple developmental processes including the development of the cardiovascular system and potentially the progression of aneurysmal disease, even perhaps in MFS, as described above. While some of the reported LDS mutations are expected to downregulate TGF beta signaling, as they reduce activity of the corresponding genes, they are not autosomal recessive but autosomal dominant. Whether simple haploinsufficiency or a novel pathological pathway is generated by the different dominant mutations causing LDS must still be determined by further research.

While mutations in the five genes mentioned above can all cause severe TAA, they often do exhibit somewhat different syndromic pathologies. For example, TGFB3 mutations may not cause arterial tortuosity in contrast to mutations in the other four genes [55, 57]. For the characteristic phenotypes of LDS patients with TGFBR1 and TGFBR2 mutations, the Montalcino Aortic Consortium published updated criteria in 2016 [57].

Animal models A recent animal model of LDS confirmed that mutations of Tgfbr1 or Tgfbr2 that are analogous to human mutations (TGFBR1 M318R and TGFBR2 G357W) act in a dominant negative way to contribute to LDS-like symptoms in mice – mostly TAA but not any of the other syndrome-like features [58]. Another study confirmed the importance of Tgfbr2 in TAA development by deleting TGFBR2 specifically in postnatal VSMC, which caused aortic damage, including moderate TAA [59]. On the other

hand, TGFBR1 deletion in VSMC caused severe aortic damage including severe TAA with 100% penetrance, strongly confirming its importance in LDS [46]. Loss of TGFBR1 seems to act through multiple pathways including the TGFBR2, the ERK (extracellular signal-regulated kinases), and the angiotensin receptor AT1R pathways [46]. These data suggest that multiple pathological pathways can be expected for generation of TAA in humans as well. SMAD3 is a downstream target of TGFBR1 and TGFBR2, and some SMAD3 mutations cause LDS in humans and indeed cause severe TAA in SMAD3−/− mice, leading to sudden rupture at death after 6–30 weeks of age [60]. In addition, TGFB2 (transforming growth factor beta 2) haploinsufficiency in mice leads to TAA confirming the finding in LDS patients [61].

At this time it is still too early to make conclusions about the proposed exact molecular mechanisms in LDS and MFS pathogenesis, especially as there are apparently contradictory findings about the importance of TGF beta signaling, as discussed above. It is also possible that some of the discrepancies are simply a consequence of incomplete analysis of the molecular pathology often relying on only one or two maker proteins supposedly proving one type of signaling over another. Thus, it may be beneficial if researchers revisit the various existing animal models to study additional components of possible signaling pathways (TGF beta, SMAD3, ERK, and angiotensin signaling). This could be facilitated by the use of functional genomic techniques such as RNAseq of the aortic tissues to generate unbiased whole genome mRNA expression profiles.

Clinical trials Because LDS is exceedingly rare and it is very difficult to recruit enough LDS patients to reach statistical power, clinical trials of LDS have been performed mostly in form of sub-studies of Marfan clinical trials (see above) and using MFS-specific medications, such as losartan and beta-blockers.

Vascular Ehlers–Danlos Syndrome (vEDS)

Vascular Ehlers–Danlos syndrome (vEDS), also called EDS type IV, is an autosomal dominant disorder caused by mutations in the COL3A1 gene [62, 63]. All EDS types together occur at a frequency of about 1 in 5000, and they are distinguished by the exact type of collagen gene that is mutated (COL1A1, COL1A2, COL3A1, COL5A1, or COL5A2). In the 1920s, individuals with EDS, such as the Indian rubber man and other circus performers, showed off the extreme elasticity of their skin and ligaments common for many types of EDS. vEDS is rare and occurs only in about 1 out of 100,000 people [63]. It is distinct from other EDS types by its arterial complications and therefore included in the syndromic FTAAD conditions. Unlike other FTAAD syndromes, large aneurysms in the aorta are rare but nevertheless ruptures occur with high frequency even in small diameter aneurysms indicating a much more fragile vessel wall than that in MFS and LDS patients [63]. Importantly, not only the aorta but many other types of arterial vessels are often affected already at a young age and therefore vEDS features a significantly more severe pathology than MFS or LDS. In addition dangerous perforations of other hollow organs, especially the sigmoid colon, are common [64].

The median life expectancy for patients with vascular EDS is 40–50 years [63]. Death is most frequently due to complications associated with vascular and hollow organ rupture. Surgical intervention, especially stent grafting, has only limited value in vEDS patients. Indeed, vascular stents and endografts are not often used, as the long-term durability of these repairs often is poor due to suboptimal graft–aortic wall interaction caused by the underlying connective tissue disease and vessel fragility. Unfortunately, even minimally invasive, relatively simple therapeutic interventions can have adverse events – even with standard tools, such as catheters and guide wires – and the need for careful intravascular manipulation cannot be stressed strongly enough.

The COL3A1 gene Mutations in this gene are inherited in an autosomal dominant manner. Interestingly, approximately 50% of cases represent new mutations that occur sporadically and lack a family history of disease but are then inherited to the next generation. The other half inherits the COL3A1 mutation from at least one parent. Women and men seem to be affected with comparable frequency. As with MFS and LDS, pregnancy can be associated with severe complication in vEDS women.

To date, more than 1000 COL3A1 mutations have been identified, and more are being added continuously, and they all can be accessed free of charge from the COL3A1 section of the online Ehlers–Danlos Syndrome Variant Database (https://eds.gene.le.ac.uk/home.php?select_db=COL3A1). This is an invaluable and very detailed resource that allows stratification for types of mutations, frequencies of occurrence, and known pathogenic effect. Most pathogenic mutations are missense mutations leading to substitutions for one of the glycine residues that are part of the many repeating G X Y (G = Glycine, X and Y representing any amino acid) triple repeats in the long triple helical region of the collagen molecule [65–67].

Animal models One of the more informative of the few animal models of vEDS shows that mice haploinsufficient for COL3A1 develop thoracic aortic aneurysms at high rate if infused with AngII by implanted pump, the same procedure used to model TAA and AAA in hyperlipidemic mice [68, 69]. This certainly confirms the crucial role of COL3A1 in aneurysm and rupture seen in vEDS patients, although the

mutation is different from those usually found in patients, which are single amino acid changes that confer a dominant negative phenotype. At this early stage, it is premature to make any definitive statements about candidate drug targets deduced from the known molecular pathology of vEDS.

Clinical trials Because of the paucity of patients, it is not surprising that few clinical trial data describing beneficial effects of candidate drugs were done, despite the great need due to the major perioperative problems associated with surgical procedures. So far only one trial has shown positive pharmacological effect for vEDS patients. It was performed in France involving 53 vEDS patients and shows beneficial effect of a beta-blocker, celiprolol, which interestingly may not act primarily through lowering of blood pressure but through stabilization of the arterial wall [70]. The originally planned 5-year study was stopped already after 5 months due to an unexpected positive effect so that all patients, including control group patients, could benefit from celiprolol [70].

Bicuspid Aortic Valve Syndrome (BAV)

Bicuspid aortic valve syndrome [24] describes an aortic valve with two rather than three leaflets [24, 71]. It is the most frequent congenital heart defect and is present in 1–2% of the population. It is also highly heritable, but so far elucidation of the mutated genes responsible has explained only a few percent of total heritability, and additional mutated loci are expected to be identified in the future.

BAV is frequently followed by aortic valve stenosis or insufficiency. Valve calcification is also observed frequently. About 20% of BAV patients develop TAAD, a significant number, given the high overall frequency of BAV.

Mutations in the signaling and transcription regulator NOTCH1 may cause an early developmental defect leading to BAV according to some genetic linkage analysis studies and functional mouse studies [72]. It is well documented that the few BAV individuals that also carry a NOTCH 1 mutation are either asymptomatic or feature valve calcification, aortic valve stenosis, coarctation, and/or hypoplastic left heart but do not usually develop TAA [24]. Further studies are needed to determine if NOTCH1 signaling plays any role in development of TAA in BAV patients.

A recent extensive large genetic linkage study testing more than 20 genes previously associated with BAV with or without TAA through numerous, mostly small, genetic linkage studies and/or animal models yielded intriguing results: based on 441 BAV patients that also had TAA, and 183 controls, only one clear genetic association with BAV/TAA syndrome could be confirmed, namely, mutations in the functionally important MH1 and MH2 domains of the transcription factor SMAD6, which could explain the molecular pathology in 2.5% of the BAV/TAA patients in the study population [24]. The NOTCH 1 gene could not be confirmed in this study to be associated with BAV/TAA [24]. Remarkably, mice lacking the mouse SMAD6 homologue also present with misplaced septation, thickening of the cardiac valves, and ossification of the outflow tract, although TAA was not yet documented [73].

Because of the considerable uncertainty about the involvement of additional proposed candidate genes that may contribute to inheritance of BAV with and without TAA, we will not discuss these here further and instead refer to recent detailed reviews of the subject [74–76].

Arterial Tortuosity Syndrome (ATS)

This very rare syndrome with autosomal recessive inheritance is caused by mutations in the SLC2A10 gene which codes for glucose transporter 10 (GLUT10) protein [77]. It is usually diagnosed in infants and consists primarily of tortuosity of the aorta and of other arteries throughout the body, such as in the pulmonary, subclavian, and renal arteries, and all of these are subject to sudden rupture. Additional clinical features in some of these patients are hyperlax skin and joints and/or dilation of the ascending aorta, thoracic aortic aneurysms, and stenosis of the ascending aorta and/or the pulmonary arteries.

ACTA2 (Alpha 2 Actin, VSMC-Specific) Syndromic FTAAD (OMIM#611788)

Mutations in the ACTA2 gene, which codes for the VSMC-specific actin, inherit in dominant fashion and cause severe early-onset FTAAD, often in children [78]. Interestingly, mutations in this gene also often cause coronary artery disease and stroke. Indeed, like other genes causing TAA, ACTA2 can cause both syndromic and non-syndromic FTAADs (see also below), depending on the exact mutation in the gene. *ACTA2* missense mutations that disrupt arginine 179 lead to a syndromic FTAAD with distinctive smooth muscle dysfunction syndrome characterized by aortic and cerebrovascular disease, fixed dilated pupils, hypotonic bladder, intestinal hypoperistalsis, and pulmonary hypertension [79]. This particular mutation causes severe and early-onset vascular disease, including TAA, and has so far only been identified as a de novo mutation in affected individuals. In addition, preliminary studies have shown correlations between specific *ACTA2* mutations and increased risk for early-onset stroke or coronary artery disease [80].

Non-syndromic Familial Thoracic Aortic Aneurysms and Dissections (Non-syndromic FTAADs)

In contrast to syndromic FTAADs, non-syndromic FTAADs lack additional unrelated symptoms, especially in children and young adults [6, 8, 81] but may acquire later in life some

weak symptoms. When such weak, often nonspecific, symptoms do occur, potentially life-threatening aneurysms have often already developed. Therefore any person with a blood relative that has experienced non-syndromic FTAAD should be genetically tested. Often this is the only way to predict and prevent potentially dangerous aneurysms. The inherited mutations that cause non-syndromic FTAAD are strikingly different from those that cause syndromic FTAAD and have been discovered more recently with the advent of modern genetic screening tools. According to the Online Mendelian Inheritance in Man (OMIM) database, there are at least 11 non-syndromic FTAAD subtypes caused by inherited mutations in at least 11 different genes. Each mutated gene by itself is sufficient to cause non-syndromic FTAAD, and by definition genetic analysis is always required to ascertain a specific genetic subtype because of the lack of an easily discernible phenotype [6, 8, 81]. Like syndromic FTAADs, most if not all non-syndromic FTAAD subtypes are inherited in an autosomal dominant manner with high penetrance.

Non-syndromic FTAAD Caused by Mutations in Genes Coding for Proteins That Are Part of the Elastin Microfibril Units in the Extracellular Matrix

FBNI *(fibrillin 1)* (OMIM#134797)

As mentioned above, in rare cases, mutations in the FBN1 gene do not cause MFS-like symptoms and instead only cause isolated FTAAD.

ELN (Elastin) (OMIM #130160)

Specific types of mutations in the ELN gene cause FTAAD. For example, individuals with triplicate copies of the ELN gene have been found to have FTAAD [82]. This is one of the most rare forms of FTAAD but with highly penetrant and autosomal dominant inheritance. Patients have also often cutis laxa (OMIM#614437). However, the most frequently observed mutations in the ELN gene do not cause FTAAD but instead cause supravalvular aortic stenosis (OMIM #185500), which is often present at birth. In some cases aortic stenosis can cause aneurysms at high age of the patient. Some types of mutations in the ELN gene cause inherited intracranial aneurysm in the absence of FTAAD [83].

FBLN4 (fibulin4) (OMIM #604633)

Patients with recessive FBLN4 mutations are predominantly characterized by aortic aneurysms, arterial tortuosity, and stenosis [84, 85]. Certain mutations in FBLN4 cause autosomal recessive cutis laxa, often in the absence of aneurysms (OMIM #614437). Mouse models with VSMC-specific KO of FBLN4 reproduce human FTAAD very well [86, 87]. The exact relationship between cutis laxa and FTAAD is subject of ongoing research.

MFAP5 (Myofibrillar-Associated Protein 5), **FTAAD Type 9** (OMIM #616166)

Very recently discovered mutations in the MFAP5 gene, coding for an extracellular matrix protein, cause FTAAD and at times mild skeletal features similar to MFS. The aneurysms and aortic dissections are caused by alterations to the structure or function of the VSMC elastin-contractile unit, of which MFAP5 is an integral part of, together with other structural components such as FBN1, ELN, and FBLN4 [90].

Non-syndromic FTAAD Caused by Mutations in Genes Coding for Proteins That Are Part of the Actin-Myosin Contractile Units in the VSMC

MYH11 (Myosin Heavy Chain 11, VSMC-Specific), FTAAD Type 4 (OMIM #132900)

MYH11 functions as key cytoskeletal protein in VSMC as do ACTA2, MYLK, and PRKG1. Heterozygous mutations in MYH11 cause severe FTAAD causing life-threatening aortic dissections [90]. These rare MYH11 mutations are often associated with ductus arteriosus [88]. Force generation by VSMC requires interactions between filaments composed of VSMC-specific isoforms of myosin heavy chain (encoded by MYH11) and of α-actin (encoded by ACTA2). MYH11 and ACTA2 mutations that disrupt this cyclic interaction cause FTAAD (see also below).

ACTA2 (Alpha 2 Actin, VSMC-Specific), FTAAD Type 6 (OMIM#611788)

ACTA2 can cause both syndromic (see above) and non-syndromic FTAAD, depending on the exact nature of the mutation in the gene. ACTA2 is the most frequently mutated gene causing non-syndromic FTAAD and is responsible for about 12–21% of such cases [89, 90]. Unlike many other genes associated with TAA, Acta2 mutations tend to cause thoracic dissections, rather than true aneurysms. The lifetime risk for an aortic event (dissection or repair) is about 76%, suggesting that additional environmental or genetic factors play a role in expression of aortic disease in individuals with ACTA2 mutations. Mutations within the ACTA2 gene at amino acid position R179 or R258 were associated with significantly increased risk for such aortic events, whereas R185Q and p.R118Q mutations showed significantly lower risk of aortic events compared with other mutations [90].

VSMC from the aorta of ACTA2 −/− mice present with a reduced number of elastic lamellae and progressive aortic root dilatation, confirming the causative role of ACTA2 in TAA [91].

MYLK (Myosin Light Chain Kinase), FTAAD Type 7, 2010 (OMIM#613780)

Mutations of the MYLK gene cause non-syndromic FTAAD [92, 93]. Individuals carrying a mutation in the MYLK gene that inactivates its function have a high risk of acute aortic dissection or rupture at an early age. Importantly, aortic events are often not preceded by obvious aortic dilatation. This means that elective surgery should be done at a lower aortic diameter than for other inherited forms of TAA. Surprisingly, in mice, the same MYLK mutations found in humans (R247C/R247C) do not present a severe phenotype; however they do cause TAA if challenged with hypertensive drugs such as angiotensin – a note of caution when trying to compare the same mutations in humans and mice [94].

PRKG1 (cGMP-Activated Protein Kinase), FTAAD Type 8 (OMIM#615436)

PRKG1 is a protein kinase, and a constitutively hyperactive mutant form of this kinase indirectly leads to dysregulation of the regulatory light chain of MYH11, thus leading to inability of the contractile cytoskeletal apparatus to generate force. Heterozygous mutations in PRKG1 genes cause severe FTAAD causing life-threatening aortic dissections [87, 93].

Non-syndromic FTAAD Caused by Mutations in Genes Coding for Proteins That Are Part of the TGF-Beta Signaling Pathway Active in VSMC and Immune Cells

TGFBR1 (Transforming Growth Factor Beta Receptor 1: Also Presents as LDS) FTAAD Type 5 (OMIM#609192)

Mutations in the TGFBR1 gene can cause LDS type 1 but can also present without the related non-aortic syndrome, thus causing isolated TAAD. It is possible that the exact nature of the mutation within the TGFBR1 gene determines whether it presents as syndromic or non-syndromic FTAAD. TGFBR1 is a complex molecule with multiple functional domains that could, if mutated separately, cause different downstream metabolic effects. No doubt the future will tell if that is the case. It is also possible that lifestyle choices and/or additional genetic factors play a role.

TGFBR2 (Transforming Growth Factor Receptor 2: Also Presents as LDS) FTAAD Type 3 (OMIM#610168)

Mutations in the TGFBR2 gene can cause LDS but, as for TGFBR1 mutations, can also cause aneurysms and dissections without the related non-aortic syndrome. The same considerations as for TGFBR1 above apply.

SMAD2 (SMAD Family Member 2) Isolated FTAAD

Recently discovered mutations in the SMAD2 gene cause early-onset thoracic aortic aneurysms [95, 96], a gene structurally and functionally similar to SMAD3 which, when mutated, can cause LDS (see above).

TGFB2 (Transforming Growth Factor Beta 2) Isolated FTAAD

Some mutations in the TGFB2 gene cause non-syndromic FTAAD rather than syndromic FTAAD (LDS; see above).

TGFB3 (Transforming Growth Factor Beta 3) Isolated FTAAD

Some mutations in the TGFB3 gene cause non-syndromic FTAAD rather than syndromic FTAAD (LDS, see above).

FTAAD Caused by Mutations in Genes Coding for Proteins That Are Part of Other Signaling Pathways

LOX (Lysyl Oxidase) (OMIM#617168), **FTAAD Type 10**

Mutations in LOX cause autosomal-dominant FTAAD in humans [97, 98]. LOX belongs to a group of copper-dependent oxidodeaminases that cross-link lysyl residues on the ECM proteins elastin and collagen, the structural proteins necessary for formation of elastic lamellae and collagen fibers in the media of the aorta [99]. Mice homozygous for a missense mutation in the LOX gene that causes FTAAD in humans die shortly after birth because of ruptured aortic aneurysms [98].

FOXE3 (Forkhead Transcription Factor 3) (OMIM#617349), **FTAAD Type 11**

Mutations in the FOXE3 gene cause autosomal dominant FTAAD [100]. In mice, FOXE3 deficiency reduced smooth muscle cell (SMC) density and impaired SMC differentiation in the ascending aorta. FOXE3 expression was induced in aortic SMCs after transverse aortic constriction, and FOXE3 deficiency increased SMC apoptosis and ascending aortic rupture with increased aortic pressure [100].

FTAAD type 1, Genetic Locus 11q23 (OMIM #607086): Mutated Gene(s) Unknown

The locus q on chromosome 11q23.3–11q24 has been shown already in 2001 to cause FTAAD at young age with extensive medial necrosis, VSMC loss, loss of elastic fibers, fibrotic remodeling, and accumulation of polysaccharides [101, 102]. However, a causative gene within this chromosomal location has yet to be identified. The difficulty may be due to incomplete penetrance of the mutation, or perhaps the mutation is not located in a gene but in a regulatory region outside of genes that regulate gene expression at a long distance. Indeed recent whole genome sequencing studies have revealed that at least eight times more DNA is reserved for active regulatory regions, such as promoters, enhancers, and non-coding RNAs, than for the protein-coding genes itself. Modern RNAseq analysis combined with whole genome sequencing and whole genome epigenetics will no doubt eventually reveal the exact mutation in locus 11q that causes non-syndromic FTAAD.

FTAAD Type 2, Genetic Locus 5q13–14, (OMIM#607087): Affected Gene(s) Unknown

Like FTAAD1, FTAAD2 presents at young age with extensive medial necrosis and is caused by a mutation whose general location, 5q13–14, is known since 2001. The exact location and nature of the causal mutation(s) have not yet been identified [103]. The same considerations as described above for locus 11q23 apply.

Cellular Pathology of the Thoracic Aorta

As detailed in Table 5.1, the cellular pathology of the dilated thoracic aortic wall is clearly distinct from the pathology of the abdominal aortic wall and is characterized by a paucity of atherosclerotic plaques and calcification, absence of intraluminal thrombus, and presence of Th1 immune cells. On the other hand, thoracic and abdominal aortic pathologies of both the non-inherited and inherited forms have important similarities: for both thoracic and abdominal aortic aneurysms, the aortic media is the predominant location of the causative injury which consists of infiltration of multiple types of inflammatory cells mostly through the adventitia; abnormal activation of metalloproteinases, such as MMP9; destruction of the elastic fibers; and loss of VSMC which together lead to structural weakness.

FTAAD, but not AAA, is caused by dominant mutations in specific genes, including those coding for proteins of the cytoskeleton as described above. Strikingly, mutations that directly affect the VSMC cytoskeleton have mostly been found in non-syndromic FTAAD, pointing toward a highly specific pathogenic mechanism. Some of these mutations seem to cause a unique pathological appearance of the aortic wall [23], and this is subject to current research. For a more detailed description of the cellular pathology of aneurysmal thoracic aortic walls including images of stained diseased aortic wall sections, visualizing the intima, media, and adventitia, the reader may be referred to several specialized reviews [23, 81, 104].

Note that the sections below on animal models for FTAAD and AAA, respectively, frequently refer to specific pathological features of the aortic media caused by either mutations in genes that affect ECM remodeling, VSMC proliferation/metabolism and/or inflammatory cells of the media, or by drugs that act on these cells via specific genetic pathways.

How Comparison of Animal Models of FTAAD with Those of Sporadic TAAD Helps Elucidate the Molecular Pathology of Sporadic TAAD

Animal models have been instrumental in the study of syndromic and non-syndromic FTAAD ever since genetically engineered mutations in the FBN1 gene were found to cause Marfan syndrome in mice (see above). Since then, almost everyone of the more than 20 genes subsequently shown to be mutated in FTAAD patients was also shown to cause TAAD in animal models, almost always mice, because of the relative ease of genetic engineering of these animals, the lower cost of animal handling, and the speed of breeding. The information from these genetic models has been useful for establishment of candidate drug targets that repress progression of TAA. Both beta-blockers and angiotensin receptor blockers (losartan) have first been proven to prevent establishment and/or progression of TAA in mice with FTAAD, and this has directly led to the – albeit modest – success of these drugs in clinical trials and in clinical practice. Several of the relevant animal models for MFS, LDS, vEDS, and ATS have already been discussed in the sections for these conditions above and will not be discussed here further, except if there are potential functional overlaps.

However two new animal models of sporadic TAAD, caused by non-genetic factors such as age, diet, smoking and others, are described below. These models would not have been possible without prior knowledge obtained from animal models of FTAAD as they recapitulate some of the molecular pathology found in FTAAD. These animal models of sporadic FTAAD are of potentially high significance as they connect findings from the study of FTAAD with the much more prevalent sporadic TAAD.

High-Fat Diet-Induced Sporadic TAAD Animal Model Involving Inflammation and the VSMC Contractile Apparatus

Interestingly, aortas from patients with sporadic TAAD (not caused by the above familial mutations but either by envi-

ronmental factors or by other yet uncharacterized mutations) show significant degeneration of contractile proteins, including MYH11, in the ascending aorta and to lesser degree also in the descending aorta [105].This suggests that degeneration of contractile proteins such as MYH11 in VSMC of the aorta of sporadic TAA patients may be an important disease causing characteristic even in the absence of a clear-cut genetic cause. Importantly, this observation links FTAAD caused by mutations in MYH11 (see above) with non-genetic TAA.

The authors further show that palmitic acid, used to simulate high-fat diet, induces caspase 1- and NLRP3-mediated inflammatory action in VSMC from TAA patient aorta removed for prophylactic surgery [105]. This was confirmed in mice with inactivating mutations in either caspase 1 or NLRP3, which resulted in reduced MYH11 degradation and attenuation of TAA generation after angiotensin challenge [105]. Finally, this study shows that TAA generation is reduced in AngII challenged in mice if anti-inflammatory glyburide is administered.

This study connects high-fat diet that causes a specific form of inflammation in the aortic media with degradation of the cytoskeleton in VSMC of the media and, thus, with the occurrence of sporadic TAA. Since VSMCs cannot generate force without connections to the extracellular matrix through focal adhesions [87], and mutations in the extracellular matrix component fibrillin 1, which links VSMC to the elastin/collagen fibrils in the matrix, also cause thoracic aortic disease (MFS) as discussed above, it is possible that disruption of the ability of the aortic VSMC to generate force through the elastin-contractile units in response to pulsatile blood flow may be a primary cause for both inherited and non-inherited thoracic aortic aneurysms and dissections.

In summary, this work is a prime example of how the study of genetic disease (FTAAD) can help elucidate the molecular mechanism of its non-genetic counterpart (sporadic TAAD) and how it can potentially assist in the development of drugs for the treatment of the non-genetic disease, by far the most frequent form of TAA.

Sporadic TAA Animal Model of NAD+ Signaling

A recent animal model of spontaneous TAA suggests that the healthy aortic media depends on an intrinsic NAMPT-NAD^+ fueling system which is necessary for ATP production, to protect against DNA damage and premature SMC senescence. In mice with NAMPT-deficient VSMC, NAD+ levels are reduced, and aortas dilate and become prone to aneurysm and rupture when challenged with angiotensin II [106]. This corresponds with the reduced levels of NAMPT found in dilated, aneurysmal aortic tissue of sporadic TAA patients [106]. VSMC in diseased aortas were not apoptotic but showed signs of senescence, including DNA double strand breaks.

The Present Pharmacological and Surgical Management of Syndromic and Non-syndromic FTAAD

While it is tempting to draw from gene defects conclusions on pathogenic pathways that are amenable to pharmacological therapy, more preclinical studies and clinical trials that test novel drug candidates will be necessary before true progress is made on drug-mediated prevention of aneurysm progression and rupture. Beta-blocker therapy is at this time still the initial medication for management of aortic aneurysm in all syndromic and non-syndromic FTAADs. Losartan may be added if beta-blocker monotherapy is not effective. Losartan may also be administered on its own if patients do not tolerate beta-blockers [107].

In contrast to prophylactic medication, the precise timing of prophylactic aortic surgery strongly depends on the diagnosis of a specific aortic disease and the availability of patient-specific genetic information, because specific FTAADs influence the choice of the surgical procedure. Major recommendations based on the genetic subtype of FTAADs are that elective surgery and invasive angiography should be avoided in vEDS and that stent graft prostheses should not be placed in native aortic tissue in MFS or LDS [107]. Further, the recommendations for the extent, type, and timing of diagnostic imaging reflect the different patterns of aortic, vascular, and systemic manifestations related to the different syndromic and non-syndromic FTAADs [107]. Additionally, there are different recommendations on the timing of elective surgery at smaller or larger aortic diameters based on the knowledge that different FTAADs, based on different genetic defects, vary in their risk for dissection or rupture [107].

The Increasing Role of Medical Genetics in the Clinical Practice of FTAADs

The explosion of knowledge regarding the genetic basis of FTAADs starting in the 1990s – and especially in the past ~5 years – has profoundly changed diagnosis and clinical treatment of these conditions, and the rapid current progress will continuously lead to further refinement of diagnosis and treatment.

Initially genetic associations with FTAADs were discovered exclusively by painstaking traditional genetic linkage analysis consisting of slowly narrowing down the approximate chromosomal location of the inherited mutation conferring a specific FTAAD in more and more affected families, requiring long-term approach and refined cytogenetic capabilities. This was followed by DNA sequencing of all the genes located in the identified broad chromosomal location that usually resulted in the discovery of a single gene whose

mutations follow Mendelian inheritance in a given affected FTAAD family, as expected from single gene disorders.

Whole exome sequencing (WES) has recently replaced much of traditional genetic linkage analysis, and a dramatic example of its success is the multiple recently identified genes that cause FTAAD, including ACTA2, MYLK, LOX, and FOXE3. Indeed, WES is on a path toward implementation in clinical practice, due to dramatically lower costs of high throughput sequencing caused by key technological advances [108–110]. The unique advantages of WES in the clinical setting are similar compared to the more comprehensive (and much more expensive) GWAS studies used in some clinical trials (see section below for GWAS studies of AAA). WES employs high throughput (HTP) DNA sequencing to simultaneously identify any type of mutation in the DNA of all ~20,000 known genes (defined as all DNA sequences that code for all-known proteins) without any preconceived ideas about which genes would be most important, and currently costs about $1000–2000 per sample.

While the human DNA coding for all the known proteins, which are by definition located in the exons, only represents about 2–3% of total human DNA, mutations in exons are especially important for FTAADs because, so far at least, FTAADs have been shown to be caused by mutations located inside these exons, directly affecting protein expression of the genes. In contrast, for AAA almost all relevant mutations are SNPs that are located in intergenic regions (introns) and not in exons, a common property of mutations that are inherited not in strictly Mendelian fashion but are predisposing for a disease in concert with non-genetic factors, such as lifestyle, age, diet, smoking, and others (see below).

One recent example for routine clinical application of WES in FTAADs was established by the Elefteriades group in 2015 at the Yale Aortic Institute who subjected 102 new and returning TAAD patients to WES [108]. The findings confirmed the presence of already known FTAAD causing mutations in many of the more than 20 genes known to be functionally associated with FTAAD (see also above). Such mutations were found in more than 20% of the patients – the rest of the patients did not seem to carry known medically important genetic alterations based on current knowledge. Importantly, in addition to known FTAAD mutations, 22 not previously reported types of mutations, mostly novel types of amino acid changes, were found in the FTAAD-associated genes described in the previous paragraphs, although their potential role in the FTAAD should await further study, especially in animal models.

The most immediate clinical benefit of WES is that FTAAD patients can be given personalized treatment depending on the gene and type of mutation causing FTAAD. Specifically, for patients with mutations prone to dissect without prior severe aneurysmal dilatation, which are mutations in the ACTA2 (FTAAD type 6), MYLK (FTAAD type 7), TGFBR1 (LDS), TGFBR2 (LDS), SMAD3(LDS), TGFB2 (LDS), and TGFB3 (LDS) genes, a policy of more frequent imaging and earlier prophylactic surgery (at lower aortic diameter) should be applied [108].

Toward Diagnosis of FTAAD via Blood Test

Since more than 90% of TAAs are asymptomatic before dissection or rupture occurs, a biomarker that could detect and monitor the progress of an early, small aneurysm would be extremely useful, especially for individuals with family members that were affected by FTAAD and that therefore are at very high risk of developing TAA.

Many potential biomarkers have been investigated for their utility in diagnosing and/or monitoring TAAs, and some are promising. None, however, are ready to be reliably used in the clinical setting [111]. D-dimer has perhaps been the most studied potential biomarker of TAAs. It is a by-product of fibrin degradation that has been shown to be up to 99% sensitive in detecting acute aortic dissections. However, the specificity of D-dimer as a test for acute aortic dissection is relatively low, as D-dimer is elevated in a number of other conditions, including pulmonary embolism and coronary thrombosis [111]. In addition, the abundance of ECM proteins such as MMPs or elastin fragments in blood may prove predictive of dangerous aortic dilatation and TAA. Immune components such as C-reactive protein and some interleukins are also being tested as biomarkers for TAA [112].

In the future, ribonucleic acid signature sequences may be reliable biomarkers of TAAs. A study looking at 33,000 mRNA expression patterns in the blood of TAA patients and comparing them with those of control patients without TAAs showed that measuring the mRNA expression of a panel of 41 genes could distinguish, with about 80% accuracy, between patients with and without TAAs based on a blood test alone [51]. In addition, microRNAs (miRNAs), short RNA molecules that function in the regulation of hundreds of genes, have recently been shown to be involved in aortic dissections.

Toward a Pharmacological Cure of FTAAD

Further delineation of the pathological pathways in inherited TAA will be needed to narrow down potential therapeutic targets. This will require more refined preclinical mouse studies testing promising drug candidates, especially those types of models that test specifically aneurysm or dissection progression rather than generation. Interesting data from a powerful recent meta-analysis of inherited AAA studies [11] (see section below for details) may also be important for

FTAAD: MMP9 was very strongly implicated in pathogenesis of AAA and appears to be an attractive drug target, and such drugs (doxycycline) already have been tested in clinical trials. Remarkably, MMP9 has been shown to be overexpressed in the media of aortas of FTAAD patients as well, although MMP9 has not been directly genetically linked to FTAAD. Further, some authors believe that MMP9 and other metalloproteinases could be promising drug targets not only for inherited FTAAD and inherited AAA but also for the much more prevalent non-inherited forms [113]. Clearly the coming years will be exciting as we may be on the cusp of defining the best drug targets for both TAA and AAA, a potentially unprecedented and life-changing advance.

Gene and Cell Therapy of TAA

Due to recent dramatic advances in gene therapy methods, direct correction of the inherited genetic defect specifically in the aortic wall may be possible within the next 10–20 years. Importantly, TAA caused by mutations in certain affected genes that are not believed to be good drug targets can possibly best be ameliorated by gene therapy. These mutations include amino acid changes in transcription factors, such as SMAD6 and FOXE3, as well as in the cytoskeletal proteins ACTA2, MYH11, and MYLK. Over the past 15 years, several different approaches of cell therapy have been used in cardiovascular disease, especially to target ischemia of the heart, but the clinical trials showed limited success so far. However improved existing and novel methods are emerging, and these should also be applicable for aortic diseases. In addition to choosing the correct cell type to repair a genetic defect, such as autologous genetically repaired vascular endothelial cells, vascular smooth muscle cells, mesenchymal stem cells, and/or macrophages, the delivery method is crucial and is often the most challenging aspect: a recent review of the use of stem cells in cardiac regeneration describes several advanced examples of using magnetic cell targeting, as well as ultrasound-mediated delivery of stem cells [114]. Such procedures could also be done for the aorta at an early stage of the disease, and if engraftment is successful and long term, they could obviate the need of life-long drug treatment or invasive and risky surgery of the patient.

Given the rapid pace of investigation in the nonsurgical treatment of TAA, it is probably only a question of time until gene/cell therapies, perhaps combined with novel drugs, are discovered that truly prevent progression of existing TAA in patients in the long term.

Once this happens, the need for surgery to treat TAA, which is associated with significant perioperative complications, will be significantly reduced.

Genetics of Abdominal Aortic Aneurysms (AAAs)

The field of AAA genetics has been rapidly progressing in the past several years, due to increasing use of modern high throughput DNA sequencing technology that enabled genome-wide association studies (GWAS). Indeed in the past several years, more than 100 independent AAA-centered genetic studies, including GWAS studies, have revealed more than 100 specific novel genetic loci that may be associated with AAA. However, only 5 of these original >100 AAA-associated genetic loci have been clearly confirmed by 2 recent large-scale meta-analyses [11, 115] that attempted to combine the data from these earlier studies. Intriguingly, one of these two meta-studies, which is the largest one published so far [11] (4972 AAA cases and 99,858 controls), also discovered four novel AAA-associated loci with very high certainty, due to its unprecedented statistical power. Indeed, this study is an impressive testament to successful international collaboration in AAA genetics. In the interest of brevity and focus, only the genetic loci supported this study [11] will be described in detail below – with the caveat that some of the previously described loci that were not confirmed may still have functional significance in genetic subpopulations.

Since the 1970s, it has been known that an important risk factor for AAA formation is a positive family history for the disease with an increased individual risk between two- and 11-fold [116–120]. It is estimated that at least 15% of all cases of AAA are in part caused by one or more inherited mutations [117]. Since AAA in general (non-inherited plus inherited) affects ~8% of males and ~1% of women over the age of 65 [2, 120, 121], genetically conditioned AAA represents about 1–2% of all people over the age of 65, a significant part of the population.

Currently, the diagnosis and management of AAA is challenging: aneurysm development and progression are mostly asymptomatic, and diagnosis is often accidental, during imaging of other medical indications. Once diagnosed there are no blood tests for monitoring aneurysm growth. Instead monitoring is done by repeated imaging until the aortic diameter approaches about 55 mm, when usually surgical intervention via open repair or endovascular stenting is performed [122]. Unfortunately open surgery is associated with significant perioperative mortality, and endovascular stenting fails in up to 20% of patients, thus requiring re-stenting for this group [122]. One typical complication is bacterial infection that can lead to septic shock if untreated [123]. Early detection is very important for success exactly as for stenting in coronary artery bypass surgery [124]. Imaging, surgical repair, and perioperative care cost at least US$20,000 per patient [122]. If no alternative treatments are found, requirement for AAA-related surgery will rise in parallel

with the global ageing population. Given these high costs, there is an urgent need for improved diagnosis, monitoring, and treatment of AAA. Optimally AAA expansion should be stopped at an early stage in order to prevent rupture completely, thus converting it from a condition treated exclusively by surgery to one mostly managed by drugs and/or cell/gene therapy.

Indeed, several novel animal models of AAA have begun validation of new therapeutic targets in vivo, and this has led to multiple recent clinical trials involving a few novel drugs. These animal models are based on the novel genetic AAA-associated loci found through genetic linkage and GWAS studies.

Most inherited AAAs are of multifactorial origin with genetic mutations as well as lifestyle choices such as diet and exercise contributing to the disease, in striking contrast to familial thoracic abdominal aneurysms (FTAADs) which show autosomal dominant inheritance with high penetrance regardless of other factors (see also below). The most important non-genetic risk factors for AAA are advanced age, male gender, cigarette smoking, hypertension, and cardiovascular risk factors, such as dyslipidemia [1].

Interestingly, some of the known AAA-predisposing mutations functionally contribute to dyslipidemia and cardiovascular disease: the best examples may be mutations affecting the expression of the SORT1 gene and to a lesser degree, the LDLR gene. However, it should be emphasized that many other AAA-predisposing mutations are not directly associated with dyslipidemia or cardiovascular disease. Indeed, several AAA-associated mutations act via remarkably diverse mechanisms that affect the immune system, the angiotensin system, extracellular matrix remodeling, and VSMC proliferation. Both the structure and function of the well-known AAA-predisposing loci have been under intense investigation. Enough functional data seem now available for several of these loci to allow the design and testing of novel drugs that potentially could prevent enlargement and rupture of existing AAA [1, 2].

Subtypes of Genetically Conditioned and/or Inherited AAA

Genetic subtypes of AAA are listed in Tables 5.1 and 5.2, as well as in more detail below, according to their associated genetic locus and mode of function, as published in [11]. This meta-study includes most previous original studies and analyzed an unprecedented 4972 AAA cases and 99,858 controls, about twice as many as the previously biggest meta-analysis [10]. Its only major bias is that many more men than women were analyzed, for the simple reason that men suffer from AAA at ~5 times higher rate than women and are thus much more easily available for screening. Surprisingly, this study confirmed only 5 of >100 previously published specific SNPs. These five SNPs have been confirmed with very high certainty, and they are located in five different genetic loci: 9p21 (CDKN2BAS/ANRIL), IL6R, SORT1, DAB2IP, and LDLR. In addition, four previously unknown SNPs in four new loci were also found by [11] to strongly associate with AAA, and these are the SMYD2, LINC00540, MMP9, and ERG loci. As shown in Tables 5.1 and 5.2, all nine strongly AAA-associated loci fall into two main subtypes, first those known to contribute to dyslipidemia and cardiovascular disease (LDLR, SORT1) and second, those not associated with dyslipidemia (IL6R, 9p21, SMYD2, LINC00540, MMP9, ERG). Confirming absence of genetic association with dyslipidemia for the second group, neither the patients nor the corresponding animal models, if available, exhibit obligate dyslipidemia or cardiovascular disease. Intense efforts are currently underway to develop novel anti-AAA drugs based on the suspected molecular mechanisms of AAA pathology of all of the proven AAA-associated loci.

Table 5.2 The nine loci strongly associated with AAA according to Jones et al. 2017 [11]

Gene locus	SNP	Major/ minor allele	Proposed primary pathogenic mechanism
LDLR	rs6511720	G* > T	Lipid metabolism
PSRC1- CELSR2-SORT1	rs602633	G* > T	Lipid metabolism
IL6R	rs4129267	C* > T	Immune response
CDKN2BAS1/ ANRIL	rs10757274	G* > A	VSMC proliferation
DAB2IP	rs10985349	C > T*	VSMC signaling and immune response
ERG	rs2836411	C > T*	Endothelial cell homeostasis
SMYD2	rs1795061	C > T*	Unknown
LINC00540	rs9316871	G* > A	Unknown
MMP9-PCIF1-ZNF335	rs3827066	C > T*	Extracellular matrix remodeling

Of note, the most recent individual AAA GWAS study, which was conducted in Japan (456 patients with aortic aneurysm, 8326 control individuals), found that the *EGFLAM* and *SPATC1L* loci are significantly associated with true aortic aneurysm, and *RNASE13* was significantly associated with dissecting aortic aneurysm [125]. What is unusual about these loci is that all three are mutated within protein-coding regions, which will strongly facilitate future functional analysis [125], in contrast to most other known AAA-associated loci which are mutated outside of protein-coding regions, making functional analysis more challenging. However, since these new protein mutations are not yet confirmed independently, they will not be further discussed here.

Since the above nine confirmed loci from the largest meta-analysis to date are contributing factors and usually not the sole factor causing AAA, it seems prudent to list the associated-AAA phenotypes not as separate diseases but as genetic subtypes of AAA. Remarkably, most of these loci

Table 5.3 The most important mouse models of AAA

AAA mouse model	Mode of AAA induction	Pathological pathway causing AAA	Human-like aspects of AAA	Disadvantages	Ref
Hph1 −/− mice deficient in the protein GTPCHI which produces tetrahydrobiopterin (BH4) a cofactor of NADPH oxidase	AngII infusion by pump for 4–6 weeks	Perturbation of endothelial nitric oxide synthase (eNOS) signaling in the aorta as well as angiotensin renin system	Leads to aneurysm formation, progression, and rupture	Unclear if the eNOS pathway acts the same way in humans. No clear genetic association of Hph1 or eNOS signaling in humans	[161]
ApoE1−/−	AngII infusion by pump for 4–6 weeks induces supra renal AAA which progresses continuously as long as AngII is infused	Perturbation of angiotensin renin system. Increased blood pressure. High-fat diet induces atherosclerosis and increases speed and frequency of AAA formation	Pathological pathways may be similar to humans. Shows also male gender bias found in humans. Focal aneurysm. Features inflammation and extracellular matrix remodeling found also in humans.	Affects suprarenal aorta not infrarenal as found in humans. No strong genetic association of human AAA with Angiotensin/renin system	[162–166]
LDLR−/−	AngII infusion by pump for 4–6 weeks	Perturbation of angiotensin renin system. Similar to ApoE1−/− mice above	See ApoE1−/− mice above	See ApoE−/− mice above	[134, 164, 166]
Apo E $^{-/-}$ TIMP-1 $^{-/-}$	30 days of cholesterol-rich diet	MMP are activated due to absence of TIMP-1 (tissue inhibitor of metalloproteinase-1	Slow induction of AAA, partly diet mediated	TIMP1 mutations not known to cause AAA in humans	[167] 2002, not repeated since
Normal mice (129/sv)	Elastase perfusion of abdominal aorta over 5 min, following surgical preparation leads to immediate AAA formation	Degrades aortic media by degradation of elastin, the major protein component of the extracellular matrix of the media. This induces chronic inflammation and infiltration of MMP9 producing macrophages over the next months	Elastin treatment in the aortic media induces MMP9 action, which is similar in human AAA: MMP9 misregulation found in AAA patients. MMP9 mutations strongly associated with human AAA	Procedure requires surgery on the aorta. Mostly an acute AAA model as most AAA resolve gradually over several weeks, while human AAA is chronic	[165, 168]
C57BL6 mice	BAPN (a lysyl oxidase inhibitor) was provided in drinking water 2 d before periaortic elastase application	Persistent irreversible AAA formation, thrombus formation, and spontaneous rupture more than 100d after elastase induction	Only model for chronic late stage aneurysm development, which is the most relevant human AAA condition. Most ruptures happen during late stage as for humans	BAPN amount needs to be balanced very carefully to prevent early AAA dissection	[169]

have been experimentally confirmed in animal models to strongly contribute to formation and progression of AAA (see Table 5.3 and detailed descriptions of individual loci in the text below). Some, but not all, of these loci are already assigned in the OMIM (Online Mendelian Inheritance in Man) database as familial abdominal aortic aneurysms type 1, 2, 3, or 4. However at this time, we find it more prudent to simply list them with their associated gene names according to their known metabolic function. See also Tables 5.1 and 5.2.

AAA-Associated Loci Affecting Lipid Metabolism

We list here only the lipid metabolism-associated loci clearly confirmed by [11] although other such loci may still be relevant for certain subpopulations not captured by this large meta-study.

LDLR *(LDL Receptor)* G* > T (rs6511720)

This single SNP G* > T (rs6511720) is one of many known mutations in the LDLR locus but was so far the only one found in GWAS studies to be strongly associated with AAA. In contrast to most other known LDLR mutations, it is not located in the protein-coding region but in the first intron of the LDLR gene and overlaps with a potential enhancer site that could regulate LDLR gene expression [126]. In contrast to many other mutations found in the LDLR locus, rs 6511720 may increase expression of the LDLR protein: it does so at least in human liver-derived cell lines and would thus potentially lead to lower, potentially cardioprotective LDL-C levels [126]. However, based on these data, it is also tempting to speculate that rs6511720 causes higher levels of the LDLR protein in macrophages that infiltrate aneurysmal

aortic walls. This would potentially lead to higher fat accumulation in the macrophages (generation of "foam cells") which in turn would lead to inflammation in the arterial wall and ultimately to AAA formation.

Consistent with the above, SNP rs6511720 has not been clearly associated with coronary artery disease and atherosclerotic plaque formation [127, 128] in striking contrast to many other SNPs in the LDLR locus which cause a reduction of LDLR activity, especially those causing familial hypercholesterolemia [127–129] (see also below).

The above strongly suggests that rs6511720 acts through a fundamentally different pathological mechanism than the many other SNPs found in the LDLR gene and that causes cardiovascular disease but no increased prevalence of AAA. The exact pathological mechanism that causes this SNP to promote AAA formation is not yet fully understood and requires significant additional research.

To begin to understand the role of rs6511720 in AAA, it is useful to consider the known LDLR function: LDLR mediates endocytosis of cholesterol-rich LDL particles from plasma and is necessary for maintenance of the optimal plasma level of LDL. LDL endocytosis occurs in many cell types including hepatocytes in the liver and macrophages that can infiltrate the aortic wall. The hepatocytes of the liver remove ~70% of LDL from the circulation. Likewise, the macrophages in the aortic wall which infiltrate during AAA formation can take up LDL from the blood using the LDLR and other receptors. LDL particles are internalized via LDLR-rich clathrin-coated pits. After internalization, the receptors dissociate from their ligands when they are exposed to lower pH in endosomes. After dissociation, the receptor recycles to the cell surface [130]. The rapid recycling of LDL receptors provides an efficient mechanism for delivery of cholesterol to cells [131, 132]. The crucial role of LDL and LDLR in maintenance of plasma lipid levels was originally discovered by Goldstein and Brown using cell culture of fibroblasts derived from patients of familial homozygous hypercholesterolemia (hoFH, see below) which lack functional LDLR [131]. It was confirmed in genetically engineered LDLR−/− mouse models (see below) and therefore immediately suggested a causal role of high plasma LDL particle levels for development of atherosclerosis.

Inactivating mutations in the LDLR locus cause familial hypercholesterolemia (FH), one of the most prevalent Mendelian disorders [129]. Interestingly, these mutations are not associated with a higher occurrence of AAA [127, 128]. These mutations usually, but not always, occur in the coding region of the very large LDLR gene, and more than 1000 different mutations have been found to cause FH. Heterozygotic FH can usually be managed by lipid lowering drugs, but the homozygotic form (hoFH) is severe and causes premature death through cardiovascular disease, and there is no satisfactory treatment available [129].

FH-like symptoms can be reproduced well in LDLR KO mice, which is very helpful for development of therapies. They include severe atherosclerosis, steatohepatitis, and high frequency of cardiovascular disease. However, in contrast to human FH patients, LDLR−/− mice also show significantly increased frequency of AAA. However, this increased AAA formation in LDLR−/− mice is conditional on angiotensin II treatment [133]. This potential difference of AAA formation frequency in LDLR−/− mice and FH patients is subject to research.

The LDLR−/− angiotensin II mouse is one of the most used and best characterized AAA animal models [134]. This model also shares many features with human AAA and has become one of the most commonly used AAA animal models. However, this mouse model does not fully recapitulate human AAA pathogenesis, in particular as homocygotic FH (hoFH) patients, all of whom are LDLR−/−, do not seem to show increased AAA occurrence.

LDLR gene therapy for hoFH patients is being performed currently only in clinical trials and attempts to deliver the normal LDLR gene to the liver – this is thought to be the only way towards a true cure of hoFH. However, this approach likely will not cure rs6511720-induced AAA as this LDLR mutation may act primarily through the macrophages in the aortic wall, as discussed above. Therefore, LDLR gene therapy for AAA may have to repair the genetic defect in macrophages instead of in the hepatocytes of the liver, an approach that seems feasible in principle (see also below).

PSRC1- CELSR2 - SORT1 G* > T(rs 602633)

The non-coding SNP G* > T (rs 602633) is one of the most strongly AAA-associated mutations [10, 11, 135] and at the same time is associated with hyperglyceridemia and coronary artery disease [136–138]. It is located close to the three genes PSRC1, CELSR2, and SORT1. Of these three, the SORT1 gene is by far the most well understood, and it has been known since 2010 that its biological expression level strongly influences risk of cardiovascular disease [139]. Interestingly, another SORT1 genetic variation at SNP rs12740374 seems to significantly mediate the variation in SORT1 gene expression and also SORT1-mediated risk of cardiovascular disease found in humans but so far has not been associated with risk of AAA [139].

In mice, macrophage SORT1 deficiency protects against atherosclerosis by reducing macrophage uptake of LDL, through lowering LDLR expression [140]. Since LDLR in the outer cell wall of macrophages is necessary for efficient uptake of LDL into macrophages, it is tempting to speculate that rs602633-mediated normal or high macrophage LDLR levels may not only lead to atherosclerosis but also to AAA, through conversion of macrophages into foam cells in the aortic wall [140].

Although much has been learned about the role of SORT1 in lipid metabolism and atherosclerosis, there is no associated SORT1 animal model of AAA. Since SNP rs 602633 is very strongly associated with AAA and also with coronary artery disease [25] and SNP rs 12740374 is strongly associated with CAD but not at all with AAA, these two SNPs, which are both located close to the SORT1 PSRC1 and CELSR2genes, clearly work through distinct mechanisms.

The clearly different disease associations of the two SNPs provide strong evidence that AAA and CAD pathologies act at least in part through separate mechanisms in humans and strongly caution against simplified assumptions that anti atherosclerotic drugs like statins would automatically be the best therapeutics for AAA although statins do seem to be somewhat beneficial. Given the extremely strong correlation of rs 602633 with human AAA, careful functional studies of the role of all three genes PSRC-CELSR2-SORT1 in AAA are well justified and likely to significantly improve our understanding of human AAA pathology.

AAA-Associated Loci Affecting the Inflammatory Response

Interleukin 6 Receptor (IL6R) C* > T(rs 4129267)

IL6R is a receptor for the pro-inflammatory cytokine interleukin 6. SNP rs 4129267 is found to be strongly associated with AAA [11] and is located close to the exon regions of the IL6R gene – but not within exons – and thus its precise function cannot be easily studied in animals. Instead current animal models study IL6R over expression or deficiency, and especially interleukin 6 (IL6, the ligand of IL6R) over expression or deficiency (see below). SNP rs 4129267 is not only strongly associated with AAA but is closely associated with occurrence of SNP rs 7529229 which causes an Asp358Ala change in IL6R [141]. In human lymphoblastoid cell lines, this Asp358Ala mutation in IL6R caused a reduction in the expression of downstream targets (STAT3, MYC, and ICAM1) in response to IL-6 stimulation [141]. Indeed, two remarkable animal models have already shown that IL6R signaling strongly influences the risk of rupture of AAA, but not de novo generation of AAA, and therefore these models may be highly relevant for risk of rupture of preexisting human AAA.

The first animal model of the role of IL6 signaling in AAA [142] is not an IL6R −/− mouse, but it is a mouse with inactive IL6, the ligand of IL6R, with expected similar phenotypes. Importantly, IL6 signaling in this model does not affect AAA generation per se: AAA generation is triggered by angiotensin II administration given to lysyl oxidase inhibitor-preconditioned mice, which stimulates CXCL1/granulocyte colony-stimulating factor expression and very rapid abdominal aortic dissection of AAA and AAD generation within 24 hours, in both IL6+/+ and IL6−/− mice at the same frequency and intensity: the dissections were initiated at the proximal site of the descending thoracic aorta and propagated distally into an abdominal site. Remarkably, only in IL6+/+ mice dissection of the aorta caused dilatation, and ~70% of the IL6+/+ mice died of aortic rupture. Importantly, in IL6+/+ mice, the adventitia of the expanded dissected aorta demonstrated high levels of interleukin-6 (IL-6) expression. Neutrophils were the major sources of IL-6. Remarkably, in IL6 −/− mice, dilatation and rupture of the dissected aorta as well as death was strongly suppressed even though the presence or absence of IL6 did not influence the timing of emergence or the initial number of AAAs or neutrophil mobilization [142].

In summary, adventitial CXCL1/granulocyte colony-stimulating factor expression in response to AAD triggers local neutrophil recruitment and activation. This leads to adventitial inflammation via IL-6 and results in aortic expansion and rupture. This model could be highly relevant for human AAA, because it is prevention of progression of existing small AAA that requires treatment in humans and not prevention of AAA generation, mostly because there is no efficient method available allowing anticipation of AAA generation in humans before it occurs [142].

Another recent noteworthy animal model of AAA confirms that inflammatory cytokine production plays a major role in AAA in expansion and progression of existing small AAA [143]. In this case downregulation of the mTOR pathway by rapamycin dramatically limits the expansion of the abdominal aorta following intraluminal elastase perfusion. Furthermore, actual reduction of aortic diameter is achieved by inhibition of the mTOR pathway, which preserves and/or restores the contractile phenotype of VSMCs and downregulates macrophage infiltration, matrix metalloproteinase expression, and inflammatory cytokine production [143]. These data highlight the importance of preservation and/or restoration of the smooth muscle cell contractile phenotype and reduction of inflammation by mTOR inhibition in AAA.

In summary, the two above mouse models of AAA implicate pro-inflammatory cells as a major driver of rupture of preexisting AAA, and thus targeted anti-inflammatory drug treatment may be a promising strategy for clinical trials.

AAA-Associated Loci Possibly Affecting Cell Proliferation and/or the Inflammatory Response or of Unknown Function

***CDKN2BAS/ANRIL* (*Part of 9p21 Locus*)** G* > A(rs 10757274)

The **CDKN2BAS and ANRIL** genes are located within the 9p21 locus that has been implicated in cardiovascular disease by a seminal GWAS study in 2007 [144] whose main conclusions have indeed been largely confirmed by multiple

follow-up GWAS studies. This 9p21 region contains multiple SNPs that span an area of about 58kB that are among the strongest risk factors ever discovered for MI, cardiovascular disease, and AAA. Homozygotes for the risk allele were estimated to make up 20–25% of Caucasians and have an approximately 30–40% increased risk of CAD.

Importantly the SNPs in the 9p21 locus are highly disease specific. For example, according to the most powerful and most recent meta-analysis of GWAS studies on AAA in 2017 [11], only the 9p21 SNP rs10757274 but not any of the other several major 9p21 SNPs is very strongly associated with AAA, while the other SNPs are only associated with MI and cardiovascular disease. The underlying pathological molecular mechanism that is triggered by SNP rs10757274 and contributes to AAA and cardiovascular disease is under intense investigation and not yet well understood, in part because it is located in an intergenic region characterized only by multiple transcription factor binding sites as well as a large non-coding RNA called ANRIL [11]. Interestingly, directly adjacent to the 58kB span, a tumor suppressor gene named CDKN2B is present.

A seminal mouse study by Leeper et al. in 2013 [145] showed that absence of CDKN2B in all tissues causes an increased aortic diameter in the elastase-driven mouse model of AAA. They also elegantly showed by bone marrow transplantation experiments that absence of CDKN2B directly caused apoptosis in VSMC of the aorta via the p53 pathway and not primarily through a defect in infiltrating immune cells [145].

This study contrasted with a later study showing that in culture, aortic smooth muscle cells obtained from mice with a 70 kb deletion encompassing the location of the human SNP rs10757274 showed excessive proliferation (instead of apoptosis) and altered regulation of the neighboring CDKN2B gene [146].

A European case control study involving 4251 patients with coronary artery disease and 4443 controls [147] replicated association for 7 separate MI-associated SNPs in the above 58 kB region of chromosome 9p21, including rs 10757274 and 10757278. In addition this study found that the large non-coding RNA (ANRIL) co-locates with the high-risk haplotype of 9p21 and is expressed in tissues and cell types that are affected by atherosclerosis, including VSMC and HVECs.

Harismendy et al. [148] identified 33 potential enhancers (short DNA sequences that promote activation of specific genes from a distance of up to several kB) in the 9p21 locus; this enhancer-rich region features a six times denser occurrence of potential enhancer sequences than the whole genome (P less than 6.55 × 10(−33)). Using a new, open-ended approach to detect long-distance interactions, they found that in human vascular endothelial cells the enhancers located close to the CAD-associated sequences of the 9p21 locus physically interact with the neighboring CDKN2B gene, consistent with the above mouse studies implicating downregulation of CDKN2B in AAA [145].

Based on the above, it will be interesting to study if drugs that upregulate ANRIL and CDKN2B can help restore the vessel wall in animal models of AAA.

DAB2IP C > T*(rs 10985349)

In humans, DAB2IP (also named AIP1) mRNA is detected in most tissues and organs but is very low or absent in blood cells. In the aortic media, it is expressed in the VSMC and is an important regulator of signal transduction of cancer-related pathways. DAB2IP acts as an adaptor, or scaffold, in protein complexes relevant for signal transduction, and it can function as a competitor, or scavenger, by binding signaling proteins and preventing their interaction with upstream activators or downstream effectors. Through these actions, DAB2IP has the potential to modulate a remarkable array of cancer-related pathways.

DAB2IP (AIP1)-deficient mice showed no obvious developmental defects including vascular development. However, they exhibited dramatically enhanced angiogenesis in two models of inflammatory angiogenesis. In one of these models, the enhanced angiogenesis observed in the DABIP-deficient mice was associated with increased VEGF-VEGFR2 signaling [149]. Consistent with this, VEGF-induced ear, cornea, and retina neovascularization were greatly augmented in DABIP KO mice, and the enhanced retinal angiogenesis was markedly diminished by overexpression of DAB2IP [149].

In a syngeneic aortic transplantation mouse model [150] in which wild-type or DAB2IP-knockout mouse aortas were transplanted into IFNγ receptor-deficient recipients and in which neointima formation was induced by intravenous administration of an adenovirus that encoded a mouse IFN-γ transgene, donor grafts from DAB2IP-knockout mice enhanced IFN-γ-induced VSMC proliferation and neointima formation. Mechanistically, knockout or knockdown of DAB2IP in VSMCs significantly enhanced IFNγ-dependent VSMC migration and proliferation, a critical step in neointima formation. Thus, DAB2IP functions as a negative regulator in IFN-γ-induced intimal formation, in part by downregulating IFN-γ-JAK2-STAT1/3-dependent migratory and proliferative signaling in VSMCs.

Taken together, these two animal models suggest that removing DAB2IP in VSMC may increase VSMC signaling and inflammation and may induce aneurysm. Drugs that prevent AAA-specific inflammation in the aortic wall should be considered in additional preclinical studies.

ERG C > T* (rs 2836411)

The recent large AAA meta-studies [4, 11] and also an earlier study [150] strongly implicate mutations in the ERG

gene: the protein product of the ERG gene physically interacts with the proteins made by the IL6R, LDLR, and MMP9 genes, which are all genes strongly associated with AAA [11] (see also above). It is particularly intriguing that each of these genes was discovered by multiple independent GWAS studies.

ERG is a transcription factor and has emerged as a major regulator of endothelial function. Multiple studies have shown that ERG plays a crucial role in promoting angiogenesis and vascular stability during development and after birth [151]. In the mature vasculature, ERG also functions to maintain endothelial homeostasis, by transactivating genes involved in key endothelial functions, while repressing expression of pro-inflammatory genes. Its homeostatic role is lineage-specific, since ectopic expression of ERG in non-endothelial tissues such as prostate is detrimental and contributes to oncogenesis.

ERG is highly expressed in differentiated quiescent endothelial cells of the aorta and of all other arteries, as well of as veins and microvasculature, and has been shown to maintain the endothelium in an anti-inflammatory state by repressing expression of pro-inflammatory molecules such as vascular cell adhesion molecule (VCAM), plasminogen activator inhibitor (PAI)-1, and interleukin (IL)-8 [152, 153]. Consistent with this, endothelial ERG expression is down-regulated by inflammatory stimuli, including tumor necrosis factor (TNF)-α and lipopolysaccharide (LPS) [154, 155]. In addition, ERG expression was lost from the endothelium near the shoulder regions of human coronary plaques which contain inflammatory infiltrate [153].

In summary, ERG is anti-inflammatory and necessary for normal homeostasis of endothelial cells, and the AAA associated ERG mutation rs 2836411 may decrease ERG activity and increase inflammation of the aortic intima and media which in turn may contribute to AAA formation. Additional research, including animal models, is required to confirm this hypothesis.

SMYD2 *C > T**(rs 1795061)

The AAA meta-study by Jones et al. [11] for the first time provided evidence that SMYD2 may be associated with AAA pathology. SMYD2 is a histone methyltransferase and may be involved in regulation of gene expression of specific genes. However in the absence of functional data regarding the role of SMYD2 in AAA, it is also possible that two other genes located nearby the AAA-associated SNP (rs 1795061) are involved. However, among the three candidate genes located near rs 1795061, SMYD2 is the best characterized gene and could be connected to AAA via its ability to regulate methylation of the heat shock protein HSP90 [156] and the fact that inhibition of HSP90 reduces AAA formation in mice [157]. Interestingly, computational network analysis based on existing database data compiled and analyzed by the consensus PathDB program revealed that SMYD2 interacts functionally with LDLR via TNF. Clearly it is premature to reach conclusions on the functional effect of (rs 1795061) on AAA and much further research is needed to clarify.

LINC00540 *G* > A*(rs 9316871)

This non-coding RNA has no known function, but a SNP located close to it was discovered in the recent meta-study with very high probability to be associated with AAA in humans [11]. rs 9316871 is not only close to LINC00540 but also to the FGF9 gene which shows increased expression in human AAA tissue. GWAS3D and eQTL analysis indicates a function of LINC00540 with FGF9 [11]. GWAS3D and eQTL (expression quantitative trait loci) analysis is similar to the consensus path DB program (see above) and combines existing GWAS DNA data with existing gene expression profile data. They are a powerful unbiased computational tool allowing determination of probable functional associations of mutations with phenotype. However, animal models lacking or overexpressing LINC00540 are still needed to study the role of this non-coding RNA in AAA in vivo.

AAA-Associated Loci Affecting ECM Remodeling

MMP9 C > T* (rs 3827066)

In addition to being very strongly implicated in AAA by multiple GWAS studies [11], computational gene network analysis reveals a central role for MMP9 in AAA [11]. MMP9 is a matrix metalloproteinase that is highly expressed in VSMC of the aortic wall. Mechanical insults, inflammatory cytokines, and other factors that act on VSMC strongly upregulate MMP9 expression and excretion, leading to immediate remodeling of the media by locally dissolving elastic laminae and other structural components of the extracellular matrix. Abnormal MMP9 overexpression can strongly contribute to eventual rupture of preexisting AAA. Computational network analysis utilizing large existing databases containing experimental gene expression data of most known genes in most known tissues has recently been devised and is commercially available as online services. Two of the most powerful network analysis tools are IPA and Consensus PathDB. IPA network analysis (IPA = Ingenuity Pathway Analysis, Qiagen) compiles and evaluates data from omics experiments, such as RNA-seq, small RNA-seq, microarrays including miRNA and SNP, metabolomics, proteomics, and small-scale experiments. Similarly, Consensus PathDB consists of a comprehensive collection of human (as well as mouse and yeast) molecular interaction data integrated from 32 different public repositories and applies computational analysis to report interaction network modules, biochemical pathways, and

functional information that are significantly enriched by the user's input.

Both IPA and Consensus PathDB programs report direct physical contact between ERG, IL6R, LDLR, and MMP9 proteins, and Consensus PathDB reveals signaling without contact (e.g., phosphorylation) between SMYD2 and LDLR as well as SMYD and MMP9 [11]. These computed outputs which are based on a huge amount of independently collected publicly available experimental data are highly significant because they establish a novel gene network that, based on GWAS studies, is directly involved in AAA formation and progression with high certainty.

In addition, two powerful animal studies of AAA have been published, showing strong involvement of MMP9 in the long-term expansion of experimentally induced AAA. In particular, these models show that pharmacological inhibition of MMP9 in the aortic wall, using imidapril administration, prevents further dilatation of experimentally induced aneurysms in mice [158]. A second related study suggests that pharmacological inhibition of necroptosis, a process intrinsic to the vasculature, using administration of small molecule drug Necrostatin1-s, stabilizes preexisting aneurysms by diminishing inflammation and promoting connective tissue repair via reduction of MMP9 activity in the aorta [159].

MMP9 is multifunctional and plays also a role in brain inflammation through modulation of the blood-brain barrier. Its overexpression is also connected to progression of certain types of cancers. Because of its role in multiple important disease processes, several small molecule drugs have already been developed that are currently in ongoing clinical trials, including AAA trials.

Animal Models of AAA

In humans, true and dissecting aneurysms of the aorta develop as a result of progressive weakening of the vessel wall. This weakening of the vessel wall is associated with and likely caused by medial degeneration, which usually starts with degeneration and fragmentation of elastic fibers, infiltration of inflammatory immune cells, as well as weakening and/or loss of smooth muscle cells through apoptosis, and also increased production of reactive oxygen intermediates causing high lipid peroxidation and general oxidative stress. Persistent growth of AAA over the years, combined with accumulation of intraluminal thrombus and an increasing number of atherosclerotic plaques, frequently occurs in humans. However AAA progression can occur in the absence of atherosclerosis in patients and animal models, and most patients with extensive atherosclerosis in the aorta indeed never develop AAA. Both the inherited and non-inherited forms of aneurysm formation are therefore clearly functionally distinct from atherosclerosis.

Ideally, a model for AAA would mirror the pathology of human disease, permitting specific investigation into the mechanisms underpinning human aneurysms. To date, no model that features all important human AAA properties exists; however specific aspects of human AAA can be studied well in animal models. For example, the arterial morphology of pigs is similar to that of humans, the coagulation pathway of sheep is analogous to humans, and primate species have similar clotting and fibrinolytic systems [122]. However, despite these advantages of large animal species, the cost of purchasing and maintaining stocks and ethical considerations have limited their use in vascular research.

In contrast, mouse models are currently by far the most important models of AAA, primarily because of their ease of genetic manipulation combined with low cost of animal husbandry and short time span till fertility. In mice AAAs typically manifest within the suprarenal aorta, while in humans they primarily affect the infrarenal aorta [160], but this difference has not been enough to justify use of large animal models.

Many AAA mouse models have been studied in detail and have indeed revolutionized our understanding of AAA (see Table 5.3). No doubt, additional mouse models with refined, more human-like AAA features will further improve our understanding of AAA pathogenesis.

Cellular Pathology of the Abdominal Aorta

In surgical pathology studies of aortas resected primarily for aneurysms, ruptured aneurysms, and dissections, the frequency and severity of atherosclerosis is much greater in abdominal aortic segments than in thoracic aortic segments [23, 170]. In adults, prominent atherosclerosis typically involves less than 10% of resected thoracic aortic segments but usually more than 80% of resected abdominal aortic segments [23, 170]. This is consistent with the finding that mutations in the LDLR and SORT1 genes are strongly associated with both atherosclerosis and AAA formation/progression, but not with TAA formation, as mentioned above. Complications of abdominal aortic atherosclerosis that may prompt surgical correction include aneurysm formation, aneurysm rupture, occlusive aortic thrombosis, fistula formation, infection, penetrating ulcer with dissection, and distal embolization of thrombus and/or plaque material.

Innate and adaptive immune cells, including neutrophils, macrophages, mast cells, natural killer cells, dendritic cells, B cells, and several types of T cells, have been identified in abdominal aortic aneurysms and have been shown to contribute to AAA development, as described in detail in [171]. Preceding aortic wall dilatation, these immune cells often enter the aorta from the microvessels of the adventitia, causing strong adventitial inflammation, and from there migrate

into the media and cause inflammation as well as breakdown of the elastin fibers through MMP9 expression by macrophages, which is strongly genetically implicated in AAA, as described above. Distinct monocyte and macrophage subsets have critical and differential roles in initiation, progression, and healing of the abdominal aortic aneurysmal process as reviewed in detail by Raffort et al. [172].

Monocytes and macrophages can also enter through lesions in the vascular endothelial cells layer of the intima and together with the vascular endothelial cells are responsible for uptake of LDL particles from the blood via the LDL receptor [173], and the gene coding for LDLR is indeed genetically strongly implicated in AAA (see above). LDL uptake often leads to foam cell formation, an important first step toward atherosclerosis that starts in the intima. It has been hypothesized that intimal plaque formation causes a compensatory inflammation of the adventitia, thus eventually causing AAA. The presence of inflammatory cells and their associated cytokines and proteases in the adventitia and media may protect from arterial narrowing by promoting outward remodeling [171, 174].

However, there is strong epidemiologic evidence against a strict causal relationship between atherosclerosis and AAA formation: it is firmly established by multiple meta-studies that diabetic patients have a significantly lower rate of AAA than the normal population, although diabetic patients show a tenfold higher propensity to atherosclerosis than the normal population [66].

Toward a Pharmacological Cure of AAA

Pharmacological treatment for AAA has been standard for many years although it only has served to slow down enlargement and rupture, not prevent it. Consistent with the strong genetic correlation of AAA with mutations affecting genes that regulate lipid metabolism (LDLR, SORT1), statins, and other blood lipid-lowering drugs as well as blood pressure-lowering drugs such as beta-blockers are often being used on diagnosed AAA patients in the hope to reduce AAA growth.

Initial clinical trials using statins to reduce dyslipidemia and atherosclerosis or beta-blockers to reduce mechanical stress did not find slowing of abdominal aortic diameter growth below ~1.5 mm per year (assuming a typical growth rate of 1.5–2.5 mm per year) [175]. More recently several clinical studies [176–180] show a significant benefit of statins, but unfortunately others do not, even though the number of enrolled subjects has been increasing to several thousand in several of these studies [181]. Of note, statins and beta-blockers are often used together, even in clinical trials, and therefore the isolated effect of these drugs is often difficult to determine.

In many countries beta-blockers and statins have become a routine treatment for AAA patients awaiting surgery. In addition, losartan, an angiotensin receptor-blocking drug that binds the AT1 receptor and also reduces blood pressure, is being used, especially when beta-blockers show insufficient results. Other completed clinical trials used antihypertensive or anti-inflammatory drugs such as perindopril, pemirolast, propranolol, and amlodipine but showed no slowing of AAA diameter growth [182].

Fortunately, population-wide AAA frequencies have been reduced somewhat in several western countries, most likely due to better diagnosis and monitoring of AAA, due to improved intraluminal stenting procedures, and perhaps also due to drug treatment [179, 180].

As mentioned above, extensive meta-analyses of recent clinical AAA trials reveal mixed results for existing AAA drugs – some seem to work better for one genetic type of AAA than for another, or there are other unexplained factors that cause often contradictory data. Therefore there is an urgent need for novel types of drugs that prevent AAA enlargement and rupture reliably and completely. At this time, the only effective treatment to prevent sudden rupture of AAA remains open surgery or catheter-based insertion of stents, as reviewed in Chaps. 19 and 22 of this book.

Fortunately, due to the recent large-scale genome-wide association studies (GWAS) of AAA that we have discussed above, many fundamentally novel animal models of AAA were published in the past ~4 years, and this has led the pharmaceutical industry to develop several new AAA drug candidates that have either already entered clinical trials or will shortly do so. These novel drugs target not only AAA-associated genetic loci involved in dyslipidemia and atherosclerosis (LDLR, SORT1) but also AAA loci that are known or suspected to affect the immune system (IL6R, ERG), extracellular matrix remodeling (MMP9), and VSMC proliferation or homeostasis (9p21/CDKN2BAS, ERG, DAB2IP). Indeed, the animal studies described above and in Tables 5.3 and 5.4 in detail show that IL6R, MMP9, and 9p21 (CDKN2BAS) can contribute to AAA generation via a different mechanism than LDLR and SORT1.

Very well-documented clinical data showing that the AAA expansion rate is significantly lower in patients with diabetes than in those without diabetes, despite the high susceptibility to advanced atherosclerosis as well as calcification in diabetic patients [65, 66], indicate that inflammation-mediated AAA formation and atherosclerosis-mediated AAA formation may not act in concert in all patients. In diabetic patients AAA calcification which is associated with stiffening of the wall may even be inversely correlated with AAA expansion [65, 183]. In addition, it has been suggested that drugs taken by almost all diabetic patients may be in part responsible for the lower AAA incidence, and this is subject to intense research [65, 66]. Multiple preclinical animal models of AAA, mostly

Table 5.4 Anti-AAA drugs tested in mouse animal models of AAA

Pre-clinical animal model and mechanism of action	Administered anti-AAA drug or agent or causative genetic change	Prevention of AAA generation	Prevention of AAA growth and rupture	Affected metabolic pathway	Human AAA-associated genes or loci	Ref
Inhibition of matrix metalloproteinases by small drug delivery using elastin antibody-coated nanoparticles	Small molecule batimastat-loaded nanoparticles	Yes	Yes	MMP remodeling of EM	MMP9	[185]
Overexpression of Sirtuin1 suppresses AAA formation in old ApoE−/− mice	Sirtuin1 transgene	Yes	Yes	VSMC proliferation and immune system	9p21, IL6R	[186]
Elevation of adiponectin levels prevent AngII-induced AAA formation	AAV adiponectin	Yes	Yes		?	[134]
Hypoxia inducible factor 1 alpha inhibition reduces AngII-induced AAA formation	Small molecule digoxin	Yes, acts in the first 10 days	No	MMP regulation	MMP9	[187]
Inhibition of receptor interacting kinase 1 ameliorates elastase-induced AAA progression	Necrostatin-1s small molecule drug	?	Yes	VSMC necroptosis	MMP9?	[159]
Factor Xa/IIa inhibitors reduce size of AAA and atherosclerosis	Small molecule dabigatran	Yes	Yes	Intraluminal thrombus formation	?	[188]
Inhibition of micro RNA-29b reduces AAA development in AngII-induced AAA in mice and also in Elastin-induced AAA in mice	Anti mi29b siRNA expression	Yes	?	Perivascular fibrosis and collagen and elastin expression. Col1a1, Col3a1, Col5a1, and Eln are miRNA29B targets	MMP9 important for extracellular matrix protein homeostasis	[189, 190]
SMAD3 deficiency promotes AAA in CaCl2-induced AAA	Mouse SMAD3−/− model	Yes	?	MMP expression and infiltration of macrophages and T cells	?	[191]
Long non-coding RNA ANRIL may be involved in development of AAA	Mouse 9p21 −/− model	Yes	?	Proliferation of VSMC?	9p21 ANRIL locus	[190]
Angiotensin receptor type 1 blockade attenuates 10 week high-fat diet-induced AAA	Telmisartan (improved over losartan) small molecule drug	?	yes	Renin-angiotensin system	?	[192]
Doxycycline may inhibit MMPs and reduce AngII-induced AAA development	Doxycycline	Yes	Yes	MMP expression in aortic media	MMP9	[163]
Cigarette smoke induces MMP9 secretion from mouse aortic VSMC	N/A	N/A	N/A	Inhibition of the JAK/STAT pathway may alleviate AAA in smokers	MMP9	[193]
Elastase-induced AAA in C57Bl6 male mice	Dietary phytoestrogens	Yes	?	Anti-inflammatory action	?	[194]
CaCl2-induced AAA in mice	Resveratrol	Yes		Anti- inflammatory	?	[195]
AngII-induced AAA in non-cholesterolemic mice. Such mice usually show little AAA	Systemic TGF beta antibodies cause strong AAA induction	Yes	?	Protects against AAA through inhibition of MMP12	?	[44]
Elastase-induced AAA in CDNK2B−/− mice	Deletion of CDKN2B causes induction of VSMC proliferation in the aorta and AAA	Yes	?	CDKN2B protects against aortic inflammation and AAA	9p21	[145]

knock-in mice with genetically engineered mutations in these loci, have shown that AAA expansion can indeed occur in the complete absence of atherosclerosis and calcification (see also Tables 5.3 and 5.4).

Perhaps the best known of the currently completed clinical trials targeting one of the new strongly AAA-associated loci (MMP9) is the long-term administration of doxycycline, an anti-inflammatory drug that is also an MMP9 inhibitor. As described above, individuals with mutations in MMP9 are predisposed to AAA, likely because they cause abnormal MMP9 expression within the extracellular matrix of the media of the aortic wall, which in turn leads to structural

weakness and, thus, aneurysms. A recent animal model has shown clearly that doxycycline can strongly reduce generation of AAA in mice and importantly also can help prevent further expansion and rupture [184]. Doxycycline was tested in an AAA clinical trial starting in 2013, but this was stopped after 1 year of administration, as doxycycline turned out to slightly *increase* the diameter of the AAA instead of stabilize or decrease it [182]. It was assumed that this increase was statistically and biologically insignificant, and an additional study is currently underway using higher doxycycline concentrations [182].

Other current clinical AAA trials test the angiotensin II blockers telmisartan and valsartan [182] which are improved versions of losartan, which has been previously used for both AAA and FTAAD to reduce hypertension and other effects of angiotensin II but with variable success so far (see above). Cyclosporine A and ticagrelor are also in clinical trial in hopes to reduce AAA growth by reducing inflammation and matrix remodeling [182].

To improve the relevance of animal models for human disease, new animal studies aim at testing the effect of novel drugs specifically on existing aneurysms rather than initiation of new aneurysms (see Table 5.4 for details). Indeed, a novel C57BL6 mouse AAA model was published in 2017 that uses oral BAPN administration combined with periaortic elastase application and that for the first time demonstrates all major stages of human AAA formation, including aneurysm formation, slow enlargement over ~ 100 days, thrombus formation, and spontaneous rupture [169]. No doubt such models will be invaluable for the development of drugs that can stop growth and rupture of diagnosed aneurysms in humans.

The most recent mouse models increasingly test drug effects on AAA progression: Table 5.4 lists more than 15 novel pharmacological approaches toward slowing AAA development as well as reducing AAA progression (many of them published within the past 3 years), including long-term treatment of existing AAA, that makes AAA pharmacology a very exciting field. Table 5.4 also lists the suspected mode of action of the treatment and the relevant characteristics of the models for human drug development.

Gene and Cell Therapy of AAA

As described above in the FTAAD section, direct correction of the genetic defect, and/or modulation of the lipid metabolism, of the extracellular matrix remodeling, and of the immune response by gene therapy could be possible within the next 10 years. Importantly, AAA caused by mutations in certain affected genes can potentially be cured by a one-time treatment with gene therapy. These include mutations in transcription factors, such as CDKN2B, DAB2IP, SMYD2, and ERG, which may not directly be targetable by drugs. One interesting way to perform cell/gene therapy in the aorta and other blood vessels was recently published for mice: the use of magnetic field-aided seeding of magnetic genetically engineered vascular endothelial cells into the aortic wall [196]. Such a procedure could be done at an early stage of the disease and could obviate the need of life-long drug treatment or invasive and risky surgery of the patient. Such procedures could also be done for the abdominal aorta at an early stage of the disease, and if engraftment is successful and long term, they could obviate the need of life-long drug treatment or invasive and risky surgery of the patient.

Given the rapid pace of investigation in the nonsurgical treatment of AAA, it is probably only a question of time until novel drugs or even gene/cell therapies are discovered that truly prevent progression of existing AAA in patients in the long term. Once this happens, the need for surgery to treat AAA, which is associated with significant perioperative complications, will be significantly reduced.

Summary and Conclusions on Abdominal Aortic Aneurysm

Familial/genetically conditioned AAA is a complex disorder that is associated with both lifestyle-associated risk factors and predisposing genes, similar to cardiovascular disease. The most recent and largest meta-analysis [11] finds strong support for statistically significant association of nine loci with AAA, four of which have never been recognized before. The nine loci are named 9p21 (CDKN2BAS/ANRIL), SORT1, IL6R, DAB2IP, LDLR, SMYD2, LINC00540, MMP9, and ERG. Since the original AAA studies that were subjected to meta-analysis proposed more than 90 candidate loci, it is clear that majority of these loci could not be confirmed after increasing statistical power [10, 11] and may either not be relevant or will have to await further studies for independent confirmation in specific patient subpopulations. This high failure rate among proposed AAA loci is not atypical of studies in medical genetics in general. Unfortunately, it is often caused by lack of statistical power, lack of sufficient normal controls, systematic error, or bias [197]. Crucially, several of the above nine genetic loci have also been clearly confirmed in multiple independent animal models, usually in the mouse. The presence of mutations in these nine loci should be determined in all AAA patients as well as their non-symptomatic blood relatives. This would allow identification of relatives with high risk of AAA. These individuals would benefit from frequent monitoring of the abdominal aorta and would be motivated to initiate preventative measures such as diet and lifestyle changes – long before an aneurysm develops. However, further research into the

function of the nine AAA-associated genes and especially the establishment and/or refinement of the corresponding animal models to allow monitoring of the effect of drugs on long-term AAA growth (and not AAA generation) is necessary to find novel candidate curative AAA drugs. Indeed, multiple current and planned clinical AAA trials promise possible future pharmacological treatment of AAA, with the potential to greatly reduce the need for surgery.

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Imaging of the Aorta

6

Caroline A. Ball and Mark G. Rabbat

Imaging plays a significant role in diagnosis and management of diseases of the aorta. Over the past decade, technologic advances have expanded the ability to diagnose, monitor, and plan interventions for various disease states. We present a description of the utility of various modalities for imaging the aorta, as well as clinical implications.

Chest X-Ray

Chest x-ray was one of the first diagnostic modalities available for imaging of the aorta. It is a widely available, inexpensive modality, which can be obtained quickly at most centers. Findings on a PA chest x-ray that indicate aortic disease include a widened mediastinum or abnormal aortic contour. The left para-aortic interface can show increased convexity due to tortuosity of the thoracic descending aorta, aneurysm, or dissection [1]. However, the standard chest x-ray has limited utility for diagnosis, and more importantly exclusion, of aortic pathologies. Sensitivity of chest x-ray to identify acute aortic syndrome ranges from 64% to 71% [2]. Specificity of the chest x-ray for diagnosis of aortic dissection is 67%, 61% for non-dissecting aneurysm, and 63% for intramural hemorrhage or penetrating ulcer [3]. Sensitivity of the chest x-ray is lower for disease that is confined to the proximal aorta, than for disease in the distal aorta, likely due to obscuring of the image due to the cardiac silhouette [3]. Abnormalities identified on chest x-ray should be followed-up with additional imaging with higher sensitivity and specificity for aortic disease.

Imaging of the aortic arch may have other utility beyond diagnosing aortic disease. Calcification of the aortic arch on chest x-ray may play a role in prediction of cardiovascular events [4] and is related to calcification throughout the aorta [5], as well as coronary artery calcification [6].

Ultrasound

Ultrasound has many applications in the detection and monitoring of aortic disease. It has a variety of benefits, including its low cost, widespread availability, and the lack of radiation or IV contrast. Ultrasound is applied using several different techniques, each of which provides imaging of specific regions within the aorta.

Transthoracic Echocardiography

Echocardiography is a useful tool for diagnosing and monitoring a range of aortic diseases, particularly at the aortic root. Standard transthoracic echocardiography (TTE) uses several views, which allows visualization of the aorta in multiple locations.

Initial survey of the aorta occurs in the parasternal long axis on echocardiogram. To obtain this image, the transducer is placed at the third or fourth intercostal space, with the notch pointed toward the patient's right shoulder. The transducer may need to be displaced superiorly, such as to the second or third intercostal space, in order to obtain aortic measurements, particularly in patients with a dilated aorta [7, 8]. Moving the transducer closer to the sternum will bring a longer segment of the ascending aorta into view [8]. Measurements should be made perpendicular to blood flow. For the parasternal long axis view in patients with a tricuspid aortic valve, this can be achieved by aligning the closure line of the visualized leaflets in the center of the aortic root. This image allows for measurement of the sinus of Valsalva, the sinotubular junction, and the ascending aorta.

There is currently debate surrounding the landmarks for measuring diameter along the aorta in echocardiography.

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Other imaging modalities, described below, have standardized measuring inner edge to inner edge. However, echocardiography has conventionally used leading edge to leading edge measurements. Reference values for aortic root measurements provided by the American Society for Echocardiography and the European Association of Cardiovascular Imaging are currently based on leading edge to leading edge measurements. It should be noted that using the inner edge to inner edge convention could modify measurements by 2–4 mm. Measurements should be obtained using 2D echocardiography, not M-Mode (Lange). Alternatively, the 2014 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for diagnosis and management of thoracic aortic disease recommend measuring internal edge to internal edge [2].

The aortic root is measured in multiple locations on TTE, with reference values listed in Table 6.1 [8]. There are reference values available for measurement at the annulus, Sinuses of Valsalva, the sinotubular junction, and the ascending aorta. The Sinuses of Valsalva, the sinotubular junction, and the ascending aorta measurements should be obtained mid-diastole, and the widest diameter of the segment being measured should be used to evaluate for aortic dilatation. Aortic diameter should be indexed to a patient's body surface area [8, 9]. However, by convention, the aortic annulus is measured in peak systole, using the inner edge to inner edge [8].

A small cross-section of the descending aorta may be visualized in the parasternal long axis view, posterior to the left atrium. While there are no standard measurements available for this segment of the aorta, it should be visually inspected for abnormalities as part of a comprehensive TTE (Fig. 6.1).

In addition to the aortic root, TTE can be used to image the aortic arch using a view from the suprasternal notch. To obtain these images, the transducer should be placed above the patient's suprasternal notch, with the transducer indicator pointed to the patient's head. From this view, the three major supra-aortic vessels, the brachiocephalic, left common carotid, and left subclavian arteries, can be seen [7]. Velocities of blood flow through the aortic arch can be recorded using both continuous wave and pulse wave Doppler signals.

Table 6.1 Standardized aortic root measurements [8]

Aortic Root	Absolute values (cm)		Indexed values (cm/m^2)	
	Men	Women	Men	Women
Annulus	2.6 ± 0.3	2.3 ± 0.2	1.3 ± 0.1	1.3 ± 0.1
Sinus of Valsalva	3.4 ± 0.3	3.0 ± 0.3	1.7 ± 0.2	1.8 ± 0.2
Sinotubular junction	2.9 ± 0.3	2.6 ± 0.3	1.5 ± 0.2	1.5 ± 0.2
Proximal ascending aorta	3.0 ± 0.4	2.7 ± 0.4	1.5 ± 0.2	1.6 ± 0.3

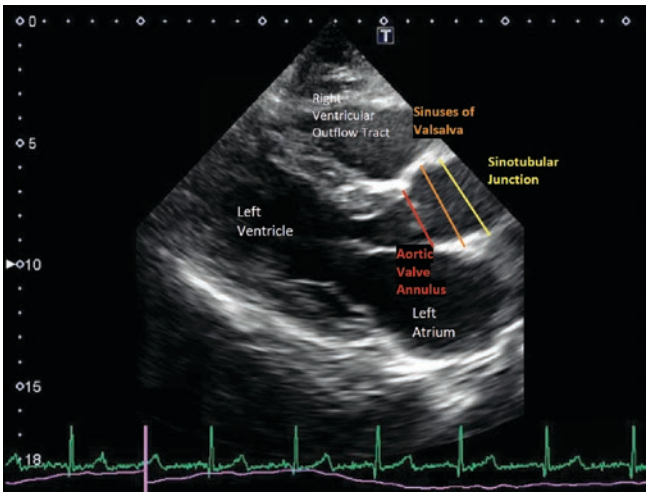

Fig. 6.1 Transthoracic echo, parasternal long axis view, diastole

Finally, portions of the abdominal aorta may be seen from the subcostal view to the left of the inferior vena cava. There are no society-recommended guidelines for imaging the abdominal aorta from this view, but abnormalities identified on this TTE view can prompt further diagnostic studies for imaging of the entire aorta.

Dilation of any one segment of the aorta as identified on TTE should prompt further imaging of the entire aorta. Measurements should be considered in the context of the patient's sex and indexed to the patient's body surface area.

TTE has additional diagnostic value for identifying and following disease processes of the aorta. First, echocardiography provides significant structural and functional information about the patient's heart, which may contribute to their aortic pathology. For example, TTE can identify a bicuspid aortic valve, which may be associated with an aortopathy.

TTE has particular utility for diagnosing and monitoring dilatation and aneurysm of the aortic root, with the benefit of being a noninvasive, relatively low-cost test without the need for radiation or contrast. Sinus of Valsalva aneurysms are a unique group of aneurysms of the aortic root that can be identified and followed on TTE. These aneurysms frequently arise from the right coronary sinus and project into the right atrium, causing the "windsock deformity." Alternatively, a sinus of Valsalva aneurysm that arises from the non-coronary cusp may be seen projecting into the interventricular septum (Fig. 6.2).

TTE can identify acute aortic dissection, although this is limited primarily to dissections of the aortic root. TTE has a sensitivity of 78–90% for identifying ascending aortic dissection, but a 31–55% sensitivity for identifying descending aortic dissection. TTE has a specificity of 87–96% for Type A aortic dissections, with a lower specificity for Type B

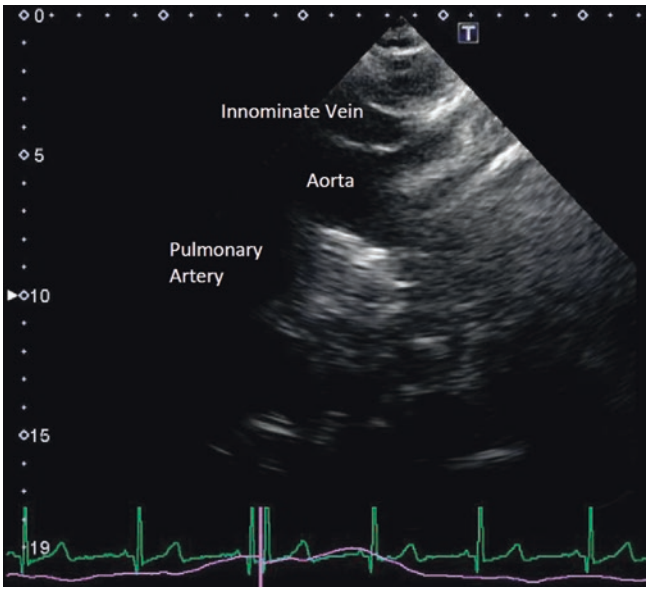

Fig. 6.2 Transthoracic echo, suprasternal notch view

aortic dissections, from 60% to 83%. The sensitivity can be improved by using ultrasound contrast agents [9]. Given its inability to visualize the entire aorta and its inferior sensitivity to other modalities listed later, TTE should not be used as the initial test to rule out aortic dissection.

Diagnosis of dissection requires identifying both a true and false lumen, including the dissection flap. The dissection flap should have motion that is independent of its surrounding structures. This flap should be contained within the lumen of the aorta. Differentiating between the true and false lumens can be challenging on 2D echocardiography, but there are several features that echocardiographers can use to identify the true and false lumen. The true lumen should expand during systole and contract during diastole. In calcified vessels, the true lumen may have surrounding calcification and have a more regular shape than the false lumen. There should be little or no spontaneous echo contrast through the true lumen, and the systolic jets should direct away from the transducer when color flow is studied through the vessel. Often, the false lumen has a wider diameter than the true lumen and may contain strand-like structures, which are referred to as "cobwebs." The false lumen may have spontaneous echo contrast or thrombus and is often bigger than the true lumen [7, 10].

After identification of aortic dissection, TTE can be used to identify complications of the dissection, such as pericardial effusion, aortic regurgitation, and wall motion abnormalities caused by dissection through the coronary ostia.

Continuous wave Doppler through the aortic arch on the suprasternal notch view can be used to identify coarctation of the aorta. There should be increased velocities across the area of coarctation, although this requires accurate Doppler signals [7, 11]. Similarly, a persistent ductus arteriosus can be identified using color Doppler [9].

Although TTE should not be used for imaging of the entire aorta, it is useful for follow-up imaging of dilatation of the aortic root, particularly in patients who will require many serial measurements [2, 9].

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) was initially developed to measure flow in the aortic arch and has remained an important modality for imaging the aorta since its inception. TEE provides an additional modality for imaging the aorta without the need for radiation or iodinated contrast exposure. TEE is a more invasive test than TTE, but has several advantages, including permitting visualization of the majority of the aorta. Similar to TTE, the aorta can be visualized in multiple views on TEE. The American Society of Echocardiography describes 28 specific views for obtaining a TEE [12]. Below, we will describe those that are relevant to imaging the aorta.

The aortic root is best visualized on TEE using the midesophageal aortic valve long-axis view and the midesophageal ascending aorta long axis view [8, 12]. The midesophageal aortic valve short axis and transgastric views can be helpful for imaging the aortic valve. The midesophageal aortic valve long axis view is obtained by inserting the transducer to the midesophagus with the transducer angle at 120–140°. From this view, the midesophageal ascending aorta long axis view can be obtained by withdrawing the probe to the upper esophagus and adjusting the transducer angle to 90–110°. The midesophageal ascending aortic short and long axis views are important for excluding aortic dissection [13] (Fig. 6.3).

A significant portion of the descending aorta can be visualized using TEE. To obtain images beginning at the upper abdominal aorta, the transducer should be inserted to the transgastric view until the aorta is no longer in view. This is around the location of the celiac trunk. Subsequently, the transducer is slowly withdrawn, allowing careful inspection of the aortic lumen. Using simultaneous multiplane imaging, the aorta can be seen in both the descending aortic long and short axis views. The probe is withdrawn to the level of the left subclavian artery, forming the upper esophageal aortic arch long and short axis views. By rotating the transducer angle from 0° (upper esophageal aortic arch long axis view) to 90–110° (upper esophageal aortic arch short axis view), the arch and descending aorta can be seen in multiple views. Additionally, from the upper esophageal aortic arch short axis view a patent ductus arteriosus or coarctation of the aorta can be identified. Other views that can be useful for imaging the aorta include the midesophageal ascending short axis and the upper esophageal aortic arch long and short axes.

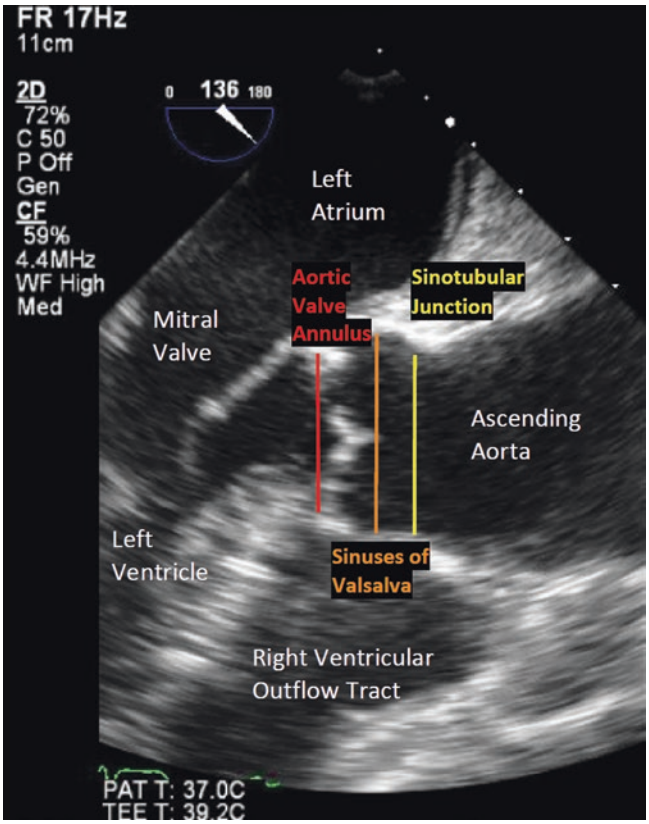

Fig. 6.3 Transesophageal echocardiogram, midesophageal aortic valve long axis view

TEE evaluation of the aorta is limited by a "blind spot" in the aortic arch, where the trachea is interposed between the esophagus and the aortic arch, causing air artifact and limiting visualization of the arch. This is of particular importance in surgery requiring cardiopulmonary bypass, as cannulation occurs in an area of the ascending aorta that may not be adequately visualized. In some situations, this "blind spot" can be overcome with the use of a fluid-filled catheter, which is referred to as an "A-View." This technique involves placing a fluid-filled intratracheal balloon down the left main stem bronchus in intubated patients to create an echo window for imaging of the aortic arch [14].

The American Society of Echocardiography recommends measuring the aortic root on TEE at several locations, including the aortic valve annulus, designated by the hinge points of the aortic leaflets, the maximal diameter in the sinus of Valsalva, and the sinotubular junction. Similar to TTE, there is no consensus on the ideal technique for measuring the aorta, but normative standards are provided for adults using the leading edge to leading edge technique. Measurements should be made using 2D echocardiography, not M-Mode [12]. Normal measurements of the aortic root are similar between TTE and TEE, and the reader is directed to Table 6.1 for standard aortic root measurements on TEE. TEE can also be used to measure the aortic arch and the descending aorta. However, TEE measurements of the descending aorta are prone to error if oblique measurements are made. Therefore, measurements should only be recorded if the aorta is visualized with circular cross-sections. Standard measurements of the descending aorta are not indexed to body surface area. Standard diameter of the aortic arch is measured proximal to the innominate artery and is 22–36 mm. Standard diameter of the descending aorta is obtained between the ligamentum arteriosum and the diaphragm and is 20–30 mm.

The American Society of Echocardiography encourages documenting any irregularities of the aortic wall, in addition to the presence and thickness of atheroma and the presence of mobile atherosclerotic elements. Locations of aortic findings should be documented relative to the left subclavian artery or relative to the incisors.

Color Doppler can be used to evaluate for abnormal flow in the thoracic aorta, particularly in the setting of atheroma or a known dissection flap. Although an emerging technique, 3D TEE has potential to improve measurements obtained by TEE.

TEE has the ability to identify atherosclerotic plaques in the aorta, which can be of particular interest in patients undergoing surgery requiring cardiopulmonary bypass. Atherosclerotic plaques appear as a thickness within the aortic wall. Whenever they are identified, they should be described with respect to their thickness and the presence of any mobile components. Several scoring systems have been implemented to better describe the stroke risk associated with each plaque. Perhaps the most widely accepted is the Katz score, which is described in Table 6.2 [15].

Based on a recent meta-analysis, standard TEE itself has limited sensitivity for aortic atherosclerosis, as low as 21%, but high specificity, up to 99% [14]. Thus, it is frequently used in conjunction with other aortic imaging techniques, such as epiaortic scanning or the A-view technique described above to identify aortic atherosclerosis. TEE can be used to identify aortic aneurysms, as well as to describe the size, location, and extent of the aneurysm, and the presence of a hematoma within the aneurysm. Whereas TEE has limited sensitivity for atherosclerosis, its sensitivity for aortic dissection is high (86–100%) and its specificity is high (90–100%) [16]. TEE is limited in its evaluation of aortic dissection by its difficulty in assessing the distal ascending aorta and the proximal aortic arch [13]. In patients with dissection, similar techniques can be used in TEE as were described for TTE for distinguishing between the true and false lumens.

Table 6.2 The Katz score for describing aortic atherosclerosis [15]

Grade	Description
I	Normal to mild intimal thickening
II	Severe intimal thickening without protruding atheroma
III	Atheroma protruding 3 to 5 mm into the lumen
IV	Atheroma protruding >5 mm into the lumen
V	Any thickness with mobile component

Abdominal Ultrasound

Abdominal aortic ultrasound is another noninvasive and inexpensive tool for imaging the aorta. Abdominal aortic ultrasound allows visualization of the abdominal aorta from the diaphragm to the bifurcation of the aorta [11]. Images are obtained using a 2.5–5.0 MHz curvilinear array transducer. The patient is placed either in the supine or left lateral decubitus position and encouraged to fast for 8–12 hours prior to the procedure to reduce intestinal gas. The abdominal aorta should be imaged in both the longitudinal and transverse planes along the entire distance from the diaphragm to the bifurcation. Measurements should be obtained in the most circular cross-sectional image possible, measured in the anterior-posterior diameter from outer edge to outer edge. Inter-observer reproducibility for measuring the abdominal aorta is ± 1.9 mm to ± 10.5 mm [11].

One of the foremost uses of abdominal ultrasound is for screening of abdominal aortic aneurysms (AAA). Abdominal ultrasound has a sensitivity of 94–100% for detecting AAA and a specificity of 98–100% [17]. Between 1988 and 1999, four major randomized controlled trials (RCT) examined screening programs for AAA. Meta-analysis of these four trials found that screening programs reduced AAA mortality by 40% after 3–5 years and a 2.7% reduction in all-cause mortality at 11–15 years follow-up [18, 19]. Each of these RCTs used a 30 mm infrarenal diameter as a cutoff for diagnosis of AAA, with surgical repair recommended for an infrarenal abdominal aortic diameter greater than 5.5 cm in men and 5.0 cm in women. However, the protocols within the RCTs used differing techniques for measurement of the AAA, including inner edge to inner edge, leading edge to leading edge, and outer edge to outer edge. The United States Preventive Services Task Force recommends a one-time ultrasonography screening for AAA in men aged 65–75 years who have ever smoked. This recommendation does not specify how the abdominal aortic diameter should be measured (Fig. 6.4).

Contrast agents are now available to enhance ultrasound images. Ultrasound contrast agents use microbubbles that reflect non-linear signals, enhancing the definition of tissue lines. Contrast agents have been used in abdominal ultrasound for enhanced imaging of AAA and for better visualizing aortic rupture [20]. Following endovascular aortic aneurysm repair, abdominal ultrasound can be used to visualize endoleaks, fractures, or progressive enlargement of an AAA as part of a surveillance program. Contrast-enhanced ultrasound is the imaging modality of choice for following these patients, as it does not require radiation, it is fast and affordable, and it has high sensitivity and specificity for diagnosing endoleaks, 98–100% and 82–93%, respectively [20].

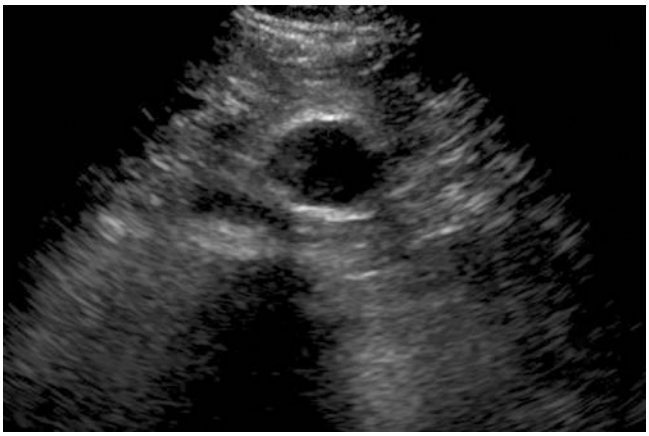

Fig. 6.4 Ultrasound of the abdominal aorta with an infrarenal aneurysm

Epiaortic Scanning

Aortic atherosclerosis is a significant risk factor for post-cardiac surgery stroke, and its identification prior to a surgical procedure can assist surgeons in forming a surgical plan. Epiaortic scanning (EAS) uses a high-frequency, linear array transducer to image the ascending aorta and the aortic arch prior to surgical manipulation of the aorta. Epiaortic scanning has the advantages of being able to image the entire aorta [21], and its use changes surgical plans 4–31% of the time, potentially reducing the risk of perioperative stroke [22]. However, epiaortic screening cannot be performed until after the sternotomy has been completed, leaving a surgeon limited time to adjust surgical planning. Additionally, introducing the ultrasound transducer to the surgical field increases risk of infection and complication. Prior to the introduction of A-view technique for TEE, epiaortic scanning was one of few methods surgeons had for visualizing aortic plaque without direct palpation of the aorta. A-view technique now allows surgeons to visualize the entire aorta prior to sternotomy.

Intravascular Ultrasound

A new area of ultrasound evaluation of the aorta is using intravascular ultrasound (IVUS). This technique involves introducing a catheter with an ultrasound probe into the patient's arterial system, most commonly through the femoral artery. The probe is inserted into the left ventricle and then slowly withdrawn to the desired level, with measurements of aortic diameter obtained along the way. This invasive approach may be of interest in the setting of transcatheter aortic valve implantation, as it provides accurate measurements of the lumen where the valve is to be implanted. Early studies demonstrate consistent aortic annular measurements obtained using IVUS and those using computed tomography (CT)

[23]. However, the correlation may be less robust in the aortic arch, where IVUS tends to measure a larger diameter compared to CT [24]. IVUS may have additional benefits in measuring variation of aortic diameter over the cardiac cycle [25].

At the time of writing, there are no specific reference standards for aortic measurements obtained by IVUS, but the reader may refer to reference standards provided for CT.

Computed Tomography

CT provides a wealth of information about the aorta. It has many advantages over other modalities, including its ability to image the entire aorta, visualizing the lumen, wall, and periaortic regions. CT can rapidly acquire high-quality images, allowing prompt diagnosis of acute aortic syndromes. Best practice CT imaging of the aorta uses ECG-gating to reduce artifact from cardiac motion, by synchronizing image acquisition to the cardiac cycle. Specifics of ECG gating are beyond the scope of this discussion [2]. CT angiography (CTA) uses iodinated contrast agents to permit improved delineation of the aorta and additional blood vessels.

Individual institutions have specific protocols for obtaining CT images of the aorta. The ACC/AHA recommend using at least four detector rows to image the thoracic aorta, with ≥3 mm thickness and a reconstruction level of 50% or less than the slice thickness with ≤50% overlap [2].

In general, imaging protocols should begin with a non-contrast image to identify the subtle changes associated with intramural hematoma, which may not be identified on contrast enhanced imaging. Next, contrast media can be introduced for improved delineation of the aortic lumen. If given, it should be injected at 3–5 mL/second via a power injector, with a total volume delivered ≤150 mL. Contrast material should be injected into the right upper extremity, as contrast delivered through the left brachiocephalic vein can result in streaking. Contrast administration is particularly important for identifying dissection flaps [2]. Imaging should extend from above the aortic arch to at least the aortoiliac bifurcation for a comprehensive aortic examination. In the setting of dissection, a field from the aortic arch to the aortoiliac bifurcation allows inspection of aortic branch vessels for malperfusion and involvement in dissection, as well as allows planning for an endovascular repair. Delayed images should be used when evaluating patients after stent-graft repair of aortic aneurysms to detect endoleaks [26]. For patients with an endoleak identified on CTA, additional imaging should be obtained with digital subtraction angiography.

Measurements obtained with CT should be performed relative to the centerline of flow to ensure that measurement occurs at a true short axis, perpendicular to the line of blood flow. More recently, the use of 3D reconstructions has allowed improved interpretation of axial section [2]. The convention in CT is to measure outer edge to outer edge. This can result in a significant discrepancy between measured aortic diameter and actual aortic lumen in the setting of intraluminal clot, aortic wall inflammation, or aortic dissection, as well as a discrepancy between measurements obtained on CT and using echocardiography (Fig. 6.5).

Due to the differences in imaging technique, there are a unique set of reference aortic diameters for CT than for echocardiography. Measurements are considered relative to the patient's age and sex. Each patient's specific measurements must be placed in the context of their clinical condition, as criteria for intervention of aortic aneurysm may be specific to disease process, such as in genetic aortopathies. Measurements should be normalized to body surface area. Reference values for aortic area as measured by CT are listed in Table 6.3 [27].

Inter-observer variability for CT evaluation of AAA is approximately 5 mm, and intra-observer variability is approximately 3 mm [11].

Imaging reports, regardless of modality used, should include several important elements, as recommended by the ACC and the AHA [2]. These elements include:

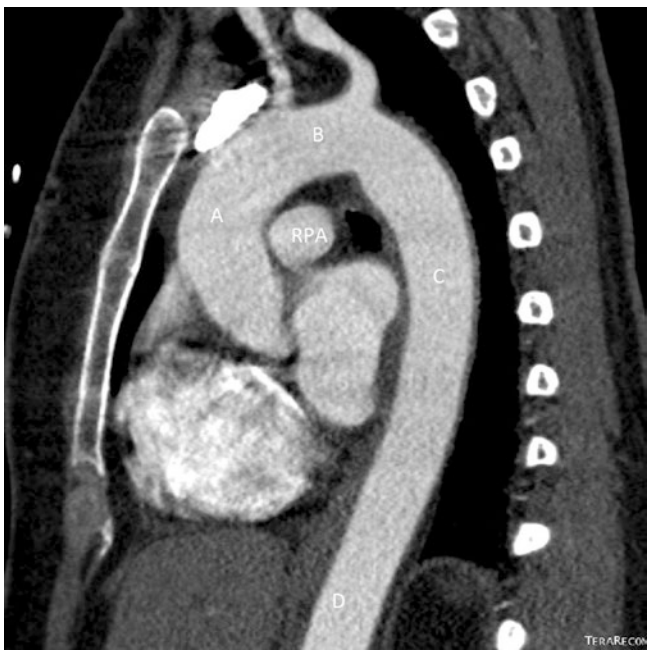

Fig. 6.5 CT image, lateral projection of the thoracic aorta. Legend: A = ascending aorta. B = aortic arch. C = thoracic descending aorta. D = abdominal descending aorta. RPA = right pulmonary artery

Table 6.3 Reference values for aortic diameter on CT [27]

	Ascending aorta		Descending aorta	
Age (years)	Male	Female	Male	Female
<45	3.9 ± 0.8	3.8 ± 0.7	2.0 ± 0.3	2.1 ± 0.3
45–54	4.4 ± 0.8	4.3 ± 0.8	2.2 ± 0.3	2.4 ± 0.4
55–64	4.7 ± 0.9	4.7 ± 0.9	2.4 ± 0.4	2.6 ± 0.4
≥65	5.2 ± 0.9	5.1 ± 0.9	2.7 ± 0.4	2.7 ± 0.4

Units are cm^2/m^2

1. The location at which the aorta is abnormal.
2. The maximum diameter of any dilatation, measured from the external wall of the aorta, perpendicular to the axis of flow, and the length of the aorta that is abnormal.
3. For patients with presumed or documented genetic syndromes at risk for aortic root disease measurements of the aortic valve, sinuses of Valsalva, sinotubular junction, and ascending aorta.
4. The presence of internal filling defects consistent with thrombus or atheroma.
5. The presence of intramural hematoma, penetrating aortic ulcer, and calcification.
6. Extension of aortic abnormality into branch vessels, including dissection and aneurysm, and secondary evidence of end-organ injury.
7. Evidence of aortic rupture, including periaortic and mediastinal hematoma, pericardial and pleural fluid, and contrast extravasation from the aortic lumen.
8. When a prior examination is available, direct image to image comparison to determine if there has been any increase in diameter.

One of the significant advantages of CT over previously described imaging modalities for the aorta is its high sensitivity and specificity. CT has a sensitivity as high as 100% and a specificity as high as 100% for diagnosis of aortic dissection [16] and a sensitivity of 90% and a specificity of 91% for AAA [17].

Due to the rapid acquisition of CT images, this modality is particularly beneficial in the trauma setting. For trauma patients, the sensitivity, specificity, and accuracy of contrast-enhanced multidetector CT for traumatic injuries are 96%, 99%, and 99%, and the negative predictive value of a non-contrast CT of the aorta approaches 100% [2]. Additionally, CT is favored over MRI for imaging of the aorta after an intervention or open surgery due to the presence of metallic closure devices and clips.

CT plays an important role in the diagnosis and management of aortic dissection, particularly with identification of the true and false lumens and the site of intimal tear. According to the International Registry of Acute Aortic Dissection, CT is the initial modality for diagnosis of aortic dissection in 61% of cases [2]. Similar to echocardiography, there are several techniques that can be used to differentiate the true from the false lumen. In highly calcified aortas, the true lumen may retain an intraluminal ring of calcification. The true lumen is generally smaller than the false lumen and will be continuous with the remainder of the aorta. "Cobwebs," linear low attenuation areas within the false lumen, are highly specific for identifying the false lumen. Thrombi may be seen in the false lumen, as well as the "beak sign," which indicates the area of intimal tear [28] (Fig. 6.6).

CT can be used to identify several specific disease conditions. Aortic rupture can be identified on CT, although the clinical situation rarely allows time for thorough examination. Aortic rupture often appears as a periaortic hematoma on a

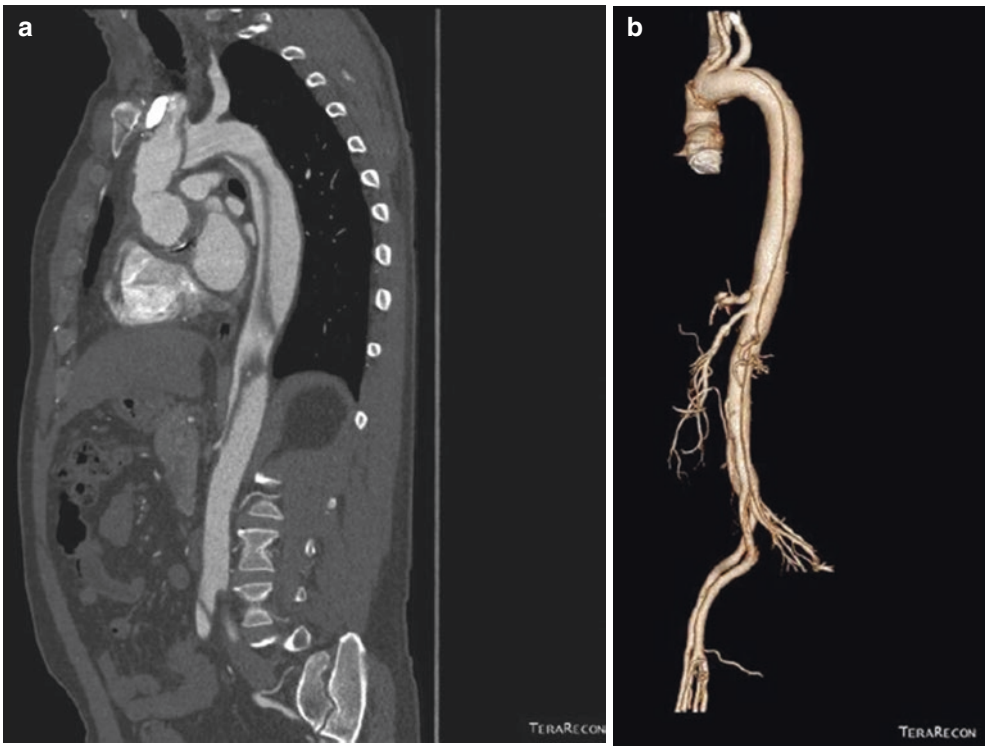

Fig. 6.6 (**a**) CT image, lateral projection of the thoracic and abdominal aorta with a large aortic dissection. (**b**) 3D reconstruction images from CT of the thoracic and abdominal aorta, with a large aortic dissection

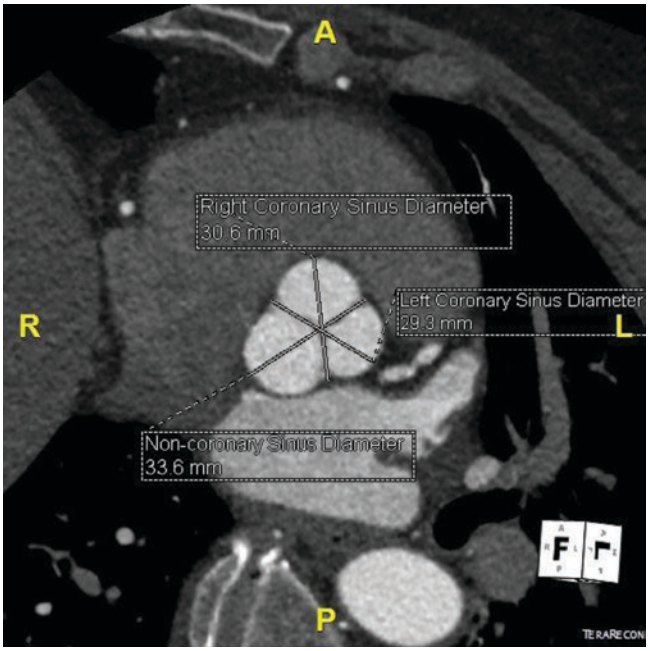

Fig. 6.7 Sinus of Valsalva diameter on CT

non-contrast image or is demonstrated by contrast extravasation into the pleura, mediastinum, or retroperitoneum. Prior to rupture, CT can identify areas of vascular instability. The "hyperattenuating crescent sign" is a high density within an aneurysm and is best seen on non-contrast studies. This represents fresh hemorrhage mixed with established mural clot. Additionally, diminishing internal thrombus may suggest dynamic vessel walls. Mycotic aneurysms can be seen on CT. Mycotic aneurysms appear saccular, with a wide neck, eccentric or multilobulated periaortic inflammation, and/or with air. Inflammatory aneurysms, more frequently seen in the abdominal aorta, present as a soft tissue ring around the aorta on cross-sectional imaging. They may be accompanied by soft tissue thickening that adhered to adjacent retroperitoneal structures, leading to loss of periaortic fat planes or medial deviation of the ureters. Penetrating aortic ulcer usually presents as an irregular, "crater-like" contrast-filled outpouching extending beyond the aortic lumen. Aortitis may present as increased wall thickening, and individual disease processes can be difficult to differentiate on CT. Giant cell arteritis tends to involve the thoracic aorta and may present with "skip lesions," whereas Takaysu's arteritis more commonly affects the left subclavian artery or the abdominal aorta [28] (Fig. 6.7).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) provides a complete image of the aorta with excellent anatomical detail. With the proper sequences, MRI has the additional benefit of providing functional imaging, including aortic valve and left ventricular function analysis. However, MRI is not readily available at all centers, and imaging techniques can take 2–4 times longer compared to a CT acquisition. Additionally, MRI requires patients to remain still in a confined space for a prolonged period, which limits its utility for patients with claustrophobia. Due to the use of magnets in image acquisition, MRI cannot be used on patients with certain metal implants [2].

While specifics of MRI are beyond the scope of this text, the reader should be aware that there are several different types of pulse sequences, combinations of radiofrequency pulses, and magnetic gradients that are used to acquire an image. Specific pulse sequences provide optimal imaging for different components of the aorta and various disease processes [29].

Protocols for obtaining MR images are specific to institutions. In general, imaging should begin with spin-echo black blood sequences to outline the shape and diameter of the aorta. Spin-echo black blood sequences also permit detection of an intimal flap in the setting of an aortic dissection. Next, gradient-echo bright blood sequences can be used to demonstrate changes in the aortic diameters throughout the cardiac cycle, as well as to detect any blood flow turbulence. Gadolinium contrast agents can be used to better delineate the vessel wall [1]. When contrast agents cannot be used, ECG-gated non-contrast steady state free precision images can be used to obtain aortic diameter [11, 30]. Source and maximal intensity projection images can be evaluated for delineation of the aortic wall and for imaging of the dissecting membrane. Time-resolved 3D flow-sensitive MRI allows visualization and measurement of blood flow patterns and shear wall stress [11]. Additionally, maximum intensity projection imaging allows visualization of collateral circulation [28]. Aortic wall inflammation can be identified using T2-weighted images by evaluating for wall edema, or by post-contrast wall enhancement [30] (Fig. 6.8).

MRI can be used to measure vessel diameter throughout the aorta. Measurements should be obtained at similar locations along the aorta as described above for CT and should be obtained perpendicular to the axis of blood flow, at the widest point of the vessel [2]. ECG gating should be used to minimize motion artifact [1]. Measurements should use the outer edge-to-outer edge technique, although this continues to be a topic for debate [31]. There are fewer published normal aortic diameter values for MRI than for other modalities. However, normal values, as obtained by Davis et al., are listed in Tables 6.4 and 6.5. Measurements should be compared to normal values for age and sex, as the aortic lumen diameter, total vessel diameter, and wall area normally increase with age [30, 32].

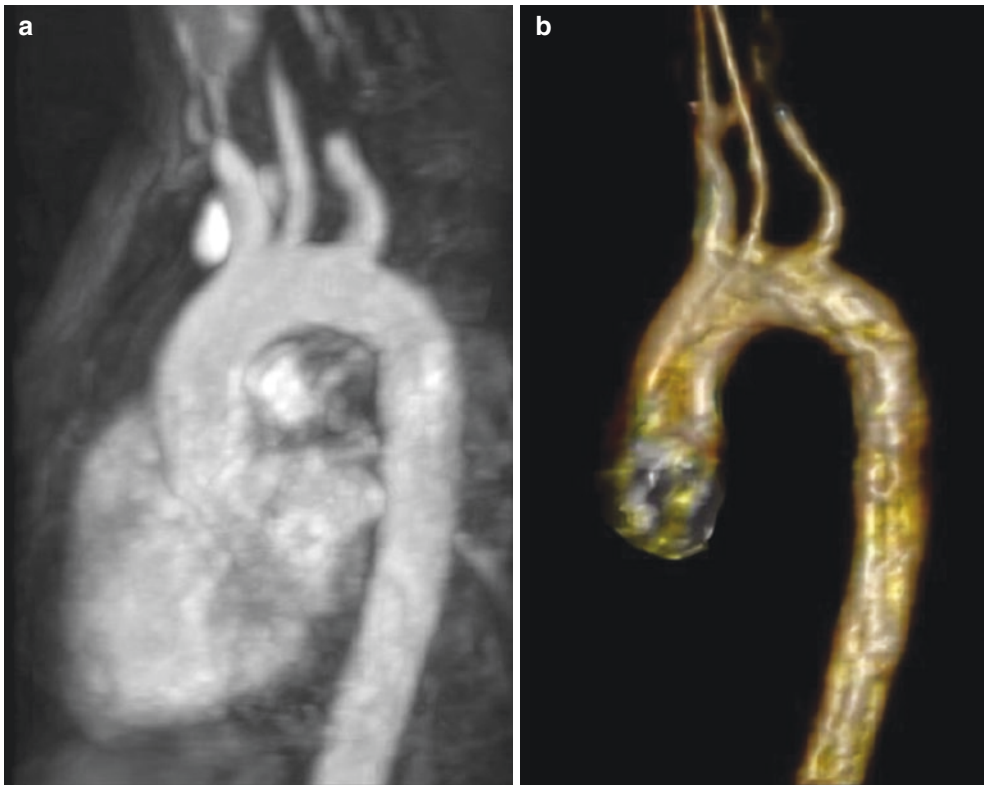

Fig. 6.8 (**a**) MR image, maximum intensity projection of the thoracic aorta. (**b**) MRI 3D reconstruction of the thoracic aorta

Table 6.4 Normal values (in mm) of the thoracic and abdominal aortic luminal diameters for men and women of different BMI categories measured on MRI at diastole [31]

	Men			Women		
BMI (kg/m²)	<25	25–29.9	>30	<25	25–29.9	>30
Aortic annulus	23.9 (18.6–29.2)	24.3 (18.9–29.7)	25.6 (20.4–30.8)	20.6 (17.4–23.8)	21.7 (18.4–25.0)	21.5 (17.2–25.8)
Aortic sinus	31.9 (24.3–39.5)	32.8 (25.2–40.4)	33.3 (24.3–42.3)	27.5 (21.9–34.2)	28.0 (21.8–34.2)	27.5 (21.3–33.7)
Sinotubular junction	24.4 (18.2–30.6)	25.7 (16.7–34.7)	26.2 (18.9–33.5)	21.6 (16.6–26.6)	22.3 (17.0–27.6)	22.1 (15.9–28.3)
Ascending aorta	26.0 (18.7–33.3)	27.4 (18.9–35.9)	28.5 (23.1–33.9)	24.7 (17.8–31.6)	26.5 (19.3–33.7)	26.6 (18.8–34.4)
Proximal descending aorta	20.1 (14.7–25.5)	20.9 (15.6–26.2)	22.2 (16.3–28.1)	18.5 (14.6–22.4)	19.2 (14.8–23.6)	19.6 (16.5–23.2)
Abdominal aorta	17.1 (12.0–22.2)	17.9 (12.8–23.0)	18.8 (14.4–23.2)	16.0 (12.1–19.9)	16.3 (12.3–20.3)	17.4 (13.9–20.9)

Values are given as (Mean [±2 SD])
BMI Body mass index

Table 6.5 Absolute and BSA-indexed normal values of ascending aortic luminal diameter for men and women of different age categories measured on MRI phase contrast images [31]

Age (years)	Men	Women
Absolute values (mm)		
45–54	31.6 (27.2–37.3)	28.8 (24.6–34.4)
55–64	32.8 (28.1–40.7)	30.1 (25.7–36.4)
65–74	34.2 (28.7–41.0)	30.6 (26.1–36.3)
75–84	34.7 (28.6–40.8)	31.1 (26.8–37.1)
Values indexed to BSA (mm/m²)		
45–54	15.9 (13.3–19.5)	16.7 (13.5–20.7)
55–64	16.8 (13.6–21.1)	17.6 (14.4–22.1)
65–74	17.8 (14.2–21.8)	18.1 (14.5–22.1)
75–84	18.6 (15.2–22.6)	19.7 (15.3–28.2)

Values are given as (Median [5th–95th percentile])
BSA Body surface area

Major society guidelines recommend MRI for repeat imaging of the aorta, particularly for any location distal to the aortic root to minimize radiation to the patient and optimize reproducibility [2].

MRI has a 95–100% sensitivity and 94–98% specificity for diagnosing aortic dissection [16]. MRI allows specific characterization of aortic atheroma with visualization of the fibrous cap, lipid core, and thrombus [22] (Fig. 6.9).

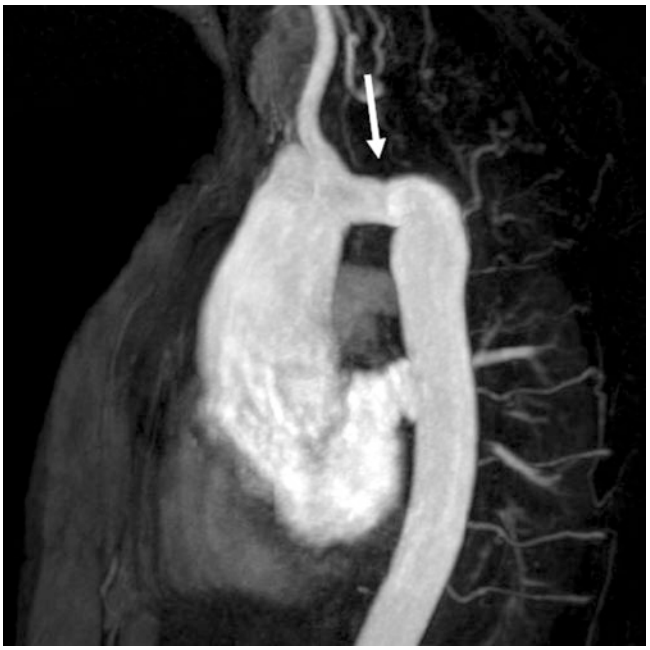

Fig. 6.9 Thoracic magnetic resonance angiogram, maximum intensity projection of the thoracic aorta demonstrating coarctation of the aorta (white arrow)

Conclusion

Significant advances in imaging techniques over the past decade have expanded the ability to noninvasively diagnose, monitor, and plan interventions for a variety of aortic pathologies. While established imaging techniques such as TTE and TEE continue to play an important role in imaging of the aorta, highly sensitive and specific modalities such as CT and MRI are playing an expanding role and are invaluable tools for the diagnosis and management of aortic diseases.

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Vascular Rings

7

Carl L. Backer

Introduction

At Ann & Robert H. Lurie Children's Hospital of Chicago, the first successful vascular ring repair was performed by the late Dr. Willis J. Potts in 1947 [1]. The patient was an 8-year-old boy who had stridor and dysphagia, which had been present essentially since birth. He had over 30 admissions to the hospital for upper respiratory tract infections and respiratory distress. Through a left thoracotomy, Potts identified a double aortic arch. The distal left aortic arch was clamped, divided, and the stumps oversewn. In addition the ligamentum arteriosum was ligated and divided. The child was discharged from the hospital 3 weeks postoperatively and his symptoms essentially disappeared.

This experience was similar to that of Dr. Robert Gross who was the first to describe a successful division of a vascular ring at Boston Children's Hospital [2]. The first patient that Gross operated on had a double aortic arch. That child was 1-year-old and had persistent wheezing and recurrent hospital admissions. Gross was also the first surgeon to describe the other most common vascular ring, right aortic arch with retroesophageal left subclavian artery and left ligamentum arteriosum [2]. Willis Potts was the first surgeon to diagnose and successfully repair an infant with a pulmonary artery sling [3]. The classification scheme for vascular rings that we use is that endorsed by the Society of Thoracic Surgeons Congenital Nomenclature and Database Project [4]. The information in this chapter is mostly based on our experience with nearly 400 vascular ring patients shown in Table 7.1.

Embryology

The embryologic origin of vascular rings was originally elucidated by the late Jesse Edwards [5]. Edwards was the first to report on the embryonic aortic arch system consisting of a ventral and dorsal aorta connected by six primitive aortic arches (Fig. 7.1). During development different portions of these arches either persist or involute. Depending on which sequence of events occurs determines the different types of vascular rings. The accuracy of Edwards' double aortic arch system has been recently shown to be correct based on fetal magnetic resonance imaging (MRI) and fetal echocardiograms that demonstrate this exact progression of development.

All patients progress through a phase of having two aortic arches, left and right (Fig. 7.2). In nearly all patients the first, second, and fifth arches regress. If the right fourth arch involutes, the patient has a ("normal") left aortic arch and no vascular ring (Fig. 7.3). If the right and left fourth arches both persist, then a double aortic arch is formed (Fig. 7.2). If the left fourth arch involutes and the right fourth arch remains, the child will have a right aortic arch (Fig. 7.4). When there is either a double aortic arch or a persistent right aortic arch, there may be various patencies or involutions of the remaining aortic arch systems creating different subsets within the major categories of vascular rings. The most common double aortic arch is when there is a dominant right aortic arch with a smaller left aortic arch. The most common right aortic arch is when there is a retroesophageal (aberrant) origin of the left subclavian artery and a left ligamentum from the descending thoracic aorta to the pulmonary artery, completing the vascular ring. However, there can be many subtle variations.

Table 7.1 Lurie Children's experience (1947–2015)

Vascular Ring	# of Patients
Double aortic arch	155
Right aortic arch/left ligamentum	172
Pulmonary artery sling	46
Total	373

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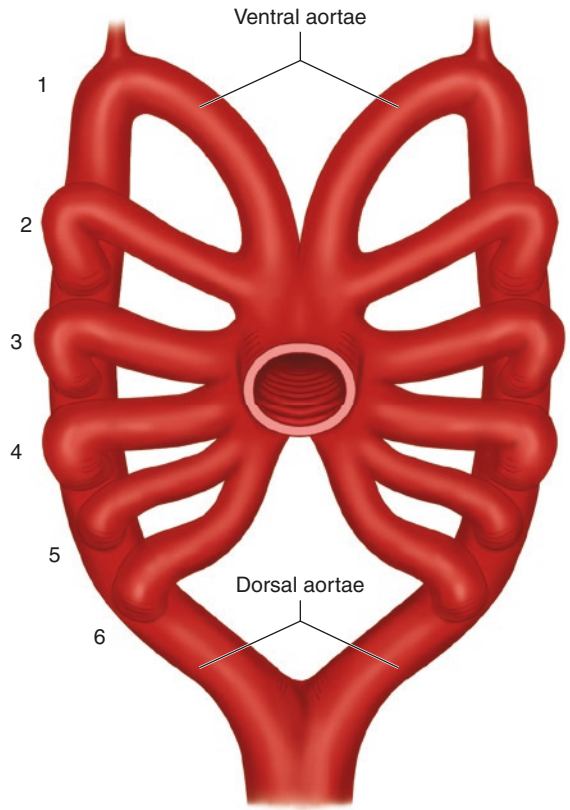

Fig. 7.1 Diagram of the embryonic aortic arches. Six pairs of aortic arches originally develop between the dorsal and ventral aorta. The first, second, and fifth arches regress. Preservation or deletion of different segments of the rudimentary arches results in either a double aortic arch, a right aortic arch, or the "normal" left aortic arch. (Reproduced with permission from Backer and Mavroudis [19])

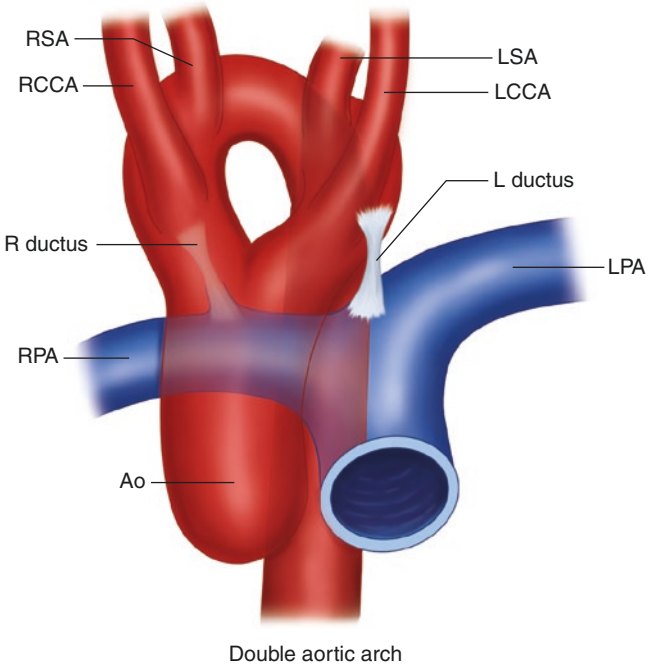

Fig. 7.2 Double aortic arch. (Ao, aorta; L, left; LCCA, left common carotid artery; LPA, left pulmonary artery; LSA, left subclavian artery; R, right; RCCA, right common carotid artery; RPA, right pulmonary artery; RSA, right subclavian artery). (Reproduced with permission from Backer and Mavroudis [19])

It is the potential for immense variability in the fine detail of these vascular rings that leads us to our recommendation for advanced medical imaging, either CT scan or MRI prior to any type of surgical intervention.

A different embryologic event occurs when pulmonary artery sling develops. In these patients the left pulmonary artery vascular bud does not connect directly to the main pulmonary artery anterior to the trachea. Instead the pulmonary artery bud courses between the esophagus and trachea to find its vascular origin from the right pulmonary artery (Fig. 7.5). It is unclear exactly what the embryologic origin of the association with tracheal stenosis is, but 2/3 of patients with a pulmonary artery sling will also have tracheal stenosis. The tracheal stenosis is caused by absence of the membranous portion of the trachea resulting in complete cartilage tracheal rings. This was referred to as the "ring/sling complex" by the radiologist, Dr. Walter E. Berdon [6].

Clinical Presentation and Diagnosis

As mentioned above when discussing the two initial patients operated on by Potts [1] and Gross [2], the most common symptoms for vascular ring patients are noisy breathing, barky cough, and dysphagia. The cough is often compared to the bark of a seal and the phrase, "seal bark cough" is a distinctive sound that these patients make. Another typical presentation is the child who has multiple admissions for upper respiratory distress thought to be secondary to asthma or some other diagnosis. We are aware of patients who have had more than 100 hospitalizations for respiratory distress prior to successful diagnosis of a double aortic arch leading to operative repair. Because of the relative infrequency of this diagnosis compared to other common respiratory problems, one requires a high index of suspicion for the diagnosis of a vascular ring.

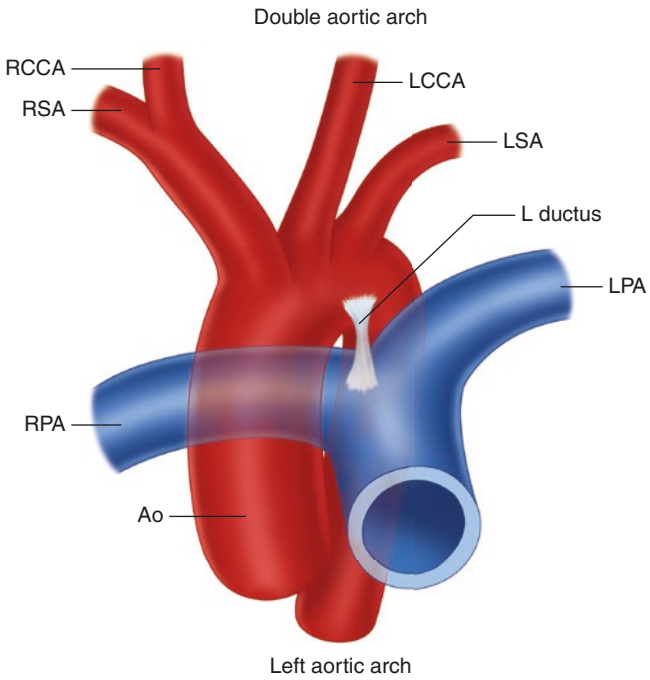

Fig. 7.3 Left ("normal") aortic arch. (Ao, aorta; L, left; LCCA, left common carotid artery; LPA, left pulmonary artery; LSA, left subclavian artery; R, right; RCCA, right common carotid artery; RPA, right pulmonary artery; RSA, right subclavian artery). (Reproduced with permission from Backer and Mavroudis [19])

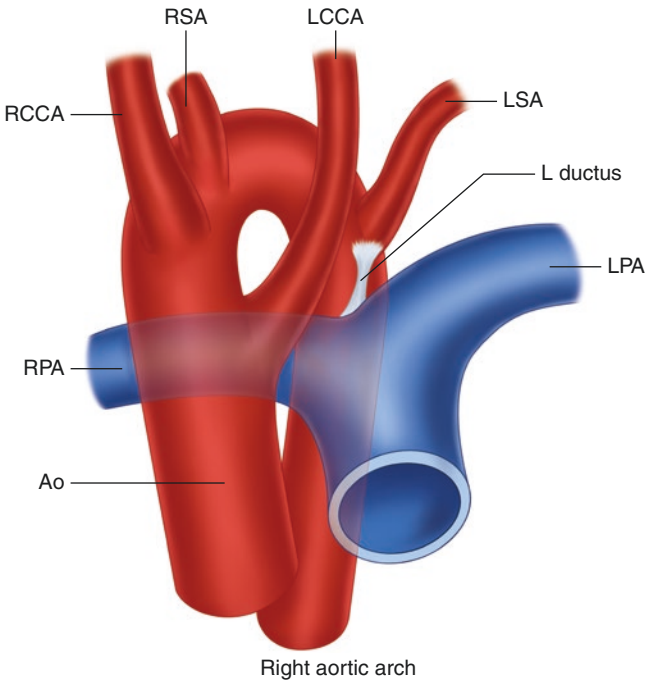

Fig. 7.4 Right aortic arch and retroesophageal (aberrant) left subclavian artery and a left ligamentum. (Ao, aorta; L, left; LCCA, left common carotid artery; LPA, left pulmonary artery; LSA, left subclavian artery; RCCA, right common carotid artery; RPA, right pulmonary artery; RSA, right subclavian artery). (Reproduced with permission from Backer and Mavroudis [19])

Another symptom is an apparent life-threatening event (ALTE) or apnea with feeding. Dysphagia does not usually become a problem until the child begins taking solid foods. Even children with relatively tight vascular rings do not usually have dysphagia or trouble with swallowing when they are taking breast milk or formula. It is when the child begins to take solid food that they sometimes, as a learned habit, will cut up their food very carefully and wash it down with plenty of liquids to alleviate the compression on the vascular ring on the esophagus.

Most patients with a true vascular ring will develop symptoms within the first year of life. Most commonly patients with double aortic arch present earlier than patients with a right aortic arch because the vascular compression is more intense when all of the structures surrounding the trachea and esophagus are truly vascular in nature.

Once the diagnosis of vascular ring is suspected the first imaging study typically obtained is a chest radiograph. It is the relationship of the transverse aortic arch to the trachea that determines whether the patient has a left or right aortic arch. The radiograph can often be helpful in demonstrating the location of the aortic arch and hence the suspicion of a vascular ring. When patients have a double aortic arch it is often difficult to tell whether the arch is right-sided or left-sided. In patients with a right aortic arch, often the trachea will be indented on the right side by the right aortic arch. What is usually absent in patients with a vascular ring is the typical knob of the left aortic arch in the left upper mediastinum. A rare presentation of patients with a pulmonary artery sling is hyperinflation of the right lung from compression of the right main bronchus.

Historically barium esophagram was the study used to diagnose vascular rings. The compressions on the column of barium by the vascular structures could be used to diagnose the vascular ring (Fig. 7.6). This however does not give the type of precise imaging in the current era which is required for planning an operative intervention. At our institution we prefer the CT scan as the procedure of choice (Fig. 7.7). The new-generation dual-source CT scans can complete an evaluation in less than 1 second without the need for intubation and with very low radiation dose. Other centers prefer MRI, but this study takes a longer period of time to obtain and often requires the child to be sedated

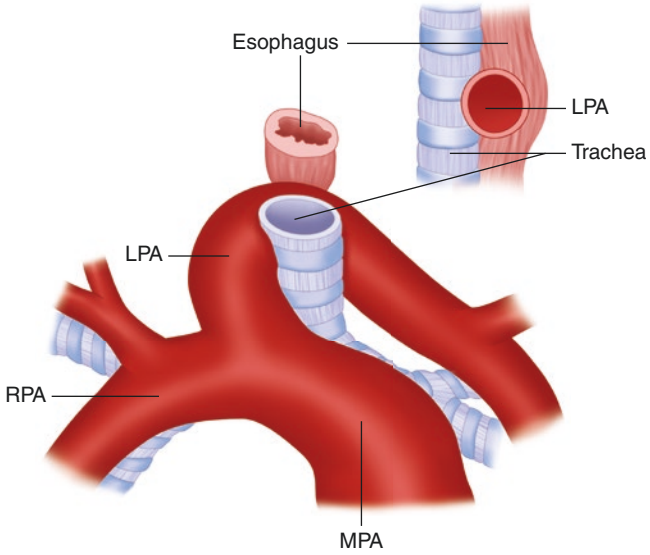

Fig. 7.5 Pulmonary artery sling. The LPA originates from the RPA and courses between the trachea and esophagus to reach the left lung. (LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery). Inset: left lateral view of anterior compression of the esophagus and posterior compression of the trachea. (Reproduced with permission from Backer and Mavroudis [19])

or intubated. In addition, the current MRI does not yield as clear a picture of the tracheal anatomy as does the CT scan [7].

The other examination that patients with a vascular ring should have is bronchoscopy. Some children who present with noisy breathing or chronic cough will undergo bronchoscopy as their first examination. Bronchoscopy examination reveals extrinsic pulsatile compression from the vascular ring structures. If bronchoscopy is suspicious for a vascular ring we then recommend proceeding with advanced medical imaging. Similarly, in the current era, many patients are diagnosed with a right aortic arch with either a fetal or postnatal echocardiogram. Echocardiography is helpful to determine whether the aortic arch is left- or right-sided but does not give precise anatomy of the ring itself. Again, for those patients, we would recommend advanced medical imaging if the diagnosis is suspected by echocardiogram. Approximately 12% of all patients with a vascular ring will have some associated cardiac pathology [7]. Hence, we obtain an echocardiogram in all of our patients with a vascular ring.

In summary, the diagnosis of patients with vascular rings should be with some form of advanced medical imaging, either CT scan or MRI. In addition we recommend bronchoscopy, either as a separate diagnostic study or immediately prior to operative intervention. Finally, we recommend an echocardiogram in all of these patients prior to the operative intervention.

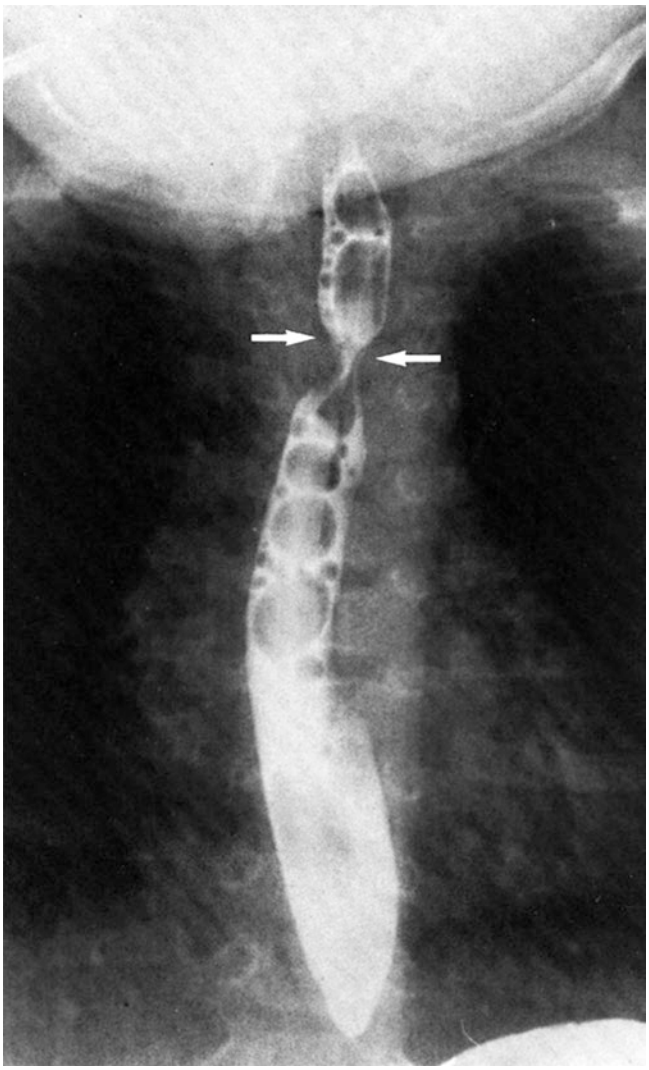

Fig. 7.6 Anteroposterior esophagram of a 4-month-old boy who presented with stridor and was found to have a double aortic arch. The arrows point to the indentation in the esophagus caused by the vascular compression. (Reproduced with permission from Backer et al. [20])

Indications for Surgery

Patients who have airway or swallowing symptoms and have a vascular ring should have surgical repair. In particular patients with double aortic arch tend to have the most severe symptoms, and early repair should be contemplated. Very rarely in patients with a right aortic arch and an aberrant left subclavian with left ligamentum the ring will be loose enough that they do not have any symptoms. We have a handful of patients in our series who we are simply observing and it does not appear that these patients will require an operative intervention. Nearly all patients with a pulmonary artery sling develop symptoms and require operative repair. There

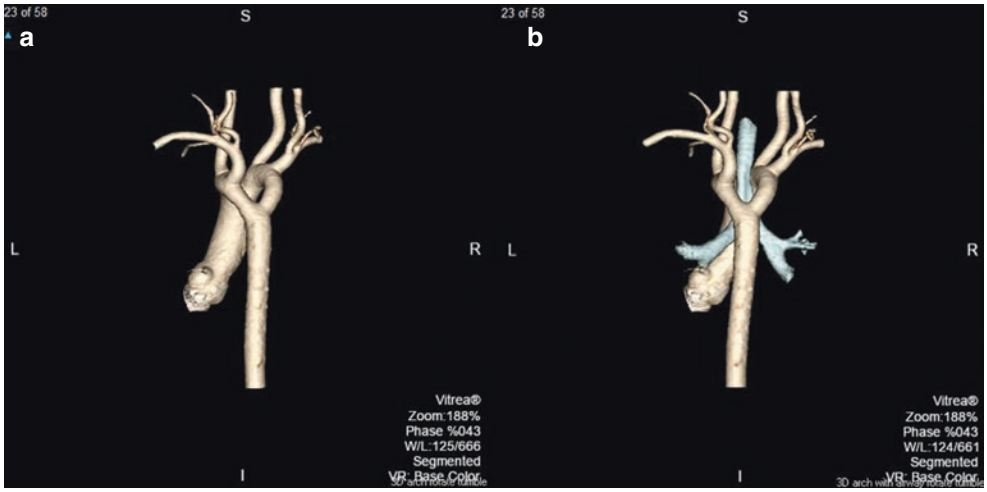

Fig. 7.7 (**a**) Three-dimensional (3D) rendering of CT scan (posterior view) of a 3-month-old infant with a double aortic arch. This patient has the rare occurrence of nearly identical right and left arches. (**b**) Posterior view shows the trachea (blue) being compressed by the vascular ring

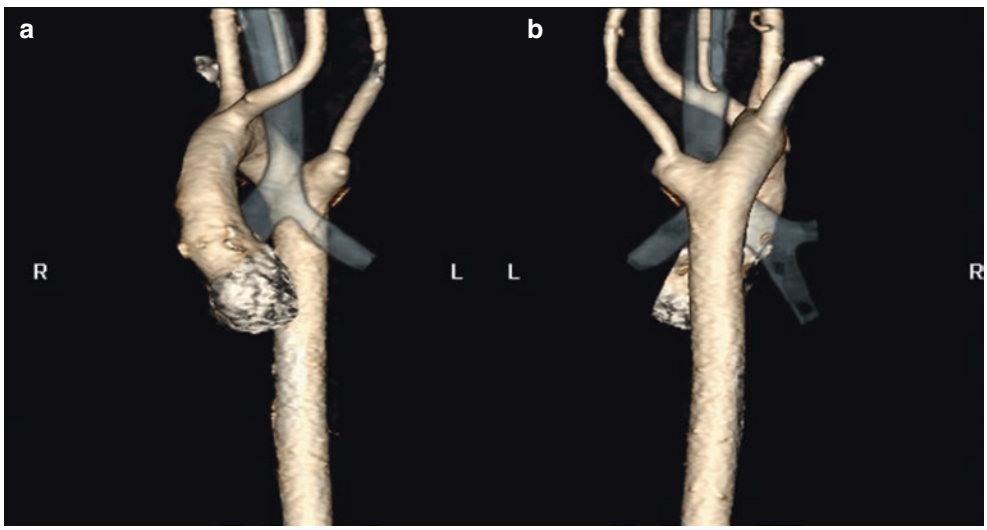

Fig. 7.8 (**a**) Three-dimensional (3D) rendering of CT scan (anterior view). Right aortic arch, retroesophageal left subclavian, large Kommerell diverticulum, ligamentum. Trachea ghosted in blue. (**b**) Same patient (posterior view). This view highlights the size of the Kommerell diverticulum

are very few case reports of adult patients with either double aortic arch or pulmonary artery sling as they nearly all develop symptoms leading to a diagnosis that will require operative intervention.

There are other rare reported complications from repaired vascular rings. We are aware of patients who have had erosion of indwelling nasogastric tubes into the esophagus. We are also aware of patients who have had catastrophic bleeding from erosion of nasogastric tubes or tracheostomy tubes into vascular ring structures. Recently there has been evidence that patients with Kommerell diverticulum are at risk of late aortic aneurysm and aortic dissection [8, 9]. Finally, patients who have severe compression of their esophagus for many years may develop dysphagia that does not resolve after release of the vascular ring. The esophageal motility appears to decrease over time if the esophagus is forced to attempt to propel food past an obstruction over a prolonged number of years.

Surgical Intervention

Right Aortic Arch

In patients with a right aortic arch, retroesophageal left subclavian artery, and a left ligamentum, the primary question to be addressed prior to surgical intervention is whether the patient has an associated Kommerell diverticulum. This will be revealed by the advanced medical imaging (Fig. 7.8). If the base of the subclavian artery is more than 1.5 times the size of the subclavian artery, we recommend resection of the diverticulum and transfer of the left subclavian artery to the left carotid artery [10, 11]. In borderline cases this can be evaluated in a stepwise fashion in the operating room.

The operation is performed with the patient in the right lateral decubitus position through a muscle-sparing left thoracotomy. We have not used double lumen endotracheal tubes in our patient population. The chest is entered through

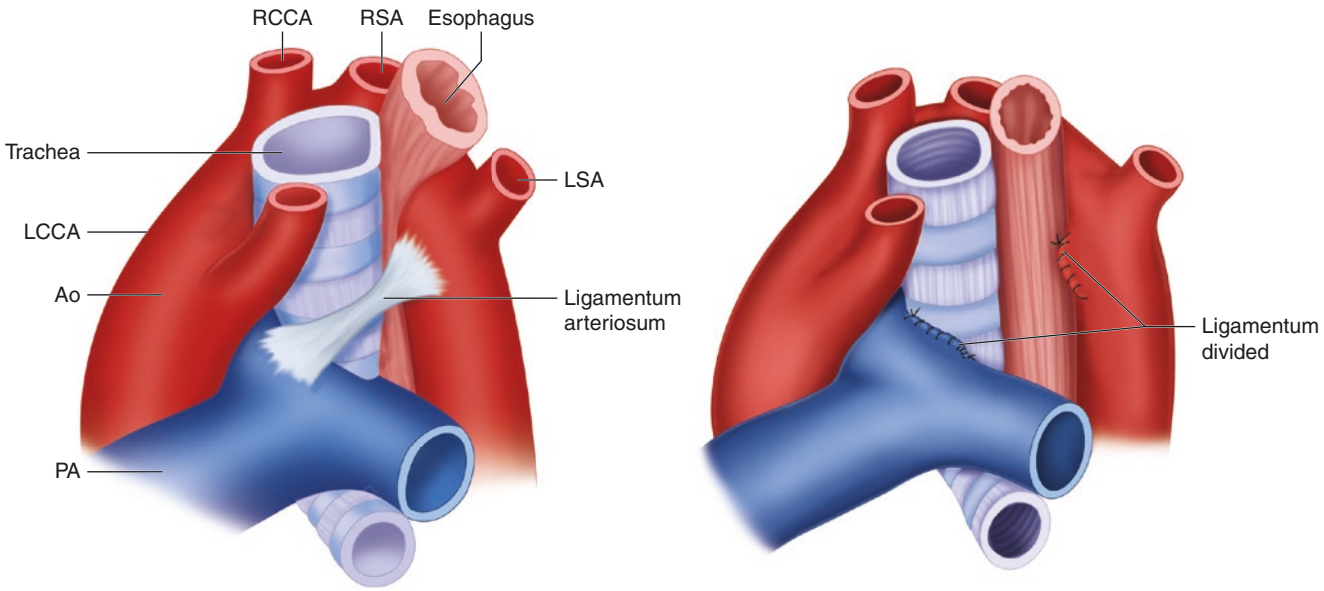

Fig. 7.9 Right aortic arch – division and oversewing of ligamentum arteriosum. (Ao, aorta; LCCA, left common carotid artery; LSA, left subclavian artery; MPA, main pulmonary artery; PA, pulmonary artery; RCCA, right common carotid artery; RSA, right subclavian artery). (Reproduced with permission from Backer and Mavroudis [19])

the fourth intercostal space. The lung is retracted anteriorly. Careful examination of the mediastinal structures is performed. In these patients the esophagus is usually immediately apparent at the typical location where one would normally see the descending thoracic aorta. Most commonly the aorta descends on the right side of the chest and is not visible from a left thoracotomy. What should be visible is the left subclavian artery and the bulge of the Kommerell diverticulum if present. The dissection begins by opening the pleura over the left subclavian artery. The left subclavian artery can be encircled with a vessel loop. Further dissection typically identifies the supreme intercostal vein and lymphatic structures crossing the area of the ligamentum and the Kommerell diverticulum. I often divide the tissues in this area between 4-0 silk ligatures to prevent any lymphatic leaks. Further dissection identifies the ligamentum arteriosum. Care must be taken to identify the recurrent laryngeal nerve and prevent any cautery injury to this nerve. This nerve originates from the vagus nerve anteriorly and then turns posteriorly beneath the ligamentum to "recur" superiorly in the tracheoesophageal groove more posteriorly. The area of the ligamentum is dissected. The ligamentum can be divided between silk ligatures or it can be divided between vascular clamps with oversewing of the stumps (Fig. 7.9). Upon division of the ligamentum one assesses how far apart the stumps of the ligamentum separate. In patients with a large Kommerell diverticulum, often the division of the ligamentum leads to very little separation of the stumps. In these cases it becomes immediately clear that the Kommerell diverticulum is an important component of the cause of the patient's symptoms. In patients with a "small" Kommerell diverticulum, should the ligamentum division lead to a separation of the stumps greater than 1–2 cm in length, it is possible that the diverticulum of Kommerell is not an important component of the vascular compression.

To proceed with Kommerell diverticulum resection, we first administer 100 units/kg of heparin intravenously. This prevents intravascular thrombosis during the procedure. In order to ensure proper orientation of the left subclavian artery at the time of reimplantation, a small marking suture is placed on the most anterior aspect of the artery prior to placing the vascular clamps. The base of the Kommerell diverticulum is occluded with a small Castañeda clamp (Fig. 7.10). This clamp can partially be placed on the descending thoracic aorta. However, it should not completely occlude the descending thoracic aorta. We prevent this from happening by monitoring the lower extremity arterial pressure with a blood pressure cuff. The left subclavian artery vascular control is obtained with a small plastic vascular clip. The left subclavian artery is then divided just distal to its origin from the Kommerell diverticulum. The Kommerell diverticulum is then resected. The resection of the diverticulum is done using staged division and oversewing techniques where the sutures for the closure of the aortic stump are partially placed prior to completely removing the diverticulum. This prevents the stump of the diverticulum

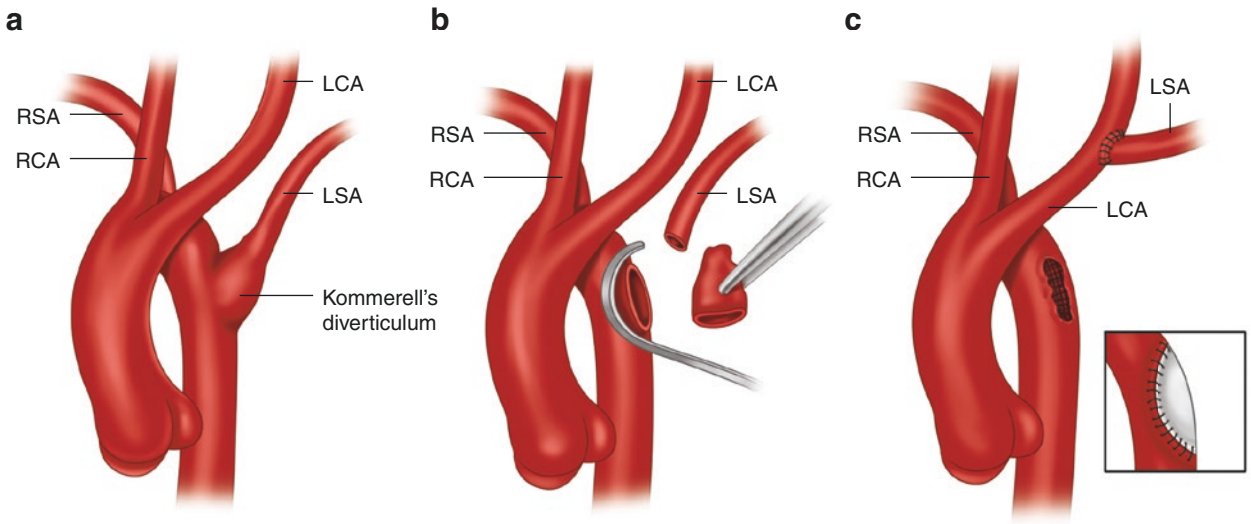

Fig. 7.10 (**a**) The typical anatomy of a patient with a right aortic arch, retroesophageal left subclavian artery, and large Kommerell diverticulum. The Kommerell diverticulum is an embryologic remnant of the left fourth aortic arch. (**b**) A schematic illustration of the resection of a Kommerell diverticulum through a left thoracotomy. There is a vascular clamp partially occluding the descending thoracic aorta at the origin of the Kommerell diverticulum. The Kommerell diverticulum has been completely resected. The clamp on the distal left subclavian artery is not illustrated. (**c**) The completed repair. The orifice where the Kommerell diverticulum was resected is usually closed primarily, or, as shown in the inset, the orifice can be patched with polytetrafluoroethylene if necessary. The left subclavian artery has been implanted into the side of the left common carotid artery with fine running polypropylene suture. (LCA, left carotid artery; LSA, left subclavian artery; RCA, right carotid artery; RSA, right subclavian artery). (Reproduced with permission from Backer et al. [10])

from retracting through the jaws of the clamp while the stumps are being oversewn. The first suture line here is a running mattress suture. The second suture line is an over-and-over baseball type suture. Prior to releasing the clamp, I place several additional interrupted mattress sutures in addition to reinforce the suture line. The sutures are not cut until the clamp has been released and the absence of substantial bleeding has been demonstrated. Should there be bleeding requiring additional sutures traction on the prolene mattress sutures can elevate the stump into the field. Careful attention to this detail is important because the stump of the Kommerell diverticulum tends to retract back into the posterior mediastinum quite rapidly and bleeding from this area can be difficult to control without the maneuvers identified above.

The left carotid artery is identified in the mediastinum by dissecting it in a plane that is posterior to the vagus nerve and anterior to the recurrent laryngeal nerve in the tracheoesophageal groove. Carefully staying in the midzone between these two nerves will allow accurate identification of the carotid artery. The carotid artery can be encircled with a right angle clamp and a vessel loop. This can then be elevated into the field. The carotid artery is then controlled with a small Castañeda clamp. The anesthesiologist should pay careful attention to the blood pressure during this maneuver. One wishes to maintain the cerebral perfusion pressure through the other carotid artery at a higher than normal level to ensure adequate cerebral blood flow through the Circle of Willis during this portion of the procedure. An opening is then made in the left carotid artery with a #15 blade. This is extended with a Potts scissors to exactly the size of the transected left subclavian artery. The subclavian artery is oriented using the previously placed adventitial marking suture. In the smaller babies (0–1 year of age), I use a 7.0 prolene suture for this anastomosis. In infants over 1 year of age we use 6.0 prolene suture. The anastomosis is performed with running suture. The clamps are temporarily released to flush air from first the subclavian artery and then the carotid artery. The suture line is then completed and the knot tied. The clamp and clip are released. Hemostasis is usually not an issue, but a small amount of Gelfoam-soaked thrombin may be used at this point. The left subclavian pulse can be monitored with pulse oximetry to ensure that the anastomosis is patent. In all patients with vascular rings, the mediastinal pleura is left open. We use one Blake drain to drain the pleural space and monitor for postoperative chylothorax and/or postoperative bleeding. The patients are extubated in the operating room and then transported to the cardiac care unit for monitoring. A rectal dose of aspirin (10 mg/kg) is administered and the patients are maintained on aspirin therapy for 6 months. The Blake drain is not removed until the patient has eaten food containing fat to ensure that there is not a chylothorax. The drain usually comes out on either postoperative day 2 or postoperative day 3.

I should mention that occasionally the diverticulum itself becomes somewhat friable in nature because of its aneurysmal dilatation. In some instances the tissue of the aneurysm does not appear adequate to hold sutures. In this case the resultant opening left by resecting the diverticulum can be patched with a small round polytetrafluoroethylene patch as shown in Fig. 7.10c. We have only had to do this in a very small number of patients.

Originally in our series, we obtained postoperative advanced medical imaging to demonstrate the patency of the anastomosis. However, we have not been performing this on a routine basis with all of the patients in the early portion of the series having a widely patent anastomosis without any aneurysm formation. Thus far in our series we have not had to reoperate on any of the patients undergoing Kommerell diverticulum resection and transfer of the left subclavian artery. To our knowledge all of the anastomoses are patent based on the pallable left radial pulse.

Double Aortic Arch

The preoperative evaluation is critically dependent on the advanced medical imaging. In patients with a double aortic arch, 80% have a right dominant arch. In these cases the surgical approach is through a left thoracotomy. In 10% of the cases, the left aortic arch is dominant. In these cases the surgical approach is through a right thoracotomy. Finally, there are a group of patients who have balanced aortic arches where the right and left arches are very similar in size (Fig. 7.11). In this case it is important to determine precisely which arch is larger, and the approach is then through the opposite chest. When the arches are equal in size, I divide the *right* arch.

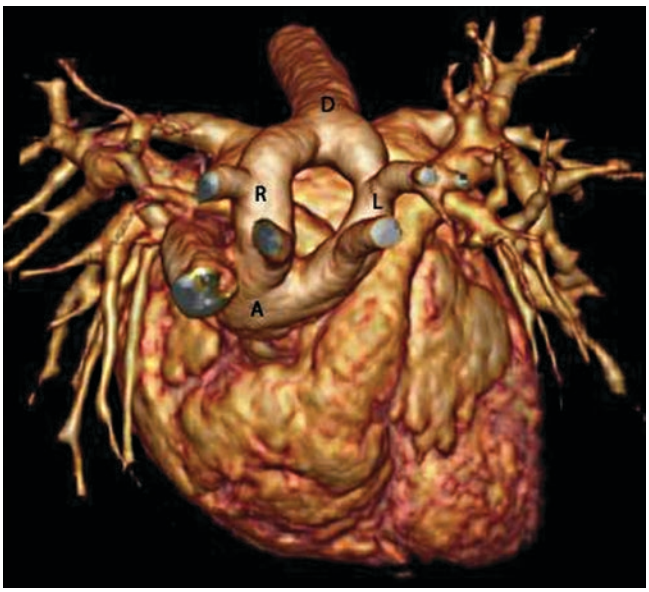

Fig. 7.11 Computed tomogram (3D reconstruction) of a child with a double aortic arch with balanced right and left arches. (A, ascending aorta; D, descending aorta; L/R, left/right arch). (Reproduced with permission from Backer et al. [21])

Similar to the operative approach for the right aortic arch the operation is performed most typically with the patient in the right lateral decubitus position through a left muscle-sparing thoracotomy (Fig. 7.12). The chest is entered through the fourth intercostal space. Again, careful external evaluation of the mediastinal pleura should be performed. In most cases the left subclavian artery can be clearly identified through the mediastinal pleura. The initial opening of the pleura is often above the left subclavian artery. This is in a vertical plane parallel to the vagus nerve. The dissection of the pleura should remain anterior closer to the vagus nerve rather than deviating posteriorly. A posterior deviation of this incision can lead to the thoracic duct or its tributaries which can be potentially injured. This would lead to a chylothorax. The first structure to be encircled with a vessel loop is usually again the left subclavian artery. At the base of the left subclavian artery, the ligamentum arteriosum and also the left aortic arch are usually found. In patients with a double aortic arch the left anterior arch serves in most instances as the blood supply to the left carotid and left subclavian artery. The area of the left aortic arch just distal to the left subclavian artery is often atretic. This is the most common site for division of the left aortic arch. The ligamentum arteriosum is mobilized. The recurrent laryngeal nerve is identified encircling the ligamentum arteriosum. The ligamentum is mobilized, doubly ligated with silk suture, and divided. Attention is then directed to dividing the left aortic arch. Even when the arch is atretic we recommend dividing it between vascular clamps. The vascular clamps should be placed at a site that preserves the antegrade blood flow to the left carotid and left subclavian arteries. Although less important now with advanced medical imaging showing the exact anatomy of the arch system, a test clamp should be performed prior to dividing the arch. The site for arch division is selected and then the clamp is temporarily placed at this site. The anesthesiologist can then check for a left radial pulse and a left carotid pulse. Pulse checking can be facilitated by the use of pulse oximetry waveforms which should be maintained during the placement of the clamps. Sufficient length should be obtained along the arch itself to place the vascular clamps. We have used a combination typically of a Castañeda clamp on the distal arch and a Potts ductus clamp on the proximal arch. The ductus clamps notably have small teeth within them that prevent the clamp from slipping. The division of the arch should be done, again using staged oversewing and division techniques. An initial incision is made in the arch after the clamps have been placed. Prolene suture used to oversew the stump is then placed; one on each side of each stump. Prior to completely dividing the arch, there should be a suture line on each stump. Should a clamp slip traction

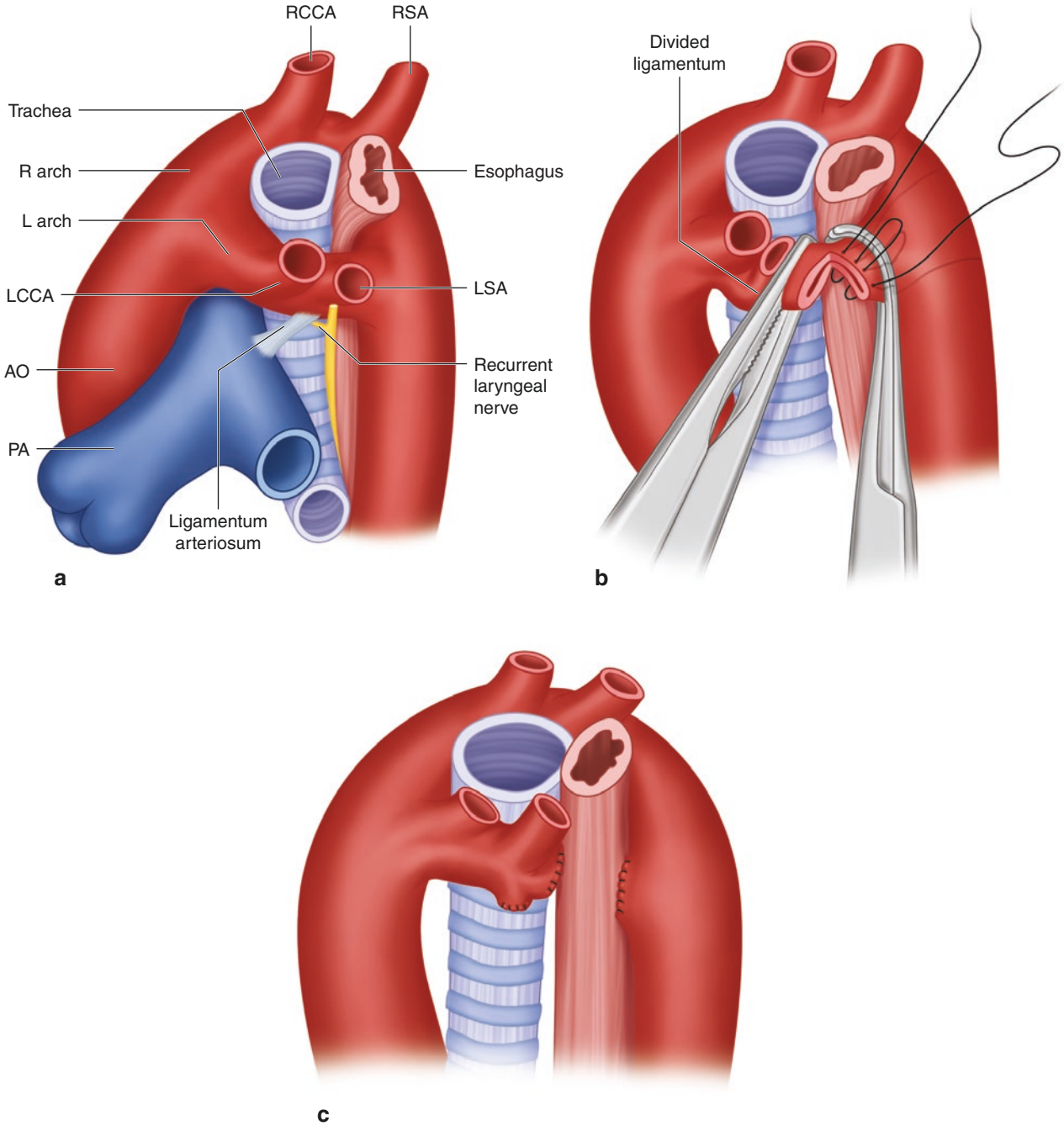

Fig. 7.12 Double aortic arch division. (**a**) Double aortic arch, right arch dominant. The ligamentum arteriosum and recurrent laryngeal nerve are also shown. (**b**) Dividing left aortic arch with a Potts ductus clamp on the anterior stump of the arch and a Castañeda clamp on the posterior stump. (**c**) Arch and ligamentum divided. (Ao, aorta; L, left; LCCA, left carotid artery; LSA, left subclavian artery; PA, pulmonary artery; R, right; RCCA, right carotid artery; RSA, right subclavian artery). (Reproduced with permission from Backer and Mavroudis [19])

on the suture would allow one to obtain control of the stump without the stump retracting into the mediastinum. The first suture line is a mattress suture. The second suture line is an over and over baseball type suture. Should the arch be widely patent with a long suture line several interrupted mattress sutures can be placed prior to clamp release. Similar to the resection of a Kommerell diverticulum these sutures are placed so the stump can be controlled should there be bleeding when the clamps are released. If there is significant bleeding the suture can be used to elevate the stump into the field and guide replacement of a vascular clamp to control the bleeding site. In most cases however with careful vascu-

lar technique, there is minimal bleeding which can be easily controlled with topical Gelfoam-thrombin. Once the clamps have been released the stumps of the divided arch usually separate widely. Again, it is also important to divide the ligamentum because leaving the ligamentum in place would then convert the double arch to a right aortic arch with a ligamentum arteriosum. The esophagus should be carefully evaluated for any adhesive bands. These adhesive bands should be lysed with electrocautery. One does need to take care here because the esophagus has no serosa. Inadvertent entry into the esophagus should be carefully avoided. At the conclusion of the procedure; again, the mediastinal pleura is left open. This decreases the chance of scar tissue leading to residual vascular ring residual compression similar to the initial vascular ring symptoms. I have had occasional experience to reoperate on a patient where the pleura was closed and in some cases this formed relatively intense scar tissue which can lead to recurrent symptoms.

The chest is then drained with a small Blake drain. This is left in place again for 2–3 days, monitoring for any bleeding or development of a chylothorax. Should a chylothorax develop the patient is treated with a low fat diet. If they have a high volume chylous output we have reoperated relatively soon. Usually one can identify the source of the chylous effusion and oversew this with fine prolene suture at the time of the reoperation. This is probably a better alternative to prolonged treatment with a fat-free diet and/or ligation of the thoracic duct through a right thoracotomy. After double arch repair, the patients are not maintained on aspirin. There has been no specific follow-up with either bronchoscopy or advanced medical imaging unless there is some unusual intraoperative concern or persistence of recurrence of symptoms.

Pulmonary Artery Sling

As mentioned in the Introduction the late Dr. Willis Potts was the first to diagnose and successfully repair a pulmonary artery sling [3]. Dr. Potts operated on a 5-month-old infant who had intermittent cyanotic spells and severe respiratory distress. Potts operated on the patient without a preoperative diagnosis. He decided to approach the patient through a right thoracotomy based on the barium esophagram. Interestingly, he was able to make the diagnosis intraoperatively after dissecting all of the vascular structures. Potts used Potts ductus clamps to occlude and then divide the left pulmonary artery. He then moved the left pulmonary artery anterior to the trachea and reimplanted it into the main pulmonary artery. The child survived the operation but was found on long-term follow-up to have an occluded left pulmonary artery [12].

The pathophysiology of pulmonary artery sling results from the left pulmonary artery originating from the right pulmonary artery. It then has to course around the distal trachea and right main stem bronchus en route to the left lung (Fig. 7.5). The resultant sling-like effect particularly on the right main stem bronchus can cause right bronchial compression leading to bronchial stenosis and bronchomalacia. In some patients this causes a ball valve effect and leads to hyperinflation of the right lung. This is the only vascular ring that causes isolated, anterior compression of the esophagus. Three-quarters of the patients with pulmonary artery sling will in addition have tracheal stenosis caused by complete cartilaginous tracheal rings [6]. The combination of tracheal stenosis and a pulmonary artery sling can lead to significant respiratory complications. Some of these patients are admitted with respiratory distress that has required intubation and ventilation.

For the critically ill infant in the intensive care unit without a diagnosis, echocardiography at the bedside can be used to initiate the diagnosis of pulmonary artery sling [13]. Some of these patients will have substantial respiratory distress and undergo bronchoscopy as a first evaluation. This will demonstrate complete tracheal rings. All children who are diagnosed with complete tracheal rings should also be assessed for the possibility of a pulmonary artery sling. Once the diagnosis is obtained and the patient is stable we have recommended advanced medical imaging either with CT or MRI to identify the precise location of the pulmonary artery sling and the relationship of the pulmonary artery to the surrounding structures [14]. Most infants with pulmonary artery sling will have symptoms and we recommend operation at the time of diagnosis. We are aware of patients who have had ALTEs from apnea secondary to pulmonary artery sling. We recommend an operative approach through a median sternotomy with the use of cardiopulmonary bypass. The initial series of patients with pulmonary artery sling were repaired through a left thoracotomy but this resulted in a very high incidence of left pulmonary artery stenosis. The anastomosis through the left chest is difficult to perform and in particular, these patients often have respiratory issues during the operation. This could lead to a hurried anastomosis which would not necessarily lead to a widely patent anastomosis. By performing the operation on cardiopulmonary bypass the anastomosis can be performed in an unhurried fashion on a decompressed main pulmonary artery. In addition, should the patient have associated complete tracheal rings the trachea can be repaired at the same time with the use of cardiopulmonary bypass. It is beyond the scope of this chapter to discuss the tracheal repair; however, I will mention that in most instances at the current time we would perform a slide tracheoplasty [14, 15]. A slide tracheoplasty is typically performed after the vascular anastomosis of the pulmonary artery sling is performed.

The operation is performed through a standard median sternotomy incision. For patients who have tracheal stenosis

that is long distance in nature, we may also perform a low-collar incision to access the upper trachea. The patient is placed on cardiopulmonary bypass with an aortic cannula and a single atrial cannula (Fig. 7.13). Cardiopulmonary bypass is initiated cooling to 34 °C. The heart is kept beating in normal sinus rhythm throughout the procedure. Once the patient is safely on cardiopulmonary bypass the left pulmonary artery is dissected and encircled with a vessel loop as it originates from the superior aspect of the right pulmonary artery. Traction on the left pulmonary artery facilitates its dissection on the right side away from the posterior aspect of the trachea. The left pulmonary artery will be coursing anterior to the esophagus and posterior to the trachea. Care must be taken during this portion of the dissection to avoid entering either the trachea or the esophagus. One of the tricky parts of the operation is to identify the left pulmonary artery on the left side of the tracheobronchial tree in the posterior mediastinum. This is facilitated by first ligating and dividing the ligamentum arteriosum. This is in the usual location. Of course the sensation is somewhat odd in that there is no left pulmonary artery adjacent to the ligamentum. That being said, the left pulmonary artery will course anteriorly to the descending thoracic aorta, which is a structure to which the ligamentum is attached. Dissecting in the area of the ligamentum stump on the descending thoracic aorta typically will identify the left pulmonary artery. This can be facilitated by traction placed on the vessel loop on the left pulmonary artery from the right side. Once the left pulmonary artery has been identified on the left side of the mediastinum it can be dissected back toward the trachea. Once the left pulmonary artery is fully mobilized the origin of the left pulmonary artery from the right pulmonary artery can be transected. Bleeding from the stump of the transected left pulmonary artery can be controlled with a plastic vascular clip. The resultant stump on the superior aspect of the right pulmonary artery is oversewn with running fine prolene suture (Fig. 7.14). This stump should be left long enough so there is no chance for stenosis of the right pulmonary artery caused by this suture line. In nearly all cases the left pulmonary artery is excessively long so leaving a small stump on the superior aspect of the right pulmonary artery is not an issue. The left pulmonary artery is then delivered from underneath the trachea, up into the anterior mediastinum on the left side. The ideal site for the reimplantation of the left pulmonary artery can be obtained by actually slightly filling the heart and allowing the main pulmonary artery to fill with blood. A site for the reimplantation is usually just adjacent to the ligated stump of the ligamentum. Again, a small Castañeda clamp can be placed in this site or the main pulmonary artery can be occluded with an angled vascular clamp (Fig. 7.15). I excise a small round patch of left pulmonary artery in order to provide a widely patent anastomosis. The left pulmonary artery should not be twisted. The left pulmonary artery is spatulated

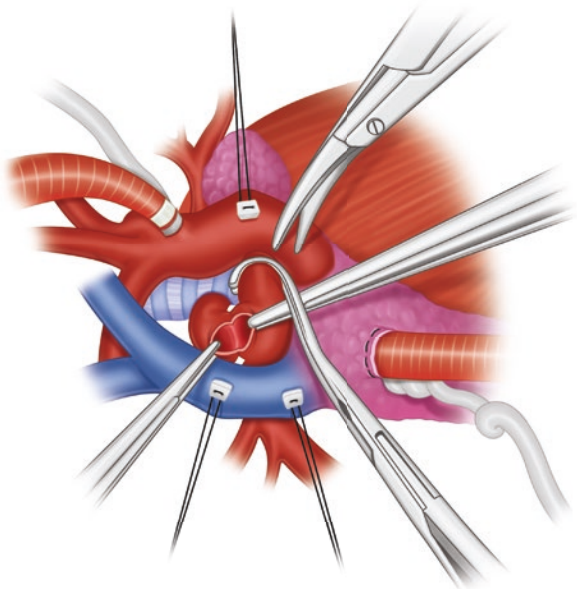

Fig. 7.13 A surgeon's view of the approach to the patient with a pulmonary artery sling. The patient has been opened with a median sternotomy and is on cardiopulmonary bypass with aortic and uniatrial venous cannulation. The aorta is being retracted to the left with a pledget supported suture. The right pulmonary artery is controlled with a vascular clamp. The left pulmonary artery has been opened at its origin from the superior aspect of the right pulmonary artery. (Reproduced with permission from Backer et al. [14])

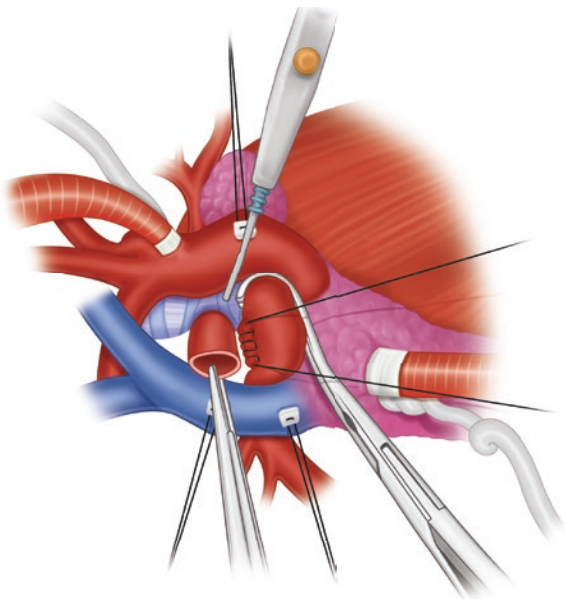

Fig. 7.14 The right pulmonary artery opening has been closed. The left pulmonary artery is being dissected under the aorta in a plane posterior to the trachea and anterior to the esophagus. (Reproduced with permission from Backer et al. [14])

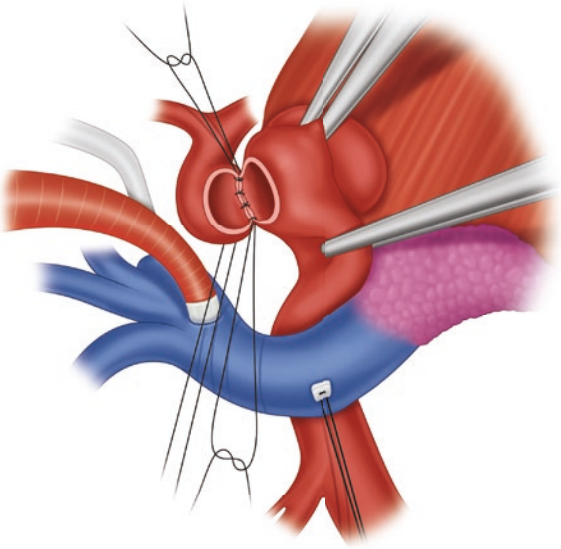

Fig. 7.15 The left pulmonary artery has now been brought up into the mediastinum on the left side of the trachea. A site for the anastomosis is determined by approximating the best natural "lie" when the main pulmonary artery was full. The anastomosis is shown in progress. (Reproduced with permission from Backer et al. [14])

and an anastomosis is then created with running absorbable PDS suture. Alternatively interrupted suture technique can be used to prevent stenosis. During this portion of the procedure, the patient can be warmed and then is ready to be weaned from cardiopulmonary bypass shortly after the completion of the anastomosis. The chest is typically closed in the standard fashion with a single mediastinal Blake drain. Again, if the patient has associated tracheal stenosis that tracheal repair is performed after the repair of pulmonary artery sling.

Aberrant Right Subclavian Artery

Aberrant origin of the left subclavian artery from the descending thoracic aorta in a patient with a left aortic arch is one of the most common vascular anomalies of the aortic arch system. By some accounts it may occur in as many as 0.5% of all humans [16]. This is *not* a vascular ring, but can be a vascular compression syndrome. The aberrant right subclavian artery usually causes no compression whatsoever on the trachea. However, it may cause compression of the esophagus. In particular, if the origin of the right subclavian artery is a Kommerell diverticulum, the Kommerell diverticulum combined with the aberrant subclavian artery may compress the esophagus. In fact, the original description of a Kommerell diverticulum by the German radiologist was in a patient with a left aortic arch and an aberrant right subclavian artery [17].

In patients who have dysphagia sometimes this aberrant subclavian artery may be considered the source of the dysphagia. However, this is rarely the case. The phrase, "dysphagia lysoria" refers to the fact that although aberrant right subclavian artery does appear that it could cause esophageal compression and dysphagia it is usually not the source of the patient's dysphagia [18].

In our series of nearly 400 patients with vascular rings, we have operated on only 2 patients with a left aortic arch and an aberrant right subclavian artery. In both cases the patients had severe dysphagia. One was associated with a large Kommerell diverticulum. In both cases the operation was performed through a right thoracotomy. The chest was entered through the 4th intercostal space. The origin of the subclavian artery from the descending thoracic aorta was dissected. The child was given 100 units/kg of heparin. The base of the subclavian artery was occluded with a Castañeda clamp. The distal subclavian artery was controlled with a fine vascular clip. The right subclavian artery was then divided and the stump oversewn using the staged division of oversewing techniques described above. The artery was marked and transferred to the right carotid artery in both of these instances.

This should be a very rare procedure. It is only after excluding all other cases of dysphagia and in patients with anatomic features showing severe compression of the esophagus that we would consider surgical repair.

Conclusion

Patients with vascular rings present with symptoms of either airway or esophageal compression. The most common presenting symptoms are noisy breathing, chronic cough, recurrent upper respiratory tract infections, and dysphagia. We currently recommend advanced medical imaging to precisely define the anatomy of the vascular ring prior to surgical intervention. In addition we recommend echocardiography and bronchoscopy. The bronchoscopy is typically performed at the time of the anesthetic for the vascular ring repair.

In our series of patients with vascular rings the most common were double aortic arch and right aortic arch with left ligamentum. Pulmonary artery sling is relatively rare compared to these other two. The most common double aortic arch is a right dominant arch. These patients are approached through a left thoracotomy with division of the smaller left arch. Patients with a right aortic arch and left ligamentum are also operated on through a left thoracotomy. These patients are treated by division of the ligamentum arteriosum. In patients with a Kommerell diverticulum serving as a source of blood to the left subclavian artery, the Kommerell diverticulum may require resection and transfer of the subclavian artery to the left carotid artery. Patients with a pulmonary

artery sling are repaired through a median sternotomy with the use of cardiopulmonary bypass. The left pulmonary artery is reimplanted into the main pulmonary artery anterior to the trachea. Very rarely patients with a left aortic arch and aberrant right subclavian have dysphagia and benefit from transfer of the right subclavian artery to the right carotid artery.

The care of patients with vascular rings requires cooperation between multiple services. This includes cardiothoracic surgery, otolaryngology, anesthesia, and critical care. In our series we have had no operative mortality from an isolated vascular ring or pulmonary artery sling since the 1950s. It is gratifying to operate on these patients in that the vast majority of them achieve freedom from their symptoms within several months of the operation.

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Coarctation of the Aorta

8

Rachel D. Torok, Michael J. Campbell, Gregory A. Fleming, and Kevin D. Hill

Introduction

Coarctation of the aorta was first described by Morgagni in 1760, and in its simplest form refers to isolated and discrete stenosis of the proximal thoracic aorta. However, coarctation may also be associated with a longer segment of narrowing, with hypoplasia of the transverse aortic arch, or with stenosis of the lower thoracic or abdominal aorta [1–3]. While more severe cases typically present in the neonatal period, aortic coarctation may be diagnosed at any age, either in isolation or in association with other cardiac defects. Crafoord was the first to perform a successful surgical repair of aortic coarctation in 1944 [4]. Since then, various surgical and transcatheter approaches have been developed, which have enabled significantly improved outcomes. In this chapter, we will focus our attention on the etiology, evaluation, and management of coarctation of the thoracic aorta and then discuss the less common presentations of abdominal aortic coarctation and pseudocoarctation.

Prevalence and Etiology

Coarctation of the aorta accounts for 5–7% of all congenital heart disease [5], with an incidence of approximately 3 cases per 10,000 births [6]. Males are more commonly affected than females [5]. Coarctation may be seen in isolation or with additional cardiac lesions, including left ventricular outflow tract lesions, such as bicuspid aortic valve, aortic valve stenosis, and hypoplastic left heart syndrome [7, 8], as well as ventricular septal defect, patent ductus arteriosus, transposition of the great arteries, and atrioventricular canal defects [9–13]. Genetic syndromes including Turner syndrome (45XO), Down syndrome (Trisomy 21), and Jacobsen syndrome (11q terminal deletion) are associated with coarctation of the aorta [14]. In neonates undergoing coarctation repair, Turner syndrome is the most common genetic syndrome (4%), followed by Down syndrome (2.1%) [15, 16]. The exact embryologic development of coarctation of the aorta is unclear, but two main hypotheses exist. One theory is that in utero, ductal tissue abnormally migrates into the aortic isthmus. With ductal constriction after birth, there is also abnormal constriction of the aortic isthmus, leading to coarctation [1]. An alternative hypothesis proposes that decreased blood flow through the ductus arteriosus leads to abnormal growth of the aortic isthmus, which acts as a vulnerable "watershed" region. This abnormal flow could be caused by proximal obstruction to flow in the left ventricular outflow tract or an abnormal angle of entry of the ductus arteriosus at the aortic isthmus [17]. This theory is supported by fetal echocardiography data, which shows a prevalence of transverse aortic arch hypoplasia in fetuses who eventually go on to have coarctation [18, 19].

Diagnosis

Clinical Presentation

Coarctation can present at any age. In the United States approximately 1 in 4 neonates requiring surgical intervention for coarctation is diagnosed prenatally [20, 21]. Neonates with "critical" or ductal dependent aortic coarctation that are not diagnosed prenatally often present with heart failure, acidosis, and shock following closure of the ductus arteriosus. Without prompt medical resuscitation and surgical intervention, death occurs rapidly in these patients [22, 23].

Patients with less severe coarctation may not be diagnosed until later in life and can present with a murmur or

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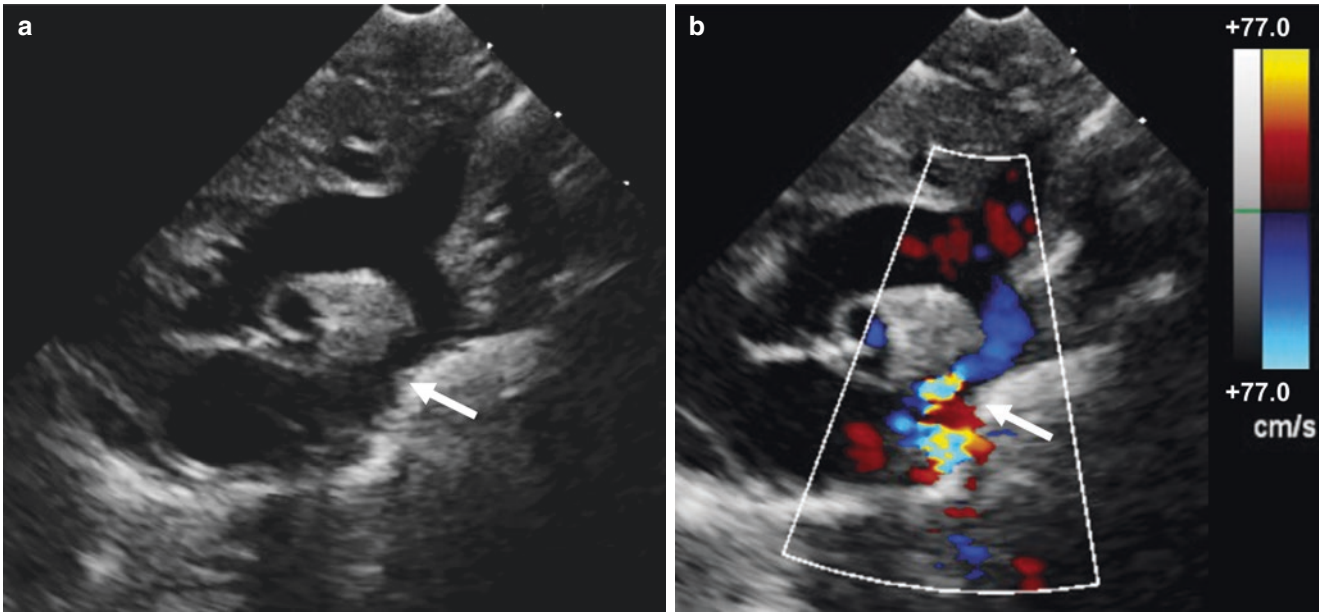

Fig. 8.1 Echocardiogram of coarctation. (**a**) Two-dimensional transthoracic echocardiogram in an 11-day-old infant with discrete coarctation (arrow). (**b**) Color Doppler of the same image demonstrating aliasing of flow at the coarctation site (arrow)

hypertension. Murmurs can be a manifestation of associated congenital heart defects (e.g. ventricular septal defects or aortic stenosis) or may be due to flow through collateral vessels that develop from the internal thoracic and subclavian arteries, thyrocervical trunks, and vertebral and anterior spinal arteries [24, 25]. In adults with previously undiagnosed coarctation, hypertension is the most common presenting symptom [26]. Frequent headaches or symptoms of claudication of the lower extremities with exertion may also be reported. In these patients, decreased lower extremity pulses or a significant systolic blood pressure gradient between the upper and lower extremities is highly suggestive of aortic coarctation [22, 26]. However, the absence of these physical exam findings does not exclude a diagnosis of coarctation, as exam findings may be diminished or even absent in the setting of significant collateral blood flow, which often develops in patients diagnosed later in life [27].

Imaging Studies

Chest x-ray may be nonspecific, especially in young patients, but in adult patients, indentation of the aorta at the site of coarctation creates a classic "3 sign," and notching of the posterior fourth to eighth ribs due to dilated intercostal arteries may also be seen [27, 28]. Electrocardiogram is often normal in infants, but in older children and adults, ventricular pressure overload typically leads to evidence of left ventricular hypertrophy [27]. Transthoracic echocardiography is the diagnostic test of choice in neonates and young children with concern for coarctation, and it enables detection of the presence and severity of aortic coarctation and any associated cardiac defects (Fig. 8.1). In adult sized patients, transthoracic echocardiography remains the initial test of choice for evaluation of coarctation [27], but echocardiographic windows may be suboptimal in this population. Computed tomography (CT) scan or magnetic resonance imaging (MRI) can provide excellent anatomic detail and are commonly used to create three-dimensional images for interventional planning (Fig. 8.2, Video 8.1). MRI has the additional benefit of defining and quantifying collateral vessel flow. Cardiac catheterization is also a valuable diagnostic tool for the diagnosis of coarctation. Although cardiac catheterization is now used less frequently as a primary diagnostic modality due to advances in other imaging modalities, such as echocardiography and MRI, catheterization remains the gold standard for quantification of pressure gradients across the region of coarctation. The addition of rotational angiography to fluoroscopic equipment will allow improved imaging of coarctation of the aorta in the catheterization lab. Moreover, transcatheter approaches are increasingly used for therapeutic intervention, particularly in older children, adolescents, and adults [27, 28].

Treatment

Fortunately, surgical and transcatheter interventions are now available for coarctation of the aorta, and the outcomes are very good. Treatment guidelines exist for both children and adults with coarctation, with intervention warranted in patients with a peak-to-peak gradient ≥20 mmHg across

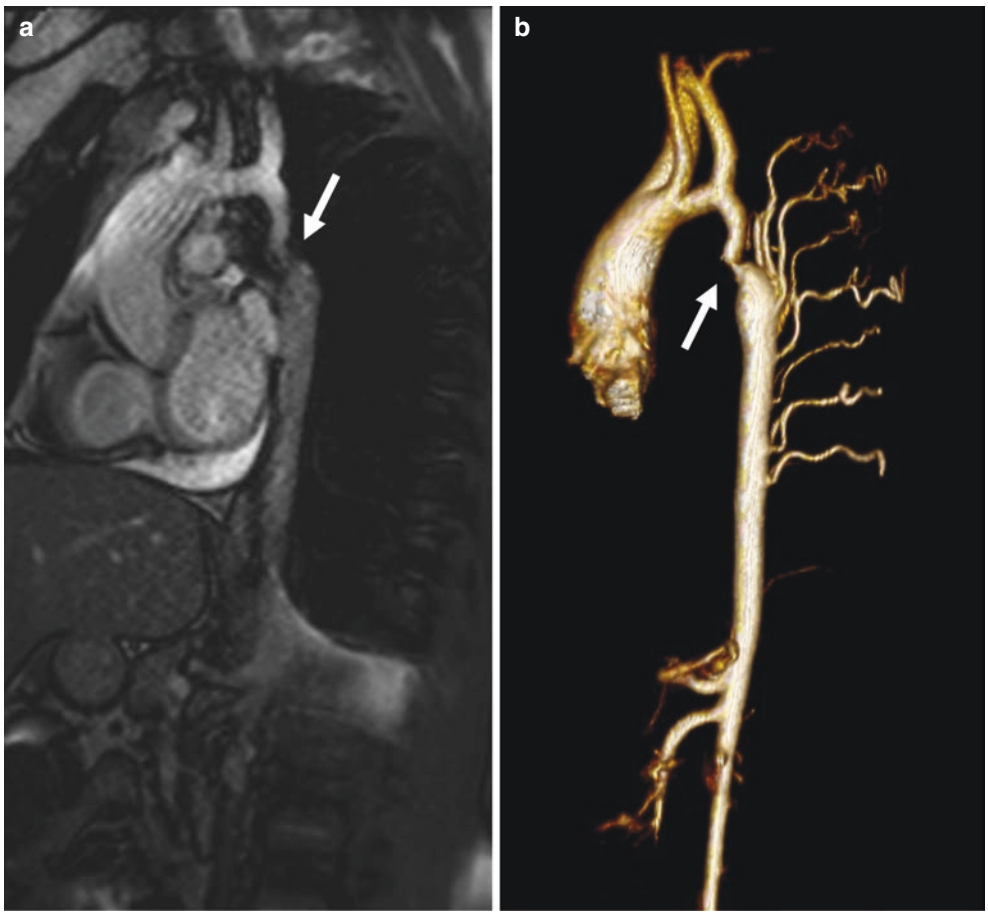

Fig. 8.2 Magnetic resonance imaging of coarctation. (**a**) Sagittal magnetic resonance image (steady-state free precession) in a 12-year-old boy showing transverse arch hypoplasia and long segment coarctation distal to the left subclavian artery (arrow). (**b**) Three-dimensional reconstruction of a gated contrasted angiogram of the same patient, again highlighting hypoplasia of the transverse arch, coarctation at the distal transverse aortic arch and isthmus (arrow), and dilated intercostal arteries functioning as collaterals

the site of coarctation. Intervention is also warranted with lesser gradients in the presence of significant anatomic evidence of stenosis and extensive collateral flow [27, 29]. Factors such as systemic hypertension, additional cardiac defects, left ventricular hypertrophy, or elevated left ventricular end diastolic pressure must also be considered when determining possible intervention [27, 29–31].

Surgical Repair

In 1944, Crafoord described resection with end-to-end anastomosis as the first surgical repair for coarctation [32] (Fig. 8.3a). Subsequent studies showed recoarctation in over half of the patients repaired with this technique, which was largely attributed to the use of a circumferential suture line [33, 34]. Gross reported using an interposition graft after resection of the segment of coarctation in 1951 [35]. While less appealing in pediatric patients due to somatic growth, this approach can be appropriate in adult patients with aneurysm, long segment coarctation, or recoarctation after primary repair [36].

As an alternative approach, Vosschulte described prosthetic patch aortoplasty for coarctation repair in 1961. In this technique, the ductal tissue is excised, a longitudinal incision across the coarctation is made, and a prosthetic patch is used to enlarge the area of stenosis (Fig. 8.3b). This technique avoids a circumferential suture line, can address longer segments of coarctation, and minimizes mobilization of the aorta and ligation of intercostal arteries [37]. Recoarctation rates of 5–12% [38] were lower compared to the resection and end-to-end anastomosis technique, but aortic aneurysm was a long-term problem with this technique, occurring in 18–51% of patients [39–42].

Subclavian flap aortoplasty was introduced in 1966 as a surgical treatment option for coarctation by Waldhausen and Nahrwold. In this approach, the left subclavian artery is ligated and divided, and the proximal left subclavian stump is folded down and used to enlarge the area of coarctation (Fig. 8.3c). This technique allows for improved growth by avoiding the use of a circumferential suture line and prosthetic material and can be used in long segment coarctation [43, 44]. However, the need to sacrifice the left subclavian artery has been a major concern with this technique, which has been associated with decreased length and muscle bulk of the left upper extremity as well as claudication with exercise [45, 46].

In 1977 Amato described a modification to Crafoord's resection and end-to-end anastomosis, called the *extended*

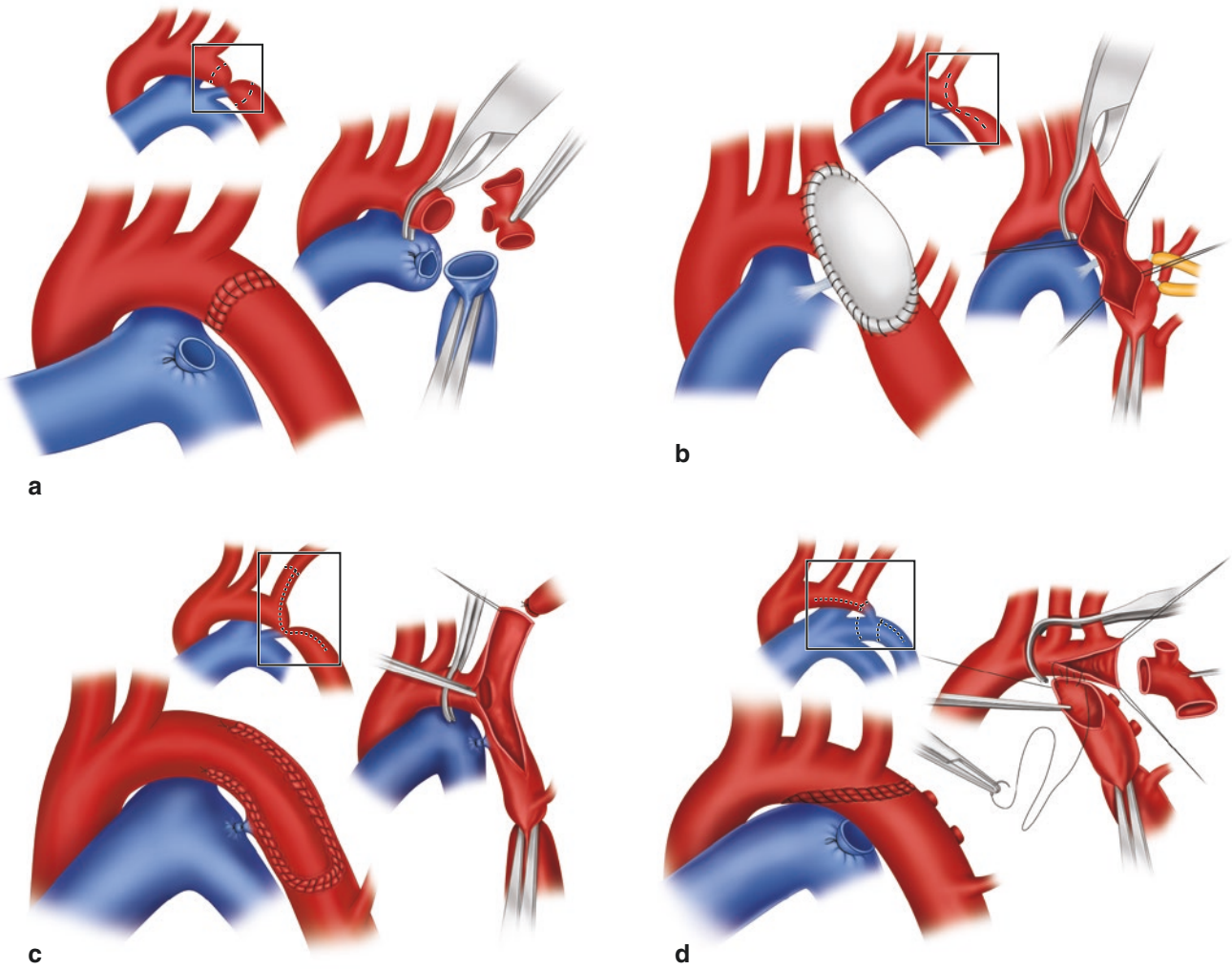

Fig. 8.3 Surgical techniques in coarctation repair. (**a**) Crafoord's original resection with end-to-end anastomosis. The coarctation is resected, and an end-to-end, circumferential anastomosis is created. (**b**) Patch aortoplasty. An incision is extended across the coarctation, followed by patch augmentation of the stenotic region. (**c**) Subclavian flap aortoplasty. The left subclavian artery is ligated and divided, and a longitudinal incision is extended from the proximal left subclavian artery beyond the area of coarctation. The proximal left subclavian flap is then folded down to enlarge the area of coarctation. (**d**) Resection with *extended* end-to-end anastomosis. The coarctation is resected using a broad, longitudinal incision, and an oblique anastomosis is used to join the undersurface of the transverse arch and descending thoracic aorta. (Adapted and reprinted from Dodge Khatami A et al. [32], with permission from John Wiley and Sons)

end-to-end technique. In the extended end-to-end approach, a broader, longitudinal incision and anastomosis across the proximal aorta is performed (Fig. 8.3d). While still avoiding prosthetic material and enabling ductal tissue resection, the wider incision is less prone to restenosis and enables enlargement of the transverse aorta [47, 48]. Currently, extended end-to-end anastomosis is one of the preferred techniques for surgical repair, due to low restenosis rates (4–11%) and low mortality rates [47, 49–51].

Finally, in neonates considerable debate has revolved around the merits of performing coarctation repair through a left thoracotomy versus a median sternotomy. While most surgeons would advocate for a left thoracotomy approach in all patients with discrete coarctation, for neonates with a hypoplastic transverse aortic arch, a slight variation of the extended end-to-end anastomosis has been called aortic arch advancement (AAA). In this procedure, a median sternotomy is performed, the infant is placed on cardiopulmonary bypass, all ductal tissue is removed, and a longitudinal incision is made on the convex aspect of the distal ascending aorta/proximal transverse arch. The descending aorta is mobilized and anastomosed in an end-to-side approach to the proximal aortic arch [52]. While one must accept the increased risks associated with cardiopulmonary bypass, compared to a left thoracotomy, proponents of the AAA approach cite overall low morbidity and mortality rates, greater exposure of the aortic arch, and lower reintervention rates [49, 52, 53].

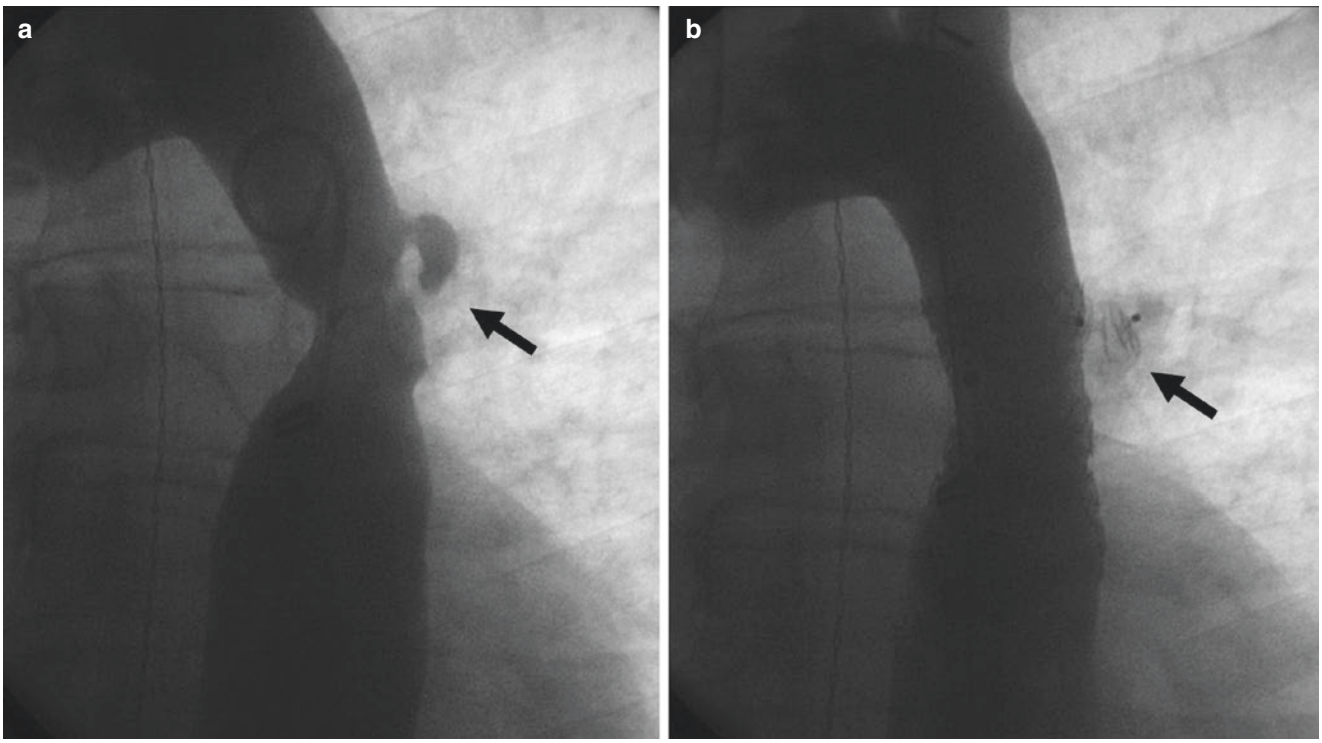

Fig. 8.4 Endovascular stent placement for coarctation. (**a**) Angiogram (LAO 30°, caudal 30°) in a 45-year-old man with a discrete coarctation and intercostal aneurysm (arrow). (**b**) Angiogram in the same projection after endovascular bare metal stent placement with no significant residual stenosis. An Amplatzer Vascular Plug II was used to successfully occlude the intercostal aneurysm (arrow)

Balloon Angioplasty: Native Coarctation

An alternative to surgical intervention for coarctation of the aorta emerged in 1982, when the use of balloon angioplasty was described by Lock [54]. Several studies have shown balloon angioplasty to be a relatively effective acute intervention for native coarctation, however recoarctation and aneurysm formation have limited the widespread adoption of balloon angioplasty in native coarctation [55–57]. In a prospective, multicenter study performed by the Congenital Cardiovascular Interventional Study Consortium (CCISC), the rate of recoarctation, defined as a systolic upper to lower extremity blood pressure gradient >15 mm Hg at intermediate term follow-up (1.5–5 years after balloon angioplasty), was 27% for native coarctation in patients greater than or equal to 10 kg. In the same study, aneurysms were observed in 8 of 21 (38%) patients with available imaging data from CT, MRI, or repeat angiography [58]. This risk of aneurysm formation was similar to that seen in a small, single-center, randomized trial comparing balloon angioplasty versus surgical repair of coarctation in 36 children (20 balloon angioplasty versus 16 surgical) ages 3–10 years of age. In this study 35% of the balloon angioplasty patients developed aneurysm, compared to none in the surgical cohort [59]. With balloon angioplasty, aneurysm formation is thought to be provoked by tearing of the intima and media during the procedure with subsequent disruption of vascular integrity [60–63].

Balloon Angioplasty: Recurrent Coarctation

In contrast to native coarctation, balloon angioplasty is typically the intervention of choice for recoarctation, especially in patients who are too small for stent placement [29]. Short-term success rates range from 80% to 93% [64], and the incidence of aortic wall injury is low at 1–2%. Fibrosis at the site of recoarctation is thought to be protective against aneurysm formation in these patients. However recoarctation remains a significant concern, with a broad incidence reported of 6–53% [65, 66].

Bare Metal Endovascular Stent Placement

Endovascular stents were introduced as a treatment option for coarctation in 1991 [67], which broadened the utility of transcatheter treatment for coarctation. Stents offer decreased rates of aortic wall injury compared to balloon angioplasty alone because stents do not require overdilation of the vessel and provide structural support to the vessel wall [5] (Fig. 8.4).

The Coarctation of the Aorta Stent Trial (COAST) has provided definitive prospective data on the safety and efficacy of stent placement for aortic coarctation. COAST began in 2007 as a multicenter, single-arm clinical trial to evaluate the safety and efficacy of the Cheatham Platinum (CP, NuMED, Hopkinton, NY) stent in children and adults with

coarctation. Because of the controversy in using endovascular stents in small children due to large sheath size and the need to accommodate for somatic growth [68, 69], patients less than 8 years of age and under 35 kg were excluded. In COAST, CP stent implantation was attempted in 105 patients from 8 to 52 years of age, with no significant acute adverse events and only one failure of stent implantation. In the catheterization lab, no patient had a significant gradient across the CP stent, and at 1 month follow-up, 99% of patients had a gradient <20 mmHg. Two-year follow-up data was available for 86% of patients, with 90% demonstrating a blood pressure gradient <20 mmHg between the upper and lower extremities. Stent fracture was relatively common, reported in 23 patients, though none of these cases had decreased stent integrity, stent migration, aortic wall injury, or hemodynamic obstruction. Aortic aneurysm was found in 6 patients, one of which spontaneously resolved. To date, there have been no reported surgical reinterventions for any COAST trial patient, but the need for stent dilation or development of aortic wall injury has prompted 19 patients to undergo repeat transcatheter intervention [70]. The COAST trial is planned to include 5 years of follow-up from stent placement, which will enable further understanding regarding the safety and efficacy of the CP stent for aortic coarctation [6].

Covered Endovascular Stents

The use of covered endovascular stents is one of the most recent transcatheter innovations for the treatment of patients with coarctation, first described in 1999. The material within the stent provides additional structural support and creates a protective barrier against shear stress and presumably subsequent aortic wall injury. When aortic aneurysm or stent fracture occur with bare metal stent placement, covered stents can serve as a rescue therapy. Covered stents can also be used as a primary treatment option for coarctation and are especially helpful in the setting of complex coarctation anatomy or when friable and calcified aortic wall tissue exists in older patients. Some limitations of covered stent placement exist, and due to the need for large sheath sizes and to accommodate for somatic growth, covered stent placement is often precluded in small children. Furthermore, caution must be taken to avoid stent occlusion of significant aortic branches, including paraspinal branches off of the descending aorta, which are often challenging to identify [71].

In 2010, the COAST II trial was developed to investigate the safety and efficacy of the covered CP stent in treating or preventing aortic wall injury in patients with coarctation. Short-term outcomes at 1-month follow-up for the COAST II trial were released in 2016. A total of 158 patients with either a history of coarctation with aortic wall injury or an increased risk of aortic wall injury underwent placement of a covered CP stent. At 1 month of follow-up, the average gradient across the aortic arch had declined from 27 ± 20 mmHg to 4 ± 6 mmHg. Complete coverage of pre-existing areas of aortic wall injury was achieved in 92% of patients, and there were no cases of acute aortic wall injury, repeat interventions, or death. This led to FDA pre-market approval of the covered CP stent in April 2016 for preventing aortic wall injury in high-risk patients with coarctation and for the treatment of existing aortic wall injury related to complications from previous interventions for coarctation. Follow-up to 24 months after covered stent placement is planned for the COAST II trial [72].

A recent randomized clinical trial was performed comparing bare CP stent placement to covered CP stent placement in 120 patients. No procedural complications occurred in either group, and at a mean follow-up of 31.1 months, the bare CP stent group had an increase in the rate of recoarctation (6.7% versus 0%) and decrease in the rate of pseudoaneurysm (0% versus 3.3%) compared to the covered CP stent group, though neither comparison reached statistical significance. In both cases of pseudoaneurysm in the covered stent group, the aneurysm developed at the proximal end of the stent and was able to be treated by placing a second covered stent. Neither case developed any further complications [73].

Management Algorithm

In the setting of various treatment options, determination of the optimal treatment strategy for coarctation of the aorta can be complicated, and there is no comprehensive evidence-based standard of care or algorithm. Guidelines from the American College of Cardiology and the American Heart Association provide some insight, but the level of evidence supporting these recommendations is suboptimal (Level B or C for all recommendations) [27, 29]. Treatment decisions must be made after careful consideration of the age at presentation, complexity of the coarctation, and whether the coarctation is native or recurrent. In general, surgical repair is preferred for infants and young children with native coarctation due to the risk of recurrent coarctation and aortic wall injury with angioplasty, the need for large sheath sizes, and challenges in accounting for somatic growth with stent placement [59]. Surgical repair may also be more appropriate at any age when repair of associated cardiac defects is indicated or in patients with complex coarctation anatomy, including those with transverse arch hypoplasia, tortuous segments of recoarctation, and distorted arterial branch anatomy [27]. For uncomplicated native coarctation in the older child or adult, stent placement with either a bare metal or covered stent can offer a less invasive approach than surgical repair with good long-term outcomes [27, 29, 74]. For recurrent coarctation, balloon angioplasty is typically per-

formed. If the anatomy is favorable, stent placement should also be considered when the chosen stent can be dilated to near adult size [29, 58].

Treatment Approach for Coarctation of the Aorta in Children and Adults

Indications for Treatment [27, 29]:
Intervention is indicated with a peak-to-peak systolic pressure gradient ≥20 mmHg across the site of coarctation upon initial presentation or in the setting of recurrent coarctation.
Intervention is also warranted with lesser gradients in the presence of significant anatomic evidence of stenosis and extensive collateral flow.
Intervention may be considered with a peak-to-peak systolic pressure gradient <20 mmHg but with systemic hypertension associated with anatomic narrowing that explains the hypertension.
Intervention may be considered with a peak-to-peak systolic pressure gradient <20 mmHg but with an elevated left ventricular end-diastolic pressure and an anatomic narrowing.

Treatment Approach:

Surgical Repair

Surgical repair is typically preferred over transcatheter approaches in infants and young children with native coarctation, all patients requiring repair of associated cardiac defects, or in the setting of complex coarctation anatomy.

Extended end-to-end anastomosis is typically the preferred surgical technique, which avoids prosthetic material, includes resection of the coarctation, and involves a wider incision that is less prone to restenosis.

In neonates with a hypoplastic transverse aortic arch, a variation of the extended end-to-end anastomosis technique, called aortic arch advancement, may be preferred.

Balloon Angioplasty

Typically balloon angioplasty is the preferred intervention for recurrent coarctation in children and adults.

Balloon angioplasty is not often used in native coarctation due to concern for recoarctation and aneurysm formation.

Endovascular Stent

For uncomplicated coarctation in the older child or adult, either a bare metal or covered endovascular stent can offer a less invasive approach than surgical repair with good long-term outcomes. If the anatomy is favorable, stent placement should be considered when the chosen stent can be dilated to near adult size.

Endovascular stents provide structural support and decreased rates of aortic wall injury and aneurysm compared to balloon angioplasty, but care must be taken to avoid overlying vital branch vessels.

Covered stents may be considered as an alternative to bare metal stents, particularly in patients felt to be at increased risk for aortic wall injury.

The use of stents in small children remains controversial due to the need for large sheath sizes and limitations in accommodating for somatic growth.

Patient Follow-Up

Without intervention, the outcome for patients with coarctation of the aorta is overwhelmingly poor. In his classic 1970 natural history study, Campbell examined autopsy and clinical records of 465 patients with coarctation who survived beyond 1 year of age, and the mean age of death was 34 years, with 75% mortality by 43 years of age. Causes of death included congestive heart failure (26%), aortic rupture (21%), bacterial endocarditis (18%), and intracranial hemorrhage (12%) [75]. Fortunately, surgical and transcatheter techniques have evolved, and outcomes for patients with repaired coarctation are now overall quite good. After coarctation repair, patients still must be followed at least annually by a cardiologist to assess for long-term issues, such as hypertension and associated left ventricular hypertrophy and dysfunction, exercise intolerance, intracranial aneurysms, and recoarctation [27].

Hypertension

Hypertension is endemic in patients with repaired aortic coarctation and represents the most common long-term morbidity [76, 77]. In a contemporary analysis of the Swedish National Registry on Congenital Heart Disease (SWEDCON), hypertension was present in 344/653 (52.7%) adults (mean age 36.9 ± 14.4 years) with a prior history of coarctation repair (mean age at repair 9.5 ± 11 years) [78]. Risk factors for hypertension in multivariable analysis included male sex (OR = 3.35 [95% CI: 1.98–5.68]), age (OR = 1.07 per year [95% CI: 1.05–1.10]), increased body mass index (OR = 1.09 per unit increase [95% CI: 1.03–1.06]), and a residual right upper to lower extremity systolic blood pressure gradient of 10–19 mm Hg (OR = 3.58 [95% CI: 1.70–7.55]) or >20 mm Hg (OR = 11.38 [95% CI: 4.03–32.11]) [78]. The etiology of such high rates of baseline and exercise-induced hypertension remain unclear but may be due to any combination of underlying arteriopathy, decreased aortic wall compliance, abnormal streaming of blood flow, or renal abnormalities [76]. In addition to traditional hypertension risk factors such as age and body mass index, the substantially increased risk of hypertension in patients with a residual blood pressure gradient serves to highlight the importance of evaluating for recoarctation as a cause of hypertension.

Intracranial Aneurysm

Adults with a history of coarctation have a five-fold increased risk of developing an intracranial aneurysm [79]. Recognizing this risk, the current American College of Cardiology and American Heart Association adult congenital guidelines recommend screening for intracranial vasculature abnormalities in patients with coarctation by CT or MRI, but the exact timing and frequency of follow-up imaging is not defined [27]. A prospective trial using CT angiography for screening of intracranial aneurysm in patients with coarctation found increased age to be the sole risk factor for

the development of intracranial aneurysm in patients with coarctation, with the fourth and fifth decade of life being the most common age at presentation [79]. While further studies are needed, this data suggests screening for intracranial aneurysm should be performed in patients with coarctation at least by the fourth decade of life.

Impact of Arch Type

Even when no evidence of recoarctation exists, patients with a history of coarctation are at risk for hypertension, vascular remodeling, and decreased left ventricular function. Some evidence suggests that the morphology of the aortic arch after coarctation repair can impact outcomes in patients who have undergone coarctation repair. Three types of aortic arch morphology have been described: (1) Romanesque with a normal, rounded aortic arch, (2) Crenel with a rectangular shaped aortic arch and normal horizontal aortic width, and (3) Gothic with an acutely angled, triangular aortic arch and an exaggerated height-to-width ratio (Fig. 8.5) [80]. Interestingly, in repaired coarctation patients, Gothic aortic arch morphology has been associated with increased prevalence of hypertension both at baseline [80] and with exercise [81]. Ou et al. demonstrated that the Gothic aortic arch morphology is also associated with other maladaptive aortic features including increased carotid artery intima-media thickness, higher aortic stiffness index, and impaired vasoreactivity proximal to the site of coarctation repair. Bruse et al. described an association between Gothic arch morphology after coarctation repair and impaired ventricular performance including lower left ventricular ejection fraction, larger indexed left ventricular end-diastolic volume, and elevated indexed left ventricular mass [82]. However, the relationship between arch morphology and long-term outcome has not been completely consistent, and other reports have shown no association between arch type and exercise induced hypertension [83, 84]. In fact, one study proposed that hypoplasia of the transverse arch and isthmus, not arch curvature, were the major factors associated with exercise induced hypertension [84]. Indeed, patients with repaired coarctation with normal or Romanesque aortic arch morphology also have significantly higher carotid artery intima-media thickness, aortic stiffness, and impaired vasoreactivity suggesting that arch morphology is not the sole determinant of abnormal arch physiology [85]. Overall, further study is needed regarding the utility of assessing arch morphology for long-term risk prediction in patients with repaired coarctation.

Consensus Follow-up Recommendations

According to guidelines from the American Heart Association and American College of Cardiology for management of adults with congenital heart disease, patients with repaired coarctation should be followed at least annually by a cardiologist, or sooner if concerns arise. In adults, it is recommended that there be consultation with a specialist in adult congenital heart disease.

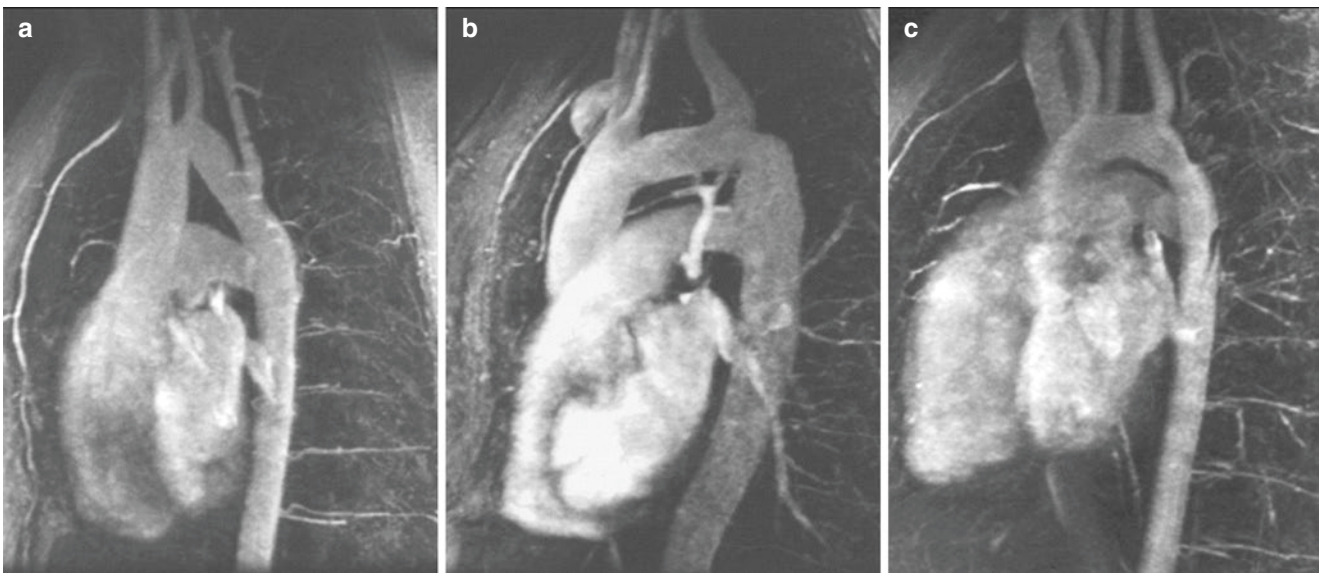

Fig. 8.5 Three described categories of arch morphology. (**a**) Gothic arch with acute angulation of the aortic arch, creating an exaggerated height-to-width ratio. (**b**) Crenel arch with rectangular shaped aortic arch and normal width. (**c**) Romanesque arch with a normal, rounded shape. (Adapted and reprinted from Ou P, et al. [85], with permission from Elsevier)

Screening for baseline and exercise induced hypertension, including evaluation for the presence of a right upper to lower extremity blood pressure gradient is recommended. Cardiac evaluation in patients with hypertension should include evaluation for associated left ventricular hypertrophy and dysfunction. Re-imaging of the repaired coarctation is recommended at least every 5 years, or sooner based on the original anatomy and symptoms, to assess for complications such as aortic aneurysm or recurrent stenosis [27]. At least by the fourth decade of life, CT or MRI angiography of the brain should be performed to assess for the presence of intracranial aneurysms. Exercise should be encouraged in patients with no significant upper to lower extremity blood pressure gradient, no evidence of aneurysm or associated heart defects, and normotension at rest and with exercise. Patients should only be restricted from activities with a large static component [86]. Although not addressed in the American Heart Association and American College of Cardiology guidelines, the European Society of Cardiology recommends consideration of reintervention regardless of symptoms for all patients with repaired coarctation and a noninvasive systolic blood pressure gradient >20 mmHg between upper and lower limbs with upper limb hypertension (>140/90 mmHg in adults), pathologic blood pressure response during exercise, or significant left ventricular hypertrophy [87]. Finally, according to the most recent American Heart Association guidelines, endocarditis prophylaxis is not routinely recommended after the first 6 months following surgical or transcatheter intervention, unless a previous history of infectious endocarditis exists [88].

Pseudocoarctation

Pseudocoarctation is a rare anomaly that refers to kinking or buckling of the aorta at the isthmus without significant obstruction to flow or development of collateral circulation (Fig. 8.6). This condition is thought to arise embryologically from abnormal compression of the third through seventh dorsal aortic segments, leading to a superiorly displaced distal aortic arch and redundancy and kinking of the aorta at the ligamentum arteriosum [89, 90]. Patients with pseudocoarctation are typically asymptomatic but may present with hypertension [91]. On routine chest x-ray pseudocoarctation may resemble a mediastinal mass due to the superior displacement of the distal transverse aortic arch. Patients with pseudocoarctation may also appear to have true coarctation on chest x-ray due to an indentation at the isthmus where the aorta is kinked, giving a classic "3 sign." In these challenging scenarios, a high degree of suspicion for pseudocoarctation must exist, prompting further evaluation [89, 92].

In isolation, pseudocoarctation is typically felt to be a benign condition due to the lack of actual obstruction to aortic blood flow. While pseudocoarctation often exists in isolation, it is important to consider the association of additional congenital heart defects, especially a bicuspid or stenotic aortic valve, which warrant further evaluation and potential intervention [93]. Furthermore, patients with pseudocoarctation are at risk for aortic aneurysm and dissection distal to the kinked segment, which is thought to be related to abnormal, turbulent blood flow beyond the area of pseudocoarctation [94]. Therefore, patients with suspected pseudocoarctation should first undergo transthoracic echocardiography to rule out associated congenital heart defects. The area of aortic kinking may be difficult to visualize by echocardiography, and CT angiography or MRI should then be performed to rule out true coarctation as well as the development of aortic aneurysm or dissection distal to the kinked segment [90, 95]. If less invasive imaging techniques remain inconclusive, cardiac catheterization should be performed, which remains the gold standard to determine the anatomy and pressure gradient across the aorta. Surgical intervention for pseudocoarctation is typically reserved for patients with significant symptoms or when concern for aortic aneurysm and/or dissection exist [90].

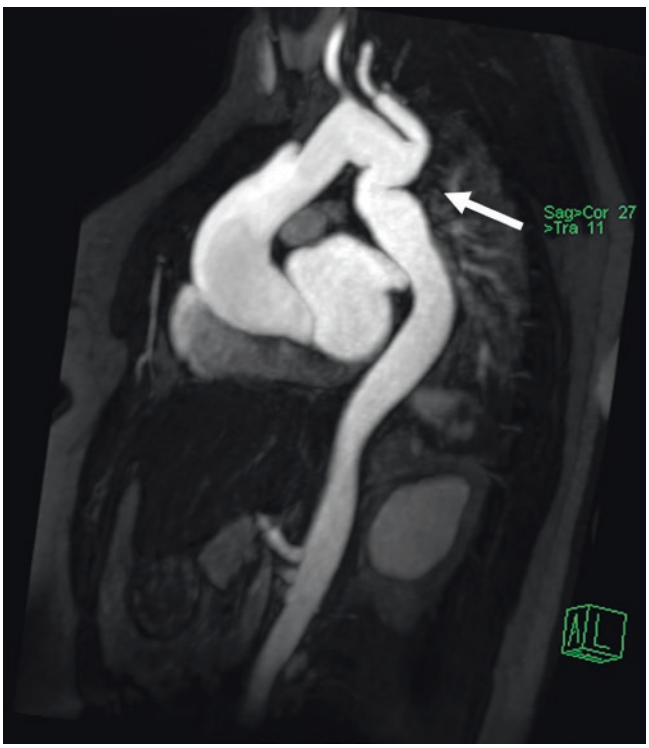

Fig. 8.6 Magnetic resonance image of pseudocoarctation. Sagittal magnetic resonance image angiogram of the thoracic aorta in a 39-year-old man with a history of pseudocoarctation demonstrating significant tortuosity of the proximal descending aorta (arrow)

Abdominal Coarctation

Abdominal coarctation, also known as Middle aortic syndrome (MAS), occurs when there is narrowing of the distal thoracic and/or the abdominal aorta (Fig. 8.7). It is a rare disease found in children and young adults, making up only 0.5–2% of all cases of aortic coarctation [96]. While uncommon, this is an important etiology for hypertension in children and young adults. A recent systematic review of MAS showed that most cases are idiopathic (64%), 15% are associated with genetic disease such as neurofibromatosis type I, Alagille syndrome, and William syndrome, and an additional 17% of cases are caused by inflammatory diseases such as Takayasu arteritis or intrauterine infection [97]. The exact embryologic development of MAS remains unclear, but one theory is that it results from abnormal fusion of the two dorsal aortas in fetal life. An inflammatory response with resultant fibrosis in the setting of an intrauterine infection prenatally or postnatal vasculitic diseases may also explain some cases of MAS [98].

Clinical Presentation

Patients with MAS most commonly present with refractory hypertension, and the severity depends on the location and degree of vessel stenosis. An abdominal bruit may be heard, and patients may have absent femoral pulses and symptoms of claudication. While stenosis of visceral vessels is quite common in MAS, reports of intestinal angina and weight loss occur rarely, though renal dysfunction occurs more commonly [97, 99].

Evaluation

As with classic coarctation, patients with MAS may demonstrate evidence of left ventricular hypertrophy on an electrocardiogram. A transthoracic echocardiogram should be obtained to assess the anatomy of the thoracic and abdominal aorta and to screen for associated intracardiac defects and end-organ damage from hypertension [98]. If an abdominal bruit exists on exam, a dedicated abdominal or renal ultrasound may also be indicated but can be of limited quality in adult patients due to technical challenges. Typically CT angiography or MRI is then utilized to better define the exact areas of the aorta that are affected, the presence of collaterals, and to define any extra-aortic vessel involvement [100, 101]. Cerebrovascular disease occurs in as many as 45% of patients with MAS and should be evaluated on CT angiography or MRI of the brain as well [102]. The abdominal aorta is the site of narrowing in 97% of cases, with only 3% of MAS affecting the distal thoracic aorta. In a large systematic review of MAS in adults by Rumman et al., 57% of the 630 reviewed cases defined the site of abdominal coarctation, and the most common site of coarctation was the suprarenal aorta

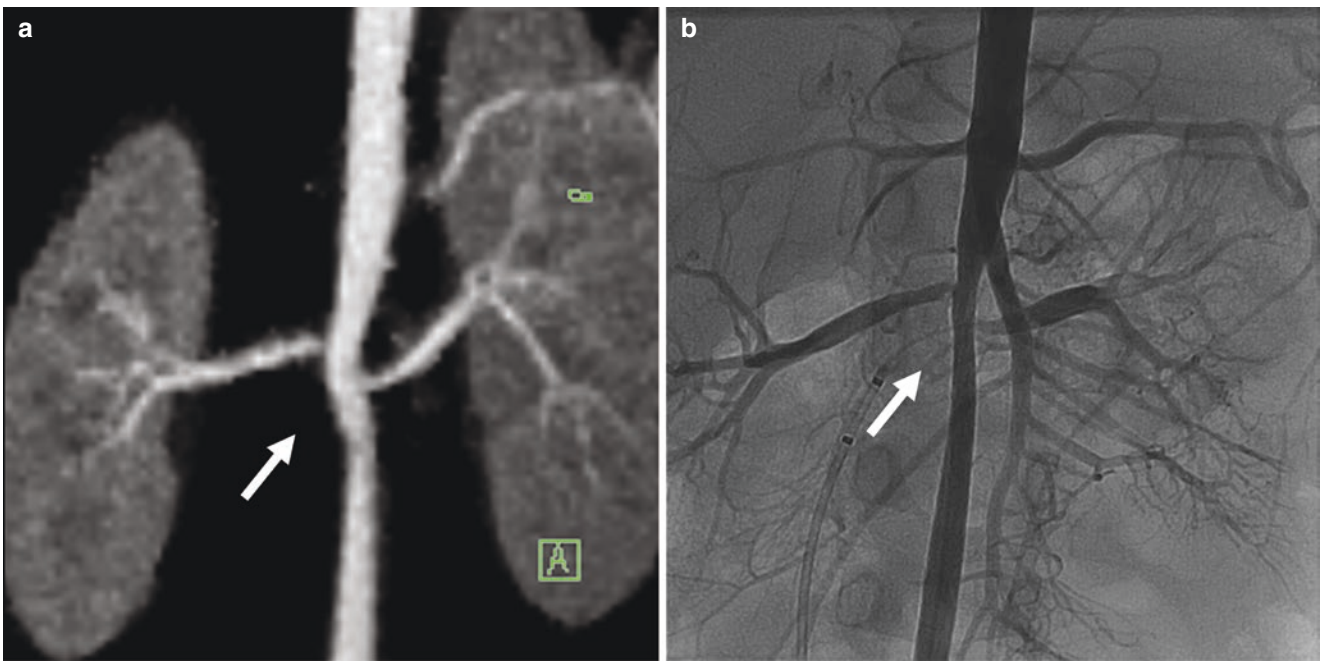

Fig. 8.7 Abdominal coarctation. (**a**) Maximum intensity projection (MIP) image of an abdominal magnetic resonance contrast angiogram in a 3-year-old girl with refractory systemic hypertension showing abdominal coarctation and bilateral renal artery stenosis (arrow). (**b**) Anterior–posterior projection of an angiogram of the descending aorta in a 6-year-old girl showing abdominal coarctation and renal artery stenosis (arrow)

(29%), followed by stenosis from the suprarenal to infrarenal aorta (12%), and the infrarenal aorta (8%). Visceral branch vessels are affected in about 70% of cases of MAS, with renal artery stenosis being the most common (66%), followed by stenosis of the superior mesenteric artery (30%) and celiac trunk (22%). Interestingly the inferior mesenteric artery is typically not affected [97].

Management

With severe hypertension being the most common symptom, antihypertensive agents are the first line treatment option in MAS. Unfortunately, there is a high rate of refractory hypertension, and in their series of 36 patients with MAS, Tummolo et al. report only an 8% success rate of medical management with antihypertensives [102]. Failure to achieve blood pressure control or evidence of end-organ damage are often cited as reasons to pursue endovascular or surgical interventions, but specific guidelines for intervention do not exist. The region and length of stenosis need to accommodate for somatic growth in young patients, extra-aortic vessel involvement, and degree of symptoms must be considered on an individual basis [97]. The use of a stent in percutaneous transluminal angioplasty (PTA) can be quite effective in relieving stenosis, but care must be taken to avoid occlusion of important visceral arteries [103]. In their systematic review of 630 adult cases of MAS, Rumman et al. reported that 28% of patients underwent PTA with or without stenting. Complications were reported in 13% of patients, mortality in 2.3%, and technical failure or need for reintervention was described in 28% of cases [97]. In their report of outcomes in 36 patients with MAS, Tummolo et al. report that 36% of patients underwent PTA, with 46% requiring repeat PTA. Because of failure to adequately control blood pressure after PTA, 53% of these patients went on to require surgical intervention [102].

Surgical options for patients with MAS include thoracoabdominal bypass grafts, patch aortoplasty, interposition aortoaortic grafts, and renal autotransplantation. In the systematic review by Rumman et al., 55% of 630 patients underwent surgical treatment for MAS, with 12% of these cases following failed endovascular intervention. Of these surgical cases, 42% were done by aortoaortic bypass, 23% involved reconstruction patch graft, and renal autotransplantation was performed in 11% of cases. While most patients tolerated surgery well, a complicated postoperative course was reported in 9% of cases, technical failure in 8%, and surgical mortality occurred in 2.9% of cases. Interestingly, cases involving arteritis were the highest risk [97]. Tummolo et al. reported 47% of their patients proceeding to surgery, with 41% of these cases following failed endovascular intervention. At mean follow-up of 5.6–7.2 years (patients who underwent surgery only versus surgery after failed PTA, respectively), 25% of patients no longer required antihypertensives, 58% required antihypertensive therapy with improved BP control, 14% of patients continued to have refractory hypertension, and 3% were reported as a technical failure. In their series of 53 patients who underwent surgical treatment for MAS, Stanley et al. reported resolved hypertension in 53% and improved hypertension in 34% of patients. There was no improvement in blood pressure in 7% of patients, who underwent repeat surgical intervention [99].

Outcome

Left untreated, MAS leads to a shortened life expectancy, typically in the fourth decade of life [103]. Residual hypertension is the most common long-term problem in MAS, and, even after endovascular or surgical intervention, hypertension is reported in over one-third of patients [97]. Restenosis, especially in-stent stenosis, and outgrowth of a previously placed stent are typical reasons for surgical reintervention after PTA [103]. In surgical patients, reintervention due to somatic growth relative to an aortic bypass graft of patch aortoplasty is not unusual, with one surgical cohort describing a reintervention rate of 6% for these reasons [99]. Exact guidelines regarding follow-up in MAS patients after intervention do not exist. However, it would seem reasonable to extrapolate recommendations for typical aortic coarctation by suggesting at least annual evaluation by a cardiologist with screening for hypertension, exercise intolerance, left ventricular hypertrophy and ventricular dysfunction. Regarding follow-up imaging, one proposed regimen is to perform at least yearly surveillance with CT angiography or MRI, and once several scans are documented to be stable, spacing imaging intervals to every 2–3 years [98].

Conclusion

Coarctation of the aorta is a very heterogeneous disease that can present at any age, sometimes requiring a high index of suspicion to make the appropriate diagnosis. Fortunately in the past 70 years, a great deal of progress has been made in the ability to both diagnose and treat aortic coarctation. Advances in echocardiography, CT, and MRI have aided the diagnosis, treatment planning, and follow-up in these patients. Modifications of various surgical techniques have led to low mortality and morbidity rates, even in the smallest patients. Development of transcatheter balloon angioplasty and subsequently endovascular stent place-

Table 8.1 Important studies and guideline statements in the treatment and outcome of coarctation in adults and children

Author	*N*	Follow-up	Outcome
Cowley et al. (2005) [59]	36	Mean 14 years	Randomized trial comparing BA and surgery for native coarctation in children. Aortic aneurysm developed in 35% of BA patients and none of the surgical patients
Carr (2006) [104]	846	Mean 36 months for catheter-based group and 7.8 years for surgical group	Meta-analysis comparing catheter versus surgical intervention for adults with coarctation. Higher risk of restenosis and need for reintervention found in catheter-based group
Forbes et al. (2007) [105]	578	Median 12 months	Retrospective multicenter analysis at intermediate follow-up after stent placement for coarctation. Exceeding a balloon/coarctation ratio of 3.5 and pre-stent BA increased risk of aortic wall injury
Warnes et al. (2008) [27]	–	–	ACC/AHA guidelines for management of coarctation in adults
Baumgartner et al. (2010) [87]	–	–	ESC guidelines for management of coarctation in adults
Holzer et al. (2010) [106]	302	3–60 months	Prospective analysis of acute, intermediate, and long-term follow-up after stent placement for coarctation using CCISC registry. At long-term follow-up, recoarctation in 20% of patients, 4% required unplanned reintervention, and 1% had aortic wall injury
Feltes et al. (2011) [29]	–	–	AHA guidelines for transcatheter intervention in children with coarctation.
Forbes et al. (2011) [107]	350	Mean 1.7 years	Multicenter observational study comparing surgery, BA, and stent placement for native coarctation in children using CCISC registry. Significantly lower acute complication rates in stent group but higher planned reintervention rates. Hemodynamic and arch imaging outcomes superior in stent and surgical patients compared to BA group.
Harris et al. (2014) [58]	130	3–60 months	Prospective, multicenter analysis of short and intermediate outcomes for BA in native and recurrent coarctation in children. Trend toward increased acute aortic wall injury and restenosis in native coarctation patients.
Sohrabi et al. (2014) [73]	120	Mean 31.1 months	Randomized clinical trial comparing covered and bare CP stents for native coarctation in adolescents and adults. Trend of increased rates of restenosis and lower rates of pseudoaneurysm in bare stent group.
Meadows et al. (2015) [70]	105	2 years	Prospective, multicenter, single-arm study assessing safety and efficacy of CP stent in children and adults with coarctation. Two-year follow-up of 86% showed 23 fractured stents with no significant clinical effects, 6 aortic aneurysms, 19 repeat catheter interventions, and no surgical interventions
Rumman et al. (2015) [97]	630	Median 4 years	Systematic review examining the features of MAS in children. There is a high prevalence of stenosis of the visceral arteries, with renal artery stenosis being most common (70% of cases). Most cases of MAS are idiopathic, but disease severity is worse in the setting of genetic or inflammatory etiologies.
Rinnström et al. (2016) [78]	653	Mean 27.4 years	Analysis of the SWEDCON registry demonstrated hypertension in 52.7% of patients with repaired coarctation. Associated risk factors for hypertension in these patients were increasing age, male sex, elevated body mass index, and a residual right upper to lower extremity systolic blood pressure gradient.

BA balloon angioplasty, *ACC* American College of Cardiology, *AHA* American Heart Association, *ESC* European Society of Cardiology, *CCISC* Congenital Cardiovascular Interventional Study Consortium, *CP* Cheatham Platinum, *MAS* middle aortic syndrome, *SWEDCON* Swedish National Registry on Congenital Heart Disease

ment have expanded treatment options and allowed less invasive approaches for some patients. However, even after seemingly uncomplicated repairs, patients with coarctation of the aorta are still at risk for long-term health issues, most notably hypertension, exercise intolerance, and left ventricular hypertrophy and dysfunction (Table 8.1). Ongoing efforts to understand and potentially mitigate these long-term problems are underway.

Conflict-of-interest Statement Fleming GA is the site principal investigator for the Covered Cheatham Platinum Stents for the Prevention or Treatment of Aortic Wall Injury Associated with Coarctation of the Aorta (COAST II) trial at Duke University Medical Center. There are no other conflicts of interest to disclose.

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Ascending Aortic Dissection, Penetrating Aortic Ulcer, and Intramural Hematoma

9

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Abbreviations

AI	Aortic insufficiency
ARR	Aortic root replacement
ATAAD	Acute type A aortic dissection
AVAR	Aortic valve and aorta replacement
AVR	Aortic valve replacement
BAV	Bicuspid aortic valve
CVA	Cerebrovascular accident
DHCA	Deep hypothermic cardiac arrest
FET	Frozen elephant trunk technique
GERAADA	German Registry for Acute Aortic Dissection Type A
IRAD	Internal Registry of Acute Aortic Dissection
MHCA	Moderate hypothermic cardiac arrest
MI	Myocardial infarction
MPS	Malperfusion syndrome
ND	Neurologic deficit
PE	Pulmonary embolism
SACP	Selective antegrade cerebral perfusion
SCAR	Supracoronary ascending aorta replacement
SCI	Spinal cord injury
STEMI	ST-elevation myocardial infarction
TAR	Total arch replacement
TEE	Transesophageal echocardiogram
TTE	Transthoracic echocardiogram
VSAR	Valve-sparing aorta replacement

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Introduction

Acute aortic dissection has been among the most lethal entities in the medical literature for centuries. In 1760, King George II died suddenly of an aortic dissection. His autopsy report published by Dr. Frank Nicholls in *Philosophical Transactions* of the Royal Society described injury to the ascending aorta resulting in tamponade [1, 2]. More than two hundred years later, Jonathan Larson, creator of the musical *Rent*, died of an aortic dissection after misdiagnosis in two separate emergency departments where he presented with chest pain [3]. Despite advances in imaging and surgical technique, acute aortic dissection, especially dissection of the ascending aorta (type A in the Stanford classification), remains a challenge to recognize and treat swiftly.

Epidemiology, Pathophysiology, and Risk Factors

The incidence of acute type A aortic dissection (ATAAD) is 3.5–6 in 100,000 but increases with age [4]. There is a male predominance and the average age of presentation is 48–67 [4]. Given the rarity of dissection, much of the data and analysis comes from registries, including the Internal Registry of Acute Aortic Dissection (IRAD) and German Registry for Acute Aortic Dissection Type A (GERAADA).

The epidemiology of younger patients with ATAAD differs from that of older patients, with more individuals having genetic conditions including Marfan syndrome (*FBN1*), Loeys-Dietz syndrome (*TGFBR1 and TGFBR2*), Ehlers-Danlos (*COL3A1*), Turner syndrome (*XO* karyotype), and other mutations affecting structural proteins that are not part of known syndromes [5]. In IRAD data, Marfan patients presenting with dissection had a mean age of 35 compared to 64 in non-Marfan patients and comprised 5% of the total group [6]. They were also more likely to present with heart failure, aortic insufficiency, and have a history of aneurysm, but less likely to have hypertension [6]. Bicuspid aortic

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valves, which are associated with or independent from genetic syndromes, increase risk for dissection due to an acquired deficiency of aortic fibrillin, upregulation of matrix metalloproteinases, and death of smooth muscle [7].

Comorbidities associated with ATAAD include those common to other cardiovascular diseases, including hypertension, smoking, chronic kidney disease, chronic obstructive pulmonary disease, and stroke [4]. Less common associated factors include inflammatory conditions such as Takayasu arteritis, giant cell arteritis, Behçet disease, systemic lupus erythematous, and rheumatoid arthritis [8]. There may be an association between fluoroquinolone antibiotic use and acute aortic dissections. Calcium channel blockers have demonstrated increased aneurysm growth and rupture in Marfan mice and this observation has been observed in Marfan and other heritable aortic aneurysm diseases in humans. Furthermore, data supporting the use of angiotensin receptor blockers (ARBs, such as losartan) in Marfan patients is inconsistent.

Classification

Aortic dissection begins as a tear in the intima which is 1–5 cm in length and starts within 10 cm of the aortic valve (Fig. 9.1) [9].

Anatomic classification follows two main schemes, Stanford and DeBakey. Stanford Type A encompasses any dissection involving the ascending aorta, while Type B involves the descending aorta only. DeBakey classifications include Type I (ascending and descending), Type II (ascending only), and Type III (descending only) (Table 9.1) [4].

Limited intimal tears of the aorta (class 3 dissection) can involve either the ascending or the descending aorta. The clinical course is thought to be similar to that of traditional aortic dissections but may be more difficult to assess on imaging.

Prognostication and surgical approach require understanding the extent of dissection. The Penn classification associates mortality with extent of organ system involvement on presentation (Fig. 9.2) [10]. Dissection without branch vessel involvement or circulatory collapse has an in-hospital mortality of 3.1% (*class a*), branch vessel malperfusion with ischemia has a mortality of 25.6% (*class b*), circulatory collapse with or without cardiac involvement has a mortality of 17.6% (*class c*), and combined *b* and *c* has a mortality of 40% (Table 9.2).

Aortic dissection can also be defined temporally, into hyperacute (0–24 hours), acute (2–7 days), subacute (8–30 days), and chronic (>30 days) phases which are associated with increasing mortality from time of symptom onset to management [11].

Diagnosis

Clinical Presentation

Chest pain is present in 79–93% of patients presenting with aortic dissection (Table 9.3) [8, 12]. Hypotension is present in 46% of patients, and it is associated with adverse events including malperfusion, death, ST changes, aortic insufficiency (AI), tamponade, and neurological deficits [13]. Back pain is seen in 47% and hypertension in 36% [8].

Classical physical exam findings in acute aortic dissection include pulse deficit and either narrow or wide pulse pressure. In an examination of IRAD patients with pulse pressure divided into quartiles (narrow, normal, mildly elevated, markedly elevated), narrow pulse pressure was associated with greater hypotension, effusion, and mortality, while widened pressure was associated with a history of hypertension and mesenteric involvement [14]. Contrary to expected results, wider pulse pressure was not associated with a greater degree of AI [14].

Pulse deficit is associated with increased in-hospital mortality neurological deficit, hypotension, shock, and tamponade [15].

Neurological symptoms are seen in up to one third of presenting patients, and can include syncope, seizure, stroke, spinal cord ischemia, hypoxic encephalopathy, and neuropathy [16].

EKG Findings

EKG findings can be used for both diagnosis and prognostication in ATAAD. Coronary involvement can be secondary to actual extension of dissection to the coronaries or can be due to occlusion of ostia by the intimal flap. Classically, dissection is considered when a patient presents with STEMI (ST-elevation myocardial infarction) on EKG, however STE is found in only 4–16% of patients [17, 18]. In a study of 233 patients presenting within 6 hours of symptom onset, 51% had ST-T changes and these patients had a more adverse presentation, including shock, tamponade, severe hypertension, and AI [17].

ST elevation indicates greater likelihood of coronary involvement according to most groups [17, 19, 20]; however one group found no greater coronary involvement when there were ischemic changes [18]. STE in avR specifically is a strong predictor of in-hospital death with an odds ratio of 23.4 [19].

Biomarkers

Biomarkers can be used to favor or exclude a diagnosis of dissection. D-dimer is the degradation product of cross-

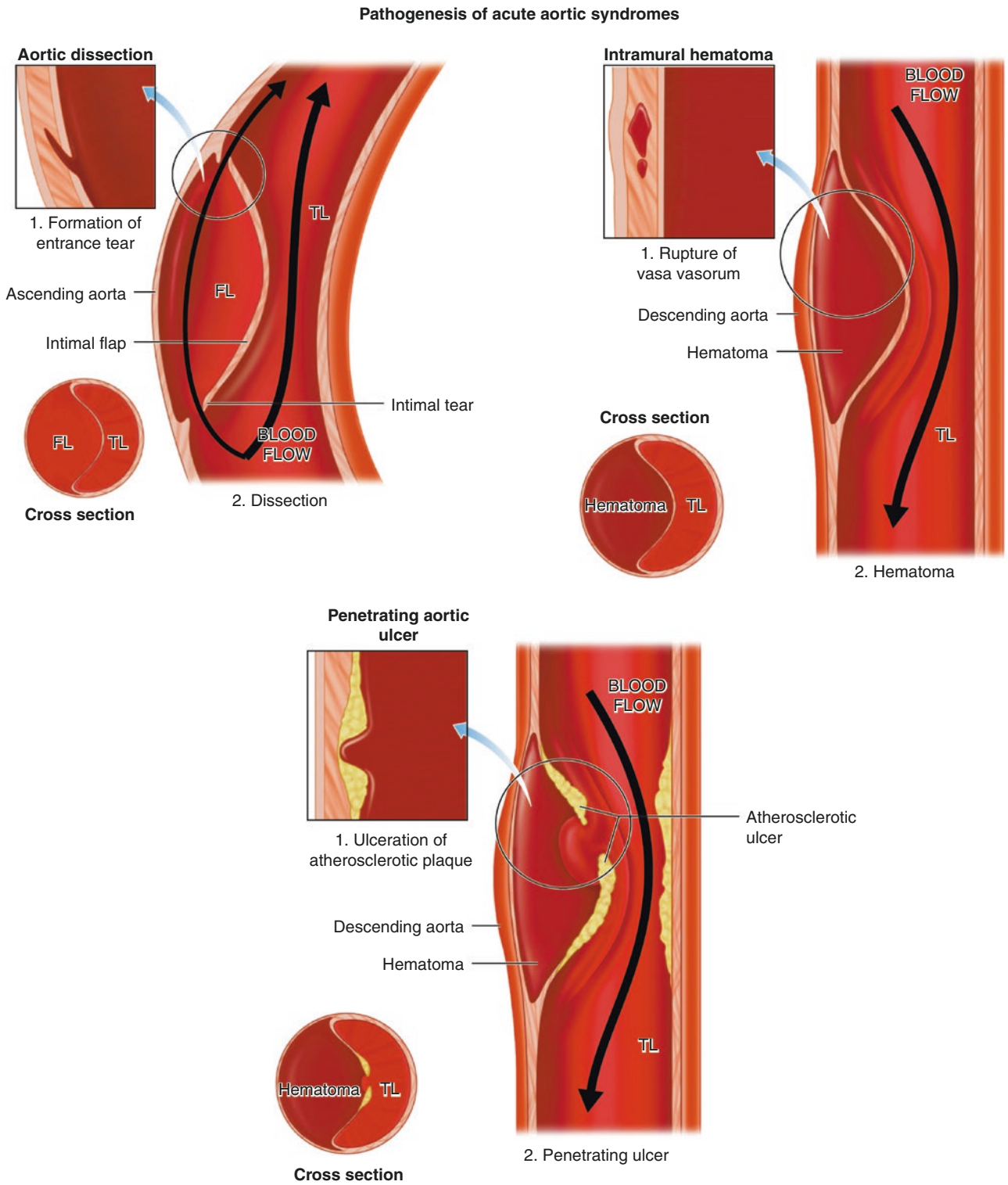

Fig. 9.1 Anatomy of the aorta and pathogenesis of acute aortic syndrome

linked fibrin and is the most widely utilized biomarker in dissection. In a meta-analysis looking at 883 AAD patients versus 1994 non-AAD patients, sensitivity was 95.2% and specificity 60.4% for a value of 500 ng/ml [21]. Short dissection, thrombosed FL, and young age are factors that may cause false negatives [21]. Elevated D-dimer is also an inde-

pendent risk factor for in-hospital mortality but not long-term mortality [22, 23]. In the IRAD Biomarkers study, ATAAD had a higher D-dimer value than other diagnoses such as myocardial infarction (MI) and pulmonary embolism (PE) [24]. Similar to PE, a level of 500 ng/mL can be used to rule out ATAAD with a NLR of 0.07 in the first day [24].

Troponin T may be an independent risk factor for in-hospital mortality, with a value greater than or equal to 0.042 ng/ml having a sensitivity of 70.8% and specificity of 76.4%. In a study of survivors versus non-survivors of ATAAD, pro-BNP had a mean value of 328 pg/ml in survivors, versus 2240 in non-survivors [25].

Other potential biomarkers which are not yet used clinically include fibrillin [5], matrix metalloproteinases [5], smooth muscle proteins [5, 8], and soluble elastin fragment [8].

Imaging

The purpose of imaging in ATAAD is not only to diagnose, but also to identify features that will be needed in downstream management – namely, site of tear, extent of rupture, and branch involvement [26]. The "classic" finding of widened mediastinum on chest x-ray was observed in only

Table 9.1 Classification of acute aortic syndromes

Stanford A (ascending +/− descending aorta)	Stanford B (descending aorta only)
DeBakey I (ascending and descending aorta)	DeBakey III (descending aorta only)
DeBakey II (ascending aorta only)	

Table 9.2 Penn classification of clinical presentation

Clinical presentation	Definition of clinical presentation class
Class a	Clinical presentation characterized by *Absence* of branch vessel malperfusion of circulatory collapse
Class b	Clinical presentation characterized by *Branch* vessel malperfusion with ischemia e.g. stroke; ischemic extremity
Class c	Clinical presentation characterized by *Circulatory* collapse with or without Cardiac involvement
Class b and c	Clinical presentation characterized by both *Branch* vessel malperfusion and *Circulatory* collapse

Reprinted from Augoustides et al. [10] with permission from Oxford University Press

Table 9.3 Acute aortic type A dissection presentation

	Frequency of occurrence
Symptoms	
Chest pain	79–93.4% [8, 12]
Back pain	47% [8]
Abrupt onset of pain	87% [13]
Neurological (syncope, seizure, stroke, spinal cord ischemia, hypoxic encephalopathy, neuropathy)	29% [16]
Syncope	16–21.6% [12]
Congestive heart failure	5% [13]
Signs	
Hypotension	29–46% [8, 13]
Hypertension	23.5–36% [8, 12]
Pulse deficit	27–32.5% [12, 13]
AI murmur	45% [8]
EKG findings	
ST-T changes	51% [18]
ST elevation	4–16% [17, 18]

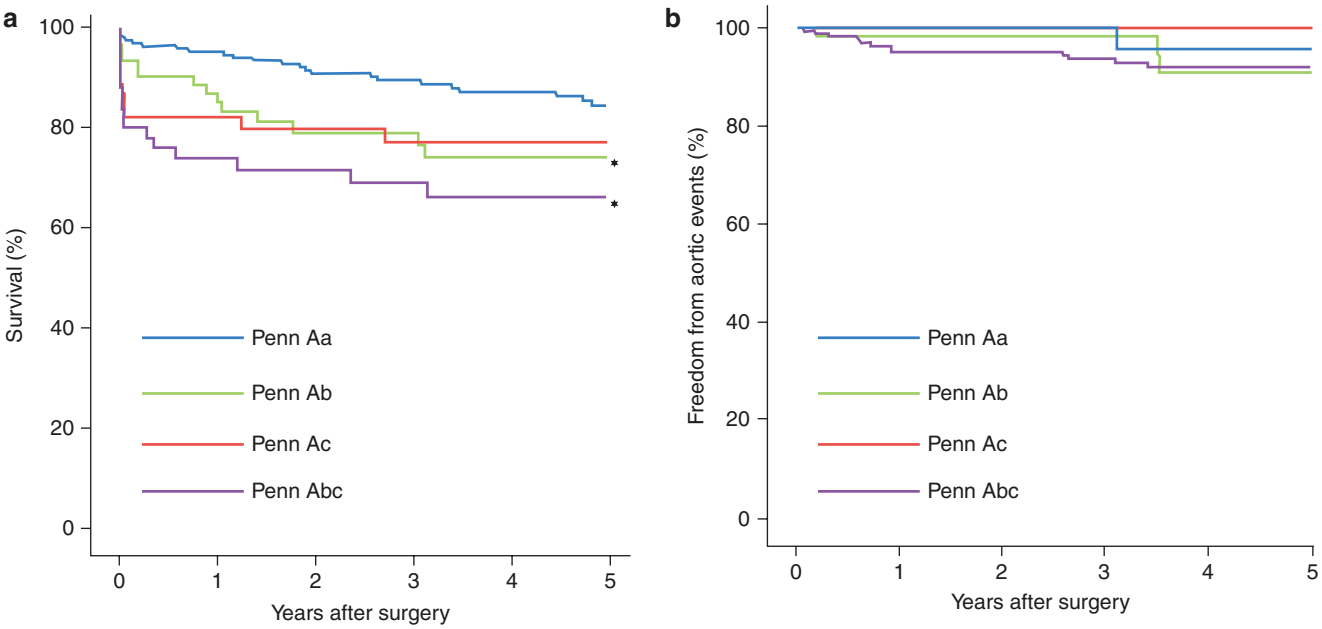

Fig. 9.2 Mortality stratified by Penn Classification (**a**) and freedom from aortic events in patients discharged with acute type A dissection (**b**). (From: Kimura [216]. Reprinted with permission from Elsevier)

37.4% of IRAD patients [27] and does not provide sufficient information for surgical planning.

CAT scan (CT) and transesophageal echocardiogram (TEE) are the most commonly used modalities, with CT having the advantage of wide availability and operator-independence [26]. During 17 years of data assessed by IRAD, CT use increased from 46% to 73% [12]. One downside to CT is that aortic flow may cause imaging artifact and be confused with a false lumen [26], but this can be minimized by using ECG-gating [28]. Features to look for include a double barrel lumen, entry tear, dilated aorta, and displaced aortic calcification [28] (Fig. 9.3). In one retrospective study, the presence of

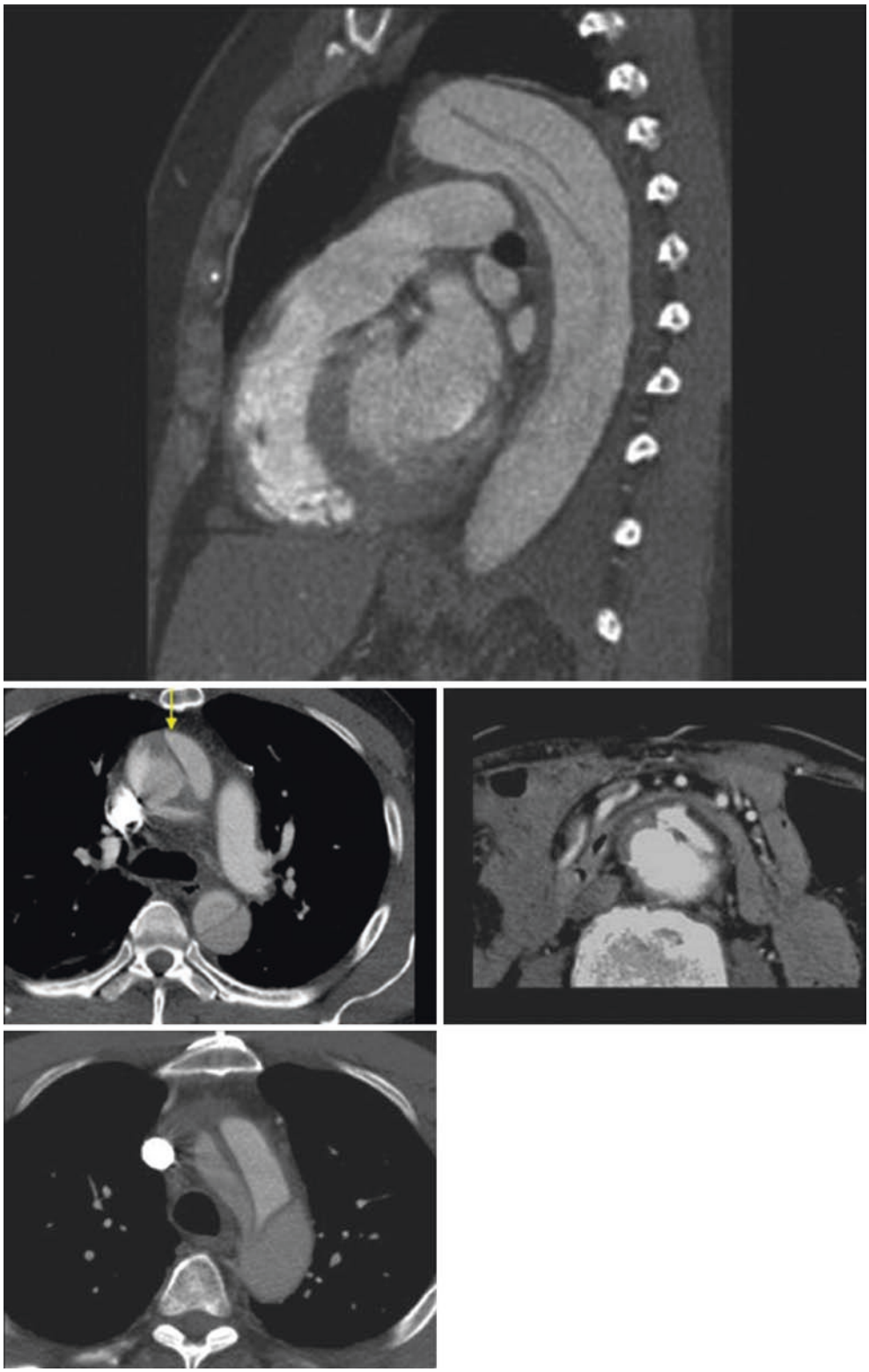

Fig. 9.3 Aortic dissection visualized on CT scan. (Images courtesy of Dr. TSA Geertsma, Ziekenhuis Gelderse Vallei, Ede, The Netherlands. Source: http://www.ultrasoundcases.info/)

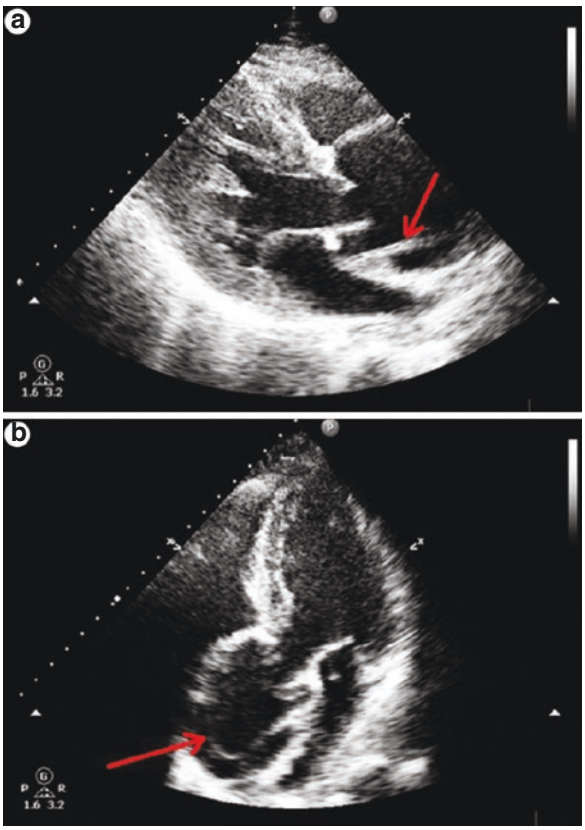

Fig. 9.4 TTE (level or aortic valve) shows tear in aortic root. (**a**) Parasternal long axis view. (**b**) Apical five-chamber view. (From Sobczyk and Nycz [217]. Open Access: © Sobczyk and Nycz; licensee BioMed Central. 2015)

a pericardial effusion and dilated ascending aorta were predictive of tear in the ascending aorta, whereas a non-thrombosed false lumen in the descending aorta predicted presence of a tear distal to the arch [29]. CT has a sensitivity and specificity of nearly 100% [30].

Transthoracic echocardiogram (TTE) (Fig. 9.4), while useful for assessing aortic insufficiency, dilatation, and effusion, has a low negative predictive value [31] and a sensitivity and specificity of 87% and 91%, respectively [28]. TEE (Fig. 9.5) is a mobile imaging modality that has strength in assessing effusion size and coronary involvement, but is less able to identify branch vessel involvement [26]. The test is operator-dependent, semi-invasive [26], and susceptible to motion artifact from reverberations off the anterior wall of the left atrium [31]. The presence of a patent false lumen on TEE is a poor prognostic factor [32]. Sensitivity for Type A dissection has been calculated at 96.8% and specificity 100% [28].

MR (Fig. 9.6) has a sensitivity of 95–100% [30] but is less widely available than other modalities, takes longer, and compromises access to patients with a life-threatening condition [33].

The responsibility of diagnosis in ATAAD typically falls on the emergency department. In a recent retrospective review of ATAAD cases, focused point-of-care cardiac ultrasound by an emergency department physician had a median diagnosis of 80 minutes versus 226 minutes in those who did not received focused ultrasound [34].

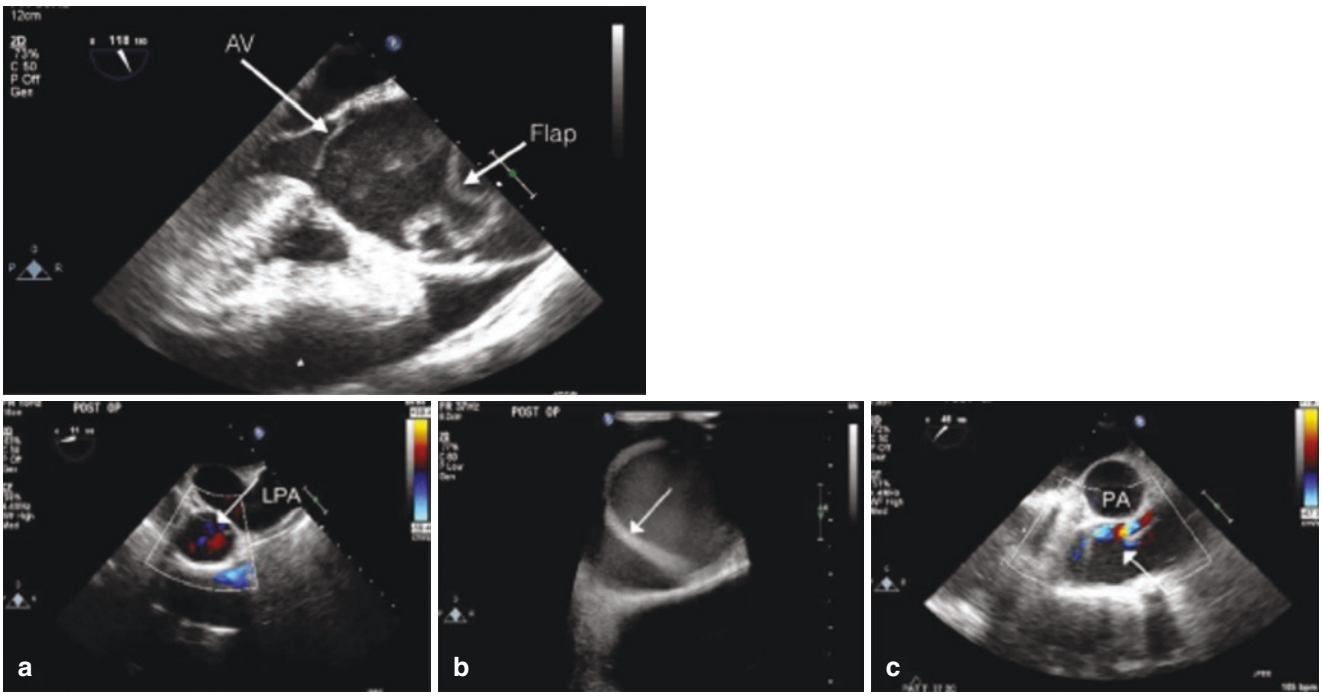

Fig. 9.5 (Row 1) Transesophageal echo long-axis view showing dissection flap (arrow) in ascending aorta. Asterisk indicates presence of hemopericadium. (Row 2) Ascending dissection shown in short-axis view (**a**), epiaortic view (**b**), and long-axis view (**c**). (Images reprinted from MacKnight et al. [26] with permission from Elsevier)

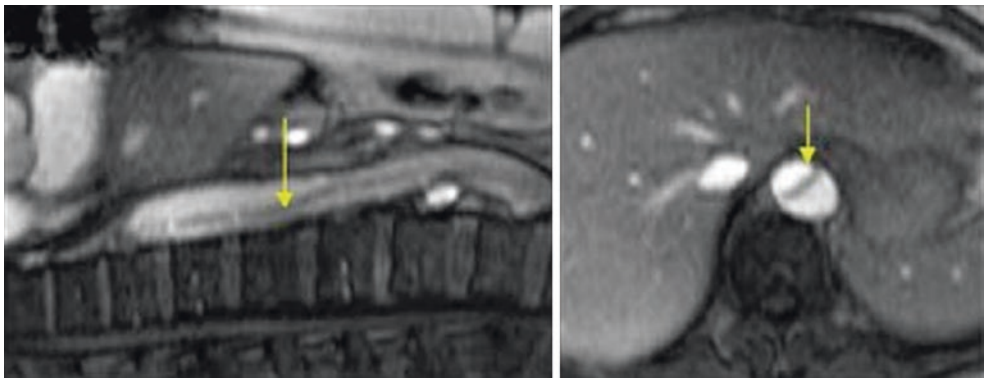

Fig. 9.6 MRI views (longitudinal, left and transverse, right) of intimal dissection. (Images courtesy of Dr. TSA Geertsma, Ziekenhuis Gelderse Vallei, Ede, The Netherlands. Source: http://www.ultrasoundcases.info/)

Diagnostic Error

Recognition of ATAAD in the face of more common chest pain syndromes is a priority in reducing mortality. Incorrect anchoring onto alternate diagnoses such as acute coronary syndrome may not only delay diagnosis, but may lead to harmful management such as use of antiplatelet or antithrombotic agents [35]. In one review of 127 patients with type A dissection, inappropriate initial diagnosis was made in 37% of cases and the median time to final diagnosis was 1.5 hours [36]. Diagnosis was further delayed in patients who had walked in and had coronary malperfusion [36].

Others have found much longer median time to diagnosis of 3–4.3 hours [37, 38]. IRAD data found that risk factors for delayed recognition include female sex, atypical pain, lack of hypotension, presentation to a non-tertiary facility, and presence of fever [37].

Diagnostic pitfalls may also be related to radiology interpretation. Chest x-ray is normal in 20–37.4% of patients [27, 39] and abnormalities on CT may be subtle, including displacement of aortic calcification or increased intimal attenuation due to thrombosis of the false lumen [39].

Management of Acute Type A Aortic Dissection

Type A aortic dissection is highly lethal, with mortality reaching 1–2% for every hour without surgical intervention [40, 41]. The guiding principles of acute type A aortic dissection management involve prompt recognition, transfer to intensive care for monitoring, and immediate impulse control – specifically reduction in heart rate, blood pressure, and LV ejection force, or *dp/dt* [40]. While patients are being evaluated for surgical intervention, or if they are deemed non-operable candidates, impulse control is achieved through the use of vasodilators, beta blockers, and calcium channel blockers. Arterial vasodilators, such as hydralazine, are relatively contraindicated as they may cause reflex tachycardia [42]. Adequate volume resuscitation and pain control should also be used to maintain a systolic blood pressure goal of 100–120 mm Hg [40].

Medical-Only Approach

Although type A aortic dissection is typically managed by immediate surgery, medical management alone is sometimes indicated. Indications for medical management alone may include stroke, severe comorbidities, prior aortic valve replacement (AVR), and late presentation more than 48–72 hours after dissection [40].

Heparinization of patients for bypass and the return of blood flow to infarcted areas of brain tissue in completed stroke are risk factors for hemorrhagic conversion [40, 43]. Therefore when stroke has been completed, risks of surgery may outweigh benefits, though the risk may be acceptable in evolving stroke [40]. A short series of four patients found that intentional delay in stroke patients before aortic surgery had beneficial outcomes [44]. On the other hand, recent data evaluating a more aggressive approach to patients with neurological injury did not show any cases of hemorrhagic conversion after anticoagulation for bypass [45].

Advanced age also increases risk for death, and outcomes in geriatric patients are described later. Age alone is not an absolute contraindication to surgery. Late presentation patients have survived the most dangerous window of dissection and can more safely undergo scheduled surgery. Previous AVR also allows delayed time until surgery, given lower likelihood that the patient will develop severe aortic insufficiency, protection of the right coronary artery from the prior graft placement, and lower risk of aortic rupture due to periaortic adhesions [40].

Centofanti et al., in a retrospective review, developed a risk equation to determine if operative benefit outweighed risk. Risk factors for mortality included age, coma, renal failure, shock, and reoperation. They found that in patients with mortality less than or equal to 58%, surgery was always beneficial [46].

Severe neurological deficit (ND), especially coma, has historically been a relative contraindication to surgery. Surgeons have become increasingly liberal when operating

on patients with neurological deficits and outcomes may be improving in this group. At one center, 8-year experience with a range of ND from comatose state to focal deficit underwent surgery, with over 50% of patients showing complete recovery. An elevated preoperative modified Rankin scale score was associated with persistent deficits [47], but even some patients with comatose state showed partial or full recovery. Notably, few comatose patients underwent surgery in this group [47]. In another recent single-center study of 24 comatose patients who underwent surgery, in-hospital mortality was similar to that of non-comatose patients, and long-term mortality was 60.3% at 5 years and 48.3% at 10 years [45]. Furthermore, Di Eusanio and colleagues published IRAD data showing that medical management alone was performed in 33.3% of coma and 24.1% of cerebrovascular accident (CVA) patients, and higher in-hospital mortality was observed in both groups compared to patients without ND. However, in those patients with ND who underwent surgical management, mortality was significantly less than in the medical management group. CVA patients had 76.2% mortality in the medical vs. 27% in the surgical group, while the coma patients strikingly had 100% mortality in the medical group vs. 44.4% in the surgical group [48]. Therefore, recent trends in management of severe neurological injury patients may begin to favor aggressive management.

Surgical Approach

Surgical repair is the mainstay of acute type A aortic dissection treatment, yet the optimal approach to surgery remains unknown. Diverse options include the extent of repair to be attempted, use of hybrid endovascular modalities, cannulation site, and cerebral perfusion strategy (Fig. 9.7).

Survival in type A aortic dissection is improved when performed by specialized aortic surgeons, rather than general cardiac surgeons. In a German study of 162 consecutive patients who underwent ATAAD surgery with a dedicated aortic team compared to a general cardiac surgery team, in-hospital mortality was 4% versus 21.8%, though surgical techniques were variable among the groups [49]. Other environmental factors which may improve outcomes include the development of an aortic dissection protocol [50] and performance of surgery at a teaching hospital [51] or a high volume center [51].

Extent of Repair and Risk of Reoperation

The over riding goal of aortic repair during type A dissection is to leave the operating room with a living patient. Repair typically involves excision of the primary entry tear in order to avoid extension of the dissection, prevent aortic rupture, and restore flow to the true lumen while obliterating the false lumen [41, 52]. As surgical techniques and outcomes have improved, the extent of repair has become open to debate, with the hope of not simply stabilizing the patient but also reducing the need for downstream intervention. Surgery may involve replacement of ascending aorta with a synthetic vascular graft and proximal arch repair only, versus extensive repair including the total arch, descending aorta, and/or root.

While proximal reoperations are most related to the degree of postoperative aortic insufficiency [53], distal reoperations are most often due to distal aneurysmal disease. At the Cleveland Clinic, 305 type A patients required 429 distal interventions during 3.8 years follow-up. The study's authors argued for more extensive repair in appropriate patients at the time of initial intervention [54]. Others have found that the descending aorta diameter grows at a rate of 1 mm/year after repair, with a risk of reoperation of 16% at 10 years [55]. In addition to distal aortic diameter, residual patency of the false lumen is predictive of late outcomes [55, 56].

Total Arch Replacement

Total arch replacement (TAR), as compared to hemiarch repair, is indicated in aneurysmal disease greater than 5 cm, arch rupture, and complex arch tear [57]. In studies comparing TAR outcomes to limited proximal repair, there was similar earlier mortality [57, 58], stroke [57], and reintervention rate [59, 60]. In most [61, 62] but not all [60, 63] studies, TAR led to increased thrombosis of the false lumen compared to hemiarch repair. In GERAADA, immediate postoperative complications such as bleeding were higher in TAR, but 30-day outcomes showed no difference compared to conservative arch repair [64]. However, one group of 188 patients, 44 with TAR, found greater risk of death and permanent neurologic injury with TAR [60].

Arch tears are uncommon and have not been extensively studied. In one center's study of 106 patients with ATAAD, 16 had arch tears and preoperative tamponade was a predictor of mortality. The rate of stroke was 6.6% and that of temporary neurologic dysfunction was 20% [65]. In another group of patients with 88 arch tears, in-hospital mortality was significantly higher for those undergoing TAR, and the authors recommended performing hemiarch repair only if the tear was limited to the lesser curvature [66].

Frozen Elephant Trunk Technique

Attempts to treat and prevent future distal aneurysmal disease at the time of ATAAD surgery has led to the increasing prevalence of graft placement in the thoracic aorta. The classic elephant trunk technique was first described by Borst in 1983 in which the arch replacement prosthesis is connected to an "elephant-trunk" piece which reaches into the distal aorta and allows a landing site for future repairs [67]. The frozen elephant trunk technique is a newer method that uses

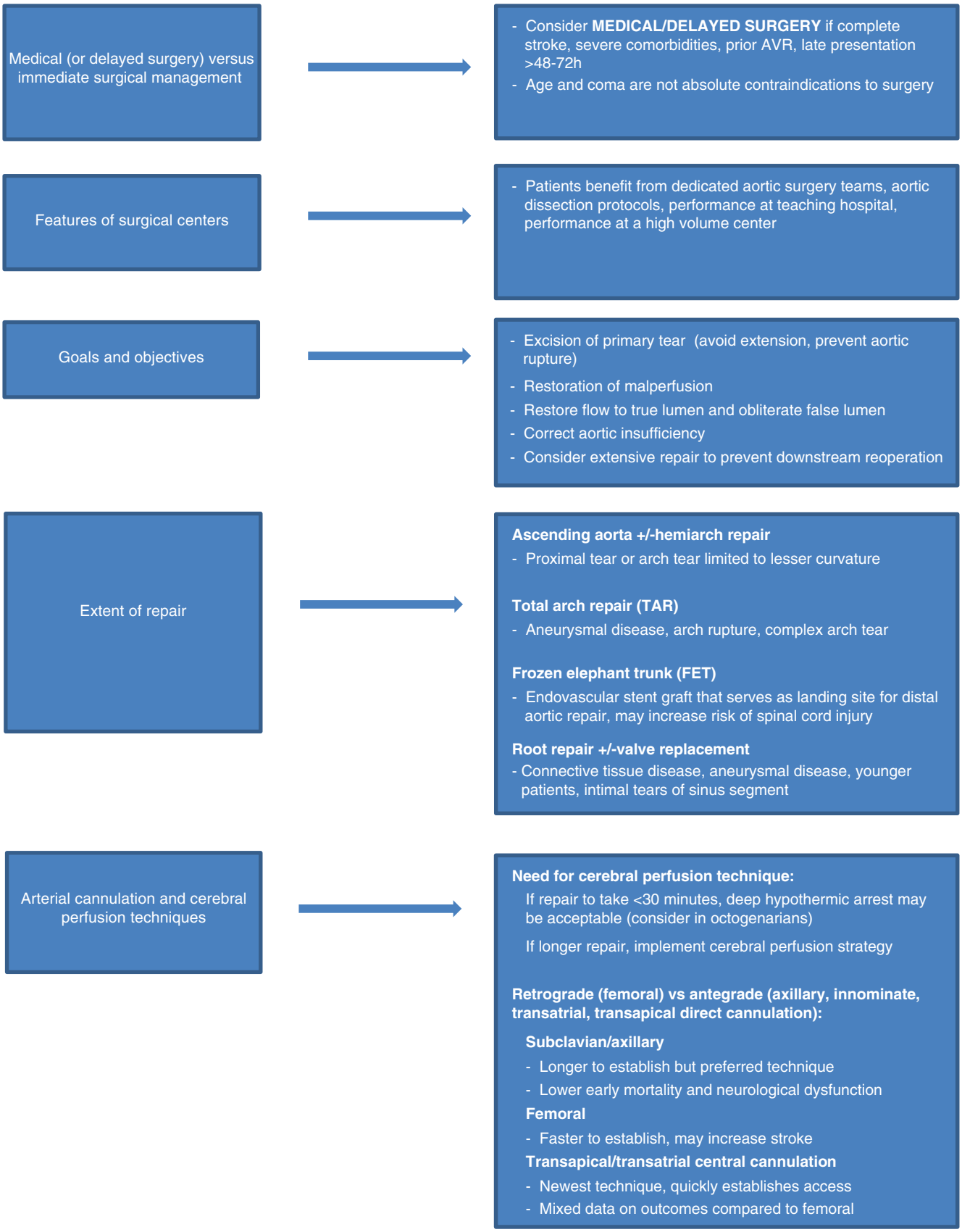

Fig. 9.7 Management algorithm for ATAAD. (Data from Dougenis [218])

an endovascular stent-graft connected to the arch graft, allowing a single-stage distal aortic repair [41, 67].

FET has enjoyed mainly positive findings, leading to a surge in its popularity. It is often described as the "new standard" for ATAAD surgery [68]. Numerous centers have found that FET either decreases or has low rates of reintervention on the distal aorta [62, 69–71]. In one analysis of 197 patients, thrombosis of the false lumen was found in all of the patients in the TAR + FET group and only 24.6% of the limited repair group ($p < 0.001$) [62].

Two meta-analyses have assessed FET outcomes. An analysis of eleven observational studies including 881 patients found acceptable in-hospital mortality at 8%, neurological outcomes of stroke 4%, and spinal cord injury (SCI) of 3% [72]. While some centers have found that FET decreases mortality [73], others have found similar in-hospital mortality to the classic ET [62, 74]. In another analysis of nine studies looking at 1872 patients comparing proximal aortic repair (ascending aorta repair +/− hemiarch) and extensive aortic repair (replacement of ascending aorta and aortic arch + elephant trunk implantation in descending aorta), hemiarch replacement had a lower early mortality than TAR. Proximal repair, however, was associated with a higher incidence of long-term aortic events such as reoperation. The long-term mortality was similar in both approaches [75].

Concerns about FET revolve around feared neurological complications, including SCI. FET requires longer bypass and surgical times, and the placement of endovascular stents increases the risk of SCI. While conventional elephant trunk surgery has a low rate of SCI, FET has ranged from 4% to 22% in patients undergoing acute repair [74, 76–78]. Additionally, a comparison of hemiarch + FET compared to TAR + FET showed similar mortality but fewer transient neurologic deficits in the hemiarch group [79].

Root

Root repair and valve replacement are another source of debate in the extent of surgery performed for acute dissection. Options for repair include a Bentall procedure with biological or mechanical aortic root replacement (ARR), or valve-sparing surgery such as the David procedure. In patients for whom the root is involved, a root-sparing technique had lower mortality compared to valve replacement (1.9 vs. 12.5%) in a group of 86 patients [80] but was similar in numerous other studies [81–87]. The greatest benefit for ARR is in patients with connective tissue disease [82, 87–89], aneurysmal disease [88, 90], younger age [89], and intimal tears of the sinus segment [88, 91].

Bicuspid and Marfan Patients

Acute type A aortic dissection occurs approximately 20 years earlier in patients with Marfan Syndrome than without, and repair for ATAAD accounts for 16–35% of aortic procedures performed in this population. Though in-hospital mortality for these patients was low in a retrospective study of repair for AATAD in Marfan Syndrome at tertiary care centers in the United States and Europe, they recommend root replacement in these patients [92].

Bicuspid aortic valve (BAV) patients who present with type A dissection are younger, have more aortic insufficiency, and have larger ascending aortic diameters than do tricuspid valve patients. Root repair is required six times more often in BAV patients [93].

Temperature and Cerebral Perfusion Technique

The German Registry for Acute Aortic Dissection Type A found that hypothermic circulatory arrest alone was appropriate if the repair could take less than 30 minutes, but once it exceeded this time limit, mortality increased three-fold. This suggests that a cerebral perfusion strategy should be implemented during more complex procedures [94].

Retrograde cerebral perfusion was one of the first adjunctive techniques introduced [95], which utilized perfusion via the SVC but could result in cerebral edema [96]. The more common adjunct now used is selective antegrade cerebral perfusion (SACP), which can be unilateral or bilateral, and involves cannulation of the head and neck vessels [94]. Antegrade technique has shown similar [97, 98] or more favorable [99, 100] outcomes compared to retrograde perfusion.

Recently, moderate levels of hypothermia >24C have been used successfully along with antegrade or retrograde cerebral perfusion methods [101]. One study of patients who underwent repair at Emory from 2004 to 2014 found similar outcomes in patients who underwent deep and moderate hypothermic circulatory arrest, with no significant difference in stroke or dialysis-dependent renal failure [102]. Moderate hypothermia may allow for a decrease in bypass time as compared to that with deep hypothermia protocols [103]. Another recent study of ATAAD repair found that there was no additional benefit of using deep hypothermic cardiac arrest (DHCA) compared to moderate hypothermic cardiac arrest (MHCA) when SACP was used [102].

Cannulation Strategy

Arterial cannulation is necessary for cardiopulmonary bypass during ATAAD surgery and can be performed in a retrograde (femoral) or antegrade (axillary, innominate, transatrial, and transapical direct cannulation of the aorta) fashion [104]. In two meta-analyses, axillary cannulation showed lower early mortality and neurological dysfunction than did femoral cannulation [105, 106]. Similarly, a best evidence topic found that femoral artery cannulation mortality and stroke occurred at rates of 6.5–40% and 3–17%, com-

pared to axillary rates of 3–8.6% and 1.75–4% [107]. The main downside to femoral access is that retrograde flow is thought to cause reverse embolization through pressure in an atheromatous descending aorta [105].

While axillary cannulation takes longer than femoral access to establish [105], central cannulation can be quickly achieved in order to establish circulatory arrest [108–110]. Some groups have found that stroke and overall mortality were lower in transatrial cannulation compared to femoral [104]. Others found no mortality or stroke reduction when comparing central cannulation to femoral cannulation [108, 109, 111]. Outcomes such as respiratory failure have mixed data, with some showing more respiratory failure with central cannulation [112], while others show shorter intubation times [113].

Outcomes

Mortality

In-hospital and long-term mortality for ATAAD remain elevated but have been improving over the last few decades [114, 115]. In type A patients who underwent surgical repair in the National Inpatient Sample, mortality decreased from 20.5% in 2003 to 14.8% in 2012 [115]. Others have found early mortality rates of 16.9–25.7% [116, 117], with predictors of in-hospital mortality including comatose state, number of malperfused organs, older age, and need for cardiopulmonary resuscitation [117, 118].

Prior cardiac surgery is also associated with significantly higher in-hospital mortality compared to patients without prior cardiac surgery, with rates varying from one third [119], to double [120], or almost triple [121] those without prior cardiac surgery.

In a multicenter Italian study spanning 33 years of follow-up, survival was 95.3% at 5 years, 92.8% at 10 years, and 52.8 at 20 years [116].

Malperfusion: Complicated and Uncomplicated Dissection

Malperfusion is a dreaded complication that can occur preoperatively, intraoperatively, or postoperatively and is associated with both perioperative and long-term mortality. Perfusion defects result when aortic side branches are compromised and can be classified as static or dynamic. Dynamic refers to malperfusion that occurs from the intimal flap decreasing blood flow to vital organ systems; restoring blood flow via the true lumen will therefore reinstate perfusion [122]. Static malperfusion syndromes (MPS) are the result of stenosis, thrombosis, or dissected artery [52]. Approximately one third of patients with ATAAD present with a malperfusion syndrome [123–126].

In a study of GERAADA patients ($n = 2137$), there was a linear correlation between the number of malperfused organs and increase of mortality of 10% [127]. Given this dramatic worsening of outcome with malperfusion, the authors argued for classifying dissection as either complicated or uncomplicated based on the presence of malperfusion. In the postoperative period, cerebral malperfusion was seen in 6.8% of patients, renal 6.8%, visceral 6.8%, peripheral 3.3%, coronary in 1.9%, and spinal 1.1%.

Complicated dissection is associated with worse survival, with patients at the University of Michigan showing median survival of 54 months if complicated versus 96 months if uncomplicated [122]. Similarly, Olsson et al. found that Penn class at presentation corresponds to mortality [128]. Other poor outcomes of complicated dissection include coma, MI, sepsis, delirium, renal failure [129], and prolonged ICU stay [124]. One look at quality of life in patients who presented with MPS found no difference from non-MPS patients, except in the case of CNS malperfusion [130].

Mesenteric ischemia has high morbidity and mortality, with 3.7% of IRAD patients showing mesenteric malperfusion on presentation. These patients showed significantly greater mortality than those without mesenteric malperfusion (62.3% vs. 23.8%) and were more likely to show malperfusion in additional organ systems including coma and renal failure [131]. Others have shown mortality that is as high as 75% [124]. Some case reports argue for addressing the mesenteric ischemia first during repair [132, 133].

In 502 patients from the Emilia-Romagna Regional Registry, 20.5% of patients presented with malperfusion, and had higher in-hospital mortality than did the non-malperfusion group (43.7% vs. 15%, $p = 0.001$). Like in the GERAADA data, multiple organ systems were associated with worse survival – single-organ malperfusion had a mortality rate of 34.7%, two systems 61.9%, and more than two 85.7% [123].

Patel et al. looked at delaying aortic repair in patients who have MPS, given a lower likelihood of surviving aortic repair. They found that patients who did survive to the aortic repair had similar mortality to those with uncomplicated dissection [125]. In a study that combined both type A and B dissections, patients with MPS had triple the operative mortality compared to uncomplicated patients [134].

Shiya et al. proposed techniques for addressing complicated dissection by system – CABG for coronary malperfusion, SCP for cerebral malperfusion, CA and SMA bypass in visceral malperfusion, and fem-fem bypass in unilateral lower extremity malperfusion [135]. Coronary malperfusion is found in 6–15% [41, 136, 137] of patients and most often compromises the right coronary artery [41].

Independent predictors for both neurologic injury and postoperative renal failure include age, prolonged cross-clamping time, and longer cerebral perfusion times. Renal failure is also predicted by preexisting renal impairment [138].

Age

Whether or not to perform surgery in older patients, who frequently have more comorbidities than younger counterparts, has been the source of debate. In patients of all ages, hemodynamic instability is predictive of poor outcomes [139].

While greater extent of repair has overall become the trend in ATAAD surgery, many centers have focused on limited repair to just the ascending aorta or hemiarch to allow for shorter surgical times in octogenarians [140–143]. Extension of the dissection into the supraaortic vessels and down to the abdominal aorta actually decreases with age [144], however if arch surgery is needed, it may be a predictor of mortality [145]. The elderly may have a non-significant trend toward more tamponade and intubation at the time of surgery [146]. A "less invasive quick replacement" technique involving no cerebral protection strategy and rapid rewarming shortened surgical times [147] and decreased mortality [148].

GERAADA found that septuagenarians had an early mortality rate of 15.8%, which was similar to the entire registry's 30-day mortality of 16.9%. Octogenarians, however, had more than double the early mortality at 34.9% [149]. Most others have found similar high perioperative mortality [142, 145, 150–152] though a few reports have found comparable in-hospital mortality to younger patients [153–155]. In IRAD, patients from 70 up to 80 had significantly decreased in-hospital mortality with surgical compared to medical management, whereas 80–90 year olds had decreased mortality with surgery (37.9% vs. 55.2%), but it failed to reach significance [156].

Discrepancies in mortality are also seen in longer term outcomes in the elderly. One year survival is 53.3–82% compared to generally more than 90% in younger patients, and five-year mortality 42.6–76% [140, 142, 157, 158]. Successful ATAAD surgery has been performed in a nonagenarian [159].

Generally, surgical treatment in the elderly is recommended given higher but acceptable perioperative mortality compared to medical management only [160]. One study found higher rates of neurological complications in the elderly which trended down with SACP [161] and others have found no significant difference in temporary neurologic dysfunction when SACP was used [162]. However, further study is needed to determine long-term outcomes, with some centers finding a decreased ability to live independently [158] while others found higher emotional well-being scores compared to younger patients [154].

On a study of root replacement in octogenarians, only some of whom had type A dissection, in-hospital mortality was similar to that in younger patients but there was greater postoperative atrial fibrillation [163].

Young patients between ages twenty and forty have lower mortality, ranging from 11% to 14% at 30 days, with mortality rising with age [144, 164]. Etiology of dissection in the young includes bicuspid aortic valve, connective tissue disease, cocaine use, and severe hypertension [164] and reoperations at the root were needed in 40% of patients [164]. These patients typically have larger aortic diameters than older patients [165]. Neurological outcomes in GERAADA did not differ among age groups [144].

Race

Little data is available on outcomes by race in acute aortic dissection. IRAD compared black and white patients, and found that the black cohort had significantly more HTN, DM, and cocaine use. They more often presented with abdominal pain and LVH on echocardiogram. Despite differences in presentation and risk factors, in-hospital and 3-year mortality between groups were similar [166].

Sex

Presenting characteristics for men and women differ in ATAAD, but whether there is a true difference in outcomes is unknown. Women experience type A dissection less frequently than do men, and therefore, fewer women are represented in registries and trial data. In 2004, IRAD included 32.1% women and showed that women presented for ATAAD at an older age than did men [167], with additional studies showing the age range for men 58–59.7 and women 67–71.5 [168, 169]. Women were more likely to present with coma, altered mental status, hypotension, and tamponade [167].

Early data showed that women had higher in-hospital mortality even after adjusting for age [167], however more recent data showed similar early and late mortality between sexes [168, 169]. One trial showed different findings, with more neurologic deficits in men and greater mortality in women [170]. Interestingly, surgeons' approaches to women may differ than approaches to men in surgical technique. In an analysis where women were an average age of 71.5 compared to 59.7 in men, women had less extensive surgery (less TAR and root surgery) and shorter surgical times. The difference in approach may be attributed to the older age at presentation of women, a finding that warrants further investigation [171].

Women are also less likely to be discharged on beta blockers than men, though not significantly [168].

The pathophysiology that explains sex-based differences is unclear. A study of aortic geometry throughout life in

patients without aortic pathology showed that women have smaller aortic dimensions at younger ages, but their aortic dimensions increase at a faster rate than men's rates [172]. When indexed by body-surface area (BSA), women's ascending aortic length increased by 2.9% per decade compared to 2.5% in men, and aortic diameter increased 3.4% in women compared to 2.6% in men. At older ages, women had higher BSA-adjusted aortic diameters than men [172].

Pregnancy

Type A dissection is rare in pregnancy but accounts for more than three-quarters of dissections that occurs in pregnant patients and has a maternal mortality of 21% [173]. The pathophysiology of pregnancy, including increased estrogen binding to aortic wall estrogen receptors and increase in cardiac output, elevates wall stress and can bring about dissection in those already at risk [173]. The third trimester, when intravascular volume has increased and hemodynamic effects of pregnancy are greatest, is when most dissections occur [174]. Marfan syndrome is associated with more than half the associated cases in the literature [173]. In a review of 75 cases of dissection in pregnancy, fetal mortality was reduced if C-section was performed concomitantly with aortic repair [173]. Current recommendations for dissection follow general guidance of cardiac surgery in pregnancy, suggesting maintaining a MAP > 70 mmHg and avoiding deep hypothermic arrest [174].

LV Function

While mortality is the major outcome of concern after type A dissection repair, long-term outcomes such as LV function have been studied. In a study of 97 patients who underwent valve-sparing aorta replacement (VSAR), supracoronary ascending aorta replacement (SCAR), and aortic valve and aorta replacement (AVAR), aortic regurgitation was greater in those who underwent only partial repairs compared to AVAR. Although immediate postoperative LV function was similar among surgical techniques, the SCAR group showed late adverse LV remodeling [175].

Iatrogenic Dissection

Iatrogenic aortic dissection is an uncommon but real complication during coronary procedures and cardiac surgery. It occurs in <0.1% of patients who undergo coronary angiography(176–178), most often when trying to engage a coronary artery, and generally has favorable outcomes despite the use of antithrombotics and antiplatelet agents [176]. Retrograde dissections typically self-sealed, while anterograde with an entry point at a coronary artery could be sealed with a stent [176]. The incidence of dissection during cardiac surgery is more common, ranging from 0.06% to 0.29% of cases [177–179] with mortality as high as 40% [179]. One group suggested that intraoperative TEE may be responsible for their observed decrease in iatrogenic dissection over time [179].

Follow-Up

In patients who survive ATAAD, serial imaging is recommended at 1 month, 3 months, 6 months, 12 months, and annually if no concerning features are found [5].

Hypertension control is the main parameter monitored in the follow-up period, with lower blood pressure and beta-blocker use associated with freedom from reoperation [180]. In one analysis of ATAAD patients, freedom from reoperation was 99%, 82%, and 79% at 1, 5, and 10 years respectively [181]. Proximal risk factors for reoperation included the use of glue and root preservation, while distal reoperation was more likely with a patent false lumen [181]. Others found that a patent false lumen was associated with significantly greater growth rate of the aorta, but this growth did not translate into higher distal reoperation rate [182]. Another group found that late reoperation wad predicted by a non-resected primary tear, Marfan syndrome, lack of beta-blocker use, and persistent hypertension [183].

Limited data is available on quality of life and changes in lifestyle after dissection. One study of survivors, which acknowledges recall bias, surveyed 82 out of 197 patients, over half of whom had ATAAD, a median of 7 years after discharge [184]. More patients said that they exercised than pre-dissection, which corresponded to lower blood pressures than those who did not exercise. While before dissection 38% of patients lifted for their occupation, only 3% (one patient) lifted afterwards [184]. Seventy-six percent of patients felt that dissection had negatively impacted their lives, due to burden of doctor visits, number of medications, activity limitations, fear, and impact on sex life. About one third self-reported depression and one third anxiety [184].

Intramural Hematoma (IMH)

Epidemiology and Presentation

IMH is an acute aortic syndrome that occurs when blood from the vasa vasorum infiltrates the medial layer [185], but there is no intimal tear and the hemorrhage does not communicate with the lumen (Fig. 9.8) [5]. Blood pools close to the adventitial layer [186] which increases the risk of tamponade [187]. IMH is classified into type A and type B like dissection, with type A having greater mortality [4] but type B comprising the majority (50–85%) of cases [187, 188].

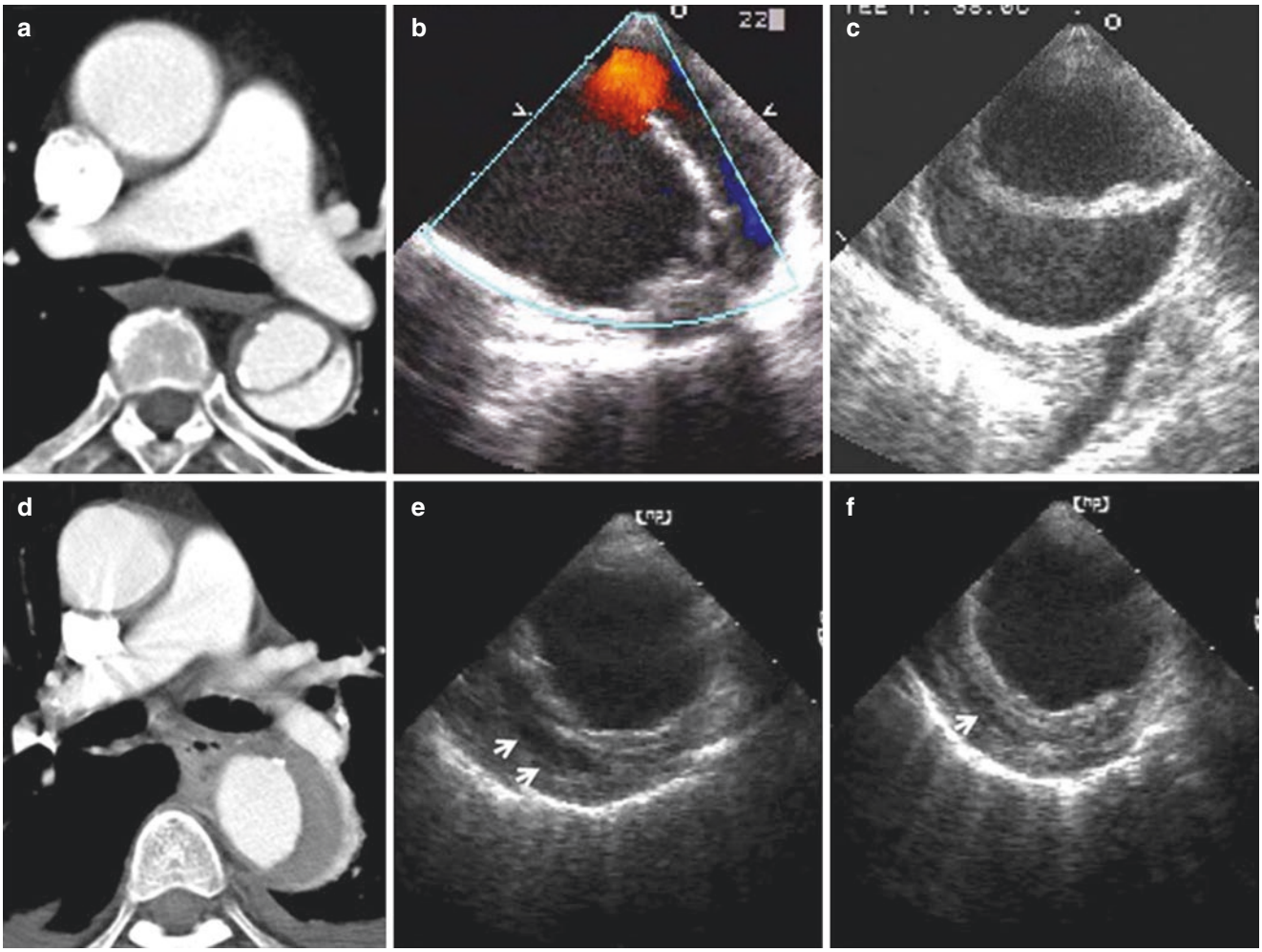

Fig. 9.8 Comparison of aortic dissection on CT and TEE (**a**–**c**) and intramural hematoma (**d**–**f**). (Reprinted from Song et al. [194] with permission from Springer)

Approximately 16–47% of patients with IMH progress to full dissection [4]. IMH patients tend to be older [189, 190], have more hypertension [191, 192], and have more pericardial effusion [190] and tamponade [191] than do classic dissection patients but are less likely to present with malperfusion [191–193], aortic insufficiency [189, 191, 193], or have Marfan syndrome [194]. Like dissection patients, IMH patients typically present with chest pain, but they are more likely to have a normal EKG [189].

Interestingly, IMH is more common in Asia where one third to one fourth of all type A dissections are the result of IMH [188].

Diagnosis, Treatment, and Outcomes

CT, MRI, and TEE are all used to diagnose IMH [195]. On noncontrast CT, IMH appears as an area of high attenuation, but it can be easily missed on first imaging due to appearing like a thrombosed false lumen [31]. IMH should result in wall thickness > 7 mm and appear crescent-shaped [187]. MRI is particularly sensitive in assessing abnormalities of the vascular wall [187].

Medical versus surgical management is controversial in type A IMH, with Western countries favoring surgical management. There are mixed outcomes looking at medical management in Asia. In a Korean registry of 165 patients, there was no significant difference in in-hospital or two-year mortality between medically and surgically managed patients [196]. A review of 328 cases of type A IMH in twelve studies also concluded that there was no significant difference in early mortality between medical and surgical approaches, however up to 40% of patients progressed to dissection or aneurysm downstream [197]. A best evidence topic, though, found that there was lower mortality in type A IMH with a surgical approach [198]. In a group of 179 patients, the medical management group had higher mortality including more emergent surgery for pericardial tamponade [199]. Others

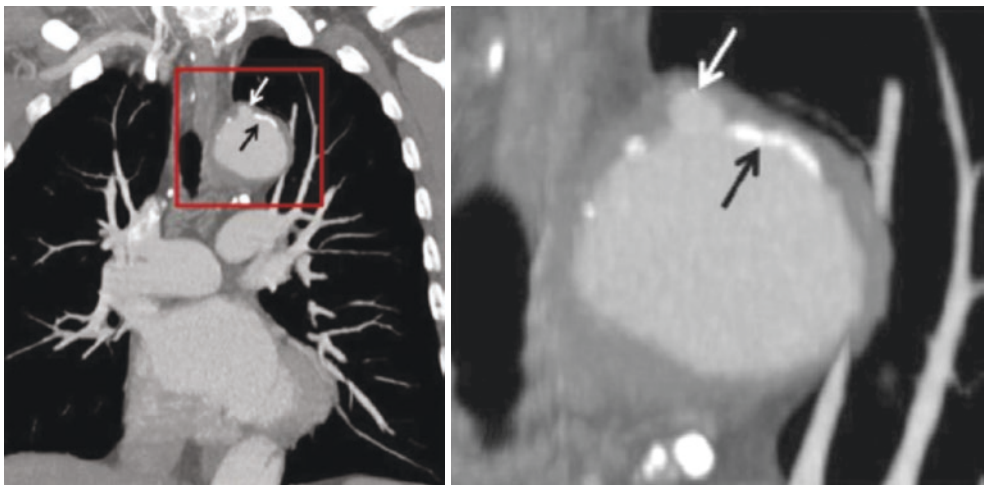

Fig. 9.9 Penetrating atherosclerotic ulcer (PAU) with outpouching (white arrow) visible through calcification (black arrow). (Reprinted from Nathan et al. [205] with permission from Elsevier)

found that up to 30% of patients progressed to true dissection when managed medically [200]. When patients are medically managed, conversion to true dissection is not always immediate, and may actually be more common after 8 days [201].

Aortic diameter > 50 mm [200, 202] or 55 mm [203] and hematoma thickness > 16 mm are predictive of adverse aortic events [203]. In a group of patients with both type A IMH and dissection, a ratio of false lumen thickness/aortic diameter > 0.98 was predictive of adverse aortic outcomes [204].

Penetrating Atherosclerotic Ulcer (PAU)

PAU is the least common acute aortic syndrome, comprising less than 10% of cases [26, 205]. PAU occurs when an atherosclerotic plaque erodes through the internal elastic lamina into the media (Fig. 9.9) [8]. It was first described as a separate entity from dissection by Stanson et al. in 1986 [206]. On pathologic examination, plaque erosion leads to medial hemorrhage and pseudoaneurysm of the aortic wall, which is distinct from cystic medial necrosis seen in dissection [207]. PAU is more likely than type A dissection to rupture the aorta, with 32–42% resulting in rupture [5, 208]. PAU may also progress to dissection [209]. The ulcers vary in depth from 4 to 30 mm and in diameter from 2 to 25 mm [209].

PAU is generally a disease of the descending thoracic aorta, occasionally the arch, and exceedingly rare to find in the ascending aorta though case reports are available [210–213]. The entity is described in more detail in the chapter on descending aortic diseases. In one study of 328 PAU detected on CTA, 27 occurred in the arch and none in the ascending aorta [205]. In another series, 2 out of 15 ulcers were in the ascending aorta [214]. Risk factors for PAU include comorbidities that contribute to atherosclerosis, including older age [214, 215], male sex [202], and hypertension [202].

Type A PAU are generally repaired surgically [215], though there is debate about how best to manage these ulcers in the descending aorta when their symptomatology varies from incidental finding to aortic rupture [202]. Increasingly, endovascular repair is being used for these lesions in the descending thoracic aorta [209].

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Descending Aortic Dissection, Penetrating Aortic Ulcer, and Intramural Hematoma (Acute and Chronic) Including Kommerell's Diverticulum

10

Marc P. Bonaca

Introduction

The descending aorta may be affected by a spectrum of entities characterized by the disruption of the aortic integrity including aortic dissection (AoD), intramural hematoma (IMH), and penetrating aortic ulcer (PAU). These entities are often diagnosed in the acute setting where they are associated with a high risk of complication including organ ischemia, rupture, and death. In patients surviving their acute presentation, they are associated with adverse remodeling leading to ischemia or aneurysm development. In addition, a rare but increasingly recognized congenital abnormality called a Kommerell's diverticulum is a cause of aneurysm in the subclavian arteries or arch and presents a management challenge for clinicians.

Diagnosis and management of these entities remains challenging due to their rarity relative to other cardiovascular complications, the non-specific nature of symptoms in the acute phase, and their lack of associated symptoms in the chronic phase even when adverse remodeling is occurring. In the acute phase, rapid diagnosis is essential as the risk of death or major complication is particularly high early in the clinical course. Establishing and characterizing the diagnosis may maximize the opportunity for successful therapeutic intervention [1, 2]. Typically, acute aortic syndromes that do not involve the ascending aorta (Type B) have been managed medically unless complications are present [3]. The role of endovascular aortic intervention including fenestration and stent grafting (TEVAR) in the management of patients with Type B acute aortic syndromes is rapidly evolving. Clinically, vigilance is necessary as patients may evolve early in their course and experience complications requiring intervention after initial triage to medical management. As patients transition to the chronic phase, multidisciplinary follow-up and serial imaging are critical for the early detection and planned treatment of adverse remodeling.

Definitions

Acute aortic syndromes involving the descending aorta include AoD, IMH, penetrating aortic ulcer (PAU), acute aneurysm expansion, and trauma [3, 4]. These entities may present alone or in combination and represent a spectrum and evolution of aortic disruption. Aortic dissection typically results from an intimal tear that allows pressurized blood into the often weakened medial layer leading to propagation of the plane front either antegrade or retrograde directions [4]. The resulting flap of tissue divides the aorta by creating a second or "false" lumen along the native or true lumen. The intimal flap may lead to complications such as malperfusion through branch vessel occlusion. The patency and degree of fenestration of the false lumen may impact patency and pressurization. The false lumen may communicate with the true lumen via one or more re-entry tears distal to the entry site, which may allow for false lumen decompression. Alternatively, there may be no or limited re-entry tears, causing the false lumen to functionally act as a "wind sock" characterized by elevated false lumen pressures. This pressurized space may lead to further propagation, outward remodeling and aneurysm formation, compromise of the true lumen, occlusion of branch vessels, or ultimately progression resulting in rupture. Observational studies have described this status of flow within the false lumen as prognostically important in patients with Type B dissection [5]. Although medial disruption is generally a unifying feature in dissection, cases of isolated intimal tears without false lumen formation do occur [6].

Intramural hematoma (IMH) results from either medial hemorrhage from ruptured vasa vasorum, progression of a PAU, or in theory a microscopic intimal tear isolated from the lumen. Isolated IMH comprises approximately 5–15% of

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acute aortic syndromes [7–10]. The natural history of IMH is variable with approximately one-third resolving spontaneously and the remaining two-thirds evolving into classic dissection, aneurysm, or pseudoaneurysm formation.

Penetrating aortic ulcers (PAU) tend to occur in the setting of atherosclerosis most commonly in the descending thoracic aorta of elderly patients. They are believed to form from inflammatory erosion of the internal elastic membrane. The natural history is variable with some healing and some progressing on to greater disruption of aortic integrity including IMH or dissection [11].

Dissection, IMH, and PAU are all associated with the disruption of the aortic integrity and are generally believed to occur along a spectrum of presentation and evolution. All can cause similar symptoms; however, by nature of the related flap and false lumen, dissection most commonly leads to complications such as malperfusion [7, 10]. Registries describe dissection as the most common followed by IMH and PAU, respectively [3]. Outcomes are best understood for patients with aortic dissection with the natural of IMH and PAU less well described by the nature of their lower frequency. Management strategies are generally similar across the three entities when involving the descending aorta [3].

Chronicity

Most often, acute aortic syndromes are identified in the acute setting. The natural history and associated risks depend on the chronicity of the disruption. Findings that are present for 2 weeks or less are defined as acute and those that are present longer are described as chronic [3]. Others have further divided the course into hyperacute (<24 hours), acute (2–7 days), subacute (8–30 days), and chronic (>30 days). These time categories have been associated with survival [12]. Mortality is highest early with rates for untreated ascending dissection described as high as 75% at 2 weeks [13].

Pathogenesis

Medial degeneration often characterized as cystic medial necrosis is generally invoked as the pathobiology underlying the development of acute aortic syndromes [3, 4]. This finding is not etiology specific and is associated with typical risk factors such as age and hypertension as well as several other disorders. In general, any process that damages the tunica media leading to degeneration will increase the risk of aneurysm or dissection. Several biological processes have been discussed as contributing to the etiology including inflammation, oxidative stress, and disrupted P53-MDM2 signaling [14, 15]. There is also an increasing appreciation of the role of transforming growth factor (TGF) B signaling [16]. A population of younger patients are at heightened risk of aortic disruption due to an underlying connective tissue disorder related to genetic disorders including Marfan Syndrome resulting from mutations in *FBN1* and elastin deficiencies, Loeys-Dietz Syndrome, Type IV Ehlers-Danlos syndrome characterized by mutations in *COL3A1*, familial thoracic aortic aneurysm syndrome (FTAAS), and bicuspid aortic valve which is often associated with an ascending aortopathy. In those with recurrent aortic dissection, approximately 5% of all dissections, Marfan is more frequently present [17]. In addition, several other conditions including Noonan's syndrome, polycystic kidney disease, and inflammatory aortopathies such as Takayasu's, Behçet's, and idiopathic aortitis are associated with increased risk of aortic syndromes [3, 4]. Pregnancy is also associated with aortic dissection with the highest incidence in the third trimester and early postpartum period [18]. This risk is greatest in those with a bicuspid aortic valve, Marfan, Ehlers–Danlos, or Turner syndrome [18–20]. In pregnant women with Turner syndrome, the risk of acute aortic syndrome is greater than 2%, and that for death is increased approximately 100-fold [18, 19].

Epidemiology and Risk Factors

Acute aortic syndromes overall occur at a frequency of between 3 and 16 cases per 100,000 person-years with those isolated to the descending aorta comprising slightly less than half of the cases. Most often, acute aortic syndromes occur in the elderly (sixth and seventh decade) with a history of hypertension [1, 2, 21, 22]. While the majority of patients (~60%) with dissection are male, events in men may occur at younger ages and community observational studies suggest that at ages above 75 years the incidence is similar for both men and women [2]. A history of uncontrolled hypertension has been described with greater frequency in patients presenting with acute aortic syndromes, suggesting that this may be a risk factor for aortic disruption [2]. Younger patients without a history of hypertension may present with acute aortic syndromes generally in the setting of a family history, connective tissue disease, vascular inflammatory disease, or trauma; therefore this diagnosis should not be discounted in the young [1, 2, 23]. Age may also influence presentation with complicated Type B dissection [21].

Acute aortic disruption may also occur in the setting of procedures (iatrogenic) or in the setting of trauma. These events may be more common in the ascending rather than the descending aorta as they have been associated with cardiac procedures [24]. Aortic transection can occur in the setting of rapid deceleration such as occurs in chest trauma and motor vehicle accidents. Cocaine ingestion may result in

abrupt increases in heart rate and/or blood pressure and has been associated with AAS, particularly among young men who smoke.

Classification

Two classification systems are used for acute aortic syndromes based on location and extent, the DeBakey classification and the Stanford Classification [25, 26]. The DeBakey system includes three types of dissection and is based on the site of origin of the dissection, while the Stanford classification includes two types and is based on the presence or absence of ascending aortic involvement. DeBakey Type I involves both the ascending and descending aorta, and/or the arch. Type II dissection involves only the ascending aorta, and type III involves only the descending aorta distal to the left subclavian artery. The Stanford classification includes Type A (involving the ascending aorta) and Type B (not involving the ascending aorta) and more closely aligns with current treatment triage algorithms. The natural history of isolated arch dissection has been less well characterized [27].

Natural History

Outcomes after acute aortic syndromes vary depending on the type, location, and the presence of complications [2]. Presentation involving the descending aorta only (Type B) is described as less common than Type A; however, increasing use of CT scans in emergency settings is increasingly identifying disruption in the descending aorta. Type B dissection overall is associated with a lower early mortality relative to Type A dissection with 30 day rates of approximately 13% [22, 28]. Risk in this group, however, is heterogenous and can be very high particularly in those with complications. Independent predictors of death included hypotension/shock at presentation, visceral ischemia, and branch vessel involvement [22]. The anatomic characteristics of the dissection and the presence of associated complications significantly impact prognosis. It has been observed that approximately 1 in 5 patients with Type B dissection develop malperfusion and require intervention during the index hospitalization [22]. A report from IRAD reported that nearly half of Type B dissections were associated with complications including the development of shock, rupture, spinal cord ischemia, mesenteric or renal ischemia, limb ischemia, recurrent or refractory pain, or uncontrolled hypertension [28]. In-hospital mortality for Type B dissection is strongly associated with the presence of complications (20% for complicated vs. 6.1% for uncomplicated, $p < 0.001$) [28]. Other predictors of mortality include age greater than 70 and the need for surgical management, although the latter is likely a reflection of the presence of complications [28]. It is important to recognize that complications may develop after presentation in patients who appear uncomplicated at the time of diagnosis and that complications may be dynamic. Identifying early, evolving, and dynamic complications in patients with Type B dissection is critical for risk stratification and timely intervention [3].

Clinical Presentation

There is no single feature in the history or on the physical exam that reliably allows for identification of dissection with definitive diagnostic evaluation dependent on imaging. Therefore, the history and exam along with a high index of suspicion are critical in appropriately selecting patients for definitive testing. Presenting symptoms may vary depending on the location and characteristics of the disruption [3, 4, 29]. The most frequently reported symptom is sudden and severe chest or back pain that is at its maximal intensity at its onset. The absence of pain, however, does not exclude the diagnosis of dissection. Pain may be severe and in some cases may be described a "tearing" [3, 4, 30]. Syncope or neurologic symptoms are generally associated with ascending dissection and are associated with poor outcomes [31]. Interscapular or back pain may also be present in patients with dissection of the descending aorta [3]. The variability and resulting lack of specificity in presenting syndrome can be challenging and can result in delayed diagnosis, particularly among patients with atypical symptoms [3, 4, 30, 32].

Like symptoms, physical findings in patients with acute aortic syndromes can also be variable and non-specific. Hypertension is common particularly for Type B dissection with presence observed in ~70% of patients. A pulse deficit is described in approximately 30% of patients and is associated with increased mortality [33]. These obstructive events are typically the result of the extension of the dissection flap into the lumen of a branch vessel (static), occlusion of the ostium of the vessel due to intermittent covering by the intimal flap (dynamic), or impaired flow into the vessel from the true lumen due to compression by the false lumen. Clinical findings associated with branch vessel involvement may range from asymptomatic to overt manifestations, including severe ischemia of the limbs or viscera [3, 33–35]. Dissections may also result in renal artery occlusion and acute renal failure or infarction. In rare cases there may be occlusion of the spinal arteries leading to paraparesis or paraplegia. Lower limb ischemia may lead to persistent or intermittent limb pain in the setting of Type B dissection. In addition, findings such as pleural effusion (reactive or hemorrhagic) typically attributed to other diagnoses may occur in as many as 15–20% of patients [1, 3].

Diagnosis

Guidelines recommend a focused history and physical exam to determine the pretest probability of aortic dissection [3]. The history should include specific questions about genetic, connective tissue, or other familial conditions associated with aortic disease. Information regarding recent aortic procedures, typical pain, or high-risk signs such as pulse deficit or other evidence of malperfusion should be obtained [3]. Risk scores based on the consensus have been evaluated and shown to be highly sensitive [36]. One study looking at time from presentation to diagnosis found a median delay of ~4 hours (intraquartile range 1.5–24 hours), suggesting that up to 25% of patients may be diagnosed more than 24 hours after presentation [30]. A delayed diagnosis is most likely in those with atypical symptoms such as syncope as well as in those with hemodynamic stability, absence of pulse deficit, and on those presenting to a non-tertiary care hospital.

The ECG is often (69%) abnormal, but generally findings are non-specific [1]. Chest X-ray is abnormal in most cases, but findings may be non-specific [1]. Findings described include widening of the mediastinum and displacement of aortic calcium. Due to the lack of sensitivity of ECG and chest X-ray, normal or non-specific findings should not preclude or delay diagnostic imaging in patients for whom acute aortic syndrome is suspected clinically [3].

Although there is growing interest in biomarkers as an adjunctive tool in patients presenting with suspected acute aortic syndromes, their clinical utility is evolving. Plasma D-Dimer, a fibrin degradation product that indicates evidence of intravascular coagulation, is routinely used in assessing the likelihood of acute pulmonary embolism and is widely available. A D-Dimer >500 ng/mL has been found in some datasets to be sensitive for acute dissection (sensitivity ~97%, negative predictive value ~96%) but with relatively poor specificity (specificity 56%, positive predictive value 60%) [37–41]. Because it is highly sensitive, D-dimer may play a role in the "rule out" acute aortic dissection [37]. Because the kinetics in this setting are not well established and D-dimer levels likely decline over time, sensitivity in patients presenting late after symptom onset may be reduced. In one study, approximately 20% of patients with confirmed aortic dissection had measured levels <400 ng/mL illustrating some variability in performance [42, 43]. Smooth muscle myosin heavy chain protein measured through a rapid assay in patients presenting early (<3 hours of symptom onset) with acute type A aortic dissection showed excellent diagnostic performance relative to conventional CT scan but did not perform as well as helical CT or MRI which would be considered standard in this setting [44, 45]. Soluble elastin fragment levels have also evaluated but the diagnostic utility has not been established [46]. Other commonly available biomarkers such as troponin and natriuretic peptides are non-specific for aortic disruption.

Rapid ascertainment of diagnostic imaging is critical establishing the diagnosis in patients with suspected aortic dissection. Multiple modalities available with preference in the acute setting for those that are highly sensitive and specific and can be obtained rapidly. Frequently, multiple imaging modalities may be required to confirm diagnosis or to characterize findings if potential complications are evolving [3].

Transthoracic echocardiography (TTE) is often readily available, non-invasive, and portable imaging modality that may be considered; however, sensitivity for type B acute aortic syndromes is ~40%. Given the low sensitivity, obtaining a TTE should not delay a diagnostic imaging study [3]. In terms of diagnostic imaging, computed tomographic angiography (CTA), magnetic resonance angiography (MRA), and trans-esophageal echocardiography (TEE) all have high sensitivity (>95%) and specificity (>95%) for acute aortic disruption although TEE may be limited in characterizing the full extent of findings in the descending aorta [3, 47–51].

CT scanning allows for characterization of the aorta and has excellent special resolution. The sensitivity (90–100%) and specificity (90%) for visualization of the intimal flap in aortic dissection are comparable to TEE [49]. Specific CT techniques allow for three-dimensional (3D) reconstruction. Dedicated aortic CT scans should account for cardiac motion through tools such as ECG gating particularly when evaluating the ascending aorta [49]. Non-contrast images should be routinely obtained to improve sensitivity for intramural hematoma. The full aorta (chest to pelvis) should be imaged to characterize the full extent of the dissection and potential complications. In some cases, patients may have renal insufficiency; however, in the critically ill patient in whom acute aortic disruption is suspected, definitive diagnosis takes priority.

Both CT and MRI have several advantages including high resolution and the ability to evaluate the entire aorta. Spatial resolution for branch vessels may be higher with CT. The sensitivity and specificity for acute aortic syndrome with MRI is nearly 100%. MRI may not be as readily available in the emergency setting or as rapidly performed as CT scanning. Both require contrast and while not nephrotoxic, MRI contrast agents are associated with complications in patients with impaired renal function.

Consultation with an imaging specialist is useful in determining how to perform optimal imaging. In some settings tests performed to exclude several acute diagnosis (e.g., pulmonary embolism, dissection, myocardial infarction) with a single CT-A are sometimes referred to as "Triple Rule-Out" scans, may be performed. Typically, these tests are associated with higher doses of radiation and the sensitivity and specificity for acute aortic dissection debated [47]. Involving an imaging specialist and describing the clinical considerations are also important in the interpretation of studies, particularly

when conducted for other diagnoses (e.g., evaluate for pulmonary embolism) where the test performed may not have sufficient diagnostic accuracy for aortic dissection [3, 51].

Treatment

Clinical Stability

All patients with suspected AAS should be treated with stabilizing medical treatment with careful consideration of their hemodynamic stability. Medical therapy is generally targeted at controlling heart rate and blood pressure (and its rate of rise, dP/dT) as potential drivers of progression. In addition, treatment of symptoms is a key aspect of early medical care [3, 52]. Evaluation targeted at early recognition of acute complications (e.g., tamponade, aortic regurgitation, and malperfusion) is necessary in selecting appropriate therapy so as not to remove a compensatory response and lead to hemodynamic instability. Unstable patients should undergo early surgical consultation ideally through a multidisciplinary approach, with rapid diagnostic imaging assessment to facilitate early management. Medical therapy in stable patients without complications and/or hemodynamic instability is discussed below.

Indications for Surgery in Acute Dissection

The need for early intervention in patients presenting with Type B AAS depends on the clinical picture and particularly the presence of complications. These are defined as limb or visceral malperfusion, indication of an unstable aorta including progression of the dissection, aortic expansion or impending rupture, or refractory pain and/or refractory hypertension. In some cases, the presence of a connective tissue disorder such as Marfan syndrome may impact the decision for prompt surgical repair. In the absence of complications, medical management and close observation is generally recommended. Although endovascular therapies for AAS are rapidly evolving, their routine use in uncomplicated Type B AAS is not recommended. When used, endovascular therapies generally include stent grafting (TEVAR) potentially supplemented by fenestration and/or branch vessel intervention. Aortic surgery in the chronic phase of dissection is usually dictated by the size of the aorta as well as the rate of change in size.

Initial Medical Management

General guidance for medical therapy is described in consensus guidelines for AAS [3]. Appropriate medical therapy should be initiated promptly in all patients with careful consideration of hemodynamic stability while definitive diagnostic studies are underway. Initial medical management of a patient with planned or likely intervention depends on clinical stability and should primarily be focused on the management of pain, reduction of blood pressure to an acceptable level, and reduction of the force of left ventricular contraction (dP/dt) [52]. Short acting parenteral therapies may be favored in the acute setting to allow titration. Close observation should occur in an intensive care setting at least in the early phase, with an arterial blood pressure monitoring.

Beta-blockers should be initiated with the goal to lower heart rate to the lowest tolerable levels generally 60 beats per minute or less. In addition, beta-blockers may reduce blood pressure although doses should not be titrated to blood pressure alone as doing so may result in intolerably low heart rate. Short acting agents such as esmolol may be useful and facilitate rapid titration. In patients with hypertension, agents with both alpha and beta antagonism such as labetalol may be preferable and can be administered intravenously in the acute setting and then converted to oral dosing. Non-dihydropyridine calcium channel blockers can be used for heart rate control in patients who cannot receive beta-blockers. As noted above, assessment for impending hemodynamic instability or acute severe aortic regurgitation is critical so as not to cause decompensation through removal of compensatory tachycardia by beta-blockade.

Once heart rate is controlled and optimized, residual hypertension should be treated with the addition of a vasodilator (e.g., angiotensin converting enzyme inhibitor or sodium nitroprusside). Vasodilators should only be considered after heart rate control as initial use results in increased heart rate and the delta of LV pressure (dP/dT). This tachycardia would be as noted above. Drives of adrenergic tone including pain and anxiety should be promptly treated.

Patients presenting with apparently uncomplicated AAS may develop complications particularly early in their course and decompensate rapidly. Intensive monitoring with frequent clinical assessments and vital signs including the use of intra-arterial monitoring should be implemented. Early serial lab exams and imaging may be useful depending on the clinical context. Evolving exams should be documented noting that complications such as branch vessel occlusion can be intermittent.

Interventional Options for Complicated Type B Dissection

Current consensus guidelines reserve intervention for Type B AAS for patients with complications [3]. Observational registries report that up to 20–40% of Type B dissections are

associated with complications [22, 28]. Endovascular treatments for complicated Type B AAS have rapidly evolved and are more frequently utilized relative to open surgery with case series describing better associated outcomes although randomized trials are lacking [53, 54]. The increasing use of endovascular repair for Type B dissection prompted an expert consensus statement from an interdisciplinary group [55]. Data from 63 studies published between 2006 and 2012 and including 6729 patients were reviewed [55]. Medical treatment for uncomplicated acute Type B dissection is recommended but complicated acute Type B dissection may be treated with TEVAR rather than surgery, when technically feasible, noting a survival benefit with the less invasive approach [55]. Fenestration to create improved false lumen outflow and depressurization is generally performed with a balloon or wire and may be useful in restoring flow to compressed or occluded branch vessels [56]. Branch vessel stenting may also be used to restore luminal flow. Endovascular stent grafts may stabilize the aorta as well as seal the proximal entry tear leading to depressurization and stabilization.

Fenestration

Data to support fenestration largely derive from case series or registries. One such case described outcomes in 40 patients presenting with AAS (10 Type A, 30 Type B), including many with malperfusion syndromes (30 renal, 22 limb, and 18 mesenteric) [56]. Successful resolution of ischemia was achieved in 93%; however, there were 9 procedural complications. Mortality at 30 days was 25% overall but deaths were largely attributed to irreversible organ damage occurring prior to intervention. Of those that survived, 83% were still alive at 29 months [56].

Another series described 35 patients with AAS characterized by malperfusion. Procedural success occurred in all patients although the majority required both fenestration and branch vessel stenting [57]. Mortality was 34% at 30 days and similar to the prior study, largely attributed to preprocedural tissue damage or stroke [57]. For those followed longitudinally, aortic dimensions remained stable in 70% at a mean of 48 months [57].

Thoracic Endovascular Aortic Repair (TEVAR)

The concept that coverage and occlusion of the proximal entry tear may reduce pressurization and resulting propagation and complications, as well as promote beneficial remodeling such as false lumen thrombosis, has prompted investigation of covered stent grafts in selected patients. One series included 12 patients with subacute or chronic Type B dissection with and indications for intervention that were treated with stent grafting. They were compared to matched controls who had been treated surgically [58]. Stent-grafting was associated with higher procedural success, shorter hospitalizations, and lower mortality rates relative to surgery [58]. The authors suggested that endovascular therapy was safe and effective alternative to surgery for patients necessitating intervention [58].

Several additional series have described outcomes after endovascular intervention in patients with Type B AAS. A meta-analysis of these series was published in 2006 [59]. Overall there were 39 studies including 609 patients who underwent endovascular intervention for Type B dissection. Overall procedural success was greater than 95% and rates of major complications and mortality were higher in those patients that required intervention in the acute setting relative to the chronic setting [59]. The authors concluded that outcomes with endovascular intervention (primarily TEVAR) compared favorably to outcomes after surgery [59]. An analysis of a series of 571 patients with acute Type B dissection from the IRAD registry that underwent intervention found that surgical repair was associated with an increased risk of mortality compared to TEVAR. The association remained even after propensity score adjustments. While not randomized, the data suggest favorable outcomes with endovascular intervention when possible [60]. A meta-analysis based on a Cochrane review included controlled trials of patients with acute Type B AAS assigned to TEVAR or surgery [61]. Overall there were five trials including 318 patients. Primary findings were that TEVAR was associated with lower short-term mortality compared with that seen with surgery; however, data on long-term outcomes was lacking [61].

In the setting of increasing utilization of endovascular intervention for Type B dissection across a spectrum of acuity and complexity, an interdisciplinary group produced a multidisciplinary consensus statement on the management of Type B dissection in 2013 [55]. Data from 63 studies spanning 2006 through 2012, which included 6729 patients, were evaluated [55]. The consensus statement recommended intensive medical therapy for uncomplicated acute Type B dissection but noted that complicated cases should be treated with an endovascular approach (TEVAR, fenestration, etc.) as opposed to surgery, when feasible noting lower associated mortality with the less invasive approach [55]. Intervention for subacute and chronic Type B dissection was recommended to only be used in the setting of complications. An endovascular approach was favored when feasible [55]. Citations included non-randomized observations IRAD including lower 5-year mortality with TEVAR compared to medical therapy [62].

No adequately powered randomized clinical trials have evaluated outcomes with TEVAR compared to surgery for acute complicated Type B dissection. Observational data suggest lower associated short-term mortality with TEVAR

compared to outcomes traditionally seen after open surgery; however, the role of patient selection in these observations limits interpretation of these findings. In addition, published data largely reflect outcomes at high-volume centers with experience in TEVAR; therefore outcomes may not be generalizable to centers with lower volume. Multidisciplinary care teams using systematic criteria for intervention systems to insure longitudinal follow-up after discharge may help to optimize care in this setting.

Intervention for Uncomplicated Type B Dissection

Current guidelines recommend medical therapy as primary treatment for Type B dissection and largely reserve intervention for Type B dissection for those who have or develop complications [3]. Longitudinal observational data that describe false lumen patency as a marker of long-term outcome [5] have led to the hypothesis that prophylactic stent grafting to cover the entry tear and promote false lumen thrombosis may improve long-term aortic-related outcomes [63]. In order to test this hypothesis, 140 patients with stable uncomplicated Type B dissection were randomly assigned to optimal medical therapy (OMT) alone or OMT plus endovascular stent grafting (TEVAR) [63]. The trial, called INSTEAD, included patients who were between 2 and 52 weeks from their acute dissection (mean 45 days for OMT group, 39 days for TEVAR + OMT). The primary endpoint was the incidence of all-cause mortality at 2 years. Secondary outcomes included the incidence of aortic death as well as imaging markers of adverse aortic remodeling. No benefit for TEVAR was seen for either the primary or secondary outcomes at 2 years [63]. An exploratory analysis that looked at 5-year outcomes in this cohort, however, suggested there may be a beneficial effect of TEVAR for all-cause mortality, aortic-related mortality, and disease progression [64]. The results raised the hypothesis that the benefits of TEVAR may take longer to become apparent. Additional prospective studies testing this hypothesis are needed to better understand the role of TEVAR in this setting.

A more recent trial called ADSORB similarly suggested benefits in terms of aortic remodeling parameters [65]. Non-randomized assessments of TEVAR for uncomplicated Type B dissection in selected patients have shown lower associated rates of aortic adverse events and mortality although the non-randomized data are hypothesis generating [66]. The concept of intervention to reduce long-term adverse remodeling has led to investigation of other endovascular therapies including neo-fenestrations with reentry devices during endovascular repair [67].

While these studies have not provided sufficient evidence to drive broad utilization of routine endovascular intervention, there is growing interest in identifying patients at long-term heightened risk for complications such as aneurysm formation that would support targeted intervention. Traditional criteria for intervention are based primarily on aortic size (>5.5 cm ascending, >5.5–6.0 cm descending), growth over time, and the presence of associated complications. Other morphologic and or patient criteria may predict aneurysm formation facilitating smaller scale preventive interventions at smaller dimensions.

Longitudinal Follow-Up

A significant proportion of patients with Type B dissection will require intervention over the long term due to the development of a complication and most frequently the development of an aneurysm [68–71]. Rates of mortality in patients with Type B dissection approach 40% at 5 years. Therefore, close follow-up is critical for all patients who have had AAS, irrespective of the type or treatment they have received (medical, surgical, endovascular) [68, 71]. Long-term longitudinal follow-up after discharge may be challenging particularly in patients who have had an intervention and may not understand their residual long-term risk [59]. Medical therapy aimed at heart rate and blood pressure control should be routinely evaluated. As in the acute setting, beta-blockers form the mainstay of medical therapy and in the outpatient setting, long-acting agents are preferred. Patient education is particularly important given the rarity of the diagnosis including information about warning symptoms guidelines for activity limitation. Serial imaging of the entire aorta should be performed including at discharge and at 1, 3, 6, and 12 months after discharge. Long-term annual imaging should be considered based on the patient's stability and the clinical context.

Prognosis

There is heterogeneity in outcomes for patients with Type B AAS in part driven by anatomic considerations and in part by patient characteristics. Several series describe that 30% of those who are initially treated medically may need intervention with 28% developing aneurysms over 5 years after discharge [68, 70]. Anatomic predictors include a large false lumen (≥22 mm) located in the upper descending thoracic aorta with rates of late aneurysm formation of over 40% and markedly higher than those without these features (42% vs. 5%, $p < 0.001$). In addition, this finding was associated with a numerical trend for higher mortality (17% vs. 5%, $p = 0.09$) [69, 70].

False lumen patency at hospital discharge is also associated with long-term outcomes [7]. The presence of partial

thrombosis of the false lumen usually indicating a patent entry tear but absence of or thrombosed re-entry tears effectively causing the false lumen to act as a pressurized "wind sock" has been associated with higher long-term mortality relative to completely patent and completely thrombosed false lumen morphologies [5]. Models of Type B dissection physiology support these observations. Hemodynamic models show higher diastolic false lumen pressures with a lack of a distal re-entry tear. These factors may influence false lumen remodeling and risk of rupture over the long term [72]. In patients with Type A dissection treated surgically, preoperative false lumen morphology is not associated with long-term outcomes [73].

Impact on aortic integrity from dissection may lead to long-term heightened risk of aneurysm formation. This risk may vary depending on location with some studies describing subsequent aneurysm formation occurring most commonly in the upper descending thoracic aorta [70]. Larger false lumen diameter and connective tissue disorder such as Marfan syndrome have also been described as independent predictors of future aneurysm formation [70].

Intramural Hematoma (IMH)

Intramural hematoma (IMH) is a collection of blood within the medial that does not communicate with the lumen. A first case and description was published in 1988 [7]. The natural history of IMH is described as similar to acute dissection; however, the true natural history is less well understood. Although intramural hematoma does not have an identifiable intimal flap as is seen in dissection, clinical presentation is generally similar [10, 74, 75]. By nature of the absence of a dissection flap, complications such as malperfusion are less likely with IMH than dissection; however, rupture and progression to dissection are possible. Some reports describe similar outcomes for patients with IMH relative to those with classic dissection [10]. Other reports, however, question this finding and have described that patients with IMH may have better survival and are more often managed without intervention [74, 76]. In terms of the epidemiology, the incidence is reported to be broadly from 0% to 25% of patients presenting with acute aortic syndromes [7]. In this registry, the descending aorta was involved most of the time (58% Type B, 42% Type A, $p < 0.001$) [7]. Overall outcomes for IMH were similar to those for dissection when matched to the same anatomic location [7]. One case series of 65 patients presenting with IMH found that associated penetrating aortic ulcer (PAU) had higher rates of adverse outcomes and progressed more frequently than those without PAU (48% vs 8% $p = 0.002$) [8]. The natural history IMH involving the descending aorta has not been well described. Some resorb spontaneously while others develop classic dissection, false aneurysm, or true aneurysm. Although experience has varied, the management of IMH should proceed according to the principles outlined for classic dissection. Long-term follow-up after IMH describes the evolution of the hematoma into aneurysm more frequently when associated with PAU. Regression is most likely with IMH occurring in a normal diameter aorta and without associated PAU.

Etiology, Pathophysiology, and Clinical Presentation

Mechanisms for IMH formation include rupture of the vasa vasorum due to medial degeneration of the aortic wall as well as extension of PAU beyond the internal elastic lamina resulting in loss of integrity of the media. The clinical presentation of IMH is similar to that of aortic dissection, and it can only be definitively distinguished by imaging. Although the risk factors and clinical presentations of classic aortic dissection and IMH are indistinguishable, certain important differences are recognized. Compared to those with typical aortic dissection, patients with IMH tend to be older, tend to have more atherosclerotic disease, and are more likely to have a distal acute aortic syndrome.

Imaging

Like dissection, the diagnosis of IMH is established through imaging. Characteristic features include a crescentic or circumferential thickening of the aortic wall indicating the presence of fresh thrombus and non-contrast imaging is important in establishing the diagnosis and differentiating from mural thrombus [3]. The diagnostic imaging approach is consistent across the spectrum of acute aortic syndrome including IMH.

Like dissection, chest X-ray findings associated with IMH are non-specific. Possible findings include an abnormal aortic silhouette and widened mediastinum although the latter in theory may be less likely in isolated IMH than in typical dissection. Displacement of intimal calcium from the aortic wall may be visible. Although IMH may be seen on a TTE, it is not sensitive enough to reliably assess for the diagnosis. Overall TEE is more sensitive than TTE and IMH may appear as an echogenic, crescent-shaped area of the aortic wall. In some cases, this thickened wall segment may be difficult to distinguish from atherosclerotic thickening, limiting the diagnostic accuracy.

On axial imaging, IMH most often appears as a crescent-shaped thickening of the wall, but often with a normal-appearing lumen. As noted above, CT imaging without contrast facilitates diagnosis of isolated IMH as the hematoma has a higher tissue density than unenhanced blood [3].

A primary feature that distinguishes IMH from typical dissection is the absence of contrast in the aortic wall. Aortography is less useful for evaluating IMH as it is based largely on the distribution of contrast and reported sensitivity for isolated IMH is described as ~20%.

Management

Initial management is the same as that for typical dissection and depends on clinical stability. The most feared consequence is an unstable aorta characterized by continued expansion and progression to typical dissection, aneurysm, and/or aortic rupture. For patients with IMH of the descending aorta, medical management and observation are recommended and outcomes reported include in-hospital mortality rates less than 10% [3, 77].

The role for endovascular therapy including TEVAR is evolving in patients with IMH. It has been described primarily in those who are thought to be at high risk of hematoma expansion and aortic rupture [78]. Type B IMH should be frequently reassessed to evaluate for progression which may require serial CT scans. Similarly, there may be low-risk patients with some studies demonstrating that a proportion of patients with IMH will resorb in the context of short-term follow-up. This is particularly the case for those with no or small associated aneurysm rather than those with increased aortic dimensions. A significant proportion of patients with IMH, however, will go on to develop adverse remodeling characterized as an enlarging aneurysm, pseudoaneurysm, classic aortic dissection, or rupture.

Penetrating Aortic Ulcer (PAU)

Penetrating aortic ulcer (PAU) may result from erosion of the internal elastic membrane usually in the setting of an inflammatory atherosclerotic plaque with penetration of the luminal blood under pressure into the media [3, 11, 79]. While some morphologic characteristics of PAU, such as depth or associated IMH, are associated with adverse prognosis, less is known about the true natural history isolated IMH [8, 80]. Increasing use of axial imaging reveals a greater prevalence of PAU in stable outpatients indicating that the true prevalence may be greater than previously appreciated. In patients with acute Type B PAU requiring intervention, TEVAR may be especially effective. Clinical considerations include refractory pain and/or uncontrolled or when imaging shows signs of instability such as propagation and/or expansion. Statin therapy is generally used given the imaging evidence of atherosclerosis. Management of patients presenting with an acute pain syndrome with evidence of PAU may be optimally managed by a multidisciplinary care team to determine whether the finding represents acute disruption or chronic findings, establishing a monitoring plan, implementing medical optimization, and considering if there is the development for the need for intervention.

Kommerell's Diverticulum

Kommerell's diverticulum is a congenital abnormality and actually is a focal aneurysm involving the origin of an aberrant subclavian artery (right or left) or directly of the isthmus of the thoracic aorta. It is believed to result from maldevelopment of the aorta and may be associated with an aberrant subclavian artery and/or aortic configuration. The pathogenesis is believed to be failure of regression of the fourth primitive dorsal arch. Kommerell's diverticulum has been classified according to criteria proposed by Salomonowitz et al. as follows: A normally configured aorta and an aneurysmal origin of an aberrant right subclavian artery is called Type 1; an anomalous right aortic arch configuration with aneurysm of the origin of an anomalous left subclavian artery is called Type 2; and a normally configured aorta with an isolated aneurysm arising from the ductal zone of the thoracic aorta and not associated with either subclavian is categorized as Type 3.

Incidence and Clinical Presentation

The reported incidence of Kommerell's diverticulum ranges from 20% to 60% of patients with anomalous subclavian artery abnormality and is likely present in <1% of the population. It is also possible that this incidence is low as more patients are diagnosed in the era of frequent axial imaging. Although children may present with respiratory symptoms, the majority of adult patients are asymptomatic from compressive symptoms. In general, this diagnosis is established in adults through incidental findings on imaging. Because the true incidence is unknown, the natural history remains poorly defined.

Management

Asymptomatic patients incidentally diagnosed with Kommerell's diverticulum are managed medically with blood pressure and heart rate reduction and then monitored for enlargement. Like aortic aneurysm, intervention is performed in order to prevent possible catastrophic complications with the main indicators being absolute diameter and rate of change. Case reports describe 4 cm or larger being a size where rupture risk is significant therefore recommendations are to intervene at a diameter above 3 cm at the base

(5 cm for total diameter) [81]. This strategy is complicated by the difficulties in establishing reliable measurements as well as the unknown natural history with some advocating for intervention at smaller diameters. Measurement techniques for this finding have been proposed [82]. The optimal intervention for this finding is debated with cases describing open surgical approaches as well as hybrid treatments including endovascular repair with bypass as well as with a periscope parallel graft [83–85]. Management and monitoring of this relatively rare entity may be provided through multidisciplinary care teams evaluating patient comorbidity and procedural risk as well as medical optimization and procedural planning.

Conclusion

Acute aortic syndromes are relatively uncommon but potentially catastrophic conditions caused by aortic disruption and associated loss of aortic integrity. Patients presenting with acute aortic syndrome may have atypical symptoms and nonspecific findings on exam. Clinicians should have a high index of suspicion in appropriate patients and proceed with definitive diagnostic imaging when indicated. Acute aortic syndromes involving the descending aorta are typically managed medically although intervention is indicated in those with malperfusion or other complications. Endovascular procedures are generally favored in this setting and are of potential utility in selected stable patients even in the absence of complications to prevent adverse remodeling. Coordinated multidisciplinary care teams providing longitudinal care from acute presentation through chronic follow-up may provide optimized care including systematic imaging, blood pressure and medical management, education, genetic screening, and interventional planning. Patients with incidentally found aortic disruption or Kommerell's diverticulum in the stable phase are also at risk of adverse remodeling and complications and should receive similar intensive multidisciplinary support.

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Ascending Aortic Aneurysm

11

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Introduction

Definition

True aortic aneurysm is commonly defined as a localized, permanent aortic dilation diameter of 50% or greater than normal, and is contained by all the layers of the normal aortic wall [1]. False aortic aneurysm is a focal dilation that consists of adventitia, some or all of the media, as well as compressed periaortic tissue, and is most frequently seen in traumatic aortic injury.

Historical Note

Denton Cooley and Michael De Bakey reported the first reported modern surgical repair of an aortic aneurysm in 1952, which described the lateral resection of a descending aortic saccular aneurysm without cardiopulmonary bypass [2]. Four years later in 1956, Cooley and De Bakey performed a replacement of the ascending aorta with a homograft with cardiopulmonary bypass [3]. Polyester conduits were introduced by De Bakey and quickly became the material of choice for artificial conduits. In 1964, Myron Wheat Jr. and colleagues resected the ascending aorta and aortic root while leaving aortic tissue around the coronary ostia, followed by the insertion of a mechanical valve tailored to accommodate the in situ coronary arteries [4]. The first composite aortic root repair with an aortic graft with attached valve was described in a patient with Marfan syndrome by Hugh Bentall and Antony De Bono in 1968 [5]. Further technical advances were developed by Christian Cabrol and colleagues, as well as Nicholas Kouchoukas and Robert Karp who described the modern technique that comprises individual coronary button reimplantation with end-to-end anastomosis [6, 7]. Valve-sparing aortic root replacement techniques, including a remodeling technique described by Sir Magdi Yacoub and a reimplantation technique developed by Tirone David, are currently performed in specialized centers.

Surgical Anatomy

The aortic root is located between the left ventricle and ascending aorta, and is an extension of the left ventricular outflow tract containing the aortic valve. The aortic root contains four distinct anatomic components: the aortic annulus and subcommissural triangles, the aortic valve cusps, sinuses of Valsalva, and the sinotubular junction (Fig. 11.1). The aortic annulus is a combination of fibrous and muscular tissue that attaches the aortic valve to the left ventricle, with approximately 55% of the circumference comprising of fibrous attachments to the anterior leaflet of the mitral valve and membranous septum, and the remaining 45% containing muscular attachment directly to the myocardium [8]. The aortic valve normally has three semilunar-shaped cusps, containing a base and a free margin, that attach to the aortic annulus forming three commissures. The area between the aortic cusps and the superior commissure are known as the subcommissural triangles.

The superior aspects of the commissures interrelate with the sinotubular junction, which is a ridge that marks the

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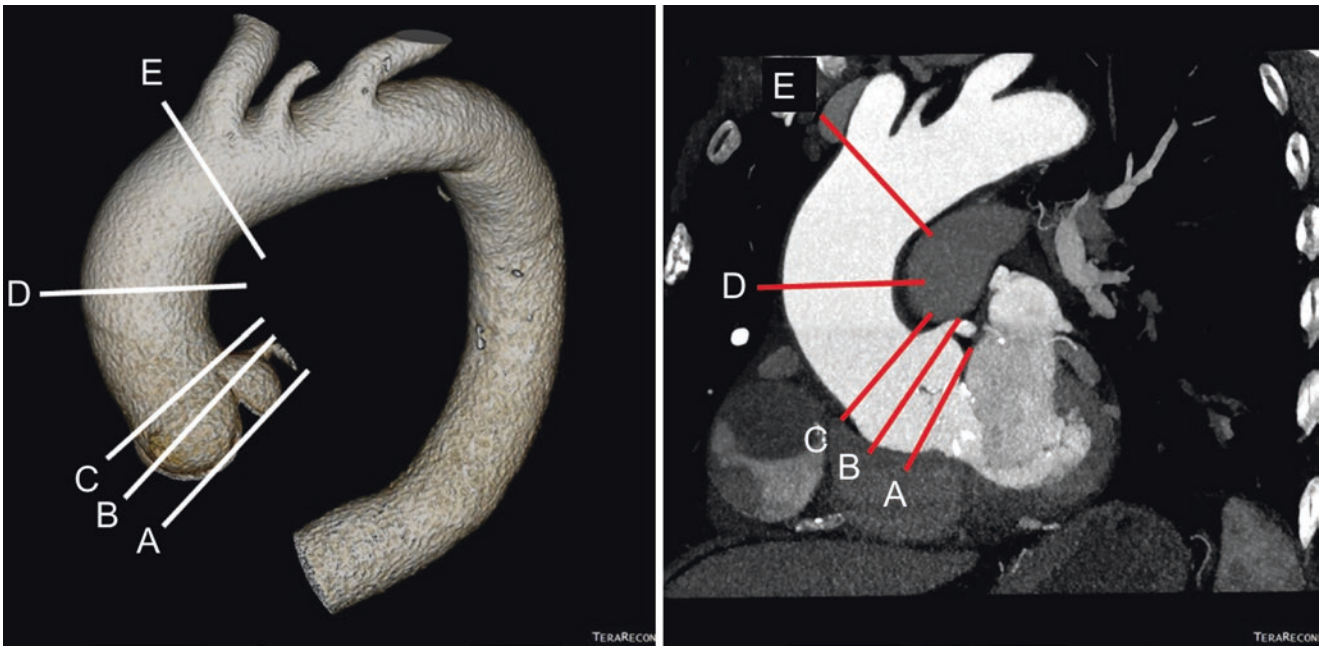

Fig. 11.1 Anatomy of the aortic root and ascending aorta (mean dimension (cm), male and female). A: aortic annulus (2.6 ± 0.3 and 2.3 ± 0.2), B: sinuses of Valsalva (3.4 ± 0.3 and 3.0 ± 0.3), C: sinotubular junction (2.9 ± 0.3 and 2.6 ± 0.3), A–C: aortic root, D: mid ascending aorta (3.0 ± 0.4 and 2.7 ± 0.4), E: aortic arch [12]

origin of the ascending aorta [9]. Slight dilation of the sinotubular junction relative to the aortic annulus frequently results in aortic insufficiency as the aortic valve cusps no longer coapt centrally. The three sinuses of Valsalva, sometimes referred to as the aortic sinuses, are located between the aortic annulus and the sinotubular junction and are associated with corresponding aortic valve cusps—the left cusp and sinus containing the ostium of the left main coronary artery, the right cusp and sinus containing the ostium of the right coronary artery, and the noncoronary cusp and sinus. The subcommissural triangles bordering the noncoronary associate with the anterior leaflet of the mitral valve, and the subcommissural triangle between the right and noncoronary sinuses mark the conduction system within the membranous septum. The relative dimensions of the three cusps are variable; however, the right and noncoronary cusps are typically larger than the left cusp [10, 11]. Larger cusps have a proportionately large annulus, sinus, and sinotubular junction. Men on average have slightly larger aortic root dimensions than women.

A study of two-dimensional (2D) echocardiographic aortic root dimensions found the mean aortic root dimensions (cm) in males and females to be 2.6 ± 0.3 and 2.3 ± 0.2 at the annulus, 3.4 ± 0.3 and 3.0 ± 0.3 at the sinuses of Valsalva, 2.9 ± 0.3 and 2.6 ± 0.3 at the sinotubular junction, and 3.0 ± 0.4 and 2.7 ± 0.4 at the proximal ascending aorta, respectively [12]. The thoracic aorta normally decreases in diameter from the aortic root distally to the diaphragmatic descending thoracic aorta. Measurement of the ascending aorta in males using computed tomography was utilized to report a mean diameter of the root, ascending, mid-descending, and diaphragmatic aorta to be 3.63, 2.85, 2.39, and 2.43 cm, respectively [1].

Epidemiology

The prevalence of ascending aortic aneurysms has been historically difficult to ascertain due to large amount of cases that go undiagnosed, as well as an underreporting in mortality statistics. Literature investigating the epidemiology of ascending aortic aneurysms is scarce. Historically, ascending aortic aneurysms were more prevalent than thoracoabdominal aortic aneurysms in the first half of the twentieth century due to increased prevalence of syphilis; however, thoracoabdominal aortic aneurysms are now more common after the advent of antibiotics [7]. A study examining thoracic aortic disease from 1987 to 2002 in Sweden, including ruptured and nonruptured thoracic aneurysm as well as acute and chronic aortic dissection, found the prevalence of aortic disease to be 16.3 per 100,000 for men and 9.1 per 100,000 for women in 2002 [13]. The incidence of aortic dissection was estimated to be six per hundred thousand persons per year in the Oxford Vascular study [14]. A trend in increased prevalence of aortic disease may be partially attributable to improved imaging techniques and screening.

Etiology and Pathophysiology

Pathology

The wall of the ascending aorta is comprised of three layers: the intima, media, and adventitia. The intima is a fragile layer of endothelial cells on a thin basal membrane. The media is a thick layer that contains an extracellular matrix containing elastin sheets, collagen, and smooth muscle. The vasa vasorum, which is a network of small blood vessels that supplies nutrients to the media, is located in the thin fibrous adventitia. The aorta contains a high degree of elastic tissue, which allows for the aorta to expand and contract, minimizing the physiologic stress of pressure shifts during the cardiac cycle. The ascending aorta has approximately twice the elastin content as the abdominal aorta and is more susceptible to age-related degeneration [15]. There are many known causes of aortic aneurysm formation, which are commonly separated into groups including age-related degeneration, congenital syndromes such as bicuspid aorta disease, Marfan syndrome, Ehlers–Danlos syndrome and Loeys–Dietz Syndrome, and infectious and noninfectious inflammatory syndromes (Fig. 11.2).

Degenerative

Degeneration of the elastic media is the most common biologic cause of aneurysm formation, and is caused by fragmentation of the extracellular matrix of the media by matrix metalloproteinases and cathepsin groups [16, 17]. As elastic layers fragment, smooth muscle cells become dysfunctional and are eventually replaced with cystic appearing mucoid material, known as cystic medial degeneration [18]. The Young–Laplace equation explains the relationship between aortic diameter and wall stress and comparable blood pressures (wall tension = pressure × radius) and helps to explain the progressively increasing rate of aortic dilation in aneu-

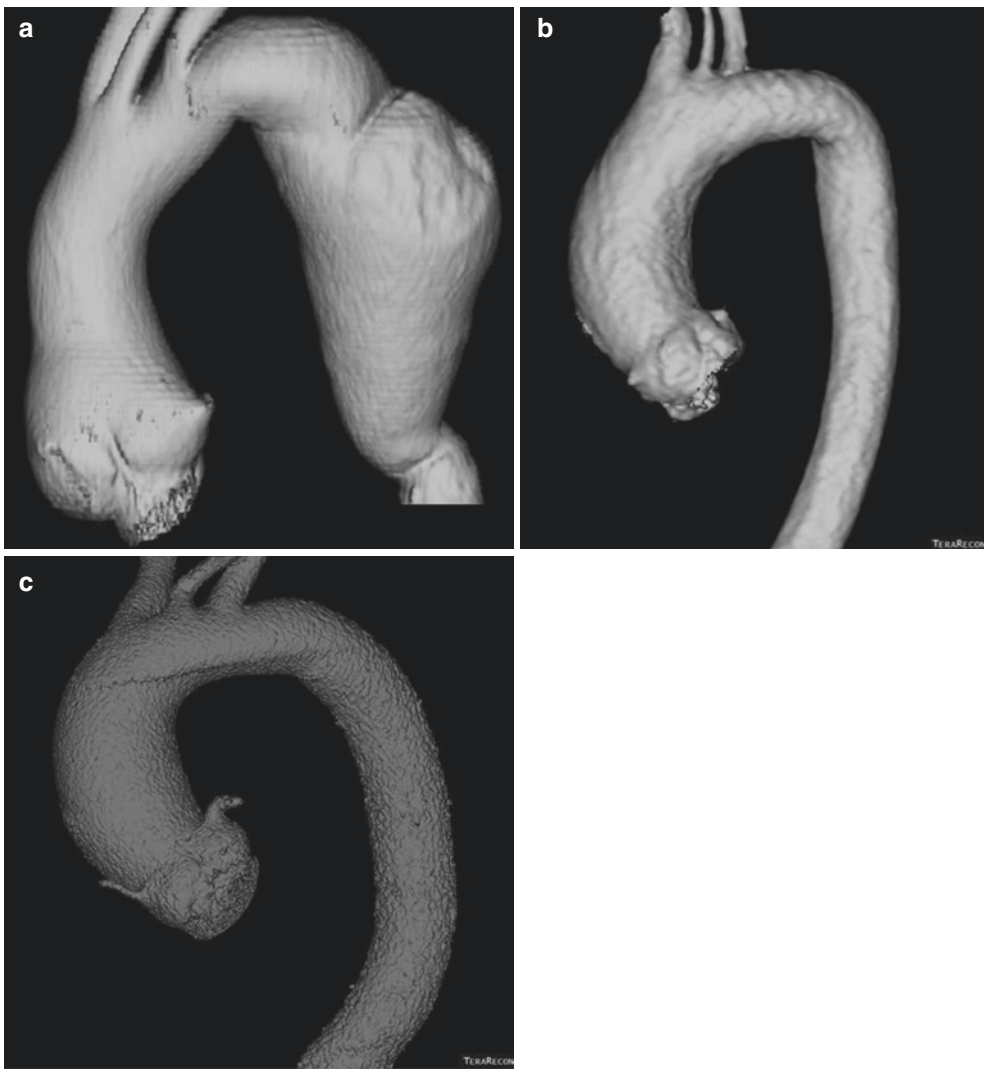

Fig. 11.2 Ascending aortic aneurysm caused by congenital syndromes. (**a**): Marfan syndrome. (**b**): Loeys–Dietz syndrome. (**c**): Bicuspid aortic valve

rysm progression. Ascending aortic aneurysms are often asymmetrical with anterior and rightward protuberance because the inner curvature of aorta is adhered to the pulmonary artery, which provides additional structural support. Dilation of the sinotubular junction and aortic annulus disturbs the coaptation of the aortic leaflets, which can progress to aortic insufficiency. Risk factors for degenerative aneurysms include smoking, hypertension, and hyperlipidemia.

Congenital

Marfan Syndrome

Marfan syndrome is a rare, autosomal-dominant multisystem disorder with high penetrance. The Ghent criteria were developed in 1996, and later revised in 2009, which comprise major and minor manifestations to aid in the diagnosis of Marfan syndrome [19]. The two most common cardiovascular features of Marfan syndrome include dilation of the ascending aorta and mitral valve prolapse, in addition to aortic arch and descending aortic aneurysms, aortic valve degeneration, and cardiomyopathy. Other manifestations include pectus excavatum, glaucoma and cataracts, hepatic and renal cysts, obstructive sleep apnea, myopathy, degenerative arthritis, osteoporosis, dural ectasia, and truncal obesity [20]. The prevalence of Marfan syndrome is about 1 per 3000–5000 individuals, without geographic or ethnic predilection. Nearly 25% of cases are sporadic due to de novo mutations [21]. Historically, Marfan syndrome was thought to be caused by mutations in the gene FNM1 coding the glycoprotein fibrillin-1 [22], resulting in elastin derangement, degeneration, and aortic aneurysm formation [23, 24]. More recently, the discovery of abnormal levels of activation of transforming growth factor β (TGF-β), which causes increased stimulation of inflammation, fibrosis, and metalloproteinases, are responsible for the clinical features of Marfan syndrome in combination with structural microfibril matrix and cell–matrix interaction abnormalities [21, 25, 26].

Aortic root dilation is often progressive and requires close surveillance. It is recommended that patients with a clinical diagnosis of Marfan syndrome and normal aortic diameter undergo annual screening transthoracic echocardiography (Fig. 11.3) with additional CT angiography or MRI every 5 years [27]. Patients with rapid progression or diameters close to surgical thresholds may require more frequent imaging. Both the absolute size of the aorta in the greatest diameter and the rate of expansion are evaluated. A recent study of the risk of an event (death/dissection) in a cohort of patients with Marfan syndrome reported risks of 0.09%/year, 0.30%, 1.33%, and 8.14% for aortic root diameters of <4.0 cm, 4.5–4.9 cm, 5.0–5.4 cm, and >5.5 cm, respectively [28]. Due to the increasing risk of dissection in larger aortic root aneurysms, it is widely accepted that prophylactic surgery should be performed when aortic diameter is greater

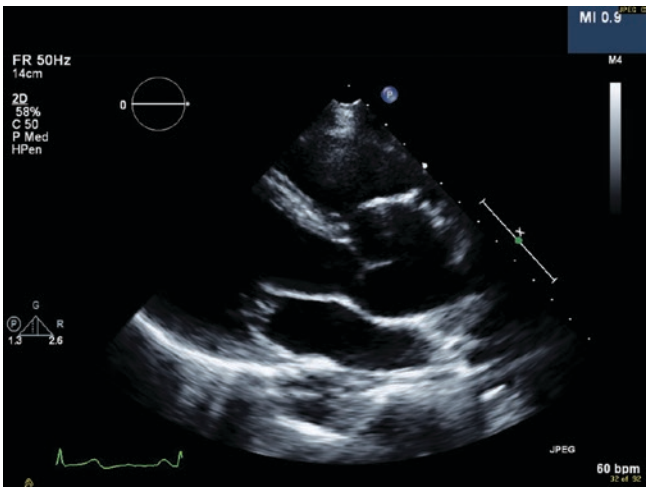

Fig. 11.3 Transthoracic echocardiogram of aortic root aneurysms in patient with Marfan syndrome

than 5.0 cm. Surgery should be considered for >4.5 cm in the presence of risk factors including family history of dissection, severe aortic regurgitation, and diameters >4.0 cm in those who desire to become pregnant [29, 30]. The average rate of aortic root dilation in patients with Marfan syndrome is variable, but is usually less than 1–2 mm per year [31]. Guidelines recommend more frequent surveillance and consideration for prophylactic aortic root replacement when dilation growth is greater than 2–5 mm/year [19, 29]. Without surgery, life expectancy in patients with Marfan syndrome is approximately 35–40 years of age, with leading causes of death mostly cardiovascular, including aortic dissection, rupture, and aortic insufficiency [32].

Medical treatment to prevent or delay the development of aortic dissection in patients with Marfan syndrome includes β-adrenergic receptor blockade, angiotensin II blockade, and historically calcium-channel blockers. The initiation of β-blocker is recommended for all Marfan patients regardless of aortic diameter if clinically appropriate [33]. Angiotensin II-receptor blockers, in addition to their well-known antihypertensive properties, act as a TGF-β antagonist and have been shown to significantly slow the rate of progressive aortic-root dilation in Marfan syndrome [34]. Calcium-channel blockers have been used in those who have had unacceptable side effects or limited response to β-blockers; however, a recently published study found that Marfan mice treated with calcium-channel blockers showed accelerated aneurysm expansion, rupture, and premature lethality [35]. In addition, retrospective analysis of a registry of humans with Marfan syndrome revealed preliminary evidence that aortic dissection and aortic surgical repair were more common in patients who had received a calcium-channel blocker than those who had been treated with other antihypertensive medication [35]. A multicenter randomized control trial compared losartan treatment in both operated and unoperated

adults with Marfan syndrome and reported a significantly decreased aortic root dilation rate in patients receiving additional losartan treatment compared to those with no additional treatment in combination with previously prescribed beta or calcium-channel blockers [36]. Lifestyle modification counseling should include not engaging in contact sports or anaerobic exercise that pronouncedly increases systemic blood pressure due to the risk of acute aortic dissection and sudden death.

Ehlers–Danlos Syndrome

Ehlers–Danlos syndrome (EDS) comprises a group of heterogeneous connective tissue disorders caused by defects in the synthesis of type III collagen. Symptoms classically include hyperelasticity and fragility of skin, joint hypermobility, obstetrical complications, platelet dysfunction, gastrointestinal rupture, and cardiovascular complications. The prevalence of EDS is estimated to be from 1 in every 10,000 to 1 in every 20,000 births [37]. The most common forms of EDS include *classical* (EDS types I, II), *hypermobile* (EDS type III), and *vascular* (EDS type IV) [38]. Vascular EDS type IV is a rare autosomal-dominant inherited connected disuse disorder resulting from mutation of the COL3A1 gene encoding type III collagen.

Cardiovascular complications of EDS type IV include dilation and/or rupture of the aortic sinus and rupture of the aorta, mitral valve prolapse, rupture of medium-sized arteries including the carotid artery, and varicose veins (Fig. 11.4).

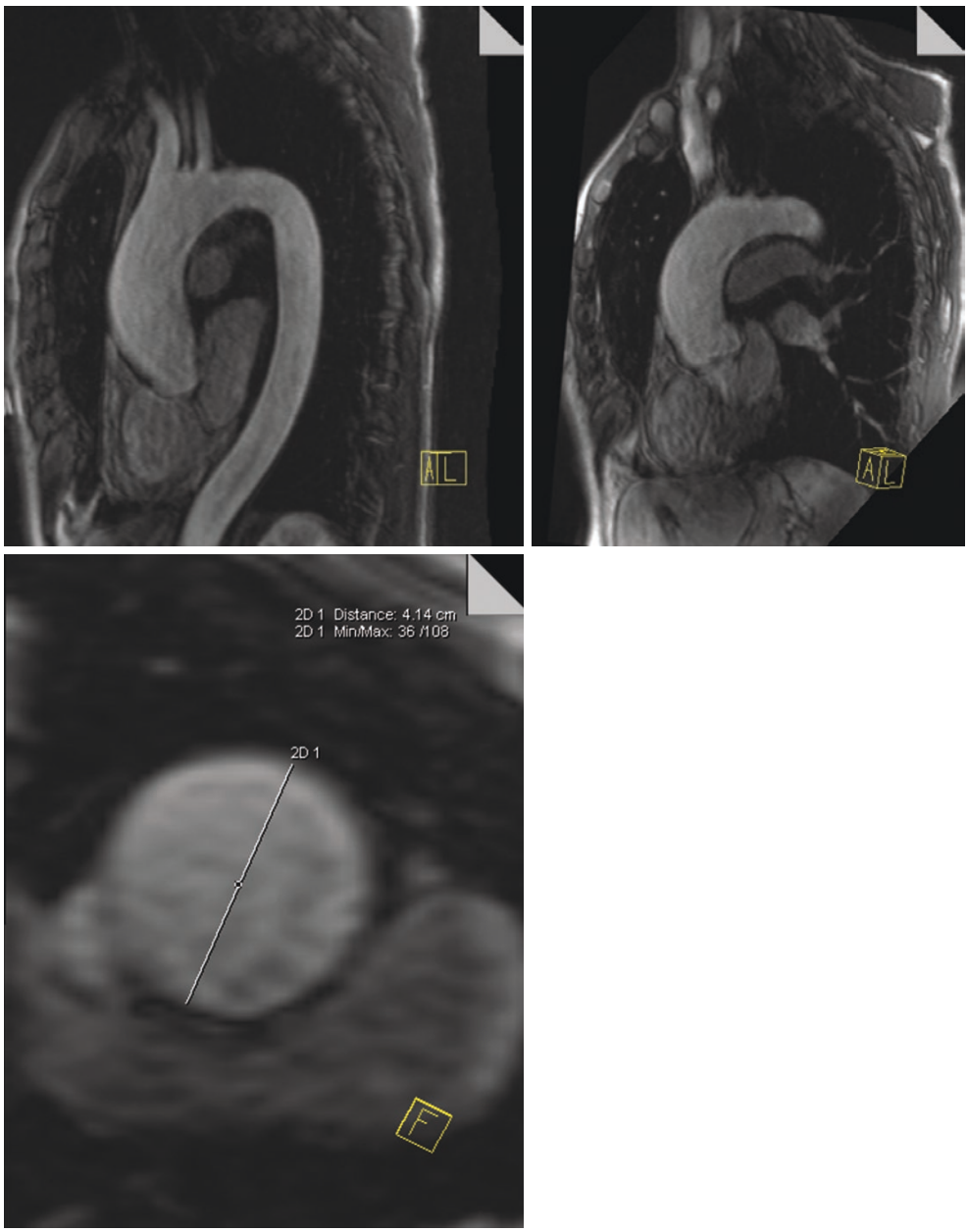

Fig. 11.4 MRI of Loeys–Dietz syndrome and ascending aortic aneurysm

Complications are rare during infancy, but occur in 25% of affected persons before the age of 20 years and 80% before the age of 40 years [39]. The presence of aortic root dilation was 28% in a study of 71 patients with EDS of any type [38]. Spontaneous rupture without dissection of the thoracic and abdominal aorta, as well as medium-sized arteries including carotid and vertebral, as well as branches of the abdominal aorta are the leading causes of death in patients with EDS type IV. Due to the risk of sudden death, close surveillance of aortic dilation is required, and prophylactic surgical repair of rapidly enlarging aneurysm may be indicated. Special precautions include delicate and atraumatic handling of tissues, use of prosthetic material, reinforced pledgeted anastomosis, and close postoperative monitoring with noninvasive imaging [40].

Loeys–Dietz Syndrome

Loeys–Dietz syndrome (LDS) is an autosomal-dominant disorder first reported to result from mutations in either transforming growth factor receptor type I or type II (TGFBR1 or TGFBR2) genes [41]. Subsequently, four different mutations have been identified and correspond to LDS type 1 through type 4, all of which alter TGF-β signaling [42]. This results in increased medial collagen and diffuse elastic fiber fragmentation and extracellular matrix deposition. Characteristics include developmental abnormalities, cleft palate, bifid uvula, scoliosis, pectus deformities, congenital heart defects, persistent patent ductus arteriosus, and atrial septal defects, in addition to aortic root aneurysm and dissection [41]. The progression of aneurysm enlargement is more rapid than other congenital syndromes and often requires prophylactic aortic root repair at smaller diameters and younger ages. Therefore, at least yearly echocardiography is recommended, and more frequently depending on the severity of the aortic disease. Medical management includes strict blood pressure control with antihypertensive medications including β-blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors. Exercise restrictions should be recommended, including avoidance of contact or competitive athletics and isometric exercises.

MacCarrick et al. recommend surgical thresholds in adults with LDS type 1, 2, and 3, to be an aortic root dimension >4.0 cm or rapidly expanding (>0.5 cm per year) or an ascending aorta/aortic arch diameter of >4.0 cm, with a low threshold for surgical intervention with growth. It is also recommended to delay surgery in children until aortic annulus is 2.0–2.2 cm to accommodate adult-sized grafting [42]. Postoperative echocardiography is recommended at 3–6 month intervals for the first year, then every 6 months to 1 year thereafter.

Bicuspid Aortic Valve Disease

Bicuspid aortic valve is a common congenital heart anomaly that occurs in approximately 1–2% of the population [43]. It more commonly affects males and is associated with Turner syndrome. Bicuspid aortic valve disease is prevalent in patients with first-degree relatives of patients with bicuspid aortic valve disease [44]. There are many suspected mechanical properties of bicuspid valves that increase the propensity of ascending aortic dilation, including significantly increased wall stress, larger dimensions of the aortic annulus and ascending aorta, independent of aneurysmal disease formation. The aortic wall in bicuspid aortic valve disease has been shown to contain increased levels of matrix metallic proteinases, elastic fragmentation, matrix disruption, and deficiency of fibrillin-1 [22, 45, 46]. Patients with bicuspid valves have a higher rate of aortic root dilation, often including the aortic arch [47] (Fig. 11.5).

Infectious

Infections may occasionally cause damage the aortic wall, which can occasionally lead to the formation of mycotic ascending aortic aneurysms. They are often associated with left-sided endocarditis, therefore sharing some of the most common organisms, such as *Staphylococcus aureus, Staphylococcus epidermidis, Salmonella,* and *Streptococcus pneumoniae* [48–50]. Syphilis was a common cause of ascending aortic aneurysm prior to the use of antibiotics. Untreated syphilis can result in the degeneration of the medial elastic fibers of the aorta, which is not reversible with antibiotic treatment. Mycotic ascending aortic aneurysms may also form in atherosclerotic aortic disease with the seeding of intraluminal clot with bacteria [49]. Computed tomography (CT) with contrast enhancement is the gold standard for diagnosis, with findings of periaortic density and adjacent gas collection signs impeding rupture [50]. Transesophageal echocardiography is often the initial imaging technique due to its role in the evaluation of infective endocarditis. Magnetic resonance imaging (MRI) with gadolinium contrast may also be beneficial. Prompt initiation of antibiotic therapy and complete surgical excision of the infected aorta is widely recommended; however, few controlled studies have been performed to guide the management of infective aortitis.

Noninfectious Inflammatory Syndromes

The most common causes of noninfectious aortitis include large-vessel vasculitides giant cell arteritis (GCA) and Takayasu arteritis, but other rheumatologic disorders such as system lupus erythematosus, rheumatoid arthritis, Wegener granulomatosis, and polyarthritis nodosum are known causes [51]. Antigen-driven cell-mediated autoimmune infiltration of the aortic media, adventitia, and vasa vasorum are present in GCA and Takayasu arteritis, which causes scarring and progresses to the destruction of the elastic lamina. Immunosuppressive therapy is the primary treatment of large-vessel vasculitis, and glucocorticoid therapy should be initiated at the time of diagnosis. Patients should be monitored closely for the common complications of

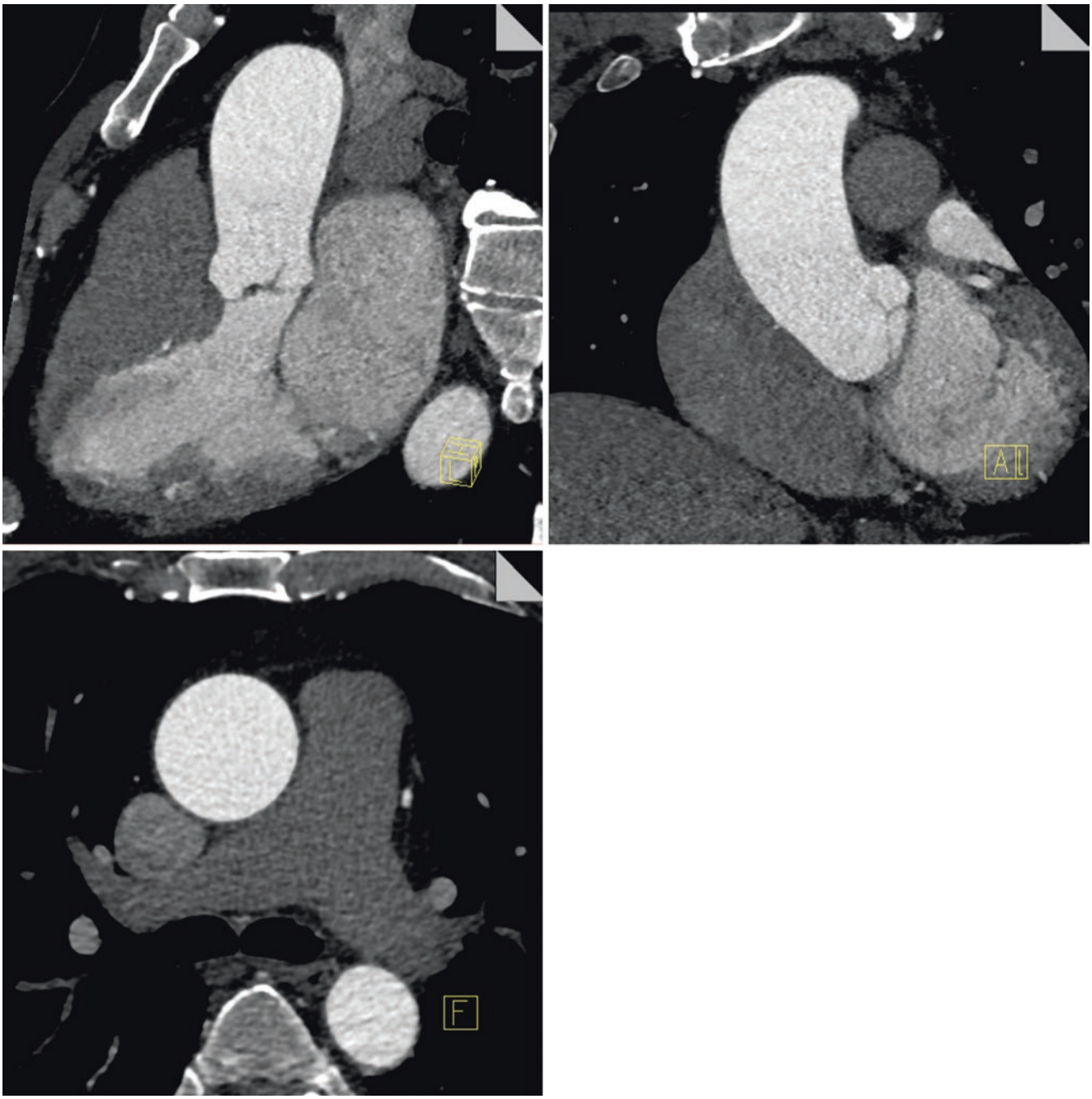

Fig. 11.5 Bicuspid aortic valve and ascending aortic aneurysm

long-term glucocorticoid therapy. Surveillance of aortic aneurysms is necessary and open aortic aneurysm repair remains the standard of treatment for enlarging aneurysms.

Clinical Presentation

Ascending aortic aneurysms are commonly asymptomatic, and are frequently discovered incidentally on radiographic studies. However, as aneurysms progress in size or involve the aortic arch they more frequently become symptomatic, with chest pain, back pain, dyspnea, dysphagia, and transient neurologic deficit. Hoarseness due to stretching of the recurrent laryngeal nerve may occur. Symptoms of heart failure may develop as dilation of the aortic root or ascending aorta disrupts coaptation of the aortic valve leaflets causing aortic regurgitation, evident by a widened pulse pressure and diastolic murmur. Acute dissection or rupture of the ascending aorta is a surgical emergency and often manifests as sudden severe anterior chest pain. Myocardial infarction, stroke, and

cardiac tamponade may result, as well as dissection down throughout the thoracoabdominal aorta causing ischemia of the kidneys or abdominal viscera. Chest X-ray is frequently obtained as initial imaging and may contain a widened mediastinum. Diagnosis is commonly obtained with chest computed tomography.

Imaging Modalities

Imaging of the aorta has evolved dramatically in the past 50 years. The advancement of echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) have allowed for many options for clinical assessment. However, each imaging modality has evolved largely independent of the others, leading to lack of standardization across the different modalities. This requires that evaluation between modalities and amongst serial studies be done cognizant of the potential limitations of each testing strategy. The best approach is to compare images directly, remeasuring if necessary to ensure consistency in approach and timing of measurement. Developing a good working relationship with advanced imaging colleagues, both Cardiology and Radiology, will ensure that clinical decisions are being made based on disease progression and not variability in measurement.

Transthoracic echocardiography is a common initial imaging strategy at most institutions due to the ease of acquisition, safety, tolerability, the ability to concurrently evaluate cardiac structure and function, and identify concurrent pathology. Compared to other aortic segments, transthoracic echocardiographic imaging of the ascending aorta is both accurate and usually reproducible, and correlates well with both transesophageal echocardiography and CT aortic diameter measurements. In addition, the negative predictive value for aortic root dilation of an optimized, diagnostic-quality transthoracic echocardiogram is high, suggesting no additional testing needed for normal aortic roots. In addition, both transthoracic echocardiography and transesophageal echocardiography have outcome data, which has driven the current guideline recommendations regarding its use. Extensive data in normal populations has allowed for gender-specific cutoffs to be developed, which are indexed to body surface area. This allows for more precise interpretation of aortic measurements tailored to individual patients. Furthermore, echocardiography allows for reliable assessment of aortic physiology as well as anatomy, specifically around distensibility and regional stiffness. This allows for assessment of dysfunction despite normal anatomy. Despite imaging-based guideline documents, there are common sources of variability that are important to identify.

Firstly, current guidelines recommend all measurements be in end-diastole. This is largely due to the relative stability of aortic hemodynamics as well as easy identification using the QRS complex, both leading to improved reproducibility. However, aortic dimensions are often the largest in end-systole, and CT and MR do not have similar guidelines as to the timing of measurement (many are nongated studies, removing this as an issue altogether). This can make comparisons of reports difficult, especially if discrepancies are found.

Secondly, current guidelines recommend measuring "leading edge to leading edge." Leading edge measurements were largely related to previous technology that made clear identification of the inner wall of the vessel difficult. However, with improved technology, harmonic imaging, and use of contrast agents, this has become less of an issue. While true inner diameter may be a more accurate representation of the size of the vessel, outcome data is largely linked with the older "leading edge to leading edge" methods. As such, guideline documents have not adjusted to reflect a change in practice. This "leading edge to leading edge" method overestimates the diameter by an average of 2 mm when compared to inner diameter measurements.

Thirdly, 2D echocardiography is angle-dependent. Depending on the orientation of the ultrasound (US) probe to the vessel, the measured diameter may underestimate or overestimate the true diameter if looked at in cross section.

Transthoracic Echocardiography

Transthoracic echocardiographic (TTE) imaging of the ascending aorta is largely done via the parasternal long-axis and suprasternal views. The parasternal long-axis view allows for the left ventricular outflow tract, aortic valve, and aortic root and a portion of the ascending aorta to be viewed in continuity. Generally, optimization of the imaging plane is achieved when both the mitral valve and aortic valve excursion are seen at the highest possible intercostal level. However, for imaging of the aorta itself efforts should be taken to maximize both aortic root and aortic dimensions given the above concerns. In this view, the aortic valve leaflets of trileaflet valve are generally seen coapting in the center of the left ventricular outflow tract, and the long axis of the aorta is seen.

Allowing for easy measurement can introduce a source of variability between different modalities. In most patients, this represents the distance between the right coronary sinus to the non-coronary sinus. Sinus-to-sinus measurements, as opposed to sinus-to-commissure measurements, tend to overestimate the aortic root size by a mean of 2 mm. Measuring in this fashion may still be helpful clinically, because it may identify sinus of Valsalva aneurysms. In addition, asymmetric enlargement of the sinuses will not necessarily be appreciated from this two-dimensional view. Three-dimensional echocardiography can help address this

issue, and some have advocated the use of an average measurement of the three individual sinus-to-sinus measurements in three-dimensional modalities. This source of variability is not inconsequential, and has been the impetus for CT-guided imaging of the aortic annulus and aortic root in most structural heart programs for transcatheter aortic valve replacements (TAVR).

Frequently, the distal ascending aorta is not completely appreciated from the parasternal long-axis view due to acoustic impedance from the left lung, and the suprasternal view is needed to identify the distal ascending aorta and arch. This view is not always obtained due to patient comfort and anatomy, but provides visualization of the distal ascending aorta and aortic arch in the vast majority of patients (>90%). Right parasternal views are needed, especially in patients with significant dilatation. Finally, apical and subcostal views can be used in selected patients, but the complete ascending aorta is not usually completely visualized in these views.

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) allows for increased spatial resolution due to higher frequency probes and the proximity of the esophagus to both the ascending and descending aorta. Furthermore, multiplane TEE probes allow for both long-axis and short-axis visualization of the aorta. TEE has been studied largely in its role in acute aortic syndromes, but can also be used in the assessment of ascending aortic aneurysms. The same issues in reproducibility occur with TEE as they do with TTE, although diagnostic image quality is generally more reliable. A specific issue with the TEE is visualization of the distal ascending aorta, arch, and great vessels due to acoustic impedance of the ultrasound image from the trachea. This theoretical "blind spot" can largely be overcome via imaging from different angles and depths to avoid air-filled structures.

Computerized Tomography

Computed tomography (both ECG gated and non-ECG gated) have rapidly become the gold standard for imaging of the entire aorta. The increased spatial resolution and rapid and reliable imaging in varied clinical scenarios have allowed for routine use of CT in this setting. The major limitation of CT-based imaging approach is the need for ionizing radiation (especially in younger patients or for serial imaging). Contrast agents are less of a concern now, especially given that iso-osmolar agents and intravenous injection allow for adequate mixing prior to the renal artery, minimizing the risk of nephrotoxicity.

Specific issues regarding imaging the aortic root and the ascending aorta largely surround artifact created by normal cardiac motion, often mimicking an aortic root dissection. This has necessitated the need for ECG gating to allow for imaging at a time when cardiac motion is minimal. In most patients with regular heart rhythm, this is achieved in end-diastole, but is adjustable, and can lead to variability in measurements.

Furthermore, the method of measurement has not been standardized. Ideally, all measurements will be made after centerline reconstructions to allow for a true cross section to be visualized. Measurements made from axial slices alone can often overestimate true dimensions. In addition, there is variability in how measurements are made. Inner diameter to inner diameter measurements likely reflect the true lumen and are most accurate. However, this can be challenging, especially in the setting of intramural hematomas, previous interventions (endovascular or open), or aortic wall thickening. Previous guidelines had suggested outer dimension to outer dimension measurements to allow for reproducibility with contrast and noncontrasted studies. However, this can significantly overestimate the true diameter. Measuring axial slices with an outer diameter to outer diameter approach will lead to the largest dimensions.

Magnetic Resonance Imaging

Magnetic resonance angiography (MRA) has been frequently been used in imaging the thoracic aorta, especially for serial assessments or a more comprehensive assessment in younger patients. The spatial resolution is less than either CT or echocardiography, especially TEE, but allows for reconstructions, as well as the lack of ionizing radiation has made it an attractive option for many patients. In addition, time-of-flight imaging allows for an MRA to be done without the need for gadolinium-based contrast agents. Patient comfort and time can limit those that tolerate MRA as an imaging modality, but evolution of this technology has limited this issue.

Unfortunately, the same issues with measurement in CT apply to MRA as well. Cardiac motion can lead to lack of spatial resolution and increased artifact, especially at the aortic root. This can be largely avoided with ECG gating and appropriate timing of acquisition. Centerline reconstruction and inner diameter to inner diameter will likely give the smallest diameter, while axial slices and outer diameter measurement will tend to overestimate the dimension.

Selecting the Appropriate Imaging Modality

Selecting the optimal imaging modality for the ascending aorta is dependent on many factors: age of patient, body habitus, need for serial testing, concurrent disease, expected

location of disease, patient compliance, and renal function. In general, an initial assessment with transthoracic echocardiography is most appropriate, especially if the disease is expected to be limited to the aortic root or proximal ascending aorta, concurrent valvular disease is suspected, or the patient has concurrent cardiovascular disease that needs to be assessed. If the transthoracic echocardiogram is normal and the ascending aorta is well visualized, additional testing should be reserved for specific clinical questions. For aortic root or ascending aortic dilation or for nondiagnostic images, assessment with CT or MRI is reasonable. The decision of which to pursue should largely be dependent on patient-specific considerations of age, need for serial testing, and patient comfort. In patients at risk for syndromic aortas, initial testing with CT or MRI is reasonable depending on patient-specific factors.

Surgical Indications

Prompt surgical evaluation and intervention is indicated in patients with symptoms suggestive of aneurysm expansion independently of size, except in cases of limited life expectancy or quality of life from comorbid conditions [30]. Indications for asymptomatic aortic aneurysm resection and replacement have developed over time. Elefteriades and colleagues at the Yale Center for Thoracic Aortic Disease have reported a threshold for dramatically increasing risk of dissection with progressive aneurysmal dilation at a size of 6 cm in the ascending aorta, and 7 cm in the descending aorta [52–54]. However, patient size is an important factor in evaluating aortic aneurysms, especially when considering operative guidelines that would apply to both small and large patients. A calculation was developed by Elefteriades et al. based on a retrospective review of patients who developed aortic dissection or rupture that incorporated body surface area and aortic aneurysm diameter [55]. Body surface area (BSA) in m^2 is calculated by the Dubois and Dubois formula:

$$\mathrm{BSA} = 0.20247\left(wgt^{0.425} \times \left(\frac{hgt}{100} \right)^{0.725} \right)$$

The aortic size index (ASI) is described as the aortic diameter (cm) divided by body surface area (m^2). Patients with ASI less than 2.75 cm/m^2 are classified as low risk (approximately 4% per year), 2.75–4.24 cm/m^2 are considered medium risk (approximately 8% per year), and greater than 4.25 cm/m^2 are high risk (approximately 20% per year) [55].

For asymptomatic adults with degenerative thoracic aneurysms, it is generally accepted that resection of the ascending aortic aneurysm is indicated at 5.5 cm or growth rate of more than 0.5 cm/year, aortic arch aneurysms should be resected at 5.5 cm, and descending aortic aneurysms may be monitored until a diameter of 6.0 cm prior to open repair [30, 56]. Lower thresholds should be considered in patients of small stature or in the cases of aortic regurgitation, and pregnancy. Surgical thresholds for repair of ascending aortic aneurysms are smaller in genetic syndromes (Table 11.1) [30, 56], such as Marfan's syndrome at 5.0 cm (4.0 cm if contemplating pregnancy) or family history of aortic dissection at smaller diameter, LDS at between 4.2 and 4.6 cm depending on imaging modality, bicuspid aortic valve at less than 5.0–5.5 cm, and EDS less than 5.0 cm but limited data is available to establish a threshold [30, 56]. Arguments have been presented that early treatment of thoracic aortic aneurysms may be beneficial in appropriate patients due to the difficulty in predicting aortic dissection, high rates of early and late mortality, emotional burden to patients, and relative safety of elective aortic surgery in the present era [57].

Table 11.1 Indications for surgical repair on asymptomatic ascending aortic aneurysms

Underlying etiology of aneurysm	Diameter (cm)
Degenerative thoracic aneurysm	5.5
If also indication for aortic valve surgery	4.5
Marfan	4.5–5.0
If desiring pregnancy	4.0
Ehlers–Danlos	4.2–4.4
Loeys–Dietz	5.0
Turner syndrome	5.0
Bicuspid valve	5.0–5.5
Mycotic aneurysm	5.5

Data from [30, 56]

Operative Technique

Ascending aortic aneurysm is a surgical disease and operative repair is essential to prevent dissection and rupture. Indications for repair are based on size, symptoms, and rate of growth. Multiple preoperative procedures are commonly performed by anesthesiologists. Venous access is obtained with a large bore central catheter, typically via the internal jugular vein with pulmonary artery pressure monitoring, as well as several large peripheral catheters. An arterial catheter is placed for hemodynamic monitoring, and both right and left radial artery access is commonly preferred in patients with aneurysms involving the aortic arch. If hypothermic circulatory arrest is planned, bilateral electroencephalographic monitoring is also employed. Transesophageal echocardiography is performed intraoperatively to evaluate cardiac function, size of aorta, and valvular function.

All patients are placed on cardiopulmonary bypass prior to repair of the aneurysm. Many repairs require concomitant aortic valve replacement, either as a separate prosthesis or using a composite graft. Choice of operative technique

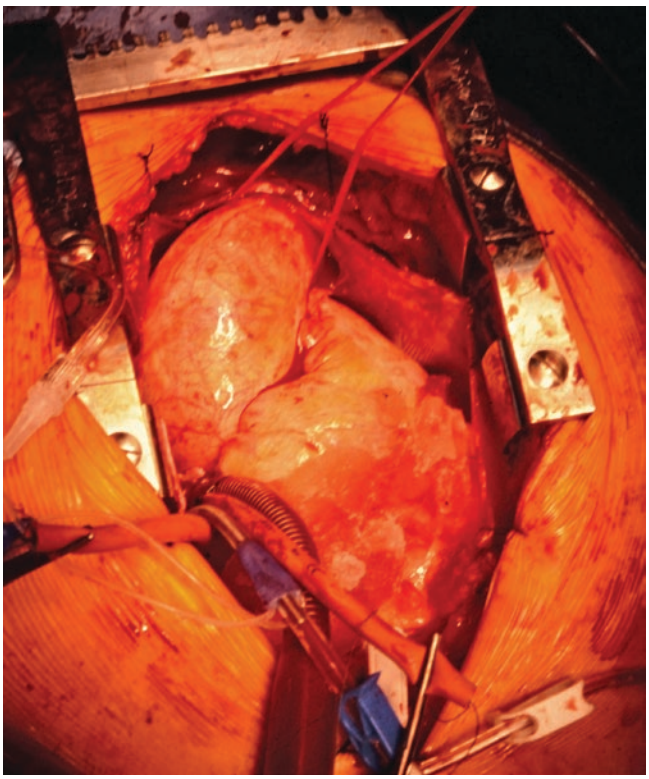

Fig. 11.6 Ascending aortic aneurysm repair

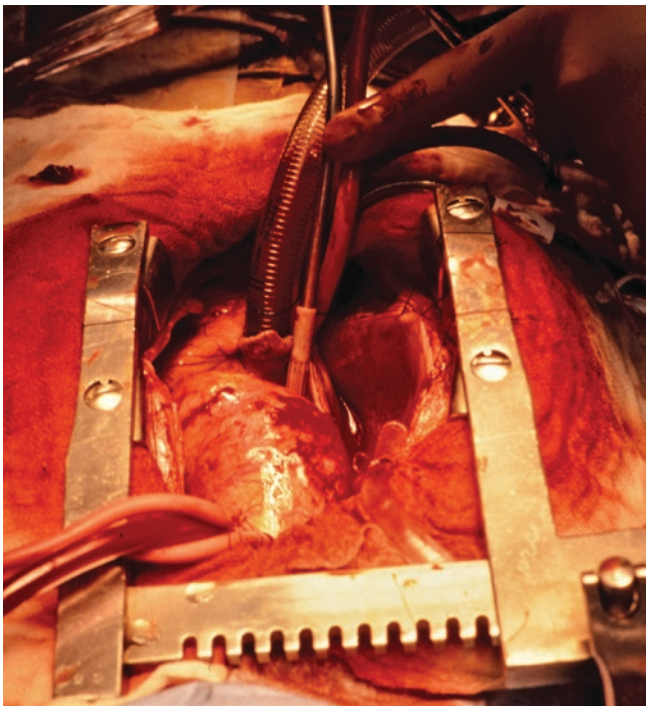

Fig. 11.7 Ascending aortic aneurysm

depends on the etiology and extent of aortic disease, as well as patient anatomy and preoperative condition (Figs. 11.6 and 11.7).

A. Isolated ascending aortic aneurysm is frequently excised and replaced with a Dacron tube graft. This procedure carries a low risk with good long-term results. However, the aortic valve is often involved and requires repair or replacement.
B. Aortic valve replacement and ascending aortic replacement with a tube graft without requiring coronary reconstruction may be performed in ascending aortic aneurysms not involving the root with concomitant aortic valve pathology, such as bicuspid aortic valve.
C. Aortic root aneurysms may require composite root replacement, which involves excision of the ascending aorta, coronary artery reimplantation, and placement of a composite valve, either mechanical (Bentall procedure) or implanted bioprosthetic. This technique is often necessary when the aneurysm involves the sinotubular junction resulting in aortic insufficiency.
D. If the aortic valve is incompetent but the cusps are normal, valve competence can be reestablished by repair of the aortic root. Valve-sparing aortic valve repairs such as the David and Yacoub procedures can be performed, which require advanced technical skill and experience and are predominantly performed at large aortic centers.

Outcomes

Early hospital mortality after elective repair of chronic ascending aortic aneurysm ranges to a high degree and is reported to be as high as 9% and recent surgical advancements have reduced operative mortality to below 3% [58–61]. Causes of early mortality and morbidity include postoperative hemorrhage, stroke, respiratory failure, myocardial dysfunction, and renal dysfunction and failure. Reoperation for bleeding ranges widely between 3% and 12%, depending on type of repair [58, 59, 62]. Preoperative risk factors for stroke include prior stroke, severe carotid artery occlusive disease, age greater than 65 years, and peripheral vascular disease [63]. Cardiopulmonary bypass is associated with acute respiratory distress syndrome and the incidence is reported to be between 0.4% and 1.7% [64, 65]. Aortic disease involving the arch carries a higher mortality [66]. Ascending aortic surgery due to diffuse atherosclerosis, which is commonly seen in cases of ascending aortic aneurysm and frequently requires concomitant coronary artery bypass grafting has higher early mortality and morbidity [67, 68]. Late mortality is variable and is dependent on patient characteristics and surgical technique. Survival rates vary from 80% to 95% at 1 year, 70% to 90% at 5 years, 60% to 75% at 10 years, and 60% at 14 years [69–71]. McCarthy et al. published a study of patients at the University of Pennsylvania who underwent elective aortic root replacement for aortic insufficiency with aneurysm and found that 95% were free of reoperation at 10 years [72]. Late mortality

in patients undergoing valve-sparing aortic root replacement at high volume centers is comparable to repair with prosthetic valves [73, 74].

Conclusion

Ascending aortic aneurysms are not uncommon and are potentially asymptomatic, and deadly.

Healthcare providers need to be aware of the patient profiles and their clinical presentations. An understanding of the strengths and limitations of the diagnostic tools available at their institutions is warranted. Recognizing the indications for surgical intervention is necessary to offer the patient the best chance for improved clinical outcomes. Timely diagnosis and delivery of appropriate medical therapy and surgical procedures is essential not only to improve survival, but reduce comorbidities and improve quality of life. However, despite a much greater understanding of the underlying etiologies, diagnostic options, and surgical techniques for ascending aortic aneurysms over the past 50 years, there remains much to learn regarding an individual patient's risk. Therefore, all prophylactic decisions for surgery should be made together with the healthcare provider and the patient, taking into consideration individual clinical and nonclinical factors.

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Aortic Arch Aneurysms

12

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Introduction

Repair of aortic arch aneurysms is especially challenging because of the complicated anatomy of this aortic segment. The need to reconstruct critical branches supplying the brain and upper extremities, the curved shape, orientation from anterior to posterior, and frequent associated aneurysm involvement with the ascending and descending aorta impose anatomic constraints that limit exposure during open procedures and challenge the tolerances of endovascular devices. Add to these challenges the critical need to perform aortic arch aneurysm repair while protecting the brain from ischemic and embolic injury. Because of these anatomic, pathologic, and technical factors, aortic arch surgery has been associated with significant morbidity and mortality and is frequently performed in specialized centers that have developed expertise in treatment of this complex entity. Modern operative techniques and endovascular approaches have reduced these risks and allowed safer, more complete repair for this challenging group of patients.

Anatomy

The aortic arch is contained within the superior mediastinum (Fig. 12.1). It is continuous with the ascending aorta and begins at the level of the second sternocostal articulation on the right side of the sternum. Its most proximal portion is directed superiorly and posteriorly, across the anterior surface of the trachea. It then travels posteriorly to the left side of the trachea before turning downward to give rise to the descending aorta at the level of the fourth thoracic vertebra.

The aortic arch normally has three branches. The most proximal and largest branch is the brachiocephalic artery, which is anterior to and to the right of the other arch vessels. The second branch is the left common carotid artery, which originates distal to and to the left of the brachiocephalic trunk. The third and most distal branch of the arch is the left subclavian artery.

Aortic arch branch vessel anomalies are common [1]. A bovine arch is the most common variant and occurs when the brachiocephalic artery shares a common origin with the left common carotid artery. A bovine arch occurs in 10–20% of the population. A thyroidea ima artery, supplying the inferior aspect of the thyroid gland, occurs in 4–10% of the population and can arise from the brachiocephalic artery, right common carotid artery, or directly from the aortic arch. Variant left vertebral arteries are present in 2–6% of the population and can arise directly from the aortic arch.

Pathophysiology

Aneurysms

The aortic arch is affected by the same pathophysiologic processes that cause aortic aneurysms in other portions of the thoracic aorta [2]. Aneurysms of the ascending aorta are most often the result of cystic medial degeneration, which appears histologically as loss of smooth muscle cells and elastic fibers within the artery wall media. Cystic medial degeneration normally occurs to some extent with aging. Hypertension and tobacco use are thought to accelerate the process.

The most common inherited disorders that cause accelerated cystic medial degeneration are Marfan syndrome and familial thoracic aortic aneurysm syndrome. The accelerated

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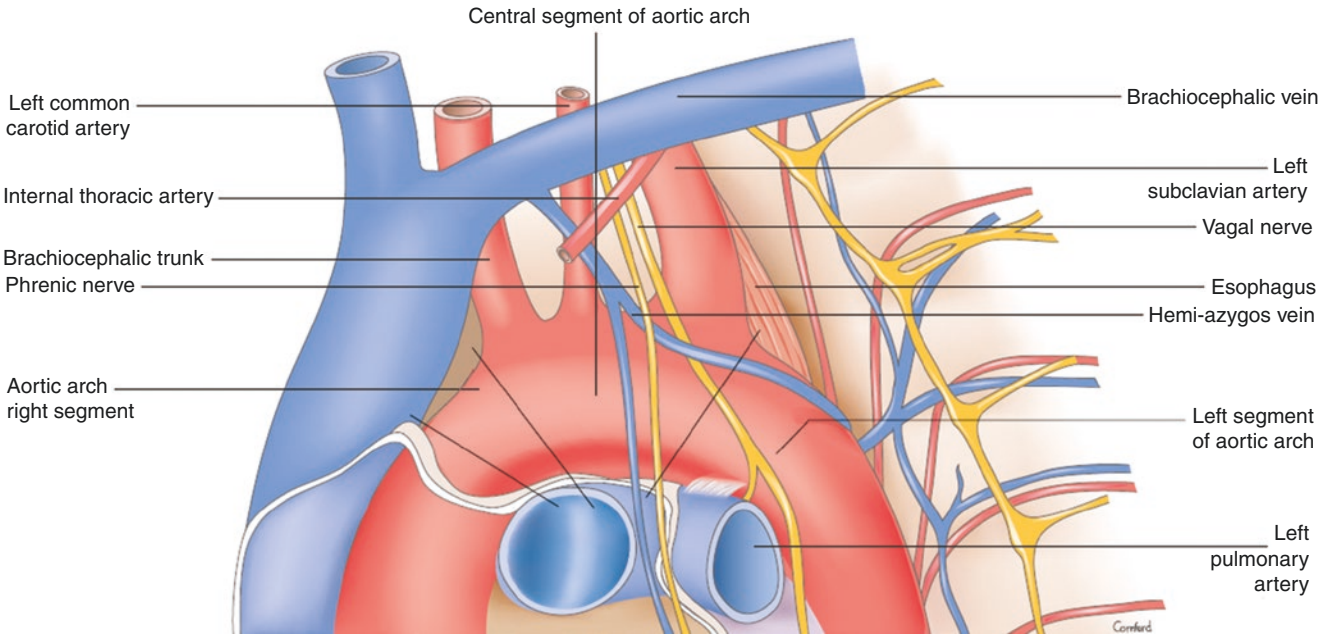


Fig. 12.1 Anterior view of the aortic arch. (Reprinted from [1], with permission from Springer)

degenerative process usually leads to early presentation during young adulthood in these patients. At least 20% of thoracic aortic aneurysms are thought to be genetically caused. Other genetic disorders associated with cystic medial degeneration and early aneurysm formations include bicuspid aortic valve, Ehlers–Danlos syndrome, Loeys–Dietz syndrome, and Turner syndrome.

In contrast to the ascending aorta, cystic medial degeneration is not typically the cause of true aneurysms involving the descending aorta. Atherosclerosis is the predominant etiology of aneurysms of the descending aorta. These aneurysms typically originate just distal to the origin of the left subclavian artery and can involve the distal aortic arch. Risk factors for atherosclerotic thoracic aneurysms include advanced age, hypertension, and tobacco use.

Aneurysms of the aortic arch are less common than aneurysms of the ascending or descending aorta. This is likely related to the pattern of involvement of the thoracic aorta with the predominant aortic pathologies, cystic medial degeneration, and atherosclerosis. Cystic medial degeneration predominantly affects the aortic root and ascending aorta while atherosclerosis predominantly affects the descending aorta. Involvement of the proximal aortic arch with cystic medial degeneration or involvement of the distal aortic arch with atherosclerosis can lead to involvement of a portion of the aortic arch with contiguous aneurysms, but whole arch involvement or isolated arch involvement is rare. Aneurysm involvement of the whole aortic arch typically signals extensive aortic involvement because it is associated with diffuse medial degenerative disease or atherosclerosis in most cases.

Syphilis was once perhaps the most common cause for ascending aortic aneurysms, but in the era of common antibiotic treatment, such aneurysms are rarely seen today. The latent period from initial spirochetal infection to aortic aneurysm formation is 10–30 years. Aneurysm formation is related to direct sprichete infection of the aortic media. Aneurysms are often saccular and involve the ascending aorta but can involve the aortic root and arch.

Chronic inflammation of the aorta is a rare cause of aortic aneurysm. Takayasu's arteritis is a rare disease of unknown etiology that causes a chronic aortitis. The disease affects women much more often than men and is diagnosed in early adulthood. It typically causes obliterative changes of the aorta or aortic branches but can cause aortic aneurysms in up to 15% of cases. Giant-cell arteritis and ankylosing spondylitis are other rare causes of aortitis that can lead to aortic aneurysm formation.

Dissections

Chronic aortic dissection is an important cause of aortic dilatation [3]. In many surgery practices, chronic dissection of the aortic arch after Stanford Type A or DeBakey Type I aortic dissection is the most common underlying pathology leading to aortic arch replacement (Fig. 12.2). When an aortic dissection occurs, it causes direct weakening of the aortic wall by forming a false lumen that is contained only by the media and adventitia of the aorta. This false lumen is typically exposed to systemic arterial pressures through fenestrations in the intimal flap between the true and false lumens. In

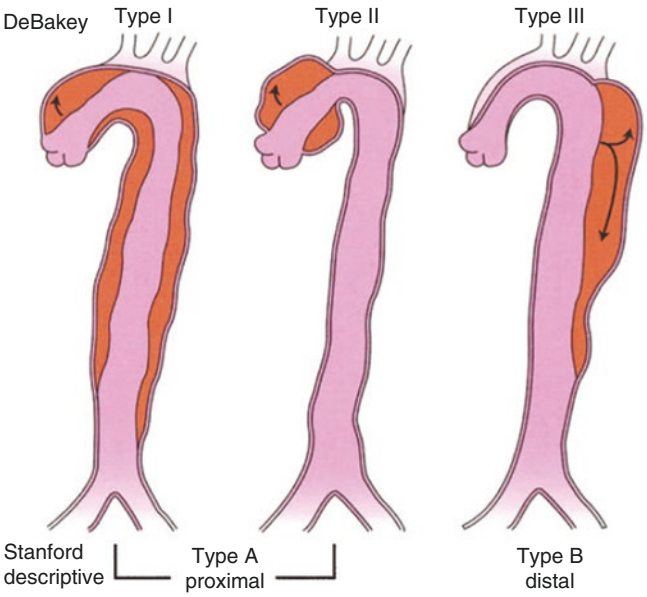


Fig. 12.2 Classification of aortic dissection by extent of aortic involvement. (From Isselbacher [29]. Reprinted with permission from Springer)

addition, because the dissected aorta is acutely enlarged at the time of dissection, the aortic wall is subjected to higher wall stress as dictated by LaPlace's Law. Further aortic growth over time begets further aortic growth by the same mechanism. Finally, many patients with chronic dissection have an underlying aortopathy that causes cystic medial degeneration and aortic growth.

Trauma

Patients suffering severe blunt chest trauma can also suffer aortic arch injuries. Typically, these injuries are the result of rapid deceleration after motor vehicle accidents or falls, leading to partial aortic transection. The aortic injury usually occurs at a point of aortic fixation within the chest, most commonly the aortic isthmus of the distal aortic arch at the site of the ligamentum arteriosum. Aortic injuries resulting from blunt trauma are typically associated with a constellation of other thoracic, abdominal, orthopedic, and central nervous system injuries. Many patients with blunt aortic injuries die from hemorrhage or other associated injuries before they can be evaluated. When the aortic injury is contained, leading to an aortic pseudoaneurysm, patients may survive to be evaluated in an emergency department. Rarely, aortic transections are not diagnosed initially and patients may develop chronic pseudoaneurysms. These pseudoaneurysms are frequently saccular and discrete. They are subject to growth over time because of their inherent weakness and high wall stress.

Presentation

Most patients with thoracic aortic aneurysms are asymptomatic. Because of this, most thoracic aneurysms are discovered incidentally at the time of chest X-ray, CT scan, MRI, or echocardiogram. Patients with aortic arch aneurysms associated with ascending aortic or aortic root aneurysms may have secondary aortic regurgitation, leading to a diastolic murmur or congestive heart failure. Patients with aortic arch aneurysms associated with bicuspid valve may also present with valve dysfunction, either aortic stenosis or regurgitation. Patients with large aortic arch or associated thoracic aneurysms may suffer a local mass effect, such as compression of the trachea or left mainstem bronchus (causing cough, wheezing, pneumonia, or pneumonitis), the esophagus (causing dysphagia), or the recurrent laryngeal nerve (causing hoarseness). Rarely, patients with nondissecting aneurysms may present with chest or back pain related to direct compression of other intrathoracic structures or erosion into bone.

The major aortic complication caused by thoracic aneurysms is dissection or rupture. Patients are typically symptomatic and have a sense of foreboding, acute onset chest or back pain, hypotension, and malperfusion of any aortic branch vessel.

Imaging

Management of thoracic aortic aneurysms is highly dependent on sizing and morphology, making imaging a critical component of the evaluation of these patients. CT and MR angiography are the preferred modalities to define aneurysm size and morphology and aortic branch anatomy. CT scans should be gated to eliminate motion artifact to allow precise aortic measurement, as changes as small as several millimeters may influence treatment decisions. When measuring aortic diameters from axial images, great care must be taken to obtain true aortic short axis measurements. This is particularly true when evaluating the aortic arch because the arch is a curved structure that is imaged off-axis in typical axial CT images. Off-axis measurements tend to overestimate the true short axis diameter of the aorta. Imaging software packages allow three-dimensional reconstruction of the aorta and manipulation to measure different segments of even a tortuous aorta along its true short axis.

When evaluating patients with ascending aortic and proximal arch aneurysms, we find CT and MR angiography of the chest to be sufficient to guide management and treatment decisions. For patients with distal arch and descending aortic involvement, cross-sectional imaging of the aorta and distal runoff vessels should be obtained through the pelvis so that the entire aorta and distal branches can be

evaluated for aneurysm involvement. Such a study also shows the suitability of the femoral and pelvic vessels for perfusion support during open repair or vascular access for transcatheter approaches.

We routinely obtain transthoracic echocardiograms in patients being considered for virtually any thoracic aortic aneurysm repair. These studies demonstrate aortic valve morphology and function. The association of aortic valve dysfunction as well as bicuspid aortic valve with thoracic aortic aneurysms makes evaluation of the aortic valve an important component in the workup of patients with thoracic aortic disease. The presence of a bicuspid aortic valve or aortic valve dysfunction may influence decisions on timing and extent of surgery.

Indications

Acute

Acute indications for aortic arch replacement include rupture of an aortic aneurysm or pseudoaneurysm. The most common indication for emergency surgery on the aortic arch is Stanford Type A dissection [4]. Emergency Type A dissection repair is undertaken to prevent free rupture of the ascending aorta or aortic root into the pericardial sac, causing cardiac tamponade. Emergency Type A dissection repair also effectively treats acute aortic regurgitation and coronary malperfusion. The standard repair for Type A dissection also involves replacement of the inferior aortic hemiarch. More extensive repair or replacement of the aortic arch in the setting of extensive dissection involvement of the arch is controversial; however, several centers support this approach. Addition of antegrade deployment of a stent graft into the proximal descending aorta (frozen elephant trunk) to the standard Type A dissection repair is another area of ongoing investigation.

Chronic

Elective aortic arch replacement is recommended for patients with large aneurysms (>6 cm) [2]. Close consideration for elective repair is given to patients with rapidly growing aneurysms (>0.5 cm/year), saccular aneurysms, and for symptomatic patients (pain or hoarseness). Smaller aneurysms (>5 cm) are considered for repair in patients with a genetically transmitted aortopathy or family history of aortic rupture or dissection. Replacement of the aortic arch is also considered at a smaller size when there is extensive aneurysm involvement of the ascending or descending aorta that mandates operative repair.

Open Aortic Arch Aneurysm Repair

Development

The advent of extracorporeal circulation and the use of hypothermia, coupled with the invention of synthetic aortic prostheses, allowed pioneers in the field to develop operations to repair thoracic aortic aneurysms. With regard to the repair of aortic arch aneurysms, the implementation of deep hypothermic circulatory arrest (DHCA) by Griepp and colleagues was a necessary development to allow neuroprotection during aortic arch surgery and this innovation was responsible for significant improvement in aortic arch surgery outcomes compared to discouraging early results [5].

Further advancements were made by Hans G. Borst, and later Lars Svenssoon, who revolutionized complex repairs of the aortic arch and proximal segments of the descending thoracic aorta by introducing the concept of the elephant trunk technique in the 1980s [6]. This consists of an open distal aortic arch anastomosis performed under DHCA with a continuous segment of aortic graft material (8–10 cm in length) left "hanging" in the proximal descending thoracic aorta aneurysm. This graft is then used to reconstruct the aortic arch to complete the first stage of the operation (Fig. 12.3). In the second stage of the repair, the proximal descending thoracic aorta is replaced through a posterolateral thoracotomy (Fig. 12.4). Control of the otherwise treacher-

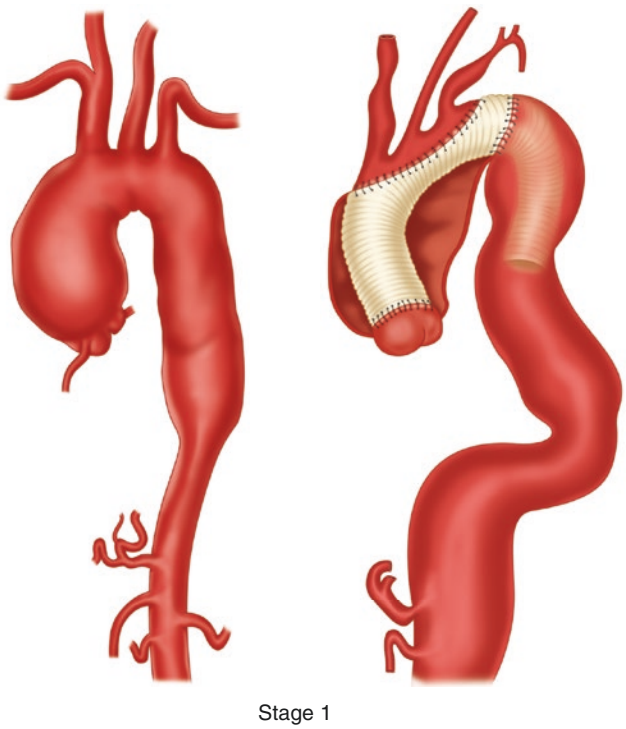


Fig. 12.3 "Elephant trunk" technique, first described by Borst in 1983. Stage 1

ous proximal descending thoracic aorta is greatly facilitated by the presence of the elephant trunk, which can be directly clamped and sewn to an aortic graft replacing the most distal portion of the descending thoracic aorta. In current practice, the second stage can be performed with endovascular techniques by landing an endostent within the elephant trunk segment proximally and distally in an area of normal aorta prior to the takeoff of the mesenteric vessels (Fig. 12.5).

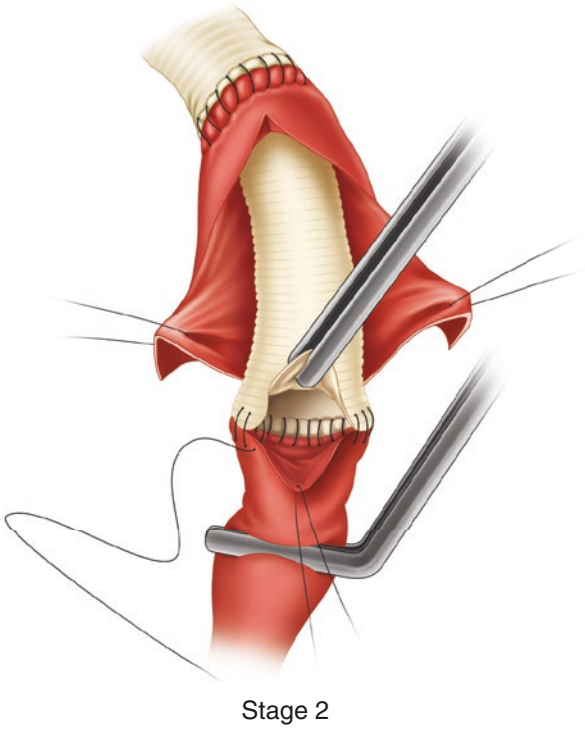


Fig. 12.4 Second stage of "elephant trunk" repair. The second stage procedure is done through a posterolateral thoracotomy or thoracoabdominal approach. The elephant trunk is accessed for proximal control of the descending aorta and used to complete aneurysm repair of the descending thoracic or thoracoabdominal aorta

Neuroprotective Strategies

Neurologic injury remains the most devastating complication of aortic arch surgery and there has been tremendous focus on developing neuroprotective strategies for use during these complex operations. There are three primary approaches used to achieve this goal. The first one is DHCA, which requires systemic cooling using cardiopulmonary bypass to below 20 °C. At this low temperature, brain metabolism is reduced to the point that circulatory support can be discontinued for 30–40 min without permanent brain injury. Once circulatory support is discontinued, the aortic cross clamp can be removed and the patient is partially exsanguinated. This allows for the distal anastomosis and arch vessel reconstruction to be performed in a bloodless field. Expediency is critical during this portion of the operation to limit the likelihood of postoperative neurocognitive deficits.

The other two approaches utilize selective brain perfusion strategies, either retrograde cerebral perfusion via the superior vena cava or selective antegrade cerebral perfusion (ACP) through the axillary artery or direct cannulation of the brachiocephalic and left carotid ostia when the aorta is splayed open [7, 8]. When ACP is used, deep hypothermia is not required and the patient can be cooled to only 23–26 °C as long as antegrade perfusion to the brain is maintained at rates between 10 and 20 ml/kg/min. Up to 90 min of moderate hypothermia (23–26 °C) is generally tolerated when

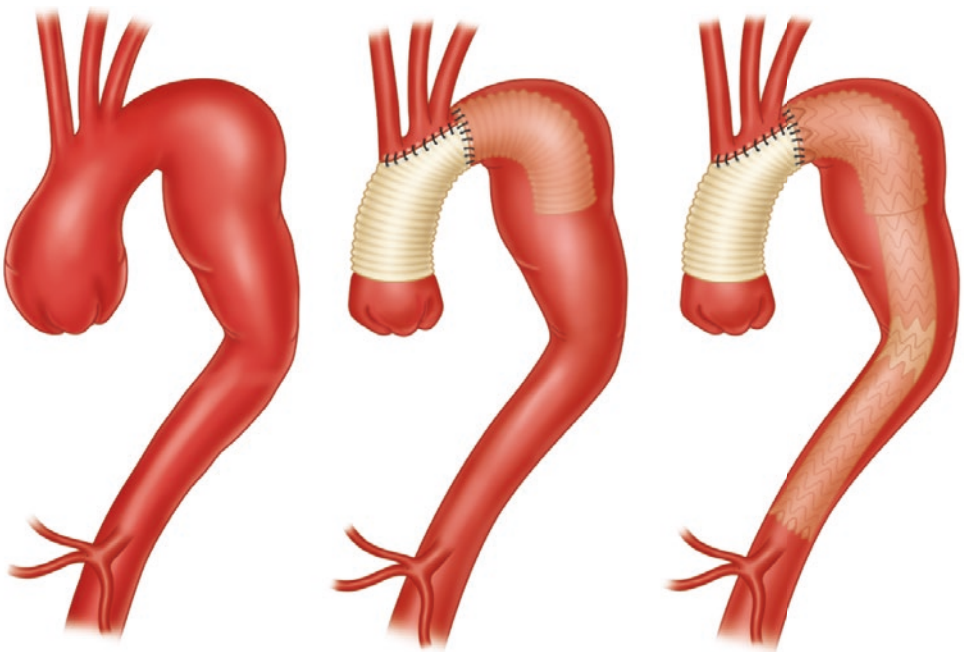


Fig. 12.5 Endovascular second stage "elephant trunk" repair. Alternatively, the second stage of the "elephant trunk" repair can be done via an endovascular approach using the elephant trunk as a proximal endostent landing zone

selective ACP is used. The authors prefer the selective ACP method as a neuroprotective strategy; however, there is no data to suggest an advantage of one over another [9–11].

Dissections and Connective Tissue Pathologies

More recently, complex aortic arch repair techniques have been used with some modifications on different types of aortic pathologies. These include complex Type A aortic dissections involving the aortic arch and supra-aortic trunks. In these cases, as well as in patients with connective tissue disorders, direct implantation of the supra-aortic trunk vessels as an island of aortic arch tissue is not advised. Rather, a branched graft is used thereby removing as much of the diseased tissue involved as possible (Fig. 12.6). Also, care must be taken to obliterate the false lumen of the distal anastomosis by using a technique such as the "Felt Sandwich" (Fig. 12.7). A more recent modification of the elephant trunk technique, the "frozen elephant trunk," offers several advantages to assure false lumen exclusion, depressurization of the aorta downstream, obliteration, and thromboexclusion, leading to shrinking of the false lumen (Fig. 12.8). This technique has potential to reduce leads the incidence of future re-interventions on the residual dissected aorta in this patient population, however prospective studies are required to demonstrate this theoretical benefit.

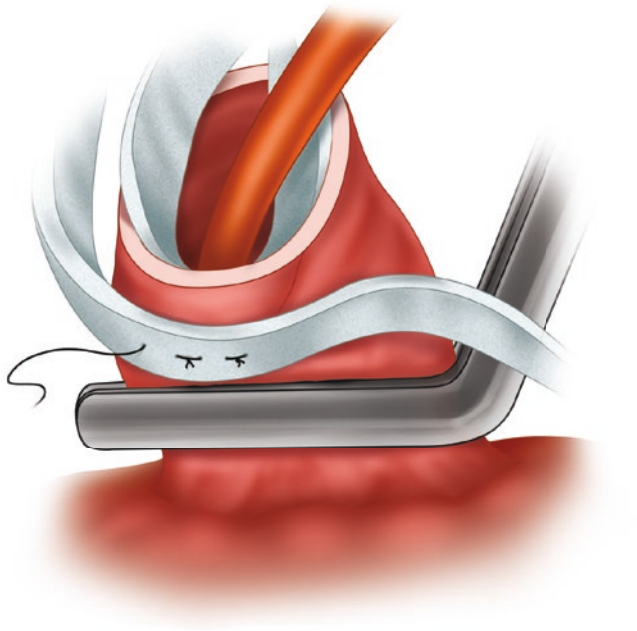


Fig. 12.7 "Felt sandwich" technique. In procedures for acute dissection, the distal aorta is prepared for anastomosis by obliterating the false lumen using bio-glue and Teflon felt strips

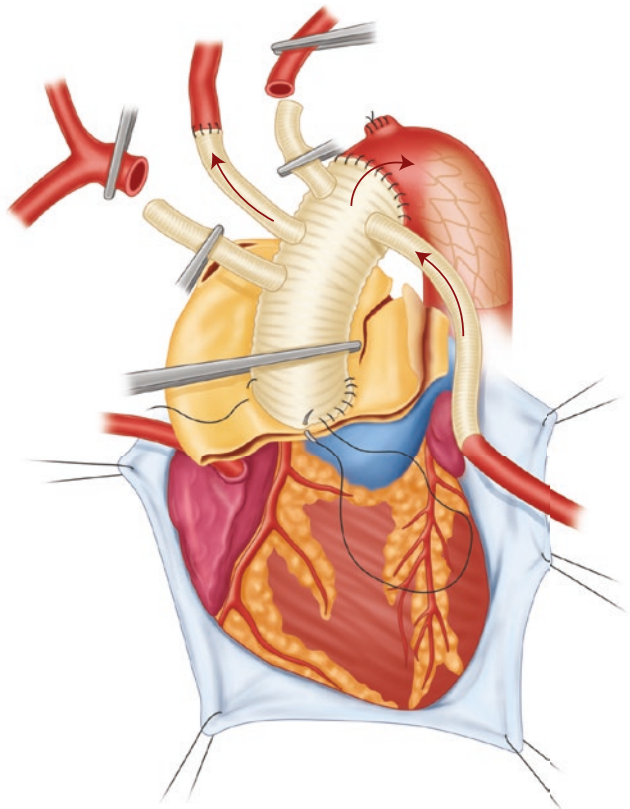


Fig. 12.6 Branched graft aortic arch repair. In cases of Type A aortic dissection involving the supra-aortic trunks or in patients with connective tissue disorders, a branched graft is used to remove as much of the diseased tissue as possible

Conduct of the Operation

The operation is performed with the patient in the supine position. All of the appropriate monitoring equipment is placed including a PA catheter and bilateral radial arterial lines. Adequacy of cerebral perfusion is assessed using Near-Infrared Spectroscopy (NIRS). Baseline levels are obtained and continuously monitored throughout the case. The patient is widely prepped and draped including the right shoulder for axillary cannulation. An incision is made over the right deltopectoral groove. Through this incision the axillary artery is dissected and encircled with a vessel loop. The patient is then given 5000 units of heparin intravenously and an 8 mm Dacron graft is anastomosed in an end-to-side fashion onto the right axillary artery (Fig. 12.9). This graft will then be connected to the arterial line of the cardiopulmonary bypass (CPB) circuit. The arterial line of the CPB circuit has a "Y" configuration to provide flow to the axillary artery and the left carotid during selective ACP. A median sternotomy is then performed to gain access to the mediastinum and the brachiocephalic vein is mobilized circumferentially, dividing the thymus branches between suture ligatures. Once this is accomplished, an umbilical tape is placed around it and used

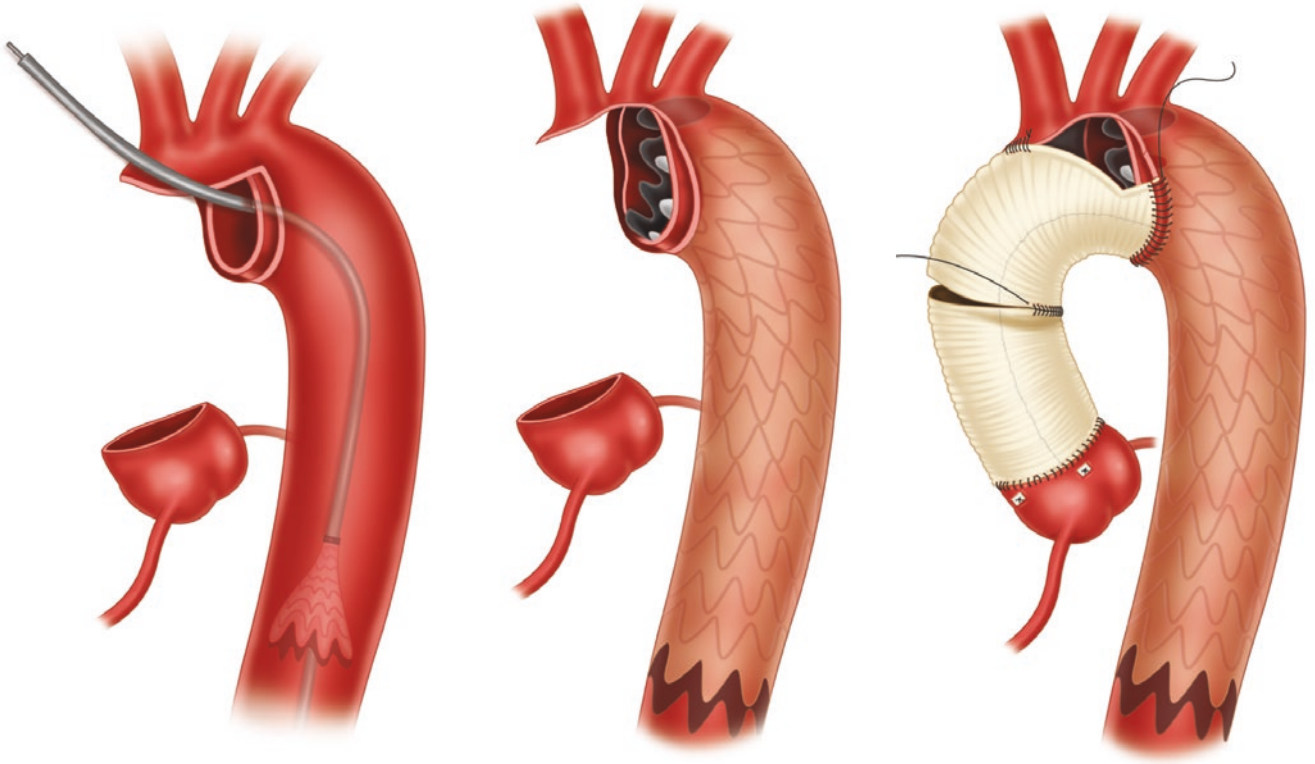
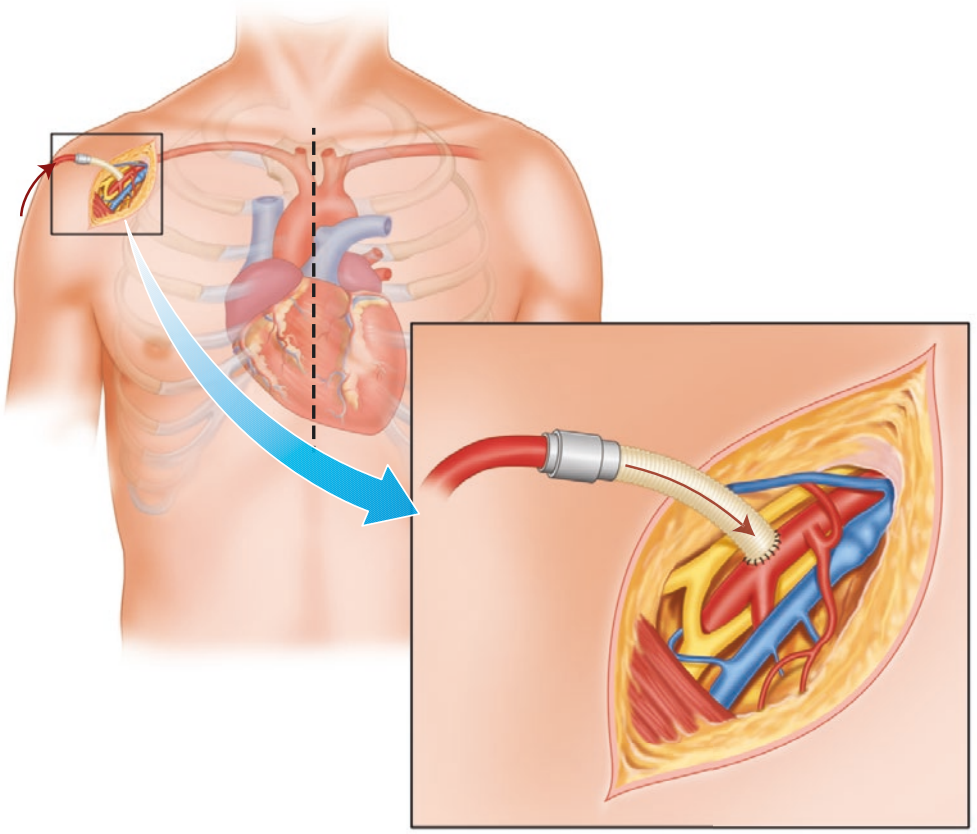


Fig. 12.8 "Frozen elephant trunk" technique. Shown here being performed at the time of Type A aortic dissection repair. The intent is to compress and exclude the false lumen, leading to thrombosis of the false lumen and reduction in overall aortic diameter

Fig. 12.9 Axillary artery dissection and cannulation. The axillary artery is dissected through an incision over the deltopectoral groove. An 8 mm Dacron graft is anastomosed to the axillary artery and used for arterial access for cardiopulmonary bypass



for traction. Next, the proximal portions of the brachiocephalic trunk and left carotid and left subclavian arteries are mobilized. This dissection is carried as close to the aortic arch as possible to avoid injury to the recurrent laryngeal nerves bilaterally. An umbilical tape with a Rummel tourniquet is placed around the brachiocephalic trunk. After this is accomplished, the rest of the thymus is divided caudally, the pericardium is opened and a pericardial well is created. The patient is then given pump dose heparin and a dual-stage venous cannula is placed through a purse-string suture in the right atrial appendage. This venous cannula is then connected to the venous line of the CPB circuit. A retrograde cardioplegia catheter is placed through the right atrium into the coronary sinus and secured.

After the Activated Clotting Time (ACT) is higher than 500 s, CPB is initiated and the patient is slowly cooled to a core temperature (bladder) of 26 °C. Once on CPB, a left ventricular (LV) vent can be placed through the right superior pulmonary vein to prevent left ventricular distension. While cooling, the heart can be arrested and any necessary procedures on the ascending aorta or aortic root can be performed. Coronary artery bypass grafting can also be performed at this time as indicated. Ten minutes prior to achieving a core temperature of 26 °C, the patient is given a bolus of steroids, mannitol, and propofol, and the head is packed in ice. After the target temperature is reached, the patient is placed in steep Trendelenburg. The pump is stopped and the Rummel on the brachiocephalic trunk is tightened. The CPB pump is then restarted at 10 ml/kg/min, thereby providing flow to the right-sided circulation of the brain. The aortic clamp is then removed and pump suckers are placed in the arch and down the descending thoracic aorta to clear the blood. With the aorta opens, the left carotid ostium is visualized and a 13 Fr balloon tipped Gundry perfusion catheter, which is attached to the "Y" arterial line of the CPB circuit, is placed into the left carotid artery. CPB flow is then increased to 20 ml/kg/min (Fig. 12.10). During this part of the operation cerebral perfusion to both brain hemispheres is monitored closely using NIRS and the antegrade flow to the brain is adjusted accordingly to maintain baseline venous saturation values.

Once adequate antegrade cerebral perfusion is established, an island of the supra-aortic trunks is created. An appropriate sized Dacron tube is invaginated, assuring at least a 10 cm segment of graft material will remain in the proximal segment of the descending thoracic aorta as the so-called elephant trunk. This invaginated tube is then sewn into the neck of the aneurysm just distal to the left subclavian with nonabsorbable suture. The invaginated segment is then retracted or pulled out of the anastomosis and a keyhole graftotomy is made along the greater curvature of the graft to sew the supra-aortic trunk island in an end-to-side fashion. Prior to completing the anastomosis, the left carotid perfusion cannula is removed and the anastomosis is completed. The patient is kept on steep Trendelenburg and the pump is stopped again. The Rummel on the brachiocephalic trunk is loosened and the pump is started again slowly, allowing the blood to exit the graft. Once de-airing of the neo-arch is completed, the aortic cross clamp is placed on the aortic graft proximal to the supra-aortic island anastomosis and full CPB is reinstituted, rewarming the patient. Rewarming is slow, even, and thorough. During this time, any necessary remaining work on the proximal ascending aorta or aortic root, including the anastomosis to the proximal end of the aortic arch graft, can be performed.

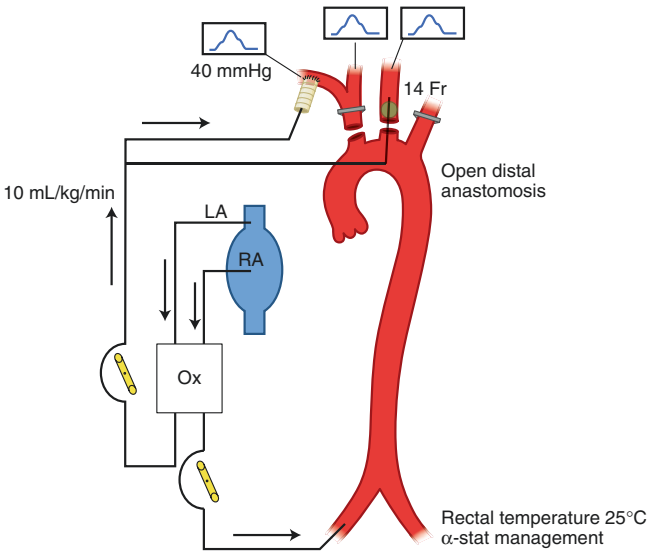


Fig. 12.10 Schematic of the cardiopulmonary bypass configuration for selective antegrade perfusion of the left and right carotid arteries during circulatory arrest and complex aortic arch repair

Outcomes

Using selective ACP and mild-to-moderate hypothermia, Svensson showed a 2% risk of stroke in patients undergoing aortic arch surgery [12, 13]. Although there are several cannulation strategies available, right axillary cannulation provides appropriate access for ACP and allows for performance of the entire procedure with a single arterial cannulation site. Studies have demonstrated that it is accessible in 97% of aortic cases [14]. Selective ACP allows arrest of systemic circulation at a higher temperature while maintaining neuroprotection through antegrade brain perfusion. Several studies have demonstrated the safety of performing a distal anastomosis at 28 °C without increased risk of stroke or lower-body morbidity [7, 15]. When comparing outcomes of renal failure, bleeding and reoperation of DHCA versus moderate hypothermic circulatory arrest with ACP there were no differences: renal failure (13.3% vs. 12.6%, $p = 0.32$) and bleeding and reoperation (10.9% vs. 13.3%, $p = 0.65$) were similar between groups. Advantages of ACP include lengthening of the period of safe circulatory arrest up to 90 min allowing the performance of complex arch repair without increased risk of brain injury [15]. Despite these advance-

ments, complex aortic arch repairs remain a challenge and are associated with a high risk of complications. However, with careful planning and a systematic approach that utilizes modern operative and neuroprotection strategies, morbidity and mortality are reduced, allowing complex aortic arch reconstructions to be performed with acceptable risk.

Endovascular and Hybrid Aortic Arch Aneurysm Repair

Open surgery remains the gold standard of treatment for aneurysms of the aortic arch. Many high volume centers have demonstrated excellent results [16]. However, these maximally invasive surgeries are often performed in elderly patients, sometimes with significant comorbid disease. These operations are technically very challenging, require a sternotomy and cardiopulmonary bypass, and frequently require hypothermic circulatory arrest. High risk patients defined as either physiologically high risk with significant comorbidities, or anatomically high risk, such as patients who have had previous sternotomy or multiple sternotomies, or patients with challenging anatomy such as anastomotic aneurysms, are often turned down for elective repair.

With proven success in the thoracic aorta with endovascular aortic stent grafting for the treatment of aneurysms and dissections, it is logical that thoracic endovascular aortic repair (TEVAR) techniques be extended to treat conditions of the aortic arch [17]. Endovascular repair of arch aneurysms often consists of hybrid operations that combine elements of endovascular stent grafting with open surgery or more recently, near-total endovascular repair of arch aneurysms.

The aortic arch presents complex anatomic challenges for endovascular repair, with curvatures and angulations that can be extreme. Inadequate apposition or conformability of the endograft in the inner curve of the aortic arch may cause difficulty with proximal seal and fixation, resulting in perioperative or postoperative Type I endoleak [18]. After placement, stent grafts in the aortic arch are subject to great dynamic strain, owing to a curved configuration, high blood flow, and pulsatile movement of the aorta, which may potentially cause migration, fracture, or disconnection of device components. Exclusion of the aneurysm sac, maintenance of cerebral perfusion, and avoidance of emboli are the primary intraoperative objectives in endovascular aortic arch aneurysm repair. Important supra-aortic vessels, such as the carotid and vertebral arteries, or coronary artery conduits arising from the internal mammary artery, must remain perfused. In addition, excessive manipulation of catheters, wires, and intravascular devices should be avoided within the confines of the aortic arch to avoid cerebral embolization with subsequent stroke or vessel wall injury, which could result in thrombus formation and dissection. These issues are particularly important for the new generation of side branch prostheses.

The success of endovascular exclusion depends on the adequacy of seal of the endograft to the aortic wall, proximal and distal to the aortic arch aneurysm. Suitable landing zones require a minimum length of 20 mm of healthy aorta. The geometry of the ascending aorta can pose specific challenges owing to a shortened inner curvature length compared to the outer curvature as well as resulting in occasional "bird-beaking" of the proximal stent–aorta interface, which can result in Type 1 endoleak. Proximal positioning must take into account the location of the coronary ostia, and oftentimes, distally placed origins of coronary artery bypass grafts. The distal landing zone can reside anywhere in the descending thoracic aorta provided it is of suitable length and diameter. Frozen elephant trunk placement of arch endografts can provide landing sites for subsequent thoracic or thoracoabdominal repair with stent grafts, or anastomotic sites for open repair. Sizing of the stent graft in the proximal landing zone requires at least 6 mm of oversizing. When the size of the ascending aorta exceeds 38 mm and is intended to be a proximal landing zone in a hybrid Zone 0 case, consideration should be given to ascending aorta replacement. Near-total arch branched grafts are relatively contraindicated in ascending aortas greater than 38 mm as this represents a potential unhealthy and unstable seal zone. Placement of an endostent in such a landing zone may result in Type 1 endoleak, aortic rupture, pseudoaneurysm formation, or retrograde Type A aortic dissection [19].

Hybrid Procedures

In hybrid repair, supra-aortic debranching is performed to provide an appropriate landing zone for the stent graft and to preserve perfusion to the supra-aortic trunks followed by stent graft deployment across the aortic arch pathology. Ischimura's classification of zones of the aortic arch is widely used to determine the preferred option of hybrid endovascular repair (Fig. 12.11). Cases are often referred to as Zone 0, 1, or 2 endovascular arch aneurysm repairs. In "Zone 0" cases, the proximal landing zone involves the orifice of the innominate artery and a prophylactic revascularization from the ascending aorta to the innominate trunk, and left common carotid artery is required with concomitant endovascular exclusion of the aneurysm commencing in the ascending aorta distal to the debranching proximal anastomosis and ending distal to the arch or descending thoracic aortic aneurysm. In "Zone 1" cases, the proximal landing zone involves the orifices of the left common carotid artery, necessitating revascularization of this vital artery, usually with an extra-anatomic carotid–carotid artery bypass along with endovascular stent grafting starting close to the distal edge of the innominate artery. In "Zone 2" cases, the proximal landing zone involves the orifice of the left subclavian artery.

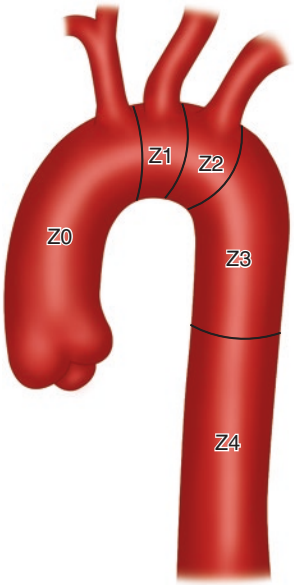


Fig. 12.11 Ischimura's classification of zones of the aortic arch. This classification system is widely used to determine the preferred option of hybrid endovascular aortic arch aneurysm repair. (Courtesy of Lena P. Abraham)

Hybrid procedures thus avoid the need for cardiopulmonary bypass or hypothermic circulatory arrest. Modifications in existing technology and new-generation devices, such as the Conformable TAG thoracic device (C-TAG, Gore & Associates), Valiant thoracic stent graft (Medtronic), Relay thoracic device (Bolton Medical), and Zenith Alpha thoracic endovascular graft (Cook Medical), have resulted in more reliable trackability and precise deployment at the distal margin of the innominate, left common carotid, and left subclavian arteries (LSA), or in the ascending aorta.

The arm's rich collateral blood supply obviates the need for mandatory revascularization, especially in an emergency setting, but restoring direct arterial flow to the subclavian artery can be important in stroke prevention as well as in the prevention of paraplegia, depending on the extent of coverage of the thoracic aorta. The decision to revascularize the left subclavian with left carotid–subclavian artery bypass has been a subject of much debate in the literature [20]. As mentioned, often the decision is based on the amount of thoracic aortic coverage required or the presence of a dominant or solitary left vertebral artery, or the presence of a functioning left internal mammary artery coronary artery bypass graft, all of which necessitate left subclavian revascularization. Clinical trials are currently underway examining the safety and feasibility of the Gore TAG Thoracic Branch Endoprosthesis (TBE device), as well as the Valiant Mona LSA Thoracic Stent Graft System, both of which feature endovascular revascularization as part of their thoracic stent graft via branches attached to their stent graft platform (Fig. 12.12). If surgical left carotid

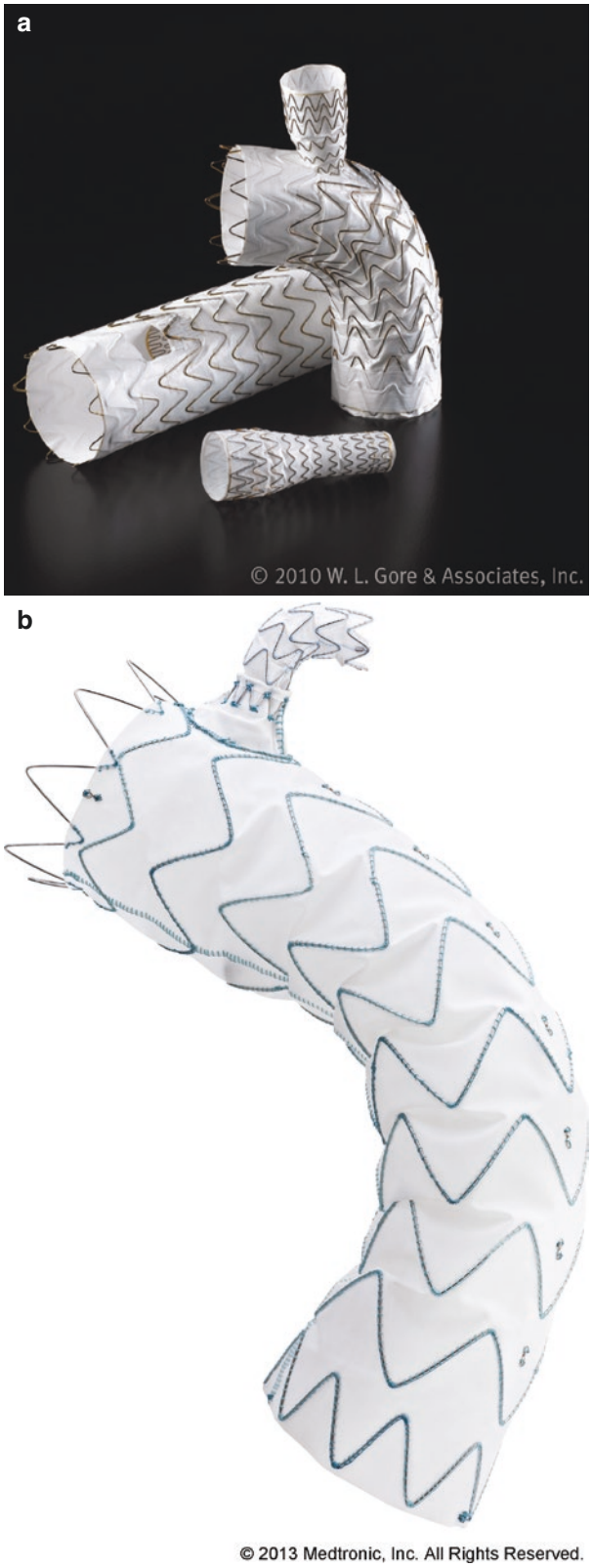


Fig. 12.12 (**a**) GORE® TAG® Thoracic Branch Endoprosthesis. (Reprinted with permission from W.L. Gore and Associates). (**b**) Medtronic Valiant Mona LSA Thoracic Stent Graft System. (Reprinted with permission from Medtronic)

subclavian bypass is performed, either proximal surgical ligation of the left subclavian artery or endovascular proximal occlusion of this artery is generally required to prevent retrograde endoleak.

Chimney or snorkel grafts (Fig. 12.13) have been proposed to extend the proximal fixation zone in the aortic arch during TEVAR repairs [21]. They have the advantage of using standard, off-the-shelf materials and being technically less demanding, but their durability and ability to effect exclusion of an arch aneurysm in the aortic arch remains questionable, despite reported early success [22, 23]. Thoracic stent graft technology is not being developed with chimney and snorkel grafts in mind, and consequently, there are presently no ideal stent grafts for this application. Until longer and more rigorous follow-up are available, chimney grafts should only be considered in emergency patients who are poor candidates for open repair or in cases of inadvertent coverage of the supra-aortic trunks.

Near-Total Arch Branched Endovascular Grafts

Near-total branched arch stent grafting offers several advantages over other approaches including avoiding the need for sternotomy, eliminating exposure to cardiopulmonary bypass, and circulatory arrest, and minimizing the extent of extra-anatomic bypass of supra-aortic vessels [24]. Several iterations of graft designs exist with the latest generation grafts being flexible enough to accommodate most arch anatomy. Branched arch endografts from Cook Medical and Bolton are available outside the United States under special access (Fig. 12.14).

The author (C.A.) has one of the largest experiences (15 cases) using the Cook Medical Arch Branched Graft in North America. Over 200 cases have been performed worldwide, and the global experience has provided valuable insight into improving stroke and mortality rates [25]. Supra-aortic branch target vessels must be of suitable diameter. The innominate artery should have a minimum diameter of 8 mm, while the left common carotid artery should have a minimum diameter of 6 mm. A custom-made branch extension limb provided by Cook Medical is usually required for the innominate artery in order to accommodate the larger diameter of the distal innominate artery. Commercially available covered stents are suitable for most carotid or subclavian arteries. Because of its accuracy and versatility, our preference is for the Atrium/ICast covered stent graft; although Bard Fluency™ and Gore Viabahn™ covered self-expanding stents are also used worldwide. The balloon expandable covered stents require lining with a bare metal self-expanding stent to add support and mitigate against tortuosity or possible kinking.

Conduct of the procedure has been described elsewhere [24]. Salient points include the need for a stiff wire buried in the left ventricle, deployment during asystole, achieved with either rapid ventricular pacing or right atrial venous balloon occlusion, and attention to the relationship of the endograft

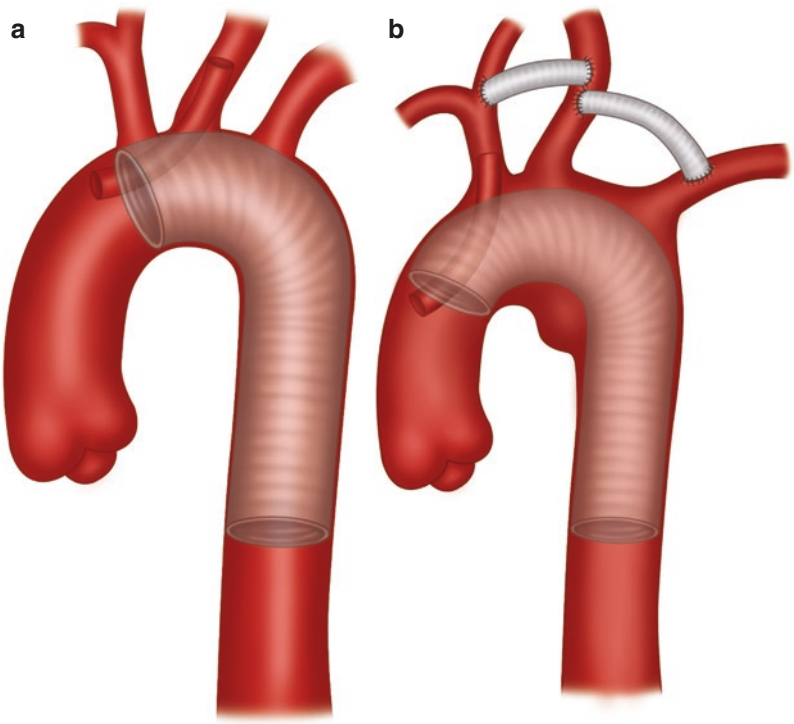


Fig. 12.13 (**a**) Snorkel Zone 1 Arch thoracic endovascular repair. (**b**) Snorkel Zone 0 Arch thoracic endovascular repair. (Courtesy of Lena P. Abraham)

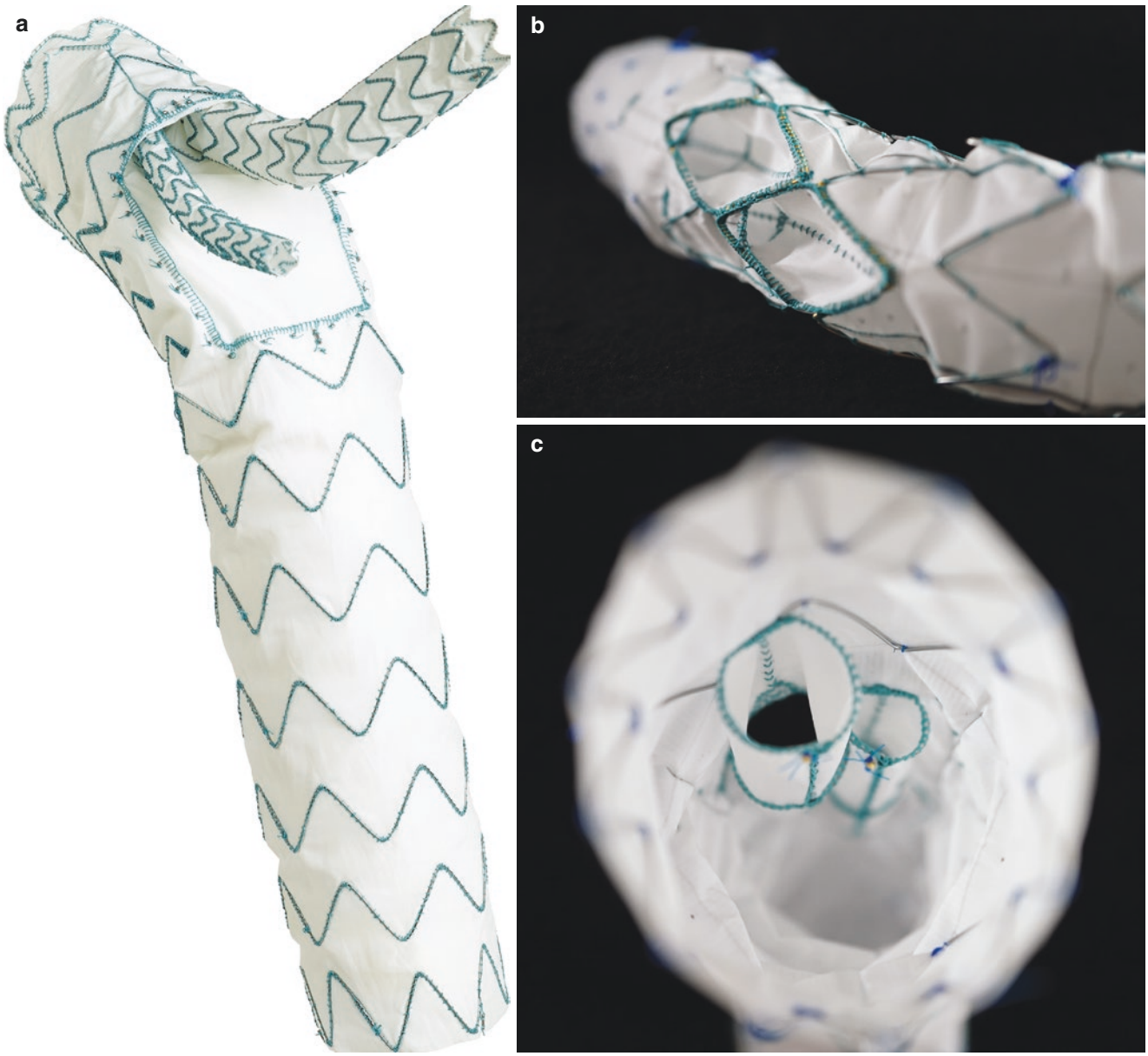


Fig. 12.14 (**a**) Bolton Relay Branch Thoracic Stent-Graft System. (Reprinted with permission from Bolton Medical). (**b**, **c**) Cook Arch Branched Graft ™. (Reprinted with permission from Cook Medical)

and its branches to the coronary arteries and supra-aortic vessels (Fig. 12.15).

The largest published series of arch branch endografting was a global experience that included 38 patients with median follow-up of 12 months [25]. The 30-day mortality of the entire cohort was 13.2%. Comparative analysis of the early experience (first 10 patients) and late experience demonstrated an interesting but not statistically significant difference in 30-day mortality (30% vs. 7.1%, $p = 0.06$). No late mortality was observed during the follow-up period. Cause of death included perioperative cardiac arrest, myocardial infarction, hemorrhagic shock, and pulmonary complications. Early procedural success was 84.2%. Failures included proximal type 1 endoleak, failure to catheterize the innominate branch, and conversion to chimney technique. On discharge, 28.8% of patients were diagnosed with an endoleak (5 Type I, 3 Type II, Type III, and 2 indeterminate), with 10.5% of patients requiring a secondary procedure. Neurological complications occurred in 16% of patients who survived the procedure. This compares to 4–12% neurological event rates seen in larger series of traditional open and hybrid repairs [26–28]. All patients in the branched arch endograft series had a full neurologic recovery (4 transient ischemic attacks, 1 stroke, 1 subarachnoid hemorrhage). In comparative analysis of the early experience (first 10 patients) compared to the late experience,

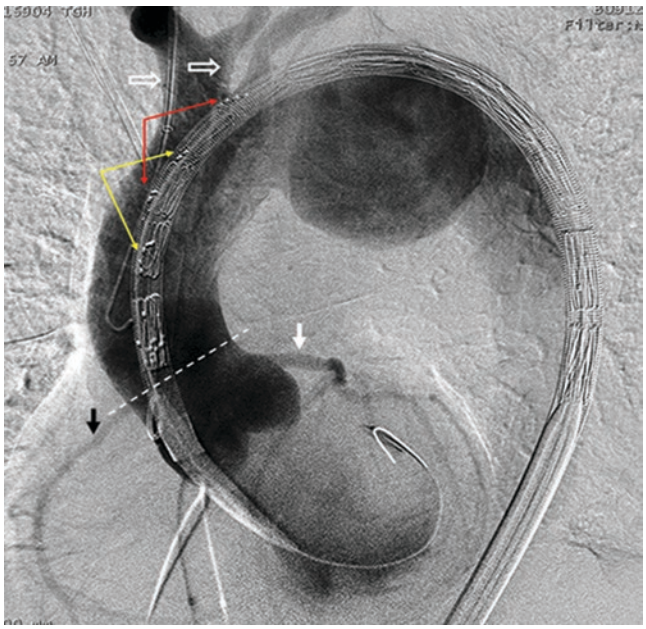


Fig. 12.15 Angiogram aortic arch demonstrating relationship of branch markings (yellow and red arrows), to origins of supra-aortic vessels (open white arrows), and proximal arch branch graft stent to origins of coronary arteries (solid white and black arrows). Note double curved lunderquist wire buried in left ventricle

there were significantly fewer intraoperative complications, less need for secondary procedures, less need for interventions for endoleaks, less operative time, and less radiation exposure. This highlights the importance of the learning curve involved with this complex procedure as well as the importance of confining these procedures to high volume regional centers.

Although a viable alternative to traditional open and hybrid repair, near-total endovascular arch stent grafting is still in its early development. The complexity of arch geometry and its branches poses unique challenges for endovascular devices and necessitates an individualized approach. These complex endovascular procedures should be reserved for patients who are not able to tolerate open or hybrid procedures for anatomic reasons, or in patients who have significant comorbidities precluding open surgery. Stroke remains an important risk in these procedures. Despite satisfactory early results, mid- to long-term studies are needed before we can recommend this treatment as a comparable alternative to standard open arch reconstruction or hybrid arch repair.

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Thoracoabdominal Aneurysms

13

Ashok Venkataraman and Jeffrey P. Schwartz

Introduction

Thoracic aortic disease is a complex process and a result of several histopathologic processes. Although abdominal aortic aneurysms (AAAs) and ascending aortic aneurysms are more common, descending thoracic aortic aneurysms (TAAs) and thoracoabdominal (TAAAs) aneurysms are not rare. The incidence has been steadily increasing and a recent study suggests an estimated incidence approaching 10.4 cases per 100,000 person-years [1]. TAA repair is associated with high morbidity and mortality. The focus of this chapter is on TAAAs defined by anatomy, arising from the left subclavian artery to the aortic bifurcation.

The earliest report of successful repairs of a thoracoabdominal aneurysm in the United States was in 1955 by Etheredge [2]. Cooley and DeBakey, known pioneers within this field, also reported total repairs via a thoracoabdominal incision utilizing a homograft conduit initially, subsequently involving knitted Dacron grafts as conduits [3]. Crawford is attributed with pioneering the evolution of techniques to include pedicled visceral segment anastomoses of celiac, superior mesenteric, and renal vessels [4]. Over the years, techniques performed at major centers today have evolved to utilize cardiopulmonary bypass, hypothermic circulatory arrest, and cerebrospinal fluid drainage amongst other novel modifications.

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Definition

Thoracoabdominal aneurysms (TAAA) result from the continuous dilation of the descending thoracic and abdominal aorta secondary to weakening and expansion of the aortic wall. By definition, the dilatation is 1.5 times its normal value [5]. TAAAs account for approximately 10% when all aneurysms of the thoracic aorta are considered [6]. Defining anatomic sizes is critical to help identify pathologic aortic growth because aortic diameter is the strongest predictor of rupture. The "hinge points" at which likelihood of rupture or dissection increases precipitously are seen at 5.5 cm for ascending and 6.5 cm for the descending aorta [7]. The challenge is weighing the risks of surgery versus that of continued surveillance and possible rupture or dissection.

With respect to TAAAs, multiple configurations occur anywhere from the origin of the left subclavian artery to the aortoiliac bifurcation. Crawford described the first classification scheme based on the anatomic extent of the aneurysm in 1986 [8]. Type I (25%) involves most of the descending thoracic aorta from the origin of the left subclavian to the suprarenal abdominal aorta. Type II (approximately 30% of all TAAAs) is the most extensive, extending from the subclavian to the aortoiliac bifurcation. Type III (<25%) involves the distal thoracic aorta to the aortoiliac bifurcation. Type IV TAAAs (<25%) are limited to the abdominal aorta below the diaphragm, including visceral and renal arteries. A Type V classification was added later referring to distal thoracic aorta extension including the celiac and superior mesenteric origins but excluding the renal arteries [9] (Fig. 13.1).

Indications for operative repair can range from elective interventions when aneurysmal size approaches a critical point to urgent or emergent surgical intervention for acute dissection, free rupture or associated complications such as visceral and extremity malperfusion.

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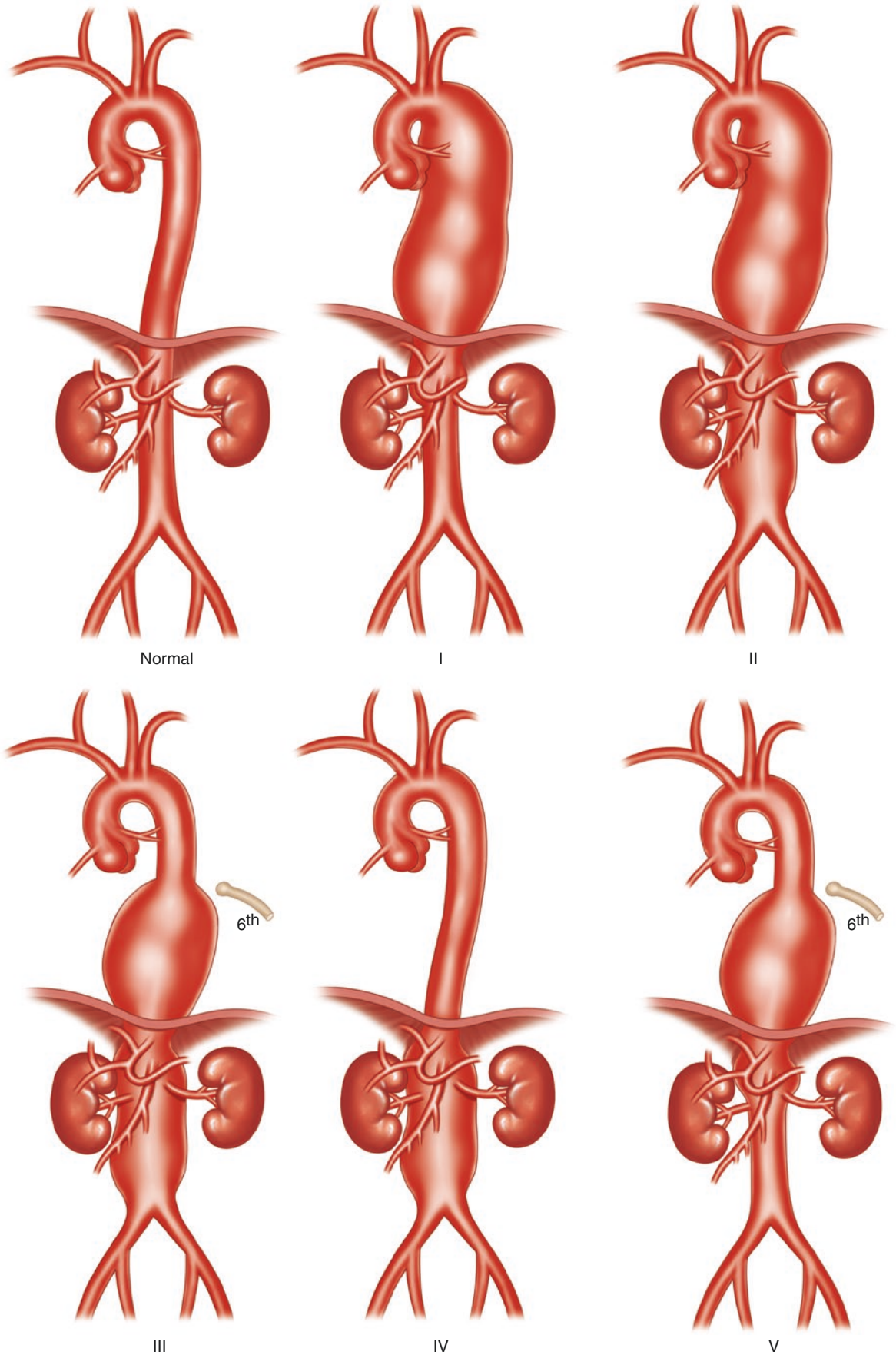

Fig. 13.1 Clark classification for thoracoabdominal aneurysm

Epidemiology

Population studies have indicated an incidence of thoracic aortic aneurysms in the range of approximately 10 new aneurysms per 100,000 person-years [1]. Up to 80% of these will eventually rupture, owing to a 10–20% 5-year survival of patients who remain untreated. The increasing prevalence of TAAAs has been attributed to several factors including an aging population, improved and more readily accessible imaging techniques, and increased patient and physician awareness [10]. Females tend to develop TAAAs later in life than men but are at a higher risk of rupture, and advanced age confers a higher risk in both sexes [11].

Pathogenesis

Development of TAAA is multifactorial, similar to that of other aneurysms, a complicated dynamic process involving both cellular and extracellular processes. Evidence suggests that extracellular matrix degradation by matric metalloproteinases (MMPs) exceeds matrix production and repair during aneurysm formation [12]. The capacitance and elasticity of the aortic wall is largely from its medial layer composed mainly of structural proteins such as collagen and elastin. Degradation of these proteins leads to medial degeneration and eventual weakening of the aortic wall [13]. Hemodynamic forces on the aortic wall, intrinsic changes in the composition of the wall and increasing stiffness and loss of elasticity lead to subsequent dilatation. A vicious cycle is created as the diameter of the aorta increases as the wall tension increases as defined by the law of Laplace, wherein the wall tension is proportional to the pressure applied by the radius of the conduit.

Medial degeneration, part of the normal aging process, is worsened by clinical conditions such as atherosclerosis and hypertension [14]. Genetic abnormalities such as Marfan's syndrome and other connective tissue disorders such as Ehlers–Danlos and Loeys–Dietz syndromes also contribute to medial degeneration [15]. Turner syndrome, polycystic kidney disease, syphilis, arteritis, and traumatic injury are amongst other disorders that are associated with aortic aneurysms in similar fashion [16]. Whilst 80% of TAAAs are secondary to medial degeneration, approximately 15–20% are caused by dissection [17].

It is postulated that atherosclerosis plays a role in aneurysm formation, particularly in the descending thoracic and abdominal aorta. True causality is unclear but the two conditions occur simultaneously in a majority of patients. Risk factors for TAAAs are thus similar to those for atherosclerosis. These include primarily smoking, hypertension, obesity, hyperlipidemia, chronic obstructive pulmonary disease (COPD), and family history. Interestingly, patients with TAAAs have a much lower incidence of coronary artery disease (CAD) (less than 30%) than those patients with abdominal aortic aneurysms (greater than 70%) [18].

Indications for Repair

The decision when to operate on a patient with a TAAA essentially involves an assessment of the likelihood of aortic rupture versus the operative risk of the individual patient. Endovascular techniques with its lower short-term mortality and morbidity continue to evolve and will in future be an important factor in the decision making for intervention. The patient's physiologic reserve and vascular anatomy determine whether open or an endovascular approach would be more suitable. Recent guidelines have been issued tailored to the when and how to repair with descending thoracic and thoracoabdominal aneurysms [19].

Natural history studies have documented an extremely high risk of rupture and death if TAAAs are left untreated and therefore all TAAAs should be considered for repair [20]. Symptomatic aneurysms regardless of size or anatomic extent should be addressed surgically. Symptoms usually present as pain and pressure that may be often described as chest pain radiating to the back or as intrascapular, with a "stabbing" or "tearing" quality. However, few patients present with symptoms prior to an acute event [21].

Size criteria have been extensively debated in the literature, with groups advocating repair anywhere between 5 and 10 cm [22]. This is further complicated by the fact that degenerative TAAAs are not uniform in size and involve segments of the aorta with varying diameters and morphology. Recent literature points toward the need for adjustment of body surface area and an evaluation of relative aortic size rather than absolute aortic size, to be incorporated into decision making about threshold for repair and the risk of rupture [23].

Elefteriades et al. have reported extensively on the natural history and rupture risk of thoracic aorta stratified by diameter and the guidelines outlined have remained the current benchmark used for intervention [24].

I. Rupture
II. Acute dissection resulting in malperfusion or other life-altering complications
III. Symptomatic states
   (a) Pain consistent with rupture and unexplained by other causes
   (b) Compression of adjacent organs
IV. Documented enlargement ≥1 cm/year or substantial growth approaching absolute size criteria
V. Absolute size >6.5 cm or >6.0 cm in patients with connective tissue disorders

All size criteria per guidelines are based on the premise that the ideal time to intervention is when the annual risk of rupture exceeds the perceived mortality of the proposed procedure.

Preoperative Workup

The physiologic stress on a patient undergoing open TAAA repair is unparalleled and as such extensive preoperative workup to ensure optimal fitness for surgery is mandatory. Pulmonary and renal function evaluation, in addition to cardiovascular risk evaluation is imperative.

Cardiac

The typical patient undergoing TAAA is elderly and the incidence of impaired myocardial function and the presence of atherosclerotic coronary disease are moderate, thereby making cardiac disease the leading cause of mortality after open TAAA repair [25]. Therefore, preoperative electrocardiogram, echocardiogram, and coronary angiography are routine. In the elective setting, coronary artery revascularization either by coronary angioplasty and stenting or by coronary artery bypass grafting may be indicated prior to intervention for the TAAA. The use of bare metal stents versus drug eluting stents should be considered particularly in view of the duration of dual antiplatelet therapy required.

Pulmonary

Pulmonary complications after open TAAA are common, and the incidence of COPD is high in this patient population (estimated between 30% and 40%) and it is associated with increased perioperative mortality [25]. Also, single lung ventilation is routinely utilized in open TAAA repair. As such, preoperative spirometry and arterial blood gas analysis is strongly recommended and performed routinely. Smoking cessation in the weeks preceding surgery, pulmonary rehabilitation to improve lung capacity, and an attempt to lose weight in obese patients has all been shown to be beneficial.

Renal

Chronic renal failure is the strongest predictor of perioperative renal failure and mortality after TAAA repair (increasing risk threefold), second only to aortic rupture [26]. Routinely assessed by laboratory tests such as blood urea nitrogen and creatinine concentrations, recent evidence indicates calculation of glomerular filtration rate is superior as a predictor of outcome after operative repair [27]. Endovascular repairs require even closer attention to preoperative renal function given the use of nephrotoxic contrast agents during these procedures.

Cerebral

Intracranial aneurysms are thought to share pathophysiologic features with TAAA and clinical association between these two conditions has been well established in recent years. Patients with TAA have a 9% prevalence of intracranial aneurysms, which is ninefold greater than the general population [28]. In light of this association, notable groups have made it a policy within their practices to image the brain of all patients prior to surgery on the thoracic aorta and obtain neurosurgical consultations should a cerebral aneurysm be identified [29].

Functional Status

Considering the surgical insult involved in open repair of TAAA, preoperative functional status of the patient is a key predictor of perioperative mortality [30]. Interestingly, advanced age alone does not impair return to normal functional status postoperatively and thus patients with asymptomatic thoracic aneurysms should not be denied elective replacement on the basis of age alone [31].

Anesthesia/Intraoperative Monitoring

Following induction of general anesthesia, a double lumen endotracheal tube is inserted. Central access is then obtained and a pulmonary artery catheter placed for hemodynamic monitoring. A Foley catheter is placed and arterial lines are placed in both upper and lower extremities (typically right radial and right femoral) to monitor both proximal and distal perfusion during aortic clamping.

Lumbar cerebrospinal fluid drains are routinely used for extensive I and II repairs, maintaining an intrathecal pressure of less than 10 mmHg (Fig. 13.2). This has been shown to appreciably lower the probability of neurological deficit [9]. In the case of a bloody insertion during the initial setting, consideration should be given for delaying surgery and admission of patient a day prior to elective surgery and placement of lumbar drain to reduce the risk of subsequent intraoperative bleeding. In the majority of cases, and particularly in Type II repairs or those requiring hypothermic circulatory arrest, electrodes are placed cranially and peripherally for monitoring of somatosensory and motor evoked potentials to assess intraoperative spinal cord protection and perfusion [32].

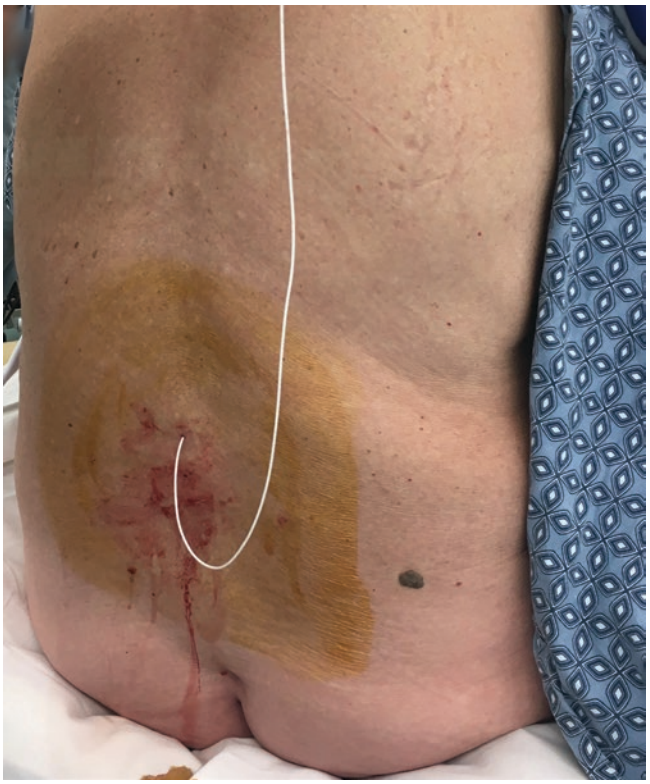

Fig. 13.2 Spinal drain inserted preoperatively

Surgical Approach

Exposure of the Thoracoabdominal Aorta

Regardless of the extent of the TAAA repair, the patient is routinely placed in the right lateral decubitus position with the operating room table flexed at the waist (Figs. 13.3 and 13.4). A beanbag is utilized to maintain appropriate position is necessary; the left arm is secured over the patient using an appropriate armrest (or a pillow and sheets are used between both extended arms). The hips and shoulders are taped down after all bony prominences are appropriately padded. The shoulders are typically rotated posteriorly 10–20° and the hips are rotated 50–60° posteriorly (flattened) with a folded sheet placed underneath the buttocks and a rolled sheet used as a shoulder roll. The right femoral arterial line is prepped into the field.

The procedure is started with exposure of the left femoral vessels after an appropriate groin incision. Access to the descending thoracic aorta and distal arch is gained by a thoracoabdominal incision (Fig. 13.5). The scapular tip is identified and marked and its location is relevant the higher the extent of the pathology is on the thoracic aorta. For exposure of the proximal descending aorta, the incision is started two fingerbreadths beneath the tip of the scapula, curved posteriorly—midway between the scapular edge and the spine. The lower extent of the incision is usually midway between the anterior superior iliac spine (ASIS) and umbilicus.

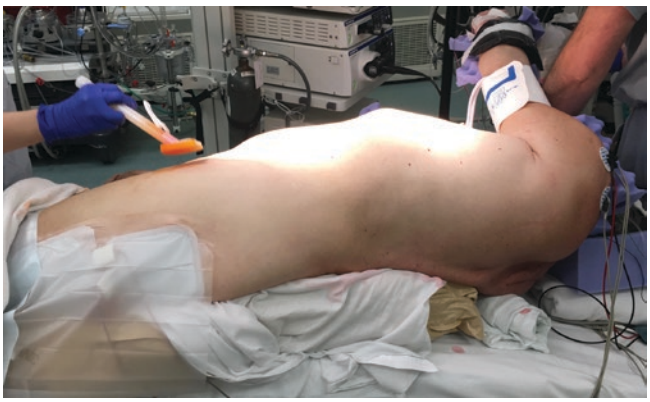

Fig. 13.3 Right lateral decubitus position, posterior view

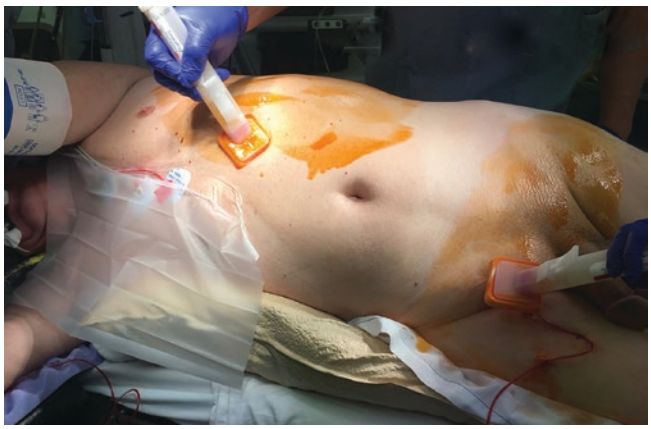

Fig. 13.4 Right lateral decubitus position, anterior view

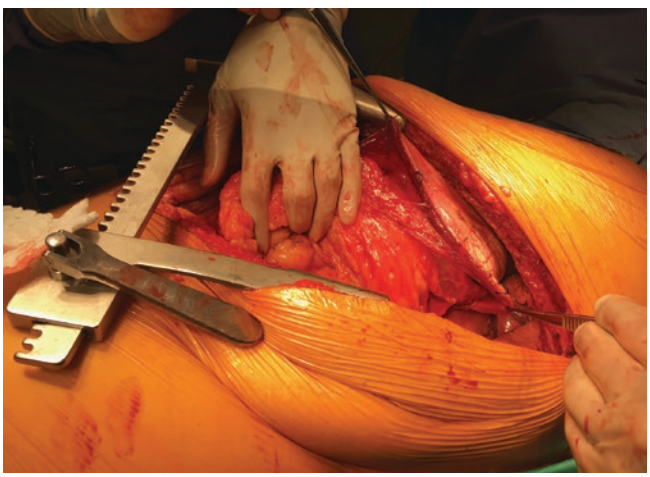

Fig. 13.5 Thoracoabdominal incision, transection of diaphragm demonstrated, followed by medial visceral rotation

The curve of the incision is along the ribs and eventually almost parallel in a long axis direction anatomically to the right of scapular tip. The level of the rib entry into the thoracic cavity is based on the proximal extent of the intended repair. Typically, the fourth or fifth interspace is appropriate

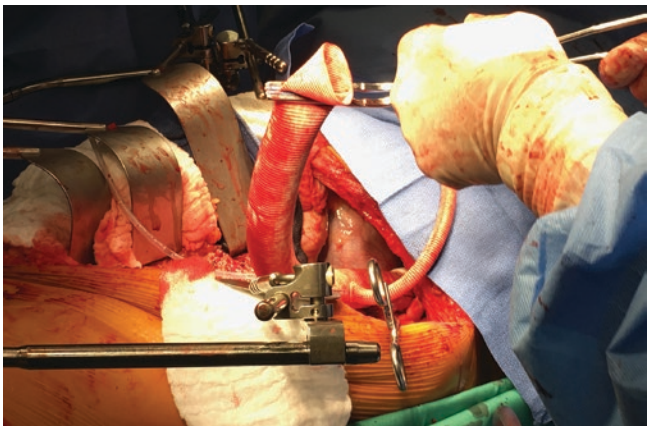

Fig. 13.6 Omni-retractor setup, and exposure

when improved exposure of the distal arch and left subclavian is required. The eight or ninth space may be utilized to approach an extent III aneurysm with little thoracic component. Oftentimes, both fifth space and an eighth space entry is required for an extent II aneurysm spanning the entire thoracoabdominal aorta.

Once the ribs are reached, the scapular fascial plane just above the ribs is mobilized all the way posteriorly. Staying on the superior aspect of the rib the thoracic cavity is entered and the posterior rib is shingled with a Guillotine. The undersurface of the diaphragm is encountered and dissecting further leads into the correct retroperitoneal plane. Once the retroperitoneum is free, the endo-GIA blue staple load is utilized to staple and transect the diaphragm circumferentially, taking care to avoid injuring the phrenic nerve. Leaving a 2–3 cm cuff of diaphragm on the chest wall and marking the staple line on either side with sutures facilitates later reapproximation of the diaphragm. This plane is then worked caudally till the psoas muscle is reached. The peritoneum is continually rolled toward the patient's right side as this plane is developed thereby executing a medial visceral rotation.

The Omni retractors are set up to provide adequate exposure within the abdominal cavity and the Finochietto rib spreaders are placed to provide intercostal exposure (Fig. 13.6). Two rib spreaders are used if a higher intercostal space (e.g., fourth interspace) is also entered for exposure. Special care and attention is directed to padded retention of the spleen to avoid capsular tear and injury.

Repair of the Thoracic Aortic Segment

The thoracic aorta is clamped sequentially and the aorta between clamps opened and a Dacron graft is sutured to the proximal descending thoracic aorta. All lower intercostal arteries from T8 to T12 are reattached either individually or together as a patch to an elliptical incision in the Dacron graft. Alternatively, an additional tube graft (10–12 mm) can be used to anastomose the intercostal vessels to the main Dacron graft.

Repair of the Abdominal Aortic Segment

The infrarenal abdominal aorta is clamped sequentially and opened. The visceral vessels are identified and perfused with cold blood via appropriately sized Pruitt balloon tipped catheters [33] (Figs. 13.7 and 13.8). The visceral vessels are then anastomosed to the Dacron graft either as an island patch or individually by using short interposition bypass grafts. Individual interposition bypass grafts tend to take longer for the anastomoses to be completed but tend to be easier to visualize and to be more hemostatic subsequently (Fig. 13.9).

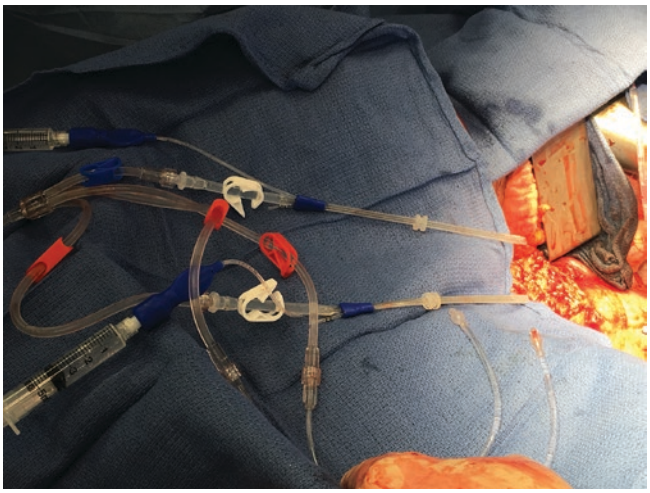

Fig. 13.7 Pruitt balloon tipped catheters

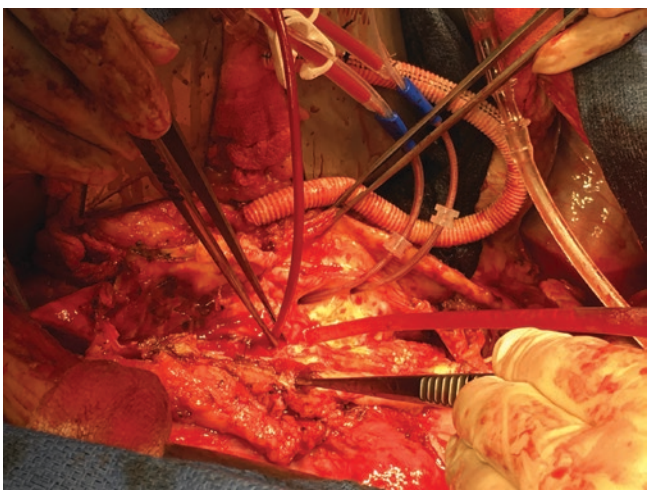

Fig. 13.8 Pruitt catheters utilized to perfuse individual mesenteric vessels

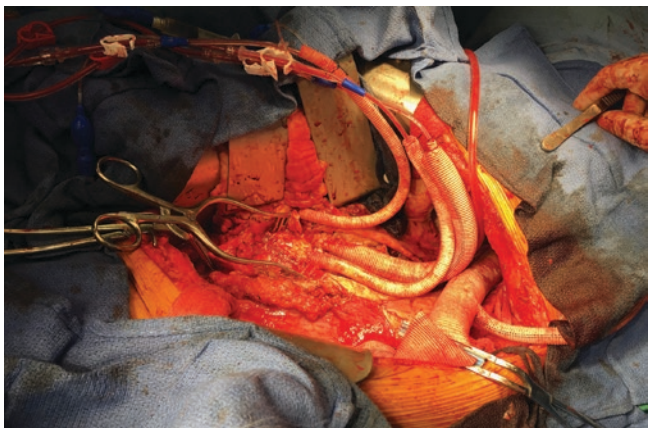

Fig. 13.9 Individual grafts anastomosed to individual mesenteric vessels and renal vessels

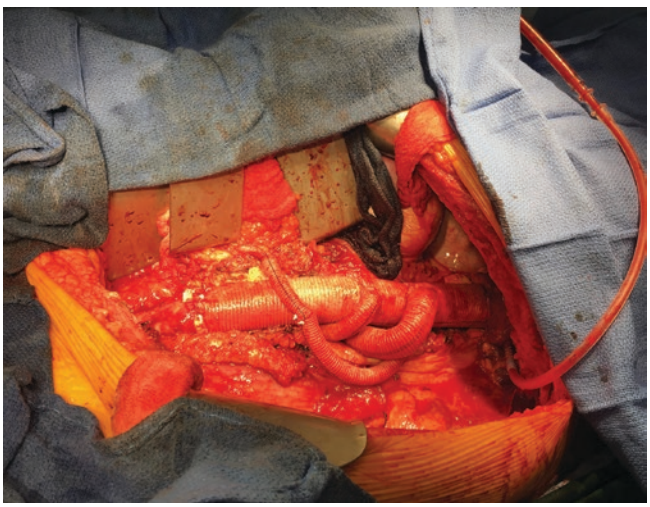

Fig. 13.10 Completely reconstructed thoracoabdominal aorta with branch side grafts to visceral and renal vessels

If an island patch technique is used, typically the left renal artery is located too far and requires a separate short interposition bypass graft. Once the visceral anastomosis is complete the clamp is moved further down the graft and flow is reestablished to the viscera and kidneys (Fig. 13.10).

Circulatory Support Options

A variety of strategies have been employed for circulatory support or extracorporeal bypass for TAAA repair. Left heart bypass (LHB) is considered the minimum and the resultant decompression of the proximal circulation in conjunction distal perfusion of the abdominal viscera, spinal cord, and lower extremities decreases complications associated with ischemia. Many groups advocate left heart bypass and use this technique as their preferred mode of circulatory support. At our institution, we commonly employ femoral–femoral cardiopulmonary bypass as described below.

Femoral–Femoral Cardiopulmonary Bypass

Our preferred approach has been to cannulate the left femoral vein with an extended venous cannula that is extended to the level of the right atrium under transesophageal guidance. Arterial cannulation is also performed via the femoral artery and full cardiopulmonary bypass is established.

Left Heart Bypass

Left atrial drainage is established via the inferior pulmonary vein. Arterial inflow is established by cannulation of the iliac system after exposure of the bifurcation, thereby providing adequate retrograde flow to the visceral segment and the spinal cord via the internal iliac system and antegrade flow to bilateral lower extremities.

Organ Protection

Neurologic Protection

The risk of postoperative neurologic deficits (paraplegia and paraparesis) has always plagued the repair of thoracoabdominal aneurysm with graft replacement since its inception. The development of a classification system for the extent of an aneurysm had revealed that extent had a direct correlation with neurological outcome in these operations. In the era of simple cross-clamp techniques, immediate survival rates were fairly impressive, but the rate of neurologic events (particularly in extent II aneurysms) remained persistently high. These poor neurologic outcomes were clearly related to the aneurysm extent, rupture, clamp time, patient age, and proximal disease. Over the years, several adjuncts have been developed to improve upon these outcomes with good results.

The technique of combined cerebrospinal fluid (CSF) drainage and distal aortic perfusion has consistently been shown to provide superior neurological outcomes. The utilization of moderate hypothermia, active visceral cooling and selective visceral perfusion, and aggressive intercostal artery reattachments has further augmented the success of these adjuncts [9]. Spinal catheters are inserted routinely by the anesthesiology team in the third of fourth lumbar space. The CSF pressure is kept at 10 mmHg or less intraoperatively, and the drain is kept in place usually for 3 days postoperatively. Because of the association of arterial blood pressure and oxy-

gen delivery to delayed neurologic deficit, we maintain mean arterial pressure (MAP) between 90 mmHg and 100 mmHg, hemoglobin above 10 mg/dl, and a cardiac index above 2.0 L/min. Urine output is closely monitored. In the event that delayed neurologic deficit occurs after removal of the CSF drain, a new CSF drain is placed urgently and drained freely for 2–3 days and the CSF pressure kept below 10 mmHg.

In current times, the overall rate of neurological events is approximately 3% compared to 15% of patients during the era of cross-clamp without adjuncts [9, 25]. The most noticeable result of adjuncts has been the significant reduction in neurologic deficits in extent II repairs, 6.6% at present compared with previous incidence of 31% [25].

Renal and Visceral Protection

Distal aortic ischemia during TAA repair carries a formidable risk of perioperative morbidity and mortality. Renal dysfunction occurs in as many as 28% of patients undergoing TAAA repairs, and necessitates dialysis in 4–11% of patients [34]. With the advancement of surgical techniques and adjuncts significant improvements in open TAAA repair have been achieved [35, 36]. The two primary approaches that have emerged to maintain distal aortic perfusion and selective visceral perfusion are that of left heart bypass (LHB) and full cardiopulmonary bypass.

Left heart bypass (LHB) is used as a closed circuit with the addition of a reservoir to salvage shed blood, and can be used to maintain distal perfusion and pressure adjusted accordingly to maintain stable hemodynamics. Visceral perfusion can be provided using either isothermic (37 °C) or cold blood (4 °C) or crystalloid of all four branching arteries [37].

Full cardiopulmonary bypass may also be used with a wide range of protective hypothermic strategies such as mild (34 °C) to profound (18 °C) systemic hypothermia, during the repair. Partial cardiopulmonary bypass with three separate roller pumps for femoral–femoral bypass, celiac axis and superior mesenteric artery perfusion, and bilateral renal perfusion has also been described [38]. In some studies, cold crystalloid perfusion was noted to protect against renal dysfunction over isothermic blood for renal perfusion [39]. In studies comparing either cold blood versus cold crystalloid for renal perfusion, no significant difference was noted between patients with regard to early death or renal failure [37]. Recent aortic guidelines recommend the use of either cold blood or cold crystalloid renal perfusion; however, the exact techniques and additives vary amongst centers [19].

Concomitant visceral and renal artery occlusive disease is present in a significant proportion of patients with TAAAs [40]. Techniques such as renal endarterectomy or the use of balloon expandable stents to improve renal and visceral blood flow have demonstrated benefits such as fewer renal failures in patients with preexisting renal dysfunction [26, 40]. The use of visceral stents in treating mesenteric and renal occlusive disease is a new strategy that is gaining acceptance [41]. The visceral stents prove useful in obliterating the false lumen associated with concomitant aortic dissections, keeping the ostia patent near patch anastomoses. Although usually safe and effective, drawbacks include risk of thrombosis, possibility of vessel perforation and stent migration.

In the literature, the incidence of renal dysfunction is highest after extent II TAAA repairs, which correlated with prolonged protected and unprotected renal ischemia times. Bowel ischemia occurred in only 1% of patients; however, it had a substantial consequent attendant mortality of 88% [34]. Thus, contemporary protective strategies enable patients to undergo open TAAA repair with substantially fewer renal and visceral ischemic complications than in previous decades.

Endovascular Repair

Endovascular aneurysm repair (EVAR) therapy offers a potential alternative for patients who are physiologically high risk for conventional surgery. Initially, advanced EVAR was limited to short-necked abdominal aortic aneurysms, but the development of the aortic endograft and bridging stent graft technology has expanded its role to include further aortic coverage [42]. Early experience with application of fenestrated and branched endografts to treat more extensive TAAA demonstrates acceptable outcomes [43]. The rates of perioperative mortality, renal failure, and spinal cord ischemia challenge outcomes attained for conventional surgery in high-volume centers [44]. Renal failure and spinal cord ischemia (SCI) remain the most concerning postoperative morbidity in complex fenestrated branched endovascular repair of TAAA. Renal failure occurred at a rate of 2.8% in some series, with an incidence of 5.5% in the subpopulation that underwent Type II repair [45]. SCI symptoms developed in 8% of patients overall, but resolved in nearly half the patients prior to hospital discharge in the same series [45]. These outcomes are comparable with the results contemporary open repair.

Staging of endovascular repair has been reported to be associated with reduced incidence and severity of SCI. Staging has its own risks. Before custom endografts were available, staging was a necessity. However, a proportion of these patients die between stages (6%) and aneurysm rupture is thought to be a causative factor [46]. From a technical standpoint, the need for the use of reinforced fenestrations in the endovascular treatment of complex TAAA may be associated with higher rate of visceral and renal endoleaks

and suboptimal patency rates [47]. Endoleaks also increase the risk and need for reinterventions, but this has not appeared to adversely affect longer-term outcomes. Evolving graft and bridging stent design improvement may help to mitigate this in future.

Hybrid Repair

The perioperative morbidity and mortality associated with open surgical repair of TAAA has always remained significant. The complications of acute renal failure (2–12%) and cardiopulmonary (4–33%) and spinal cord ischemia (1–15%) are significant and are increased when preoperative pulmonary and renal impairment is present [48]. Complete endovascular exclusion of TAAA, while feasible, remains a technique that is in evolution and has its shortcomings as discussed above. Therefore, a hybrid approach mixing stable endovascular exclusion of TAAAs after open visceral bypass has evolved into a viable treatment option. The general premise of the hybrid approach is based on the reduced physiologic stress of operating through one visceral cavity rather than two (abdomen and thorax), thereby reducing complications and improving ultimate outcome.

Visceral hybrid TAAA repair utilizes retrograde revascularization of the visceral and renal arteries via an open abdominal approach. This preparatory operation then enables an endovascular stent-graft to exclude the TAAA including the visceral aortic segment. Compared to open techniques, this approach reduces visceral ischemia time. Spinal cord ischemia, attributed to aortic cross-clamping, intraoperative hypotension and reperfusion injury are theoretically minimized. The avoidance of a thoracotomy confers significant physiologic advantages in most patients, particularly those with preoperative pulmonary impairment. There exists the possibility of interval aneurysm degeneration and rupture between two operations in the staged hybrid approach. Proponents of this technique thus advocate its use in patients considered high risk such as those with chronic obstructive pulmonary disease, coronary artery disease, or chronic renal insufficiency [49]. These groups typically stage the open debranching operation 2–4 months prior to the endovascular procedure, citing the avoidance of fluid shifts and hemodynamic instability, which can result in a higher risk of paraplegia if performed concomitantly with endografting [49].

Summary

The outcomes of open TAAA repair have greatly improved over the years and contemporary 30-day survival rates are quoted over 90%. The highest survival rate published to date was also the largest series ever reported, indicating that high volume centers can achieve the best outcomes in this complex disease process. Whilst sounding less invasive, hybrid and endovascular approaches still carry the significant risk of morbidity and mortality compared with the open procedures. It is reasonable to assume that with increased use of endovascular techniques, an era will arrive in which TAAAs may be more universally treated with less invasive techniques. At present, open repair remains the best option for the majority of patients to achieve good long-term results.

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Abdominal Aortic Aneurysms

14

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Abbreviations

^{18}F-FDG	^{18}F-fluoro-deoxy-glucose
AAA	Abdominal aortic aneurysm
ACE	Angiotensin-converting enzyme
ADAM	Aneurysm Detection and Management
CAD	Coronary artery disease
CAESAR	Comparison of surveillance versus aortic endografting for small aneurysm repair
CEUS	Contrast-enhanced ultrasonography
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CTA	Computed tomographic angiography
DREAM	Dutch Randomized Endovascular Aneurysm Management
DUS	Duplex ultrasound
EVAR	Endovascular aneurysm repair
FAST	Focused Assessment with Sonography in Trauma
HR	Hazard ratio
IAAA	Inflammatory abdominal aortic aneurysm
MMP	Matrix metalloproteinases
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
OR	Odds ratio
OVER	Open Versus Endovascular Repair
PAD	Peripheral artery disease
PET	Positron emission tomography
PIVOTAL	Positive Impact of Endovascular Options for treating Aneurysms Early
SPECT	Single-photon emission computer tomography
UKSAT	UK Small Aneurysm Trial
US	Ultrasound
USPSTF	US Preventative Services Task Force

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Introduction and Definitions

Aneurysm derives from the Greek word ανευρυσμα (aneurusma), meaning widening, and can be defined as a permanent and irreversible localized dilatation of a vessel. An abdominal aortic aneurysm (AAA) is a permanent, localized dilatation of the abdominal aorta that exceeds the normal diameter by 50%.

The abdominal aorta begins at the level of the diaphragm and extends to its bifurcation into the left and right common iliac arteries. Normal aortic diameter varies with age, gender, and body habitus, but the average diameter of the adult human infrarenal aorta is about 2.0 cm and typically less than 3.0 cm. Thus, for the majority of patients, an infrarenal aorta with a maximum diameter ≥ 3.0 cm is considered aneurysmal [1].

Anatomy of the Abdominal Aorta

The abdominal aorta is a retroperitoneal structure that begins superiorly at the diaphragm and extends down to the level of the forth lumbar vertebra, where it bifurcates into the right and left common iliac arteries (Fig. 14.1) [3]. The aorta lies slightly left of midline, with the inferior vena cava adjacent to it on the right. The branches of the aorta include (superior to inferior) the left and right inferior phrenic arteries, left and

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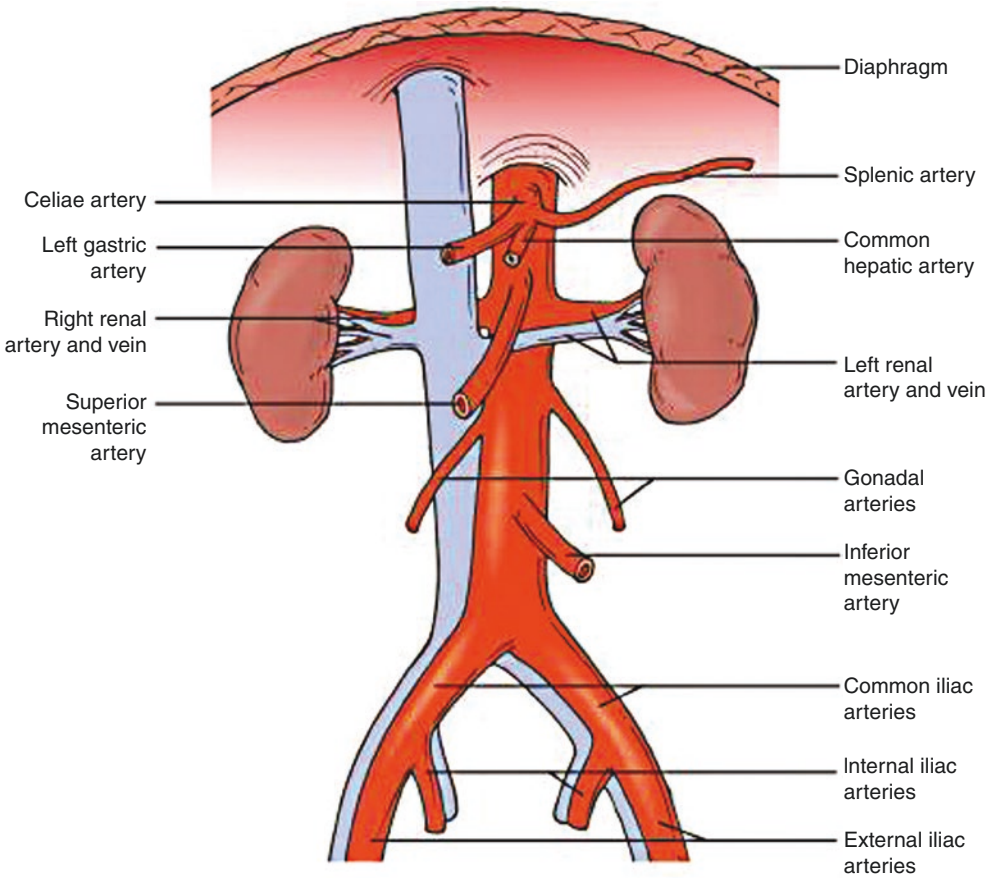

Fig. 14.1 Anatomy of the abdominal aorta. (From Tainter [2]. Reprinted with permission from Elsevier)

right middle suprarenal arteries, the celiac axis, superior mesenteric artery, left and right renal arteries, left and right gonadal arteries, inferior mesenteric artery, left and right common iliac artery, middle sacral artery, and the paired lumbar arteries. The common iliac artery bifurcates into the external iliac and internal iliac arteries at the pelvic inlet.

Similar to other arteries, the aortic wall is divided into three layers (from external to lumen): the tunica externa (or tunica adventitia), tunica media, and tunica intima. The vascular supply to the tunica externa and tunica media is provided by an extensive network of small blood vessels known as the vasa vasorum [3].

Classification

Aneurysms can be categorized by morphological characteristics, location, or etiology. The following are terms that define aneurysms based on morphology (Fig. 14.2) [5].

- *True aneurysm*: An aneurysm that involves all three layers of the arterial wall (intima, media, and adventitia).
- *False aneurysm (pseudoaneurysm):* A collection of blood or hematoma that has leaked out of the artery but is then confined by the surrounding tissue.
- *Fusiform aneurysm:* The circumference of the artery is impacted by the aneurysm (most aneurysms are fusiform).
- *Saccular aneurysm:* Only a part of the circumference of the artery is impacted by the aneurysm.
- *Inflammatory aneurysm:* Characterized by extensive perianeurysmal and retroperitoneal fibrosis and dense adhesions to adjacent abdominal organs [1].
- *Infectious (mycotic) aneurysm:* Aneurysm caused by an infectious agent, most commonly bacterial (most commonly *Staphylococcus aureus*, *Salmonella*, and *Streptococcus pneumonia*) [6].

Another commonly used classification modality is based on location within the aorta (Fig. 14.3) [8]:

- *Suprarenal aneurysm:* Involves the origins of one or more visceral arteries but does not extend into the chest.
- *Pararenal aneurysm*: The renal arteries arise from the aneurysmal aorta; however, the aorta at the level of the superior mesenteric artery is not aneurysmal.
- *Juxtarenal aneurysm*: Originates just beyond the origins of the renal arteries. There is no segment of nonaneurysmal aorta distal to the renal arteries, but the aorta at the level of the renal arteries is not aneurysmal.

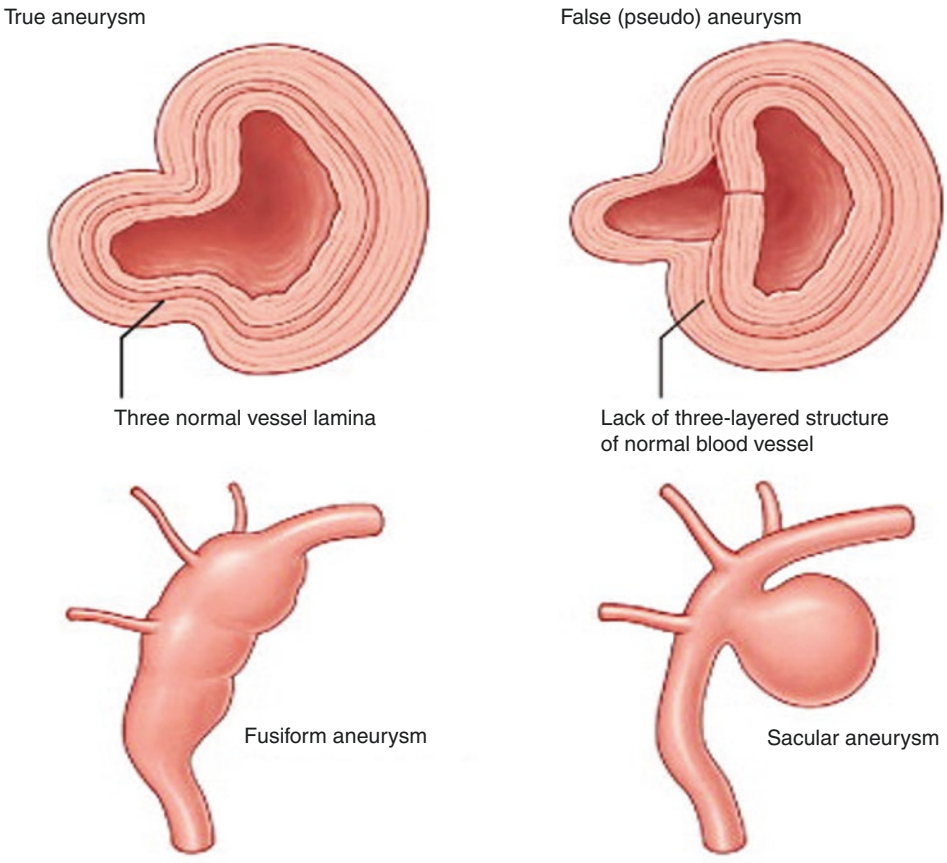

Fig. 14.2 Aneurysm morphologies. (From Netscher et al. [4]. Reprinted with permission from Elsevier)

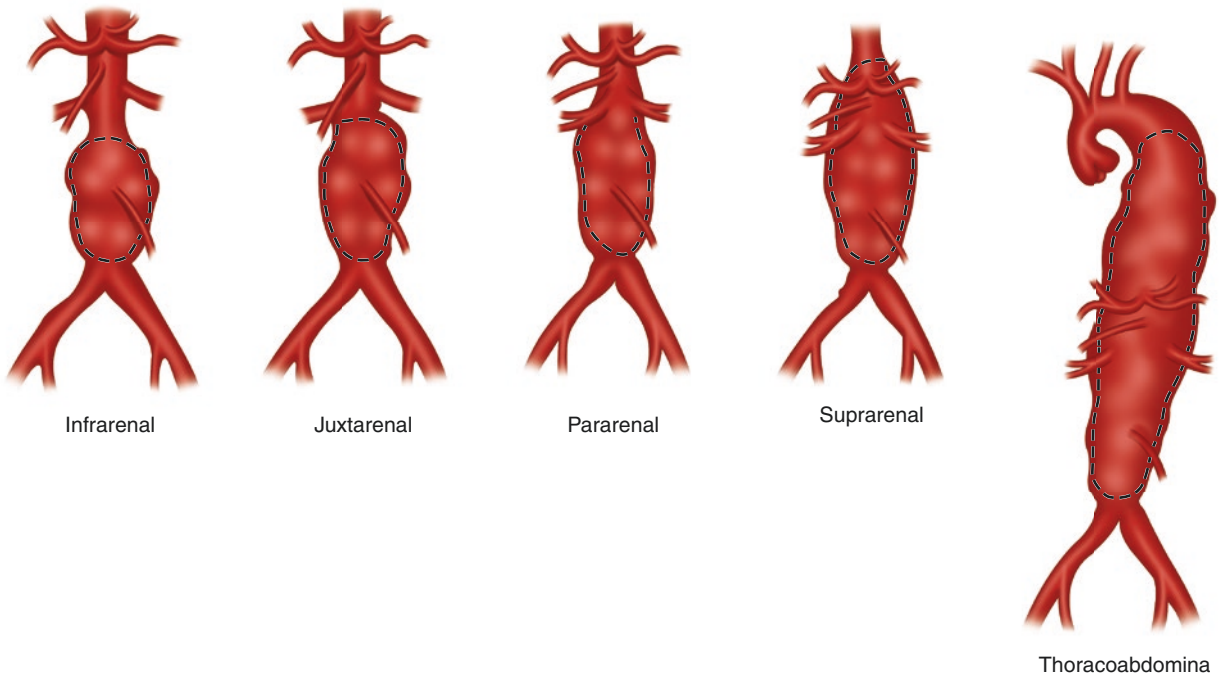

Fig. 14.3 Abdominal aortic aneurysms described by their location in relation to the renal arteries. (From Goldstone [7]. Reprinted with permission from Elsevier)

- *Infrarenal aneurysm:* Originates distal to the renal arteries. There is a segment of nonaneurysmal aorta that extends distal to the origins of the renal arteries.
- *Thoracoabdominal aneurysm:* Originates in the chest and may involve the visceral or renal vessels.

Abdominal aortic aneurysms (AAA) most often affect the segment of aorta between the renal and inferior mesenteric arteries [9].

Pathophysiology

The development of abdominal aortic aneurysms is associated with alterations of the connective tissue in the aortic wall. Elastic fibers and fibrillar collagen are the main determinants of the mechanical properties of the aorta. Elastin and associated proteins form a network of elastic fibers responsible for the viscoelastic properties of the aorta. Elastin is stabilized by cross-links between the molecules and is degraded by specific proteases that display elastase activity. Elastic fibers associated with smooth muscle cells are most abundant in the media of the aortic wall. Collagen, in polymeric form, is also a significant component of the media and the surrounding fibrous adventitia.

One of the major histological features of aneurysmal tissue is fragmentation of elastic fibers and a decreased concentration of elastin. The loss of elastic fibers seems to be an early step in aneurysm formation. Although elastin fragmentation and medial attenuation are the most important characteristics of the wall of an aneurysm, the adventitial tissue, in which collagen is predominant, is responsible for the resistance of the aorta in the absence of medial elastin. Therefore, while loss of elastin leads to aneurysm formation, collagen degradation is thought to be the ultimate cause of aneurysm rupture [5].

Collagen production continues throughout life and is even increased in the aneurysmal wall. Besides enhanced collagen synthesis, however, collagenolytic activity is increased in AAA as well. This increased lytic activity is why several hereditary connective tissue disorders (e.g., Ehlers-Danlos and Marfan's syndromes) are associated with aneurysm formation at an early age [8].

The alteration of elastin and collagen in the aortic wall is dependent on production of proteases by nearby vascular wall cells (medial smooth muscle cells and adventitial fibroblasts) and by the cells of the lymphomonocytic infiltrate. These inflammatory cells in the media and adventitia come from the aortic blood and from a medial neovascularization, which characterizes abdominal aortic aneurysms. Leukocyte recruitment into the aortic wall is promoted by elastin degradation fragments as well as proinflammatory cytokines, chemokines, and prostaglandin derivatives produced by both the resident mesenchymal cells and the inflammatory cells themselves. Elastic and collagen fibers are degraded by proteolytic enzymes mostly represented by matrix metalloproteinases (MMP) locally activated by either other MMP or by plasmin generated by plasminogen activators.

Besides rarefaction of its extracellular matrix, the elastic media also undergo a reduction in the density of smooth muscle cells, which is regarded as a key event in the development of abdominal aortic aneurysms. Smooth muscle cells participate in vascular wall remodeling through localized expression of various extracellular matrix proteins as well as proteases and their inhibitors. Additionally, smooth muscle cells have a protective role against inflammation and proteolysis.

The development of abdominal aortic aneurysms is also associated with a mural thrombus in a number of patients. By contrast with arterial occlusive diseases, blood flow is maintained in aortic aneurysms resulting in a persistent remodeling activity of the components of the thrombus. Although the thrombus can substantially reduce aneurysmal wall stress, its increasing thickness leads to local hypoxia at the inner layer of the media, which can induce increased medial neovascularization and inflammation. This appears to play a role in aneurysmal degeneration associated with an adherent thrombus [1]. Some data suggests that thrombus may actually increase risk of aneurysm rupture, presumably due to localized tissue hypoxia and diminished wall strength [10–13].

Risk Factors

The common risk factors of AAA are smoking, male gender, white race, older age, chronic obstructive pulmonary disease (COPD), hypertension, dyslipidemia, coronary artery disease (CAD), peripheral artery disease (PAD), and positive family history [14]. Interestingly, although diabetes mellitus is a risk factor for PAD and CAD, it has been found to be a negative risk factor for AAA development and growth [15, 16].

Age

Elastin is not synthesized in the adult aorta. With a half-life of 70 years, the amount of elastin in the aortic wall decreases with age. The age-related alterations in the vessel wall affect the mechanical properties of the aorta. This explains why AAA is primarily a disease of the elderly [8].

Atherosclerosis

The historical association of AAA with atherosclerosis has now expanded into a multifactorial causation for the disease.

It is unclear why atherosclerosis, normally causing narrowing of the arterial lumen, should in some cases result in dilation. There are epidemiological differences between patients with obstructive vascular and aneurysmal disease. Histological examination of the aneurysm wall reveals a chronic adventitial and medial inflammatory infiltrate of varying intensity. This distinguishes AAA from the purely atherosclerotic aorta, in which inflammatory cells are mainly associated with plaque. Patients with obstructive peripheral vascular disease also carry an increased risk for AAA. It is also important to remember that both AAA and peripheral arterial disease share many common risk factors (such as age, gender, smoking, hypertension, and hyperlipidemia, among others) [8].

Smoking

Smoking is the risk factor most strongly associated with AAA. Men who currently smoke more than 25 cigarettes per day have a 15-fold increased risk of AAA (hazard ratio [HR] 14.6, 95% CI 9.6–22) compared with men who have never smoked [17]. A smoker's risk of developing AAA continues for at least 10 years following smoking cessation. In spite of this association, however, no causative link has been proven between smoking and AAA formation. The mechanism by which cigarette smoking contributes to aneurysm formation is independent of atherosclerosis. Theories behind the pathophysiology include disruption in collagen synthesis, altered expression of metalloproteinases, and the response to oxidative stress [18].

Patients with smoking history are more likely to develop COPD. As is the case in AAA, COPD is driven by excess matrix turnover and proteolysis. A large meta-analysis recently showed a 1.8-fold increase prevalence and incidence of AAA in patients with COPD compared to those without it [19]. Further, some studies suggest that COPD increases the risk of AAA rupture [20].

Gender

Men are at much higher risk of AAA than women. The reasons for this are unclear, but it is likely to be a function of hormonal factors, genetic susceptibility, and risk factor exposure [18].

Hypertension

Hypertension enhances the growth rate of aneurysms and is associated with an increased prevalence of AAA, which indicates that an increased load on the aortic wall may be involved in pathogenesis [5]. Hypertension also increases rupture risk in patients with established AAAs [14].

Hyperlipidemia

High-serum total cholesterol has a positive association with AAA prevalence, whereas high-density lipoprotein cholesterol has an inverse association. This correlation may be related to the increased risk of atherosclerosis, or may in part be a direct factor [21]. Similarly, obesity has also been shown to be an independent risk factor [18].

Family History/Genetic Factors

Positive family history has been shown to be a major risk factor for development of abdominal aortic aneurysm. A study by Larsson and colleagues showed the overall relative risk of AAA associated with family history compared to no family history was 1.9 (95% confidence interval [CI] 1.6–2.2) [22].

The development of AAAs is unlikely to be related to a single gene mutation, and multiple genetic factors are implicated. Susceptibility genes, rather than causal gene mutations, are likely to be important, particularly those regulating inflammatory mediators, tissue proteases, and smooth muscle cell biology [18].

Alcohol Intake

High levels of alcohol intake (>30 g/day) have been associated with increased risk of AAA (OR 1.65, 95% CI 1.03–2.64) [17]. The mechanism through which alcohol exposure increases the risk of AAA is unclear, but could be through upregulation of matrix metalloproteinases and focal elastin degradation.

Primary Disorders of the Aorta

A fraction of the cases of AAA are the direct consequence of disorders of the aorta itself or disruptions in the integrity of the aorta. Some of these causes include trauma, acute infection (bacterial or fungal), chronic infection (tuberculosis), inflammatory diseases (Behçet and Takayasu disease), and connective tissue disorders (Marfan's syndrome, Ehlers-Danlos type IV) [1].

In spite of the nomenclature, mycotic aneurysms are most often caused by bacterial pathogens, with fungi rarely being associated. The most commonly implicated organisms include *Staphylococcus aureus*, *Salmonella*, and

Streptococcus pneumonia. Syphilis (*T. pallidum*) once caused up to 50% of infected aneurysms [6].

The source of infection may be due to the direct inoculation of vessel wall or spread from an adjacent source of infection, which contributes to degradation or focal erosion of the arterial wall. Mycotic aneurysms may also arise from hematogenous spread [23].

Presentation

Nonruptured Abdominal Aortic Aneurysm

Nonruptured abdominal aortic aneurysms (AAA) are asymptomatic in most patients. Often the initial diagnosis is made as an incidental finding on abdominal ultrasound, abdominal computed tomography, or abdominal magnetic resonance imaging utilized for other purposes. When symptoms are present, they may include nonspecific abdominal pain, lower back pain, and mid-abdominal or flank pain with radiation to the back, groin, or scrotum [1]. The pain may be described as a gnawing sensation with episodes lasting hours to days [24]. Aneurysmal pain is typically not exacerbated by movement, though patients may be more comfortable in certain positions [25]. The presence of these symptoms is usually secondary to direct pressure or distention of intra-abdominal structures adjacent to the aorta [1]. Development of new or worsening pain that is severe, persistent, and/or localized to the back, lower abdomen, buttocks, or lower extremities may forebode impending rupture [25].

On physical exam, a pulsatile, typically nontender, mass can be present. Palpation of an AAA has been demonstrated to be safe and does not precipitate rupture [25]. The sensitivity of abdominal palpation is variable due to variabilities in AAA size and patient body habitus [26, 27]. Sensitivity of abdominal palpation in 15 studies of patients screened for AAA with both palpation and ultrasound was 29% for AAA 3.0–3.9 cm, 50% for 4.0–4.9 cm, and 76% for AAA ≥ 5 cm. The positive predictive value was 43% for AAA > 3.0 cm [26]. Abdominal obesity reduces sensitivity. One study demonstrated that palpation for AAA in patients with an abdominal girth of less than 100 cm (40-inch waistline) was 91% versus just 53% in patients with a girth of 100 cm or more ($p < 0.001$) [27].

Mycotic aneurysms are a distinct entity that classically present with a triad of fever, abdominal pain, and a palpable abdominal mass; however, the majority of patients with mycotic aneurysms do not have this triad of symptoms [28]. Laboratory evaluation reveals elevation of inflammatory markers such as erythrocyte sedimentation rate [29]. Blood cultures are positive in 50–90% of cases and can remain positive in spite of appropriate antimicrobial therapy [28].

Ruptured Abdominal Aortic Aneurysm

Ruptured AAAs classically present with the triad of abdominal or back pain, a pulsatile abdominal mass, and hypotension, though this triad is present in only about 33–50% of presentations [1, 25]. Alternatively, presenting symptoms may be secondary to hemorrhagic shock post rupture. These symptoms can include hypotension, vasoconstriction, mottled skin, diaphoresis, altered mental status, and oliguria. Terminal symptoms maybe are manifested by arrhythmias and/or cardiac arrest [25].

The clinical presentation varies depending on location of rupture. Rupture involving anterolateral wall into the peritoneal cavity causes abdominal distention and is usually rapidly fatal. Most patients with AAA rupture who survive long enough to reach medical attention have rupture of the posterolateral wall into the retroperitoneal space. On physical exam, ecchymosis in the flanks (Grey Turner sign) may be seen. A small tear can temporarily seal the rupture mitigating initial blood loss. Within hours, the rupture progresses necessitating acute intervention.

Rarely, an AAA can rupture into the inferior vena cava forming an aortocaval fistula. The triad of abdominal or lower back pain, an abdominal bruit, and a pulsatile abdominal mass is characteristic; however, this triad is found in the minority of patients. Other possible symptoms include lower extremity edema, congestive heart failure, hypotension, and hematuria [30]. Rarely, an aortocaval fistula may form leading to hematuria or shock [31, 32]. Rupture into the gastrointestinal tract or the formation of an aortoenteric fistula presents as massive gastrointestinal hemorrhage [25].

Imaging

There are many modalities to screen, confirm, and monitor AAA. This section will discuss ultrasound, computed tomographic angiography and rotational angiography, magnetic resonance imaging, as well as newer techniques such as three-dimensional reconstruction and wall stress calculation.

Ultrasound

Ultrasound (US) is the most common imaging modality for AAA due to ease of use, relative accuracy, cost, and absence of radiation [33]. Routine evaluation measures the anteroposterior, transverse, and longitudinal dimensions of the suprarenal, juxtarenal, pararenal, and infrarenal aorta. Iliac arteries should be included. Bowel gas or abdominal fat may block the suprarenal aorta or iliac arteries and for these reasons may misjudge the extent of an AAA. If possible, patients

Table 14.1 Screening recommendations for abdominal aortic aneurysms from several societies

Society	Recommended groups	Not recommended or insufficient data
US Preventative Services Task Force	Men age 65–75 who have ever smoked	Women
	Men age 65–75 who have never smoked with select histories	
American College of Cardiology and American Heart Association	Men age 65–75 who have ever smoked	Men who have never smoked Women
	Men age 60 or older who are the sibling or offspring of a person with AAA	
Society for Vascular Surgery	Men age 55 or older with family history of AAA	
	Men age 65 or older	
	Women age 65 or older who have ever smoked or have family history of AAA	
American College of Preventive Medicine	Men age 65–75 who have ever smoked	Women
Canadian Society of Vascular Surgery	Men age 65–75 who are candidates for surgery and willing to participate	
	Women age 65 or older with risk factors for AAA	
European Society for Vascular Surgery	Men age 65 or older	
	Men at high risk	

should fast prior to examination to reduce bowel gas interference. Despite these factors, it is rare to be unable to image the aorta properly, with less than 2% of studies limited by technical factors [34]. If US is unable to provide reliable images, an alternative imaging modality should be pursued.

While dependent on operator experience and patient characteristics, there is less than 5 mm inter-rater variability of AAA size in more than 80% of cases [35], though some prior studies have shown US can underestimate the size of a AAA by up to 1 cm when compared directly with CT angiography [36, 37]. Generally, US is used as the initial diagnostic test for screening and surveillance of AAA. The US Preventative Services Taskforce (USPSTF) recommends a one-time screening US for men age 65–75 with a smoking history. See Table 14.1 for additional screening recommendations. US is also very useful when patients present to the emergency department with hemodynamic instability in the setting of either a known or unknown AAA. While not a requirement prior to diagnosis, bedside ultrasonography can be performed, while patient is still in emergency department or in route to the operating room without causing unnecessary delay. Emergency department physicians have become much more comfortable with the abdominal US due to continued use of the Focused Assessment with Sonography in Trauma (FAST) exam and can quickly identify abnormal findings, such as an enlarged aorta, abdominal ascites, or retroperitoneal hematoma [38].

Spiral Computed Tomographic and Angiography

Spiral computed tomographic and computed tomographic angiography (CT and CTA) studies are costlier than US and expose the patient to radiation and intravenous contrast; however, they provide more anatomic detail, which is needed for perioperative planning [35, 37]. Different methods, such as magnification, electronic calipers, and other standardized techniques, have brought variability to less than 2 mm in 90% of cases. Three-dimensional reconstruction is added to assess for symmetry as a tortuous aorta can show oblique cross sections and AAA diameters could be overestimated.

CT is recommended in hemodynamically stable patient suspected of having an AAA or aneurysm rupture [39]. Signs of rupture on CT include an indistinct aortic wall, retroperitoneal hematoma, extravasation of intravenous contrast, retroperitoneal stranding, or loss of the fat plane between the aorta and surrounding tissue (Fig. 14.4, Table 14.2). If rupture is not seen, it may reveal certain findings associated with unstable aneurysms suggesting impending rupture such as crescent sign, discontinuous circumaortic calcification, aor-

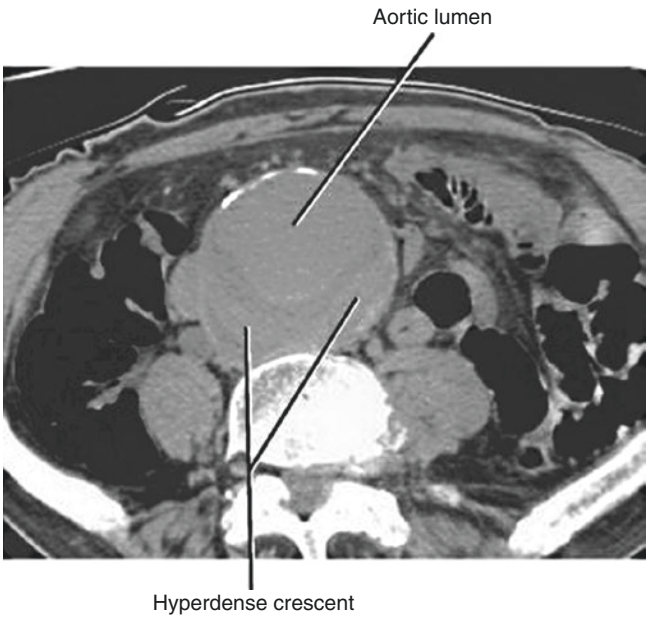

Fig. 14.4 The crescent sign and drape sign seen on CT are suggestive of impending rupture. (From Dalrymple et al. [40]. Reprinted with permission from Elsevier)

tic bulges or blebs, and aortic draping. Combined with aneurysm size of 5 cm or greater, these signs have been shown to be predictive of impending rupture [41].

CT imaging of the aortic wall can also show signs of inflammation or infection consistent with an inflammatory or mycotic aneurysm [42, 43]. The aorta can become primarily infected by bacteria and cause a rapidly expanding AAA, or a pre-existing AAA can be secondarily infected. Features that suggest infected aneurysm include soft tissue inflammation surrounding the aorta, perivascular fluid collection, an AAA with air around the vessel or intramurally, or multilobular, eccentric, or saccular AAA. An inflammatory AAA (IAAA) can show thickening of the adventitia, defined on CT as greater than a 1 cm ring surrounding the aorta. Fibrosis or adherence to adjacent structures, such as the duodenum, ureters, and generalized retroperitoneum, may be seen. Though inflammation is present, periaortic air or fluid is not seen as noted for infected aneurysms.

Table 14.2 Signs of impending abdominal aortic aneurysm rupture on CT scan

Crescent sign	Acute intramural or mural thrombus (Fig. 14.4)
Discontinuous circumaortic calcifications	Noncontiguous calcified plaques along endothelial vascular surface
Aortic bulges/blebs	Outpouchings from vascular wall
Aortic draping	Posterior wall of aortic aneurysm drapes or molds to anterior surface of vertebral bodies (Fig. 14.4)

Recent guidelines from the American Heart Association recommend CTA as the initial imaging modality when there is suspicion for a mycotic aneurysm (Class IIa, level of evidence B). Findings suggestive of a mycotic aneurysm on CTA include a saccular appearance, an irregular lobular contour, minimal or absent calcifications, periaortic soft tissue stranding, and periaortic gas [28].

Currently, CTA is the most commonly used imaging modality for preoperative planning and endografting (Fig. 14.5). It can be used in both elective and acute settings and can exclude rupture. It also images the renal and iliac arteries more accurately than US, which is beneficial for preoperative planning as the presence of juxtarenal or suprarenal aneurysms can affect placement of vascular cross-clamps or help determine which type of graft is used (fenestrated or branched). Rotational angiography before and after EVAR is commonly used. Benefits include confirmation of rupture within the operating room, and the images can be used for operative planning and graft sizing. However, image quality may be less than spiral CT angiography, and branch vessels (renal and iliacs) may not display as well [44].

Regular follow-up imaging of postoperative EVAR is typically done with CT and usually performed for the life of the patient. Monitoring is performed to detect aneurysm expansion, graft deformation or migration, and endoleaks. CTA may be more sensitive than spiral CT in detecting endoleaks.

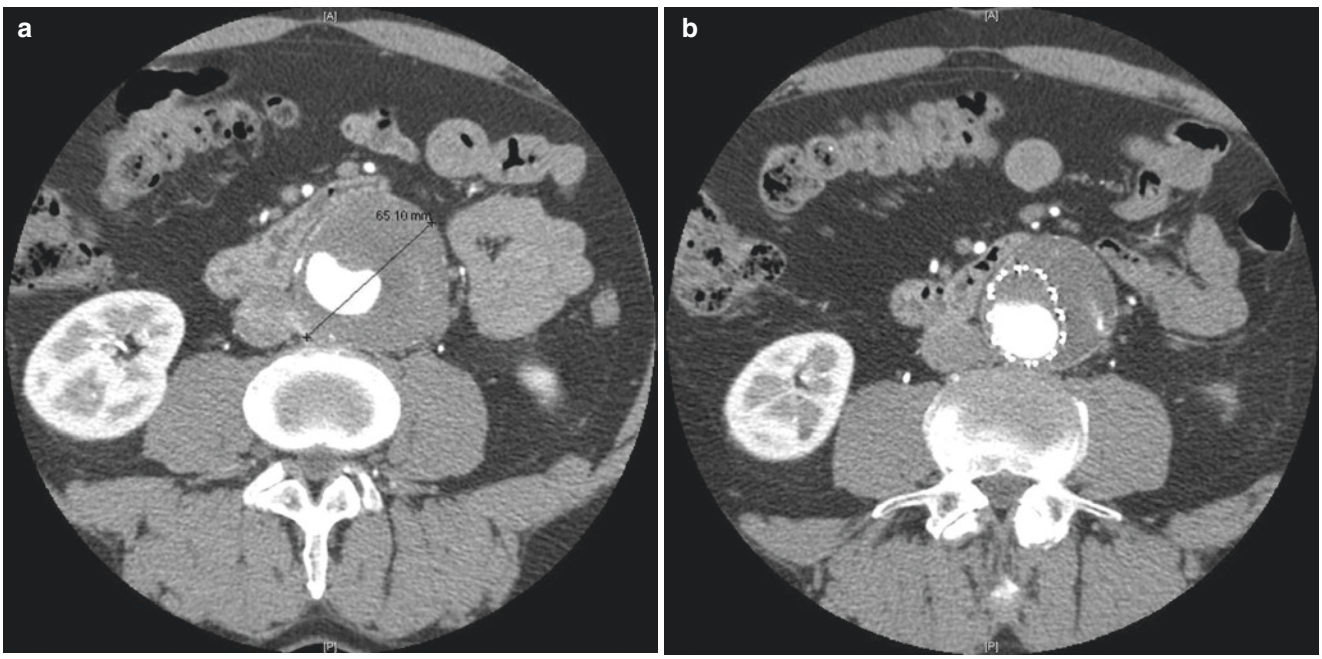

Fig. 14.5 (**a**) CT angiography demonstrating an infrarenal abdominal aortic aneurysm measuring up to 6.5 cm in diameter. (**b**) CT angiography performed following EVAR

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are accurate in determining size and morphology of AAA, but increased cost, time, and less standardized techniques make it a less favorable study compared to CT and US. Moreover, MRI/MRA does not visualize calcium plaque as well as CT. It does have the benefit of no radiation exposure, and it was previously thought that gadolinium contrast would be safe in patient with renal insufficiency until studies described a link with nephrogenic sclerosing fibrosis [45]. Nevertheless, gadolinium does prove useful if intravenous contrast is precluded due to allergies or other reasons.

Other Modalities

Commonly AAA may be incidentally seen on nonvascular imaging studies that were performed for other reasons. Plain film x-rays can delineate the abdominal aorta if enough calcified plaque is present or a large-enough soft tissue density is visualized, signaling presence of an aneurysm. While aneurysm presence or size may be inferred from other imaging, dedicated vascular imaging should be performed to confirm details.

While US, CT, and MR have become standardized imaging modalities for assessing AAA, functional and molecular imaging are becoming more prevalent and may aid in learning the pathophysiology behind AAA.

Functional imaging can reveal the physiological changes within an organ or tissue via radiolabeled tracers or probes. With AAA, this is most commonly performed with single-photon emission computer tomography (SPECT). SPECT imaging using radiolabeled red blood cells or platelets has been performed for years for noninvasive vascular flow studies, though their sensitivity in detecting AAA or leak has been surpassed by CT and MR. Radiolabeled leukocytes can also be used to detect inflammatory AAA.

Molecular imaging may provide insight into the earlier biomolecular and mechanical changes of the aorta prior to aneurysm formation [46]. Molecular probes can be used to mark different molecular processes at different stages of disease. This could help determine other factors that lead to growth and rupture aside from the anatomic characteristics currently known. SPECT and optical imaging can be performed for this purpose; however, PET nuclear imaging may have the most promise. PET, primarily used as the gold standard in cancer diagnosis and surveillance, can be used to show wall inflammation and instability using the same ^{18}F-fluoro-deoxy-glucose (^{18}F-FDG) radiotracer [47]. Increased metabolic activity can indicate infection or inflammatory processes within the aortic wall which may help pursue repair when other anatomic imaging suggests surveillance. Other studies show that asymptomatic AAA shows increased ^{18}F-FDG uptake compared to nonaneurysmal controls irrespective of AAA size, alluding to additional factors that contribute to AAA pathophysiology outside of anatomical characteristics [48].

Surveillance

AAAs are frequently asymptomatic until they rupture, and the overall mortality of a ruptured AAA approaches 85–90% with improvement to 50–70% in patients who are able to reach the hospital [32]. By contrast, elective aneurysm repair, whether a surgical or endovascular approach, is associated with an overall 30-day mortality of less than 5%. Additionally, given the ease and availability of a low-cost, low-risk, and high accuracy test (ultrasonography), it follows that screening of appropriate patients prior to development of symptoms may help to prevent undue mortality, particularly given that AAAs have a significant asymptomatic phase. One meta-analysis of four randomized controlled trials (RCTs) of screening for AAAs in older men demonstrated a significant decrease in AAA-related mortality and emergency operations (with an expected increase in elective procedures) in both mid-term and long-term analysis [49].

The USPSTF released recommendations in 2005 and again in 2014 to screen men and women aged 65–75 both with and without a history of smoking [50, 51]. Men in this age group with a smoking history would benefit from one-time screening for AAA (grade B recommendation), and this is largely based on the aforementioned RCTs. Selective screening for nonsmoking men may demonstrate a small net benefit (grade C recommendation), and it is the low prevalence (approximately 2%) in this population that decreases the absolute benefit [52]. There is insufficient data to assess the benefits of AAA screening in women in this age group with a smoking history as only one RCT demonstrated no difference in AAA-related mortality, though the trial was underpowered to detect these differences [53]. Women who have never smoked have a lower prevalence than men (less than 1%) and do not benefit from screening [52]. Additional screening recommendations from national guidelines are outlined in Table 14.1.

Once an AAA is detected, it is primarily the diameter of the aneurysm which determines subsequent evaluation. While the annual risk of rupture of AAAs < 5.5 cm is ≤1.0%, those from 5.5 to 5.9 cm have a risk of 9.4%, 6.0–6.9 cm have a risk of 10.2%, and ≥7.0 cm have a risk of 32.5% (Table 14.3) [54–56]. Generally, referral for elective repair is indicated in patients with AAA diameter ≥ 5.5 cm with a high level of evidence, as this was the cut-off used in multiple

Table 14.3 Abdominal aortic aneurysm size and risk of rupture

Aneurysm size (cm)	Annual risk of aneurysm rupture (%)
<5.5	≤1
5.5–5.9	9.4
6.0–6.9	10.2
≥7.0	32.5

Table 14.4 Surveillance interval recommendations from the Society for Vascular Surgery for varying abdominal aortic aneurysm sizes

AAA size (cm)	Surveillance interval
<2.6	No surveillance necessary
2.6–2.9	5 years
3.0–3.4	3 years
3.5–4.4	1 year
4.5–5.4	6 months

screening trials [51, 57]. For patients with diameters < 4 cm, surveillance is generally recommended.

There is still debate regarding the intermediate patients with AAA diameters between 4 and 5.4 cm, and the decision to treat may depend on other risk factors and clinical variables. The UKSAT and ADAM trials demonstrated equivalent long-term survival in both surgical and surveillance groups, though there may be a trend toward improved survival in younger patients with larger aneurysms [54, 58]. The CAESAR and PIVOTAL trials compared surveillance with endovascular repair, and neither trial showed a clear benefit of EVAR over surveillance in AAAs with diameters < 5.5 cm [59, 60]. Current guidelines recommend ultrasound surveillance at varying intervals depending on the size of the AAA (Table 14.4) [57]. Due to inter-observer variability in ultrasound measurements, there has been some interest in using CT to monitor AAA growth [61], though ultrasound remains favored due to its relative cost and lack of radiation exposure.

Following repair of the AAA, imaging surveillance is still necessary given complications of the repair itself. The concerning complication of surgical repair is late paranastomotic aneurysm formation, the risk of which increases over time and approximates 1%, 5%, and 20% in patients 5, 10, and 15 years following surgical repair, respectively [57]. The Society for Vascular Surgery therefore recommends screening with CT imaging at five-year intervals following open surgical intervention.

For endovascular aneurysm repair (EVAR), the primary concern for postprocedural surveillance is monitoring for endoleak, the most frequent complication following EVAR. Endoleak is persistent blood flow in the aneurysm sac outside the endograft. There are five types of endoleak that have been described (Table 14.5) [57]. Type I endoleak occurs as a result of incomplete sealing at the end of the stent graft and is associated with continuous risk of rupture; therefore, these should be repaired at the time of EVAR. Type II

Table 14.5 Endoleak definitions [29]

Endoleak	Description
Ia	Incomplete seal at the proximal graft attachment site
Ib	Incomplete seal at the distal graft attachment site
II	Retrograde filling of aneurysm sac by collateral vessels (e.g., inferior mesenteric or lumbar arteries)
III	Leak at the attachment site of the modular components; graft tear
IV	Benign leak due to porosity of the graft material
V	"Endotension"; no endoleak detected, but there is persistent pressurization of the aneurysm sac; can lead to sac enlargement or rupture

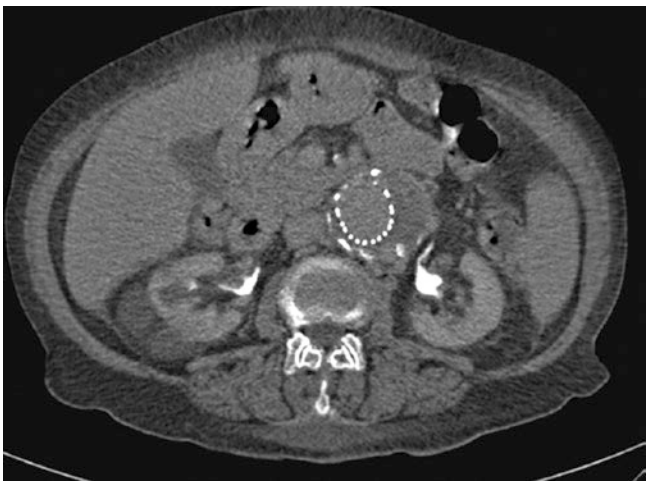

Fig. 14.6 Type II endoleak. Contrast is seen filling the aortic sac, most likely due to filling from a lumbar vessel. (From Titus [62]. Reprinted with permission from Springer)

endoleaks are the most common and describe retrograde filling of the sac by collateral vessels (Fig. 14.6). These may resolve spontaneously or persist, and repair may be indicated depending on the patient, aneurysm size, vessels involved, and other factors, though generally risk of rupture is uncommon. Type III endoleaks are the result of poorly seated components, degradation, disconnection, or erosion of the material and should be treated. Type IV endoleaks refer to benign leak due to porosity of the graft material itself and do not need treatment. Finally, type V endoleak, also known as endotension, leads to persistently elevated pressures in the aneurysm sac. While no endoleak is noted in endotension, it can result in aneurysmal sac enlargement and rupture [29].

The EUROSTAR registry demonstrated many of these initial concerns when published in 2000 [63]. The cumulative rate of rupture was approximately 1% per year, and rate of late conversion to open surgical repair was about 2% per year; endoleak was noted to be a statistically significant risk factor for both endpoints of late failure.

CT angiography (CTA) remains the gold standard for postprocedural surveillance following EVAR with current recommendations suggesting 1-month, 6-month, and

12-month surveillance postrepair with annual lifelong screening thereafter [57]. Given the risks associated with this extensive radiation exposure, recent studies have investigated alternate forms of imaging for postrepair surveillance. Duplex ultrasound (DUS) was compared to CTA in a study of 132 patients and found a sensitivity and specificity of 86% and 67%, respectively [64]. The limitation was a significant number of false positives, with a positive predictive value of only 45%. A recent study of contrast-enhanced ultrasonography (CEUS) comparing DUS, CEUS, and CTA found significantly improved sensitivity and specificity for CEUS of 93% and 95%, respectively [65]. DUS was inferior to CTA in this study ($p = 0.002$), but CEUS and CTA were equivalent, and all endoleaks that required intervention detected on CTA were also detected on CEUS. Endoleaks missed by CEUS were type II without sac expansion that did not require intervention. Prior studies of CEUS did not demonstrate as strong results that were limited by low sensitivity and high false positive rates, possibly highlighting the importance of ultrasonographer technique and experience (in addition to patient habitus limitations) when performing these studies [66, 67]. Magnetic resonance angiography (MRA) has also been shown to be comparable to CTA and may be an alternative to patients with nitinol stents or iodinated contrast allergies, and though lacking in radiation, it is obviously limited by cost [68].

One recent study by Garg et al. interestingly questions the current dogma on postrepair surveillance [69]. Approximately 10,000 patients from a Medicare database who had underwent EVAR were retrospectively evaluated for long-term outcomes including mortality, late rupture, and reintervention with a mean follow-up of 6 years. Two cohorts divided into complete or incomplete surveillance based on follow-up imaging ("complete" defined as at least 1 imaging event within 15 months of repair and every 15 months thereafter), and these were propensity matched based on demographic variables. Incomplete surveillance was seen in about 50% of patients after propensity score matching. Analysis of outcomes demonstrated no statistical significant differences in aneurysm-related mortality between the two groups. Moreover, the incomplete surveillance group was noted to have lower rates of complication, reintervention, and all-cause mortality. The authors suggest that patients with other comorbidities may undergo more surveillance, are more likely to receive additional imaging not necessarily for surveillance, and are overall subject to increased mortality.

Treatment Options

Ruptured abdominal aortic aneurysms are associated with a mortality of 80–90% overall and approximately 50–70% among those that reach the hospital [70, 71]. The aim of therapy is therefore to prevent aneurysm rupture. While this goal is reached through several modalities, including behavioral modifications, pharmacologic therapies, screening, and surveillance, the mainstay of treatment is elective surgical or endovascular repair of the aneurysm.

Behavioral Modifications

Cigarette smoking is strongly associated with the presence of abdominal aortic aneurysms. In a cohort study examining more than 3 million patients, duration and amount of cigarette smoking were both directly correlated with the presence of an AAA. Among patients that quit smoking, the risk of aneurysm formation decreased over time; those that quit less than 5 years prior had an odds ratio of AAA formation of 0.87 (95% CI 0.84–0.912) compared with current smokers; those that quit greater than 10 years prior had an odds ratio of 0.42 (95% CI 0.41–0.43) [72].

Patients with AAA should be encouraged to participate in moderate physical activity as a means of decreasing their overall risk of cardiovascular morbidity and death. Some data has shown that blood flow to AAA increases with exercise [73]. Animal models demonstrated that increased blood flow to AAAs was associated with limited aneurysm expansion [74]. When viewed in concert, it seems plausible that exercise may limit aneurysm expansion; however to date, this has not been demonstrated clinically [75].

Although exercise increases blood pressure and wall tension, which theoretically could lead to expansion and rupture, there is currently no data to suggest this is the case. One study examined 262 patients with an abdominal aortic aneurysm (mean size 5.5 cm ± 1.1 cm) undergoing stress test. Only one patient suffered aneurysm rupture in the 72 hours following stress testing (aneurysm diameter was 6.1 cm in that patient), and the authors therefore concluded treadmill exercise could safely be performed [76].

Pharmacologic Interventions

In searching for a pharmacologic intervention that can slow the rate of AAA expansion, many classes of medications have been investigated, including beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, anti-platelets, and antibiotics. While some have shown promise in animal studies, to date no class of medications has definitively been found to slow the rate of expansion of abdominal aortic aneurysms [77–82]. One study found the use of ACE inhibitors to be associated with increased rate of growth of AAA [78]. Another study examined the effect of propranolol on the growth rate of AAA, and found it to have no impact (growth of 0.26 cm/year with pla-

cebo versus 0.22 cm/year with propranolol, $p = 0.11$). Further, the patients taking propranolol had worse quality of life scores and had no improvement in mortality [77].

As AAA is a cardiovascular disease risk equivalent, it is recommended that these patients be placed on aspirin. Additionally, while statins have not been found to slow the rate of AAA expansion, statin therapy has been associated with improved survival following surgical or endovascular repair of AAA [83].

Surgical and Endovascular Aneurysm Repair

When indicated, abdominal aortic aneurysm repair is the gold standard of treatment. This can be accomplished either via open surgical repair or EVAR. In open surgical repair, a midline abdominal incision or a retroperitoneal incision is made. Once isolated, the abdominal aortic aneurysm is replaced with a prosthetic graft or tube [83]. In EVAR, an endograft is inserted via the femoral or iliac arteries, thereby excluding any blood flow in the aneurysm sac (Figs. 14.7 and 14.8) [84, 85].

There have been several major trials that have compared EVAR and open surgical repair. In the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, 351 patients were randomized to either open surgical repair or EVAR. While there was no significant difference in the primary endpoint (a composite of operative mortality and moderate or severe complications), there was a nonsignificant reduction in mortality at 30 days with EVAR [86]. At 2 years of follow-up, however, this reduction in mortality was no longer evident (cumulative survival rate of 89.6% versus 89.7% in open versus EVAR, respectively). Further, while aneurysm-related death was significantly lower in the EVAR group, this was entirely accounted for by differences in perioperative mortality [87]. In subsequent follow-up at 6 years, there was still no difference in survival between the two groups; however, more patients initially randomized to the EVAR group had required secondary interventions (freedom from intervention was 81.9% for open repair versus 70.4% for endovascular repair). Additionally, a larger proportion of secondary interventions performed in the EVAR group were due to graft-related indications, while the majority of secondary interventions in the open repair group were hernia repairs [88].

The UK Endovascular Aneurysm Repair trial 1 (EVAR trial 1) found similar results [89, 90]. In this trial, 1082 patients were randomly assigned to either EVAR or open repair. Thirty-day mortality was significantly lower in the EVAR group when compared to the open repair group (1.7% versus 4.7% respectively, odds ratio of 0.35, $p = 0.009$) [90]. At 4 years of follow-up, all-cause mortality was not significantly different between the two groups. There was, however, a persistent reduction in aneurysm-related mortality in the EVAR group that was attributable to the observed reduction in perioperative mortality [89]. Recently, the EVAR trial 1 investigators reported that at a mean of 12.7 years of follow-up, there was no difference in overall mortality or aneurysm-related mortality. Of note, there was an increase in late mortality from aneurysm-related deaths in the EVAR group [91].

The Open Versus Endovascular Repair (OVER) study trial also assessed whether endovascular repair may have benefit over open repair. At an interim assessment at 2 years, there was no significant difference in mortality between the groups [92]. Once again, perioperative mortality was lower in the endovascular group than the open surgical repair group. Notably, mortality rates overall were much lower in this more recent trial, with 30-day mortality following EVAR of 0.5% (compared with 2.1% in EVAR-1 and 1.2% in DREAM trial) and 3.0% following open surgical repair (compared with 6.2% in EVAR-1 and 4.6% in DREAM trial). At the conclusion of the 9-year follow-up period, there was no difference in survival between the two groups. Interestingly, younger patients seemed to derive more benefit from EVAR compared with older patients [93].

Timing of Intervention

Given the catastrophic consequences of rupture of an abdominal aortic aneurysm, the mainstay of therapy is either surgical or endovascular repair prior to rupture. However, both of these surgeries carry significant perioperative risks, including death. Therefore, it is appropriate to intervene on an AAA only when it carries a significant risk of rupture. A great deal of research has been conducted to delineate the optimum time for intervention.

In the UK Small Aneurysm Trial, 1090 patients with an AAA of 4.0–5.5 cm were randomized to either ultrasound surveillance or early elective surgery. Those that were randomized to ultrasound surveillance underwent surgery if the AAA grew to greater than 5.5 cm, grew more than 1 cm in a year, became tender, or repair of an iliac or thoracic aneurysm was needed. At the end of 6 years of follow-up, about one third of patients in each group had died. Further, the rate of death in the first 6 months following randomization was 2.5 times higher for the early surgery group due to perioperative mortality [94]. A similar trial performed in the United States randomized 1136 patients to early surgery or ultrasound surveillance. Once again, no difference in outcomes with early surgery or routine ultrasound surveillance was observed at a mean of 4.9 years of follow-up [54].

Data also suggests that there is no benefit to EVAR for aneurysms less than 5.5 cm in diameter. The CAESAR trial randomized 360 patients with AAA sized 4.1–5.4 cm to early

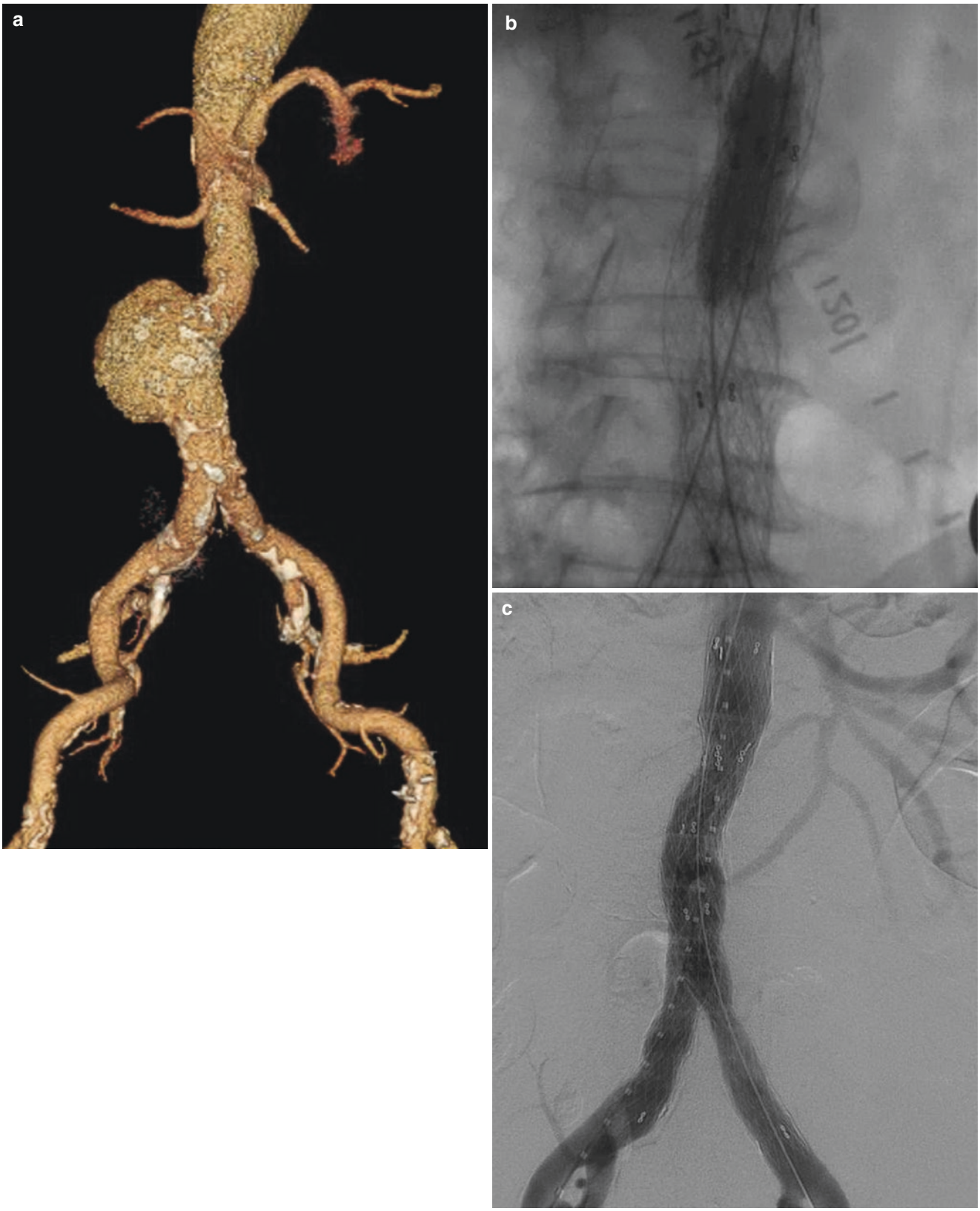

Fig. 14.7 (**a**) CT angiography demonstrating an infrarenal abdominal aortic aneurysm measuring up to 5.9 cm in diameter. (**b**) and (**c**) This patient underwent EVAR with excellent results

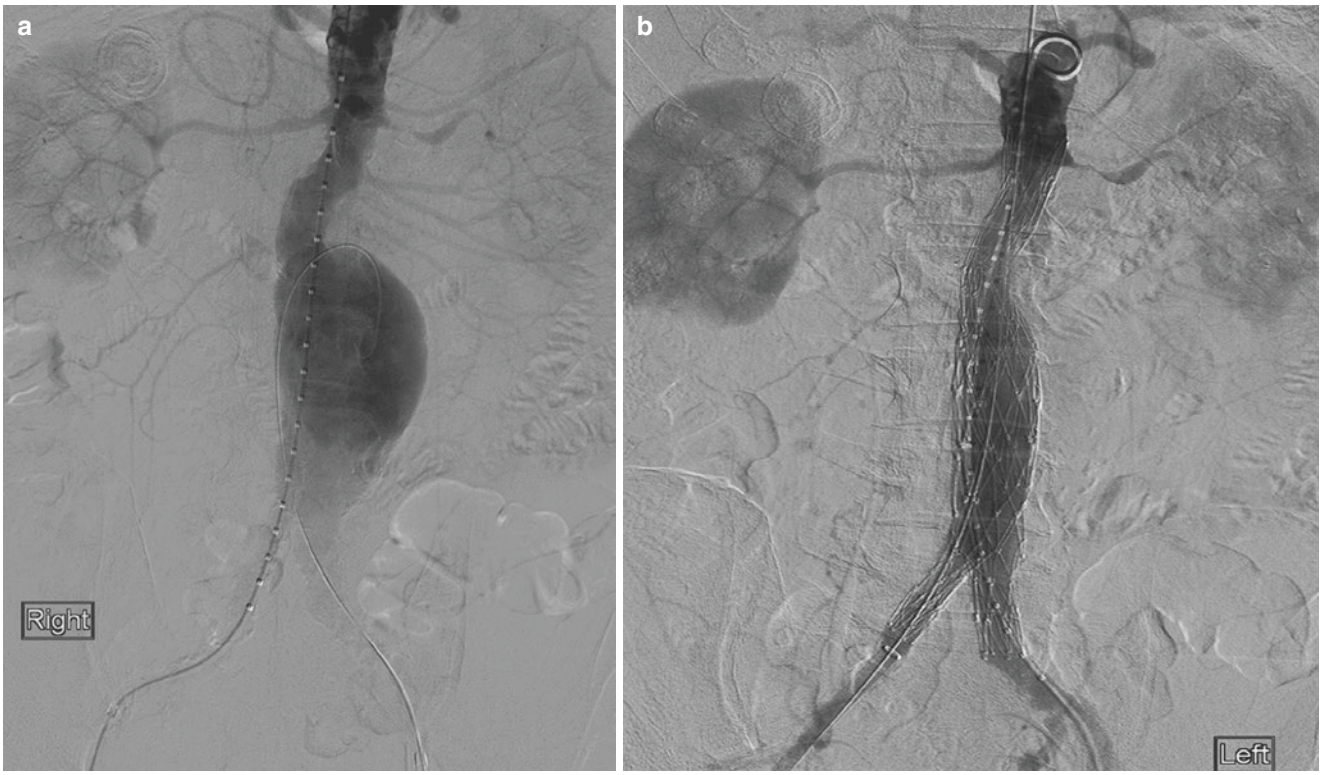

Fig. 14.8 (**a**) Aortogram showing a large infrarenal abdominal aortic aneurysm. (**b**) Completion aortogram demonstrating aneurysm sac exclusion. (From Annambhotla [84]. Reprinted with permission from Springer)

EVAR or ultrasound surveillance. At 54 months of follow-up, there was no difference in all-cause mortality [59]. The PIVOTAL trial, which randomized 728 patients with AAA sized 4.0–5.0 cm to early EVAR or ultrasound surveillance, also found no difference in overall mortality after a mean follow-up period of 20 months [60].

Current Guidelines

The European Society for Vascular Surgery recommends ultrasound surveillance for small abdominal aortic aneurysms (4.0–5.5 cm) and referral to a vascular surgeon when the AAA grows to greater than 5.5 cm in men (greater than 5.0 cm in women), the rate of growth is greater than 1 cm in a year, or the patient develops symptoms [95]. These recommendations are the same for open surgical repair and EVAR. Likewise, the American College of Cardiology and American Heart Association (AHA) guidelines recommend repair of infrarenal or juxtarenal AAAs measuring 5.5 cm or larger and imaging surveillance every 6–12 months for those AAAs measuring 4.0–5.4 cm [96].

In spite of the current guidelines, significant variability in the timing of surgical or endovascular intervention remains. A recent study compared practice patterns and outcomes for AAAs in the United States and England. The study found that aneurysm repair was less common in England than the United States; however, aneurysm-related death was more common in England (odds ratio of 3.6, $p < 0.001$). Further, the mean aneurysm diameter at the time of repair was larger in England than in the United States (6.37 cm vs. 5.83 cm, respectively, $p < 0.001$) [97].

Special Considerations

Juxtarenal, Suprarenal, and Thoracoabdominal Aneurysms

While the use of EVAR is well established for the treatment of infrarenal abdominal aortic aneurysms, until recently it was not used for treatment of juxtarenal or suprarenal AAAs. Technical advances have allowed an expansion of EVAR into these territories which were previously exclusive to surgical repair. A retrospective analysis of endovascular aneurysm repair of juxtarenal, suprarenal, and thoracoabdominal aneurysms with a fenestrated aortic endograft found it to be safe and effective for patients deemed too high risk for surgical repair [98]. Alternatively, chimney grafts have been found to be a suitable alternative intervention in those patients who are not eligible for fenestrated endografts [99].

Mycotic Aneurysms

Treatment of mycotic aneurysms is multidimensional and includes antibiotic therapy directed at common organisms, as well as surgical or endovascular intervention. The most common pathogens include *Salmonella* and *Staphylococcus* [100]. As such, treatment with beta-lactam antibiotics is indicated. Due to the increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin is frequently part of the antibiotic regimen [101]. According to recent AHA guidelines, antimicrobial therapy should be continued for 6 weeks to 6 months (Class IIb, level of evidence B), and in some cases, lifelong suppressive therapy may be considered [28].

Surgery is the cornerstone of treatment for mycotic abdominal aortic aneurysms. Options for intervention include resection of the aneurysm with extra-anatomic revascularization or in situ reconstruction. The AHA recommends resection and in situ revascularization in most cases (Class IIa; level of evidence B), with extra-anatomic revascularization reserved for patients with gross pus in the operative field, retroperitoneal or psoas abscess, vertebral osteomyelitis, ongoing signs of fever in spite of preoperative antibiotics, and certain patients with aortoenteric fistula (Class IIb, level of evidence C) [28]. While EVAR has been used for treatment in patient with prohibitive surgical risk, mortality is worse than with open repair and is therefore reserved for those with prohibitive surgical risk [102].

Inflammatory Aneurysms

Inflammatory aneurysms can be treated with either EVAR or open surgical repair, though EVAR is currently favored as surgical repair of inflammatory aneurysms, it is technically difficult and associated with worse outcomes [103]. One recent meta-analysis that included 999 patients than underwent open surgical repair and 121 patients that underwent EVAR for management of an inflammatory AAA found a reduction in mortality at 1 year with EVAR (2% versus 14%, $p = 0.002$) [104]. If open surgical repair is pursued, a retroperitoneal approach is preferred as the most inflamed section of the aneurysm is typically the anterior most aspect [57].

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Abdominal Aortic Occlusive Disease

15

Sungho Lim and Paul R. Crisostomo

Introduction

Atherosclerosis of the abdominal aorta or iliac arteries is one of the most common causes of lower extremity ischemia. The first implication of the disease was uncovered in the late eighteenth century by British anatomist John Hunter. However, two more centuries passed before Rene Leriche described a patient with claudication and erectile dysfunction in 1948, ultimately linking clinical symptoms with pathophysiology and anatomy [1].

Surgical revascularization of aortoiliac artery was first described by Wylie et al. in San Francisco in 1952 [2]. Since then, tremendous advances have occurred in synthetic graft conduits, tissue engineering, and, most recently, percutaneous endovascular devices which allow a wide range of treatment options based on patient morbidity and anatomic defect. This chapter will review clinical characteristics of abdominal aortic occlusive disease and contemporary management.

Epidemiology

The majority of patients with aortic occlusive disease present with diffuse disease involving multi-level peripheral vasculature including femoropopliteal or infrapopliteal vessels. This subset of patients with diffuse multi-level disease are typically older, more likely male, with a higher prevalence of diabetes and hypertension and with concomitant coronary artery disease, cerebrovascular disease, and visceral atherosclerosis [3, 4]. Such patients with multi-vessel disease often present with ischemic pain, tissue loss, or gangrene. Not surprisingly, their life expectancy is lower than their age-matched counterpart [5]. In contrast, patients with isolated aortoiliac disease are generally younger and more likely female with a high prevalence of smoking or dyslipidemia [6].

"Hypoplastic aortic syndrome" or "small aorta syndrome" is a particularly virulent form of aortic atherosclerosis often found in young, small stature women who smoke [6]. This disease particularly involves the infrarenal aorta proximal to the aortic bifurcation. Radiographic findings are typically atretic or narrowed vasculature with diffuse calcific atherosclerosis. Due to the diminutive size of the aorta and iliac vessels, durability of either endovascular intervention or local endarterectomy is generally inferior, particularly in the presence of continued cigarette use.

Pathophysiology

Aortoiliac atherosclerosis typically starts at the iliac bifurcation and extends proximally and distally. Degree of the progression may vary but ultimately could occlude aortic blood flow over time. Starrett et al. demonstrated one-third of patients experienced proximal disease progression up to the level of renal artery in the period of 6–10 years [7]. In the same study, they also demonstrated a 30–40% chance of profunda femoris or superficial femoral artery distal involvement [7].

Due to the relatively slow progression of atherosclerosis, collateral circulation often develops. The primary compensatory vessels to the lower extremity include the internal thoracic artery (mammary) to the inferior epigastric artery and the intercostal and lumbar artery to the deep circumflex artery. Additional colonic collaterals arise from the SMA to the IMA via the marginal artery of Drummond and the arc of Riolan. Pelvic collaterals from the IMA to the hypogastric include the superior rectal to the middle rectal, the iliolumbar to the lumbar, and the lateral sacral to the median sacral artery. It is important to recognize these compensatory pathways and to preserve them during reconstruction.

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Clinical Presentation

Chronic atherosclerosis of the aortoiliac segment often accompanies infrainguinal arterial disease. Thus, this disease most frequently manifests as lower extremity arterial insufficiency. Symptoms vary widely depending on location of concomitant disease and degree of collateralization.

Patients with multi-level disease can present with typical lower extremity arterial insufficiency symptoms such as leg claudication, tissue loss, or gangrene. In contrast, patients with isolated aortoiliac segment disease may present with pelvic or buttock claudication. In male aortoiliac disease patients, up to 30% experience difficulty achieving and maintaining an erection owing to decreased perfusion of the internal pudendal artery. The constellation of symptoms associated with distal aortic occlusion, including pelvic claudication, atrophy of the leg muscles, impotence, and decreased femoral pulses, is known as Leriche's syndrome [1].

Diagnosis

Patient History

Conducting a complete history and identifying cardiovascular risk factors are important in the diagnosis. Atherosclerosis is a pathologic process related with aging (Fig. 15.1). Hypertension, diabetes, dyslipidemia, chronic kidney disease, and cigarette smoking are classic risk factors that must be identified and addressed. It is critical to control these modifiable factors to slow the progression of the atherosclerosis.

Male gender and non-Hispanic black race are known unmodifiable risk factors for atherosclerosis. In patients who lack these classic risk factors, hyperhomocysteinemia, hypercoagulability, and hyperfibrinogenemia should be investigated.

Risk Factors for Atherosclerosis [8]

- Advanced age.
- Race (non-Hispanic blacks).
- Male gender.
- Hyperfibrinogenemia.
- Diabetes mellitus.
- Hyperhomocysteinemia.
- Smoking.
- Hypercoagulability.
- Hypertension.
- Elevated C-reactive protein.
- Dyslipidemia.
- Chronic renal insufficiency.

Physical Examination

Physical examination begins with inspection. Aortoiliac disease may cause ischemic changes of the pelvis/buttocks and/or the lower extremities. Visual signs of ischemia include pallor, muscular atrophy, and cyanosis or skin mottling.

Palpation and comparison of femoral pulses is the quickest and the most important way to diagnose aortoiliac occlusive disease. Grading a pulse is subjective, simply described as (1) normal, diminished, or absent and (2) symmetric versus asymmetric. If a pulse is not palpable, further assessment using Doppler should be pursued. The Doppler signal can be described as triphasic, biphasic, or monophasic. Palpation of the lower extremity is also helpful to assess the level of skin temperature and neurologic (motor and sensory) status.

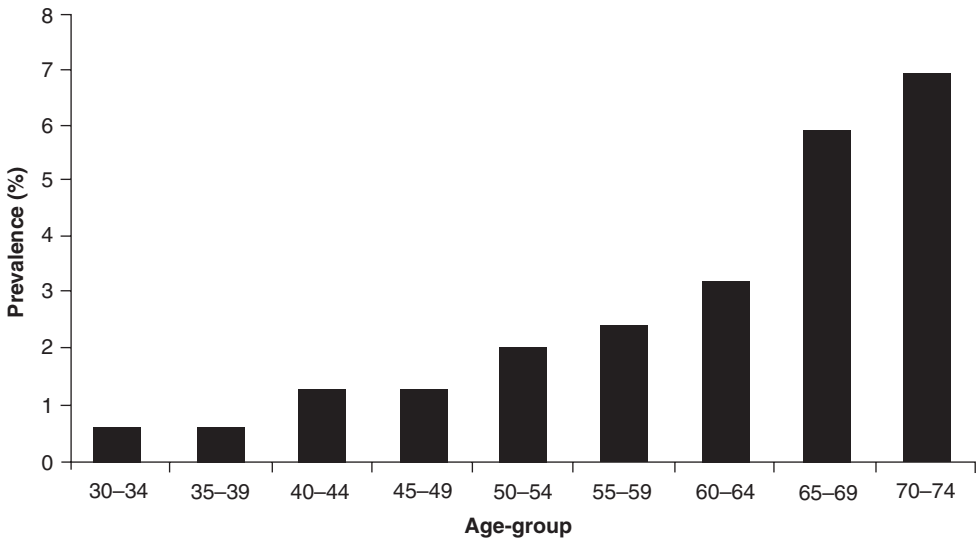


Fig. 15.1 Prevalence of symptomatic peripheral arterial disease. (From Norgren et al. [8]. Reprinted with permission from Elsevier)

Auscultation of the abdomen commonly reveals bruits when significant stenosis of the aorta or its branch is present. Middle to lower abdominal bruits may present with aortoiliac occlusive disease, whereas epigastric or paramedian bruits can indicate visceral vessel stenosis or renal artery stenosis, respectively.

Patients with aortoiliac occlusive disease and robust collateral formation may have a deceiving lack of distinct physical examination findings. In that case, an exercise trial may augment changes in pulses or bruit. Lumbar disc herniation, spinal stenosis, or arthritis of the hip or knee joint should be included in the differential diagnosis. Discomfort related with certain positions, or prolonged standing in elderly often arises from neurogenic or musculoskeletal origins.

Vascular Laboratory

Non-invasive hemodynamic vascular laboratory testing begins with ankle-brachial index (ABI). Segmental systolic blood pressure measurement and pulse volume recording (PVR) may aid in locating the area of concern. A difference of systolic blood pressure between the upper arm and proximal thigh more than 20 mmHg reflects significant stenosis in the aortoiliac or proximal femoral arteries. Further reduction of blood pressure in the distal segments or decreased PVR or ABI indicates concomitant outflow disease. The combination of a thorough history and physical examination with vascular laboratory testing often provides sufficient clinical data to decide upon the necessity of revascularization.

Duplex ultrasound (DUS) is the most commonly used diagnostic imaging study for delineating extremity vascular abnormalities. However, evaluation of aortoiliac, renal, and visceral arteries is somewhat limited mainly due to overlying bowel gas. Patient factors such as obesity or tortuosity of the vessel also complicate visualization and make it difficult to determine the precise anatomic location of the disease and its severity.

Axial Imaging

Computed tomographic angiography (CTA) is the gold standard imaging modality for aortoiliac disease in our institution. CTA is a non-invasive alternative to standard angiography and can be obtained quickly [9]. With recent advances in multi-detector CT scan, high-quality images with sub-millimeter spatial resolution are now available. Disadvantages of CT scan include radiation exposure, risk of contrast-induced nephropathy, and hypersensitivity to iodine contrast.

In some institutions, magnetic resonance angiography (MRA) has become the imaging study of choice. MRA is an excellent diagnostic study for aortoiliac occlusive disease with sensitivity and specificity near 95% [10]. MRA can even be obtained without contrast, utilizing time of flight. MRA can be a reliable guide for percutaneous or open intervention of the aortoiliac disease. However, MRA has a tendency to overestimate the degree of stenosis and has limited evaluation of the severity of calcific disease. In addition, MRI cannot be utilized for patients with certain metallic implants such as cardiac pacemaker or defibrillator.

Arteriography

Despite recent technical advances in CT or MRI with increased speed and accuracy, diagnostic catheter-based arteriography remains a valuable tool in a physician's armamentarium. Femoral approach is the preferred way in our institution; however, brachial approach may be necessary in long-segment, near-occlusive, or occlusive aortic or bi-iliac disease. Real-time angiographic imaging utilizing lateral or oblique views may delineate the contribution of accessory renal vessels (Can they be sacrificed?), IMA vs SMA perfusion (IMA reimplantation?), and lumbar vessels for spinal perfusion (risk of paralysis?) and/or clarify whether radiographic stenosis are truly hemodynamically significant. For example, the presence of superior mesenteric artery occlusion, hypogastric occlusion, or prominent inferior mesenteric artery may require preservation of the inferior mesenteric artery during aortic reconstruction to avoid bowel ischemia.

Treatment Modalities

Conservative Management

Smoking

Smoking cessation is without question desirable in aortic occlusive disease to slow down the progression of atherosclerosis. Smoking cessation is associated with reduced risks of amputation, myocardial infarction, and mortality in this patient population [11, 12].

Dyslipidemia

Use of statin has demonstrated a significant reduction of adverse cardiovascular event in patient with atherosclerosis [13–15]. Low-density lipoprotein cholesterol should be controlled under 100 mg/dL or to 70 mg/dL in very high-risk patients [16].

Diabetes

It is unclear whether aggressive diabetic control decreases adverse cardiovascular events. However, atherosclerosis tends to be more complicated, and amputation rate is higher

in diabetic patient. This may be related to susceptibility to infection in this population and higher prevalence of distal sensory neuropathy from poor diabetic control.

Hypertension

Hypertension is recognized as a risk factor of atherosclerosis; however, relative risk for atherosclerosis is less for hypertension than dyslipidemia or smoking. Treatment for hypertension is associated with low cardiovascular complications, stroke, or death [17].

Antiplatelet Therapy

The American Heart Association and the Society for Vascular Surgery recommend the use of an antiplatelet agent in peripheral arterial occlusive disease [16, 18]. The same can be applied to aortoiliac atherosclerotic disease. Dual antiplatelet therapy can be applied at the physician's discretion, but there is a lack of evidence to date that combination therapy is more effective than a single-agent therapy [19].

Supervised Exercise Therapy

Exercise therapy may improve intermittent claudication. A meta-analysis of 1200 patients demonstrated overall improvement of walking distance without improvement of ankle-brachial index [20]. The precise mechanism of action is still unknown, but it is thought to be related with nitric oxide-related vasodilation and improved bioenergetics of skeletal muscle. However, severe cardiopulmonary disease or arthritis may preclude adequate exercise participation.

Medical Therapy

Medical therapy aims for symptomatic relief of claudication. There are two Food and Drug Administration (FDA)-approved medications – pentoxifylline and cilostazol – whereas the Royal College of Physicians in the UK identified naftidrofuryl as the drug of choice over those two drugs. Naftidrofuryl is widely available in the European countries but has not been FDA approved in the USA.

Pharmacodynamics of pentoxifylline includes reducing blood viscosity and enhancing peripheral perfusion and tissue oxygenation. Multicenter prospective randomized trial proved its efficacy over placebo [21]. Pentoxifylline can be begun at 400 mg three times daily with maximum dose of 1800 mg/day. Side effects of this medication include hypertension, nausea, vomiting, and headache.

Cilostazol is a phosphodiesterase inhibitor that induces vasodilation and suppresses platelet aggregation. In addition to routine antiplatelet therapy, cilostazol (100 mg twice daily) can contribute to increased overall pain-free ambulatory distance in as short as 4 weeks [22]. However, this agent can exacerbate congestive heart failure and is contraindicated in a patient with any level of heart failure.

A multicenter, randomized, double-blind, parallel-group study compared cilostazol and pentoxifylline and found that while cilostazol significantly improved walking distance, pentoxifylline was not significantly different than placebo [23].

Decision-Making to Intervention

The natural history of atherosclerosis in aortoiliac disease is a slow arterial process that impairs walking ability. With maximum medical treatment and exercise therapy, the chance of developing severe ischemic symptoms such as rest pain or tissue loss is relatively low (<5%) [8, 24]. Thus, the majority of patients need just reassurance from their physician. However, patients with advanced ischemic symptoms or claudication that significantly impacts their daily living or occupation should be under consideration for intervention.

It is important to recognize that determining the degree of functional impairment is not straightforward. Patient perception of functional impairment may vary according to their baseline activity. For example, mild to moderate claudication in an active man may have a greater impact, while severe claudication in a sedentary patient may be less significant. Patient morbidity is another important aspect to be considered. Patients with severe arthritis or spinal degenerative disease might not benefit from invasive vascular intervention, whereas patients with severe coronary artery disease or pulmonary compromise may suffer from postoperative significant morbidity or mortality.

Open revascularization has traditionally demonstrated improved patency over endovascular intervention at the expense of higher morbidity and mortality although supporting data comparing the two strategies are still poor. The TransAtlantic Inter Society Consensus (TASC) document first in 2000, then in 2007, and most recently updated in 2015, classified anatomic patterns of disease severity from types A through D for aortoiliac, femoropopliteal, and infrapopliteal segments [25] (Fig. 15.2). Initially, the TASC working group advocated endovascular intervention for TASC type A lesions and open surgical treatment for TASC type D lesions. However, the latest TASC II update in 2015 recognized that with modern advances in endovascular instruments and practitioner skill, an endovascular first approach has become the predominant modality when revascularization is decided. Moreover, hybrid open and endovascular procedures may be suitable for complex anatomy.

Endovascular Intervention

Arterial Access

Lesions at the aortic bifurcation or common iliac arteries can be treated with the usual retrograde approach from the common femoral arteries. Occlusions that cannot be crossed

Type A lesions

- Unilateral or bilateral stenoses of CIA
- Unilateral or bilateral single short (≤3 cm) stenosis of EIA

Type B lesions:

- Short (≤3cm) stenosis of infrarenal aorta
- Unilateral CIA occlusion
- Single or multiple stenosis totaling 3-10 cm involving the EIA not extending into the CFA
- Unilateral EIA occlusion not involving the origins of internal iliac or CFA

Type C lesions

- Bilateral CIA occlusions
- Bilateral EIA stenoses 3–10 cm long not extending into the CFA
- Unilateral EIA stenosis extending into the CFA
- Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA
- Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA

Type D lesions

- Infra-renal aortoiliac occlusion
- Diffuse disease involving the aorta and both iliac arteries requiring treatment
- Diffuse multiple stenoses involving the unilateral CIA, EIA, and CFA
- Unilateral occlusions of both CIA and EIA
- Bilateral occlusions of EIA
- Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery

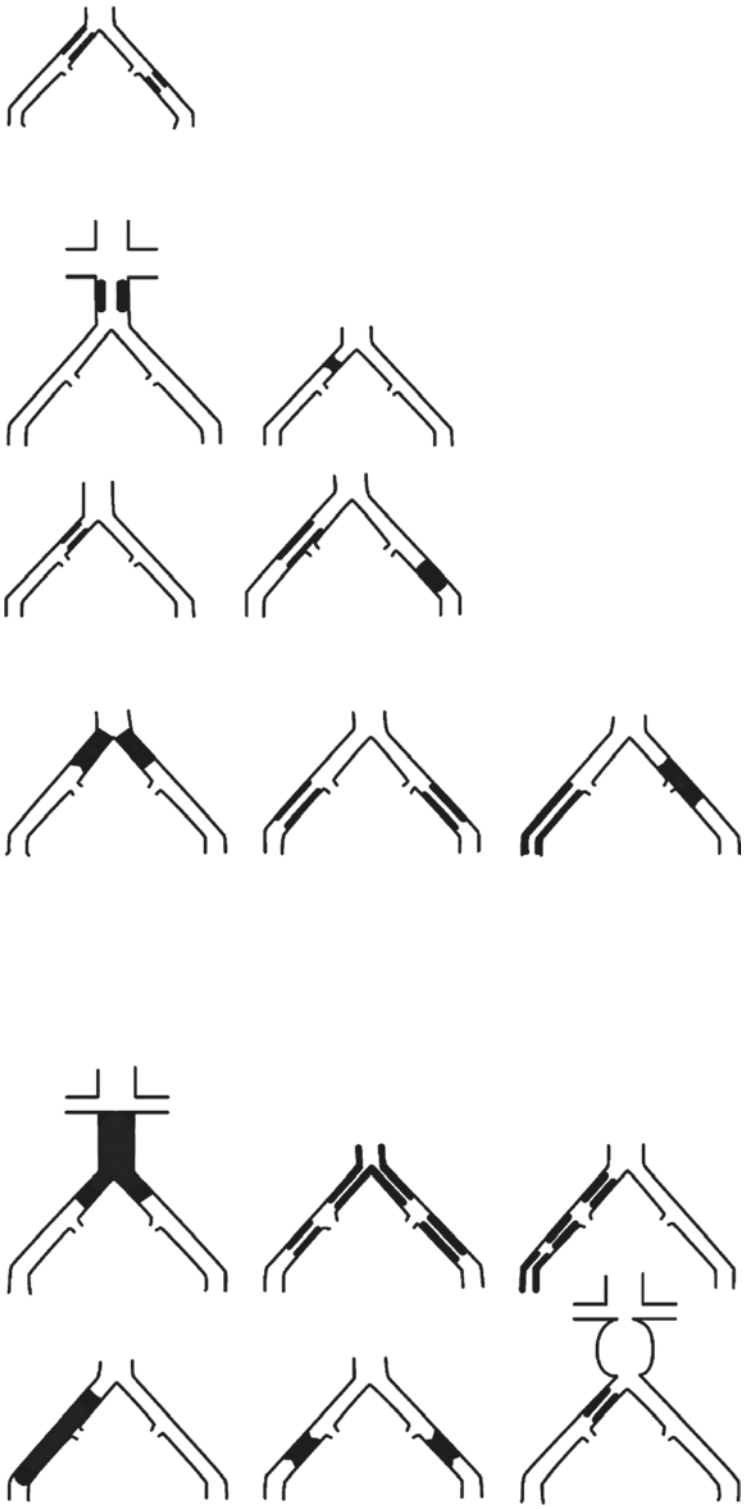


Fig. 15.2 TransAtlantic Inter-Societal Classification of aortoiliac lesions. (From Norgren et al. [8]. Reprinted with permission from Elsevier)

from the ipsilateral femoral retrograde approach may require contralateral femoral artery or brachial artery access and subsequent antegrade approach. A left brachial artery approach may also decrease the risk of an aortic dissection, but this patient population not infrequently exhibits concomitant left subclavian artery stenosis that may require pretreatment prior to aortoiliac intervention.

After access is obtained, a diagnostic angiographic evaluation should be performed prior to intervention. Aortogram and pelvic images are essential to evaluate extent of the dis-

ease. A contralateral oblique view opens the iliac bifurcation, whereas an ipsilateral oblique view helps to clarify the femoral bifurcation. Infrainguinal runoffs also should be evaluated prior to intervention in case of distal embolization during the course of intervention.

Crossing the Lesion

An angled GLIDEWIRE (Terumo Medical Corp, Somerset, NJ) and angled support catheter are the prototypical methods for crossing an iliac stenosis. Chronic total occlusions (CTO) often require a variety of wires, catheters, and sheath support. The most difficult part of the occlusion is the proximal cap. After the wire is fully crossed over, true lumen location should be confirmed with contrast injection. Blood draw as confirmation may be false. A variety of CTO devices exist, some of which allow re-entry from a subintimal plane to the true lumen (Fig. 15.3).

Aortic Bifurcation Disease

Lesions at the aortic bifurcation traditionally are treated with kissing iliac balloon and stent placement. Even in scenarios with unilateral disease, if the lesion is close to the aortic bifurcation, simultaneous bilateral intervention has been advocated to prevent contralateral iliac dissection or thrombus dislodgement and subsequent embolism. Contralateral prophylactic treatment has also been recommended in order to treat spill over plaque originating from the aorta [26, 27]. However, a retrospective of 175 patients with unilateral iliac artery lesions treated with unilateral method revealed about 1% risk of contralateral extremity complications [28].

Selection of Balloon and Stent

Plain old balloon angioplasty (POBA) is inferior in patency to balloon angioplasty and stent within the aortoiliac system [29–31]. The optimal vessel diameter is often derived from the normal equivalent segment on the contralateral side. A calibration imaging system can also be useful to facilitate measuring size and length of the lesion. Balloons and stents should be large enough to cover the diseased segment completely but small enough not to injure normal vessels and aortic branches. Five to ten percent oversize of the balloon and stent is recommended except for a heavily calcified lesion that may rupture with larger devices.

A variety of stents are commercially available which fall into two main deployment categories: balloon-expandable and self-expanding. Selection of a stent often depends on device availability and the operator's familiarity. However, it is noteworthy that a balloon-expandable stent is advantageous when precise stent placement is necessary. Such is the case in bilateral common iliac lesions which need kissing stents to be deployed precisely at the same level to allow equal opposition. In contrast, when the stent must follow a tortuous path or is to be placed from the contralateral side, a self-expanding stent provides greater flexibility. The external iliac artery often benefits from self-expanding stent placement.

A covered stent graft is a metal stent covered with Dacron or polytetrafluorethylene (PTFE) which initially was developed for exclusion of an aneurysmal segment or treatment of an iatrogenic perforation or rupture. Covered stents exclude the diseased segments from the circulation and, theoretically, may reduce in-stent restenosis. Although limited studies

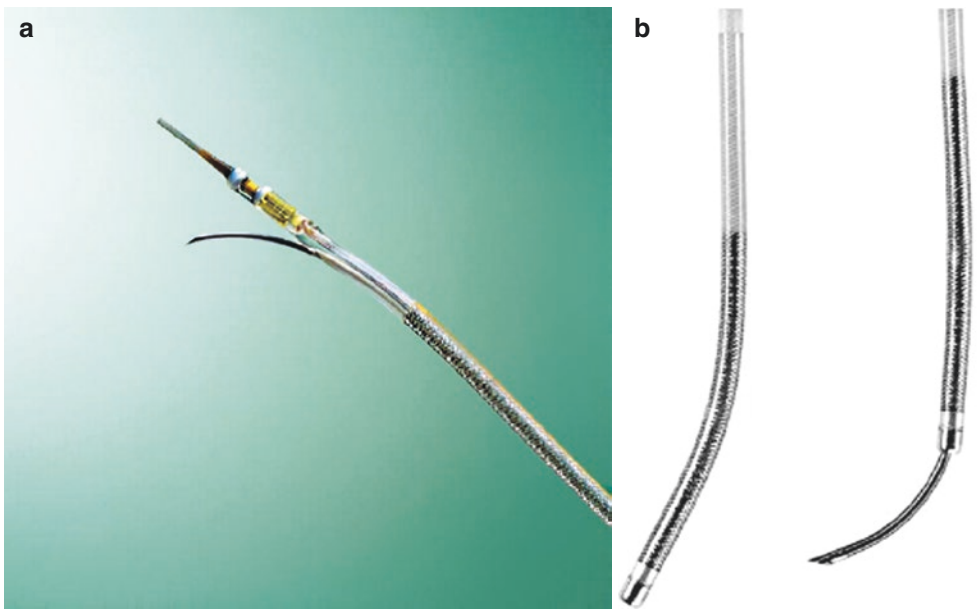


Fig. 15.3 Reentry catheters. (**a**) Pioneer catheter with needle deployed. (**b**) Outback LTD catheter. (Right: with needle retracted. Left: with needle deployed). (From Jacobs et al. [42]. Reprinted with permission from Elsevier)

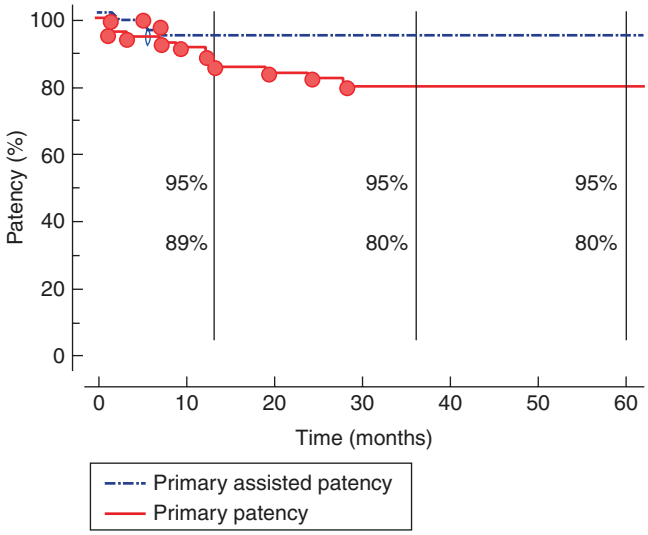


Fig. 15.4 Comparison of primary patency between stents and stent grafts. (From Chang et al. [32]. Reprinted with permission from Elsevier)

have been conducted in patients with aortoiliac atherosclerotic disease, primary and primary-assisted patency rate at 5 years are 80% and 95% which are superior to bare-metal stents [32] (Fig. 15.4).

Drug-eluting stents (DES) were initially developed for the treatment of coronary artery disease. A drug such as paclitaxel or sirolimus delivered via stent inhibits restenosis and improves long-term patency. DES and drug-coated balloons (DCB) have similarly been FDA approved for the treatment of femoropopliteal artery disease [33–35]. These newer-generation balloons and stents have been recommended over their nondrug coated counterparts but may require extended dual antiplatelet therapy [36]. Although these newer drug-coated devices have been used off label in the external iliac artery, data for the aortoiliac segment is lacking.

Concomitant Femoral Artery Disease

With coexisting severe common femoral artery disease, the artery can be accessed utilizing a hybrid femoral open cut down allowing arterial puncture under direct visualization. At the end of the intervention, proximal and distal control is obtained and the femoral artery can be endarterectomized using a longitudinal arteriotomy and closed with a patch angioplasty. This will improve inflow perfusion to the ipsilateral leg and better maintain graft patency [32].

Postoperative Care

Aspirin therapy should be initiated and continued indefinitely. Dual antiplatelet is recommended for at least 30 days. Clinical surveillance with physical exam, ABI, and duplex ultrasonography should be performed immediate postop (30 days) and every 6 months at least 1 year and annually thereafter.

Results of Endovascular Revascularization

The technical success rate of endovascular interventions in the aortoiliac segment is very high in many reports. However, maintaining long-term patency requires dedicated surveillance and may need multiple secondary interventions. Although a variety of factors can affect the outcome, the TASC classification well represents outcomes referencing disease location and severity [37]. Endovascular long-term outcomes are better in TASC A and B lesions compared to TASC C or D lesions. Cumulative primary patency of all lesions was 83% at 5 years (Fig. 15.5). Although many TASC D lesions can be treated successfully with an endovascular approach, open surgical revascularization especially in patients suitable for the procedure should be discussed.

Open Surgical Revascularization

In general, open surgical repair carries a higher perioperative morbidity and mortality compared to minimally invasive endovascular revascularization. Thus, cardiopulmonary comorbidities and renal function have to be assessed and optimized prior to operation. Coagulation profile should be checked routinely. Preoperative coronary evaluation may be necessary and is an important modifiable risk factor in patients undergoing open vascular procedures. Preoperative nuclear cardiac stress test has been used in our institution frequently given most of aortic occlusive patients cannot complete an exercise stress test and are at high risk for postoperative myocardial infarction. Full assessment of the peripheral vasculature is indicated because the condition of the distal runoffs influence the outcome of the aortoiliac intervention. Sometimes, concurrent distal bypass may be indicated.

Intraoperatively, appropriate antibiotic prophylaxis should be administered before the incision and through the perioperative period. Invasive arterial blood pressure monitoring is routine in many hospitals.

Direct Surgical Revascularization (Aorto-Bifemoral Bypass)

Initial Approach and Groin Dissection

The patient is placed in supine position. Bilateral groin incisions are made. The choices of groin incisions are predominated by preoperative findings and patient factors. Oblique

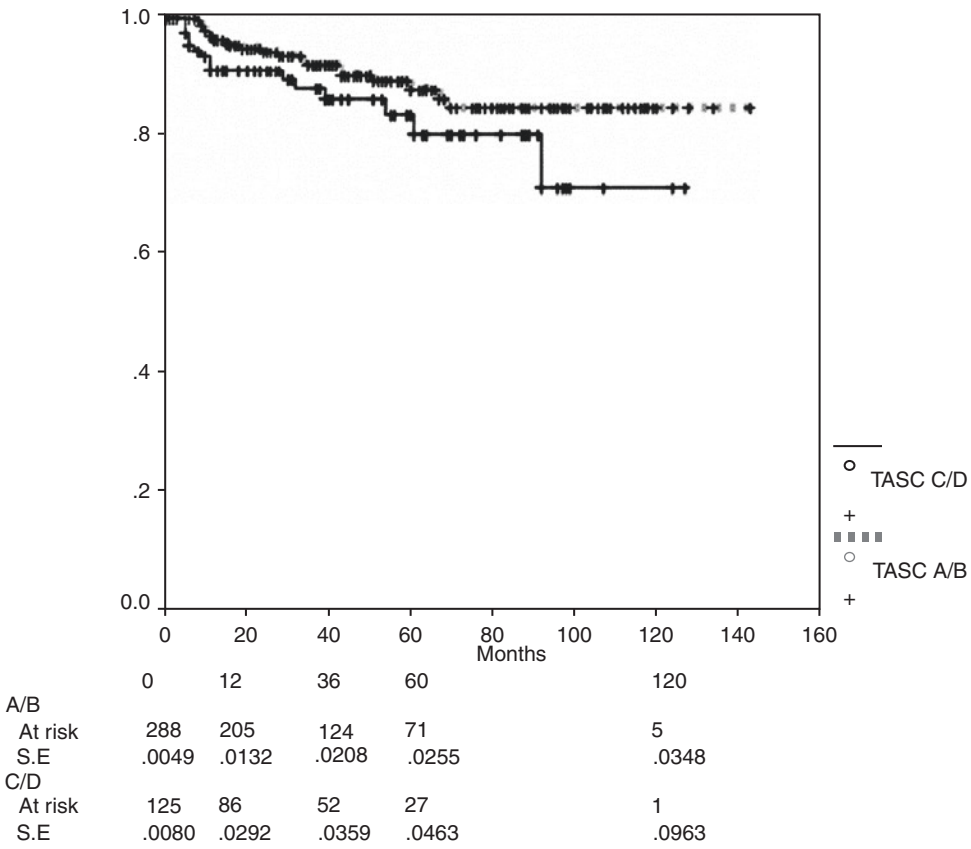


Fig. 15.5 Long-term patency of endovascular interventions. Cumulative primary patency was 83% at 5 years. (From Ichihashi et al. [37]. Reprinted with permission from Elsevier)

incisions may reduce postoperative infection and can be performed even in patients needing profunda femoral endarterectomy (Fig. 15.6). Longitudinal incision is a more traditional femoral exposure which provides technical flexibility to approach more proximal and distal femoral artery. The common, superficial, and deep (profundal) femoral arteries are dissected free and controlled with loops. The inferior border of the inguinal ligament rarely needs to be divided to create enough space for tunneling of the graft.

Abdominal Dissection

A midline abdominal incision is made from subxiphoid to a point just below the umbilicus. If the common iliac exposure is required, the incision can be extended to the suprapubic area. Multiple prior abdominal operations or history of peritonitis increases the risk of enterotomy during lysis of adhesions. In these patients, retroperitoneal or high thoracoabdominal approach may be warranted. Greater omentum and the transverse colon are retracted carefully cephalad and secured with a wet towel. An Omni wall retractor may allow for greater flexibility. Excessive traction is avoided to prevent injury to the middle colic branch of the superior mesenteric artery. The small bowel and the sigmoid colon are moved to the patient right and left, respectively. When possible, the small bowel is not eviscerated to prevent unnecessary fluid loss and bowel edema. The peritoneum between the duodenum and the inferior mesenteric vein is incised dissected along the long axis of the aorta beyond the level of the IMA. Care is taken not to injure autonomic nerve fibers on the anterolateral aspect of the aorta. The ligament of Treitz is divided, and the fourth portion of the duodenum is mobilized and dissection continued cephalad until the left renal vein is exposed (Fig. 15.7). After completion of the dissection, tunnels are made by gentle blunt dissection using fingers, simultaneously from the groin and the pelvis. The tunnel should be constructed along the iliac artery, posterior to the ureter to avoid hydroureter from mechanical obstruction from the iliac graft limb. A Penrose drain, umbilical tape, red rubber catheter, or an aortic clamp can be passed through to facilitate future passage of the graft limbs (Fig. 15.8).

After systemic heparinization, the aorta is clamped just caudal to the left renal vein and the aorta is transected. In contrast to aneurysmal aortic patients, aortic occlusive chronic disease often does not create hemodynamic changes with initial aortic cross clamp. Patent lumbar branches are ligated. The distal aortic end is oversewn with 3–0 polypropylene sutures. When possible, this is done immediately above the IMA to allow for the retrograde perfusion of the IMA after reconstruction (Fig. 15.9).

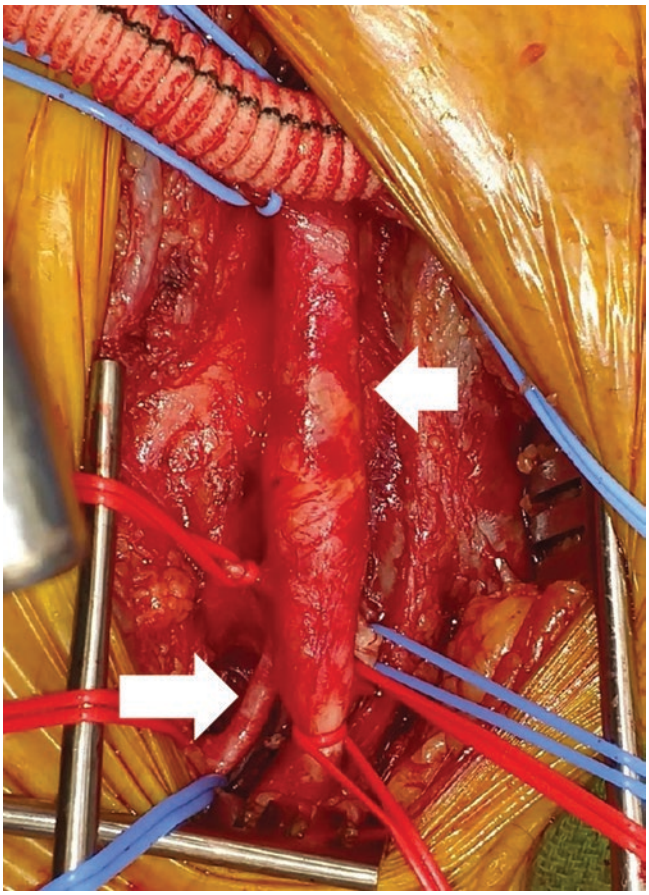


Fig. 15.6 Oblique groin incisions for femoral artery exposure (Short arrow: Common femoral artery, Long arrow: Profunda femoral artery)

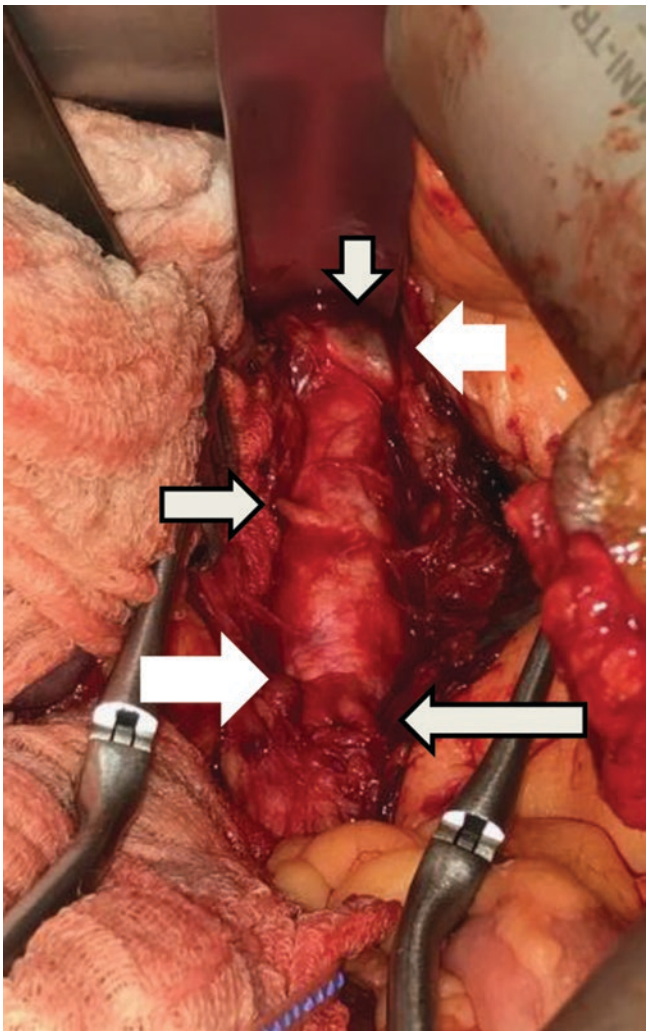


Fig. 15.7 Intraoperative exposure of the aorta (Short arrow: Renal vein, Middle arrow: Accessory right renal artery, Long arrow: Inferior mesenteric artery)

Graft Anastomosis

Most surgeons prefer Dacron grafts for ease of use and hemostasis, but PTFE conduits are also available and may have decreased aortoenteric fistula complications. The standard proximal aortic anastomosis is an end-to-end anastomosis using 3–0 running sutures from the posterior aortic wall toward the anterior wall. The end-to-side anastomosis can be applied when preservation of a large accessory renal artery or a patent inferior mesenteric artery is required (Fig. 15.10). Configuration of the standard end-to-end anastomosis poses less peri-anastomotic turbulence or anastomotic aneurysm formation. Graft-enteric fistula can be more prevalent in an end-to-side anastomosis since the graft lies more prominently toward the peritoneum, although the data is lacking.

Then, the graft limbs are passed through the previously created tunnels. Longitudinal femoral arteriotomy is made and an end-to-side anastomosis is made using 5–0 or 6–0 running vascular sutures. When possible, this arteriotomy should be elongated onto the PFA (Fig. 15.11) as the natural history of prototypical PAD is that SFA disease will develop in the not too distant future. In some instances, femoral endarterectomy is required with bovine patch angioplasty (Fig. 15.12). Upon the completion of the anastomosis, the anesthesia team has to be alerted prior to removal of vascular clamp.

Other Anatomic Revascularization

Aortoiliac Endarterectomy

Patients with limited disease in the distal aorta or proximal common iliac artery are considered for this procedure. After the dissection of the aortic wall, endarterectomy is performed using a longitudinal incision in the distal aorta and onto the common iliac arteries as needed (Fig. 15.13). Advantages of the procedure include lack of prosthetic material and exceedingly low potential for graft infection. However, this is performed very infrequently today, given the tremendous advances in endovascular angioplasty and stent procedures.

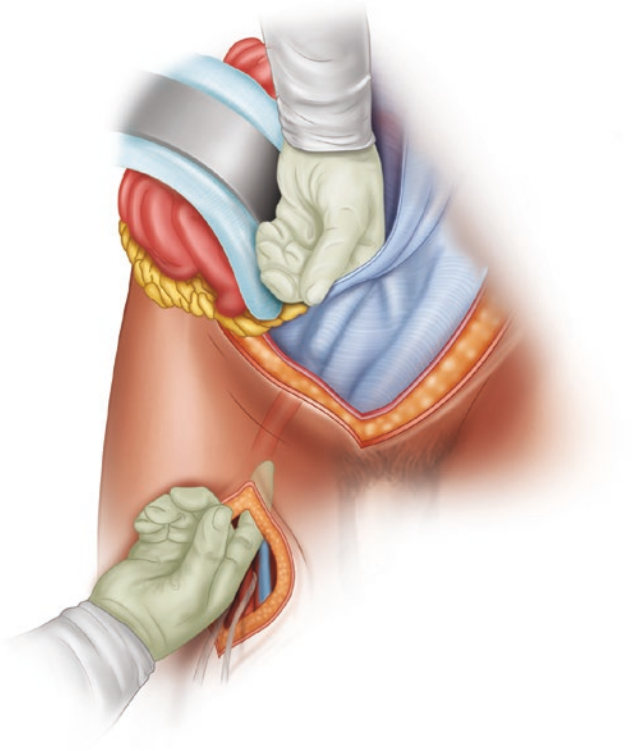


Fig. 15.8 Creation of tunnel between the aorta and the femoral artery. Tunnel should be placed underneath the ureter to avoid hydroureter

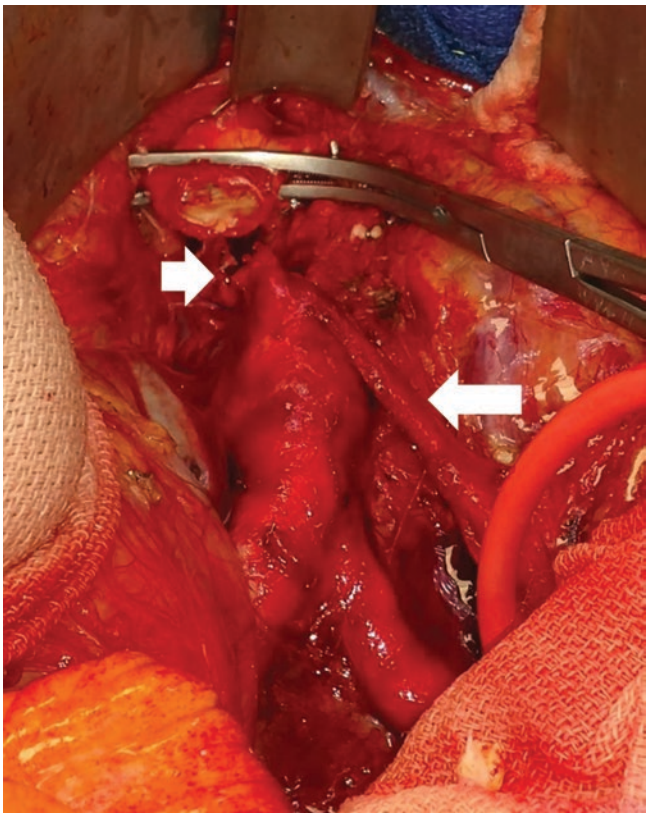
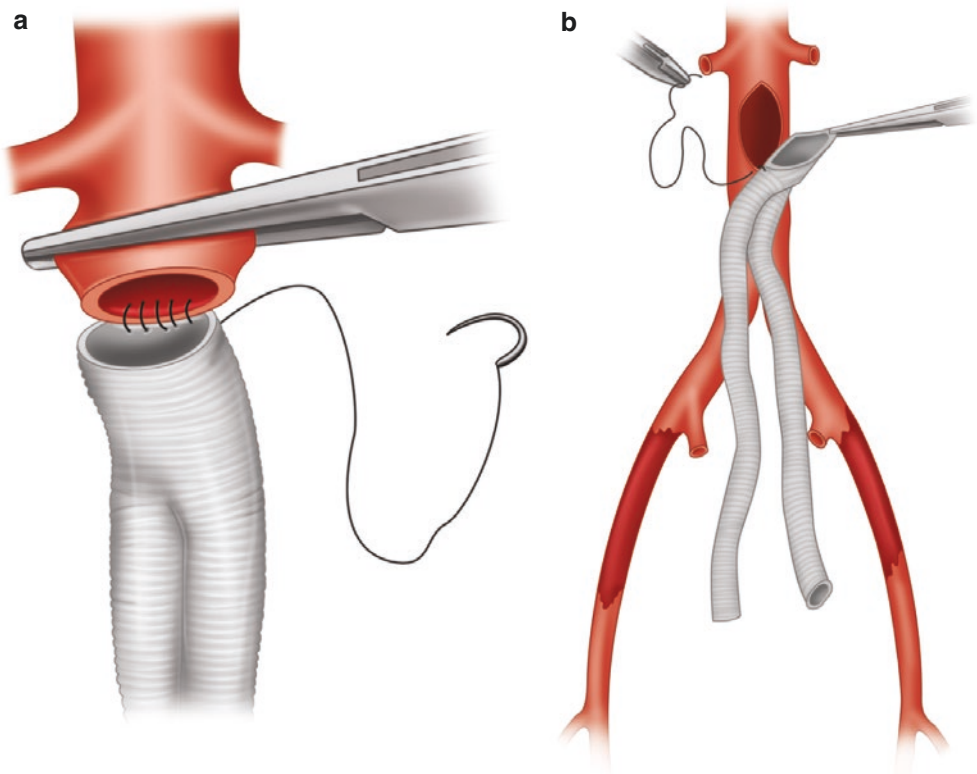


Fig. 15.9 Proximal aortic control and transected aorta. (Short arrow: Oversewn aortic stump, Long arrow: IMA)

Fig. 15.10 Aorto-femoral graft proximal anastomosis (**a**) End-to-end anastomosis, (**b**) End-to-side anastomosis)



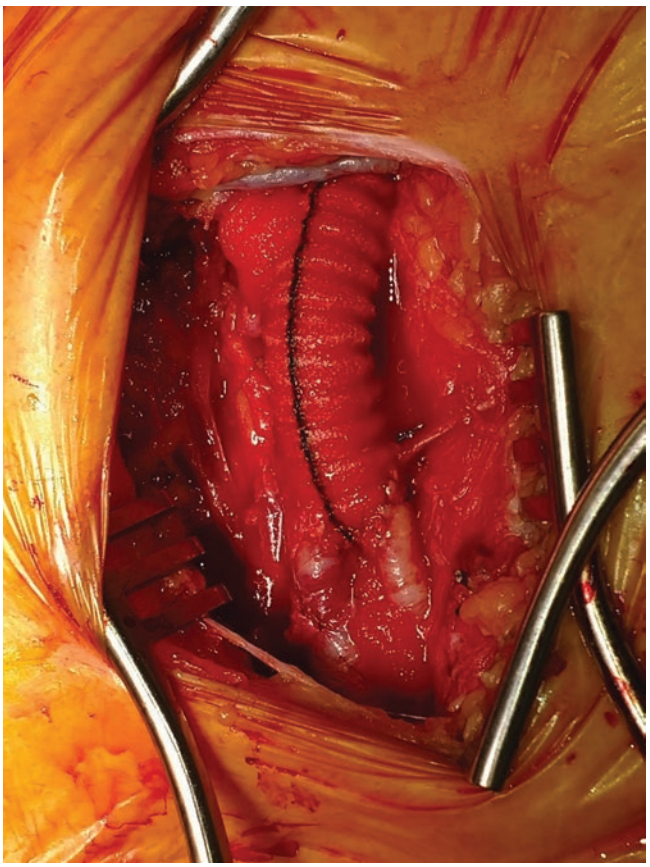


Fig. 15.11 Femoral arteriotomy onto the profundal femoris and anastomosis

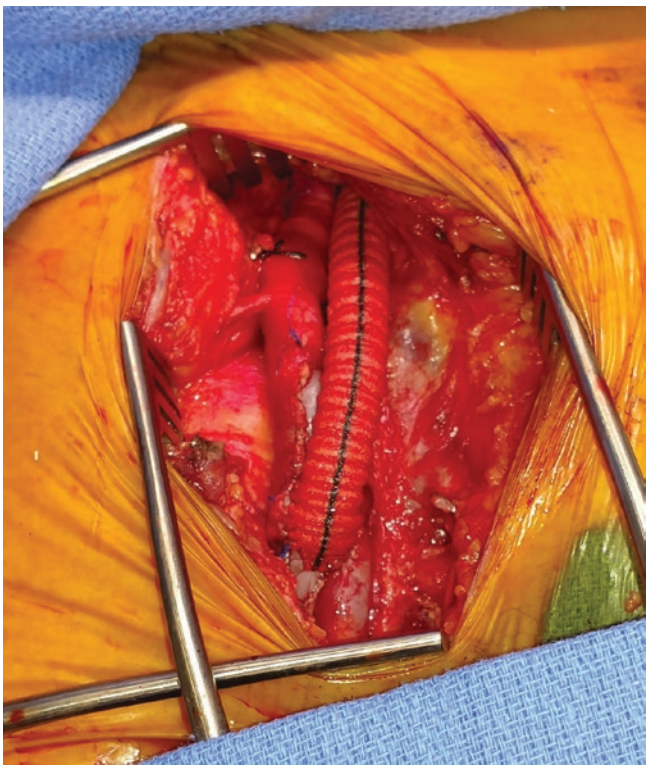


Fig. 15.12 Femoral anastomosis after bovine patch angioplasty

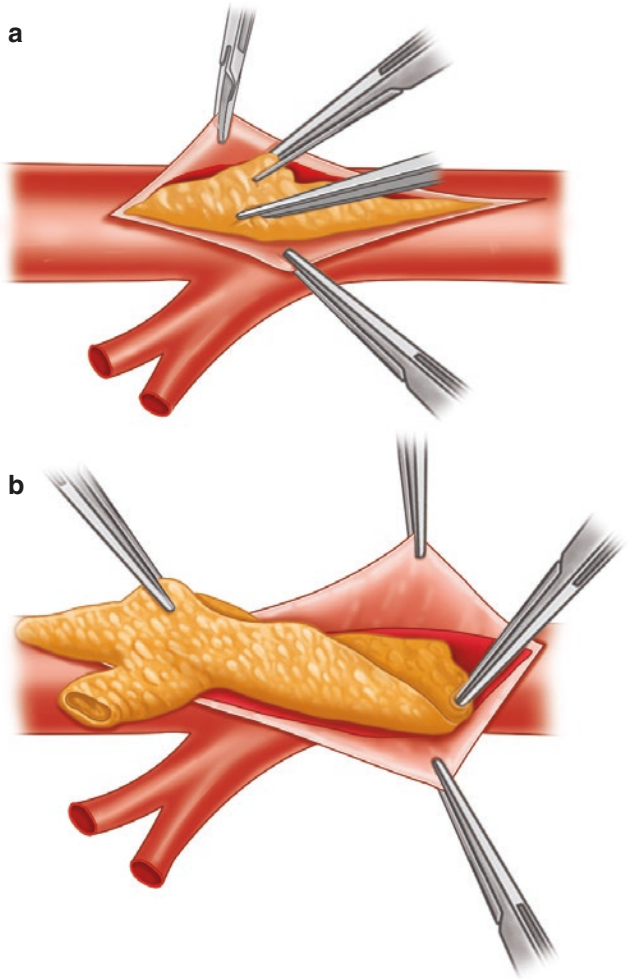


Fig. 15.13 Techniques of aortoiliac endarterectomy. (**a**) Initial separation of the plaque. (**b**) Endarterectomy is terminated by feathering to a tapered endpoint. If not, may need tacking sutures

Iliofemoral Bypass

With advances in catheter-based procedures, unilateral iliac disease rarely requires open surgical reconstruction. When endovascular intervention is impossible, unilateral iliofemoral bypass or extra-anatomical bypasses such as femoral-femoral or axilla-femoral bypass are viable options. Surgical technique of the iliofemoral bypass is similar to aorto-femoral bypass.

Extra-Anatomic Revascularization

Extra-anatomic revascularization was developed as an alternative to direct aorto-bifemoral bypass for patients with high comorbidities or with hostile abdomen from previous major abdominal surgery, infection, or radiation. The first femoral-femoral bypass was described by Freeman in 1952 [38] followed by introduction of axillo-femoral bypass in 1963 [39, 40]. After many years of experience and retrospective studies, these extra-anatomic bypasses have proven to be a safe and durable alternative of direct surgical revascularization.

Femoral-Femoral Bypass

Femoral-femoral bypass can be used in unilateral iliac disease when the donor iliac artery can supply enough blood flow to both donor and recipient legs (Fig. 15.14). Typical bilateral femoral incisions can be made (See Aorto-bifemoral Approach). The common, superficial, and deep femoral arteries are dissected and ready to be controlled.

Then the plane for tunneling of the bypass graft is created in the immediate prefascial subcutaneous layer. Similar to aorto-bifemoral bypass, blunt dissection using surgeon's finger from both sides is usually enough to create the space. Then a DeBakey aortic clamp or ring forceps can be used to pull the graft from one side to the other. At this time, attention should be paid to reduce risk of graft kinking or injury to hollow viscus in an unexpected hernia. An 8-mm diameter externally supported ringed PTFE graft is our preferred choice of graft.

After appropriate systemic anticoagulation was obtained, bilateral femoral arteries and their branches are controlled and longitudinal arteriotomy is made. The size of the arteriotomy is usually 2.5 to 3 times larger than diameter of the graft. End-to-side anastomosis is created using 5–0 or 6–0 vascular sutures in running fashion. Prior to completion of anastomosis, brief release of the arterial clamp and vessel loop will allow expulsion of air and other debris.

A sterile handheld Doppler will help to confirm successful inflow into the recipient femoral vessels. The incisions should be closed with at least two layers, preferably more, given the high incidence of wound infection.

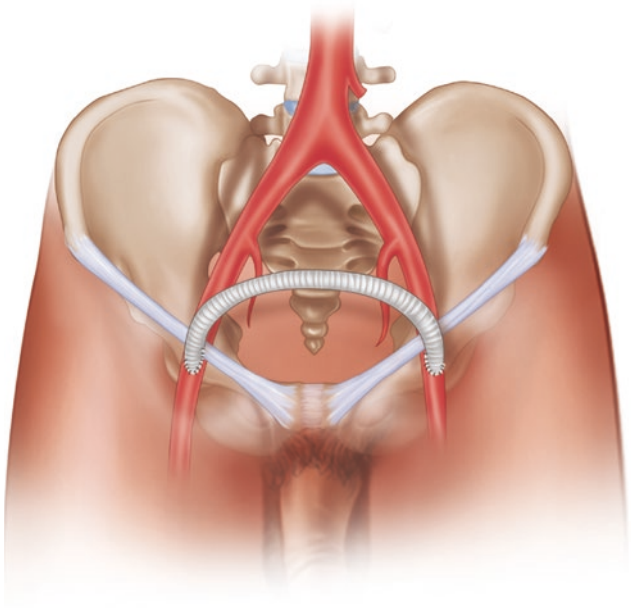


Fig. 15.14 Typical configuration of femoral-femoral bypass

Axillo-Femoral Bypass

Axillo-femoral bypass is another option for patients who are precluded from anatomic bypass or femoral-femoral bypass and often performed as axillo-bifemoral bypass in a patient.

Either axillary artery may be a donor artery. In the case of an axillo-unifemoral bypass, the ipsilateral axillary artery is almost always the donor vessel. With any evidence of donor artery stenosis (e.g., unequal arm blood pressure measurements), preoperative duplex ultrasonography or CT angiography is warranted.

A soft roll or gel pad is placed underneath the chest with the patient in supine position to increase the working area underneath the clavicle. Wide prepping and draping including ipsilateral neck, clavicle, chest, and sternum is necessary. In an obese patient, it may be necessary to abduct and prep the arm into the surgical field. Infraclavicular transverse incision is made below the mid to lateral clavicular area. The deep fascia is incised and pectoralis major muscle fibers are split. After mobilizing the axillary vein which is anterior, the axillary artery is dissected free close to clavicle.

After typical femoral dissection, a subcutaneous tunnel is created between the axillary artery and the ipsilateral groin. The tunnel should traverse below the pectoralis minor and medial to the ASIS. A tunneler can be used, but depending on the height of the patient, a counter incision at the lateral mid-thorax may be needed. An 8-mm externally ringed PTFE graft is the conduit of choice with premade axillo-bifemoral PTFE conduits available to decrease intraoperative time.

Appropriate systemic anticoagulation is achieved; end-to-side anastomosis is created using 5–0 or 6–0 vascular sutures in running fashion. Since the axillary artery can be easily pulled or kinked with arm abduction, medial placement of the proximal anastomosis close to the subclavian artery is recommended to limit tension of the graft with arm movement [41]. Femoral anastomosis and wound closure are the same as femoral-femoral bypass.

Results of Surgical Revascularization

In the most recent series, aorto-femoral bypass graft showed nearly 90% graft patency at 5 years (Table 15.1). Type of approach (transperitoneal vs retroperitoneal) or type of anastomosis (end-to-end vs end-to-side) does not appreciably alter the results.

Extra-anatomic bypass, in general, is inferior in longer-term outcome although this still revealed acceptable 5-year patency rate up to approximately 70%. Thus, these interventions should be reserved for patients who are not good candidates for direct aortic revascularization.

Table 15.1 Result of surgical revascularization

Procedure	5-year patency (%)	Perioperative morbidity (%)	Operative mortality (%)
Aorto-femoral bypass	80–95	10–30	2–4
Ilio-femoral bypass	80–90	10–25	1–3
Femoro-femoral bypass	55–85	10–25	1–3
Axillo-bifemoral bypass	50–75	10–40	1–4
Axillo-femoral bypass	45–70	10–40	1–4

Conclusion

Aortoiliac occlusive disease is a slow irreversible process of atherosclerosis. Modifiable risk factors such as hypertension, diabetes, dyslipidemia, and cigarette use have to be addressed early. Patients with lower extremity ischemic symptoms need a careful assessment of perioperative risk factors and a discussion of endovascular options. However, open surgical revascularization remains a viable option for patients with advanced disease or failed endovascular therapy.

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Inflammatory and Connective Tissue Disorders of the Aorta

16

Brittany S. Panico, Ambrose F. Panico, and Robert S. Dieter

Giant Cell Arteritis

Giant cell arteritis (GCA) is a chronic systemic vasculitis that preferentially affects large- and medium-sized arteries with well-developed wall layers and adventitial vasa vasorum [1]. The vasculitis is characterized by granulomatous involvement of the aorta and main branches in which inflammation leads to luminal occlusion, stenosis, and marked disruption in the vascular wall integrity and distal blood flow [2]. Intimal hyperplasia occurs sporadically along the length of the muscular arteries which causes stenosis and occlusion, resulting in a variety of ischemic complications [3]. Conversely, when the aorta is affected, the inflammatory process leads to dilation and aneurysm formation with a predilection for the thoracic aorta [3, 4]. GCA is well known to occur in close association with polymyalgia rheumatica (PMR), and these two syndromes are commonly observed together.

Epidemiology

Giant cell arteritis is the most common of the large-vessel vasculitides (Fig. 16.1) and occurs almost exclusively in the elderly. Patients are typically over 50 years of age, with peak incidence between age 70 and 80 years. Like most other rheumatologic conditions, women are more often affected than men and account for approximately 65 to 75% of patients diagnosed with GCA [1]. The highest frequencies have been reported in populations of Scandinavian and Northern European descent. The annual incidence of GCA in Olmsted County, Minnesota, is 17 per 100,000 persons over the age of 50, which is similar to that reported in Scandinavian countries [1, 6]. In Southern Europe and the Mediterranean, incidence rates are fewer than 10 per 100,000 persons over 50 years of age [1, 3, 7]. There are very few reported cases of GCA in patients of Latino, Asian, Middle Eastern, and African American descent [7]. This high degree of variability among population-based cohorts suggests there may be a genetic predisposition in certain populations. The overall mortality rate in patients with GCA and PMR is similar to that expected in general populations of the same age and sex [7].

Polymyalgia rheumatica has a similar age, sex, and genetic distribution as giant cell arteritis, and diagnostic criteria for both syndromes include age greater than 50 years [8–11]. Despite the many similarities between the two syndromes, the prevalence of PMR is 1 per 133 persons over the age of 50 years [6, 8].

Large-vessel involvement in GCA is likely underestimated in the literature, in part due to the frequent delay in diagnosis and lack of typical cranial symptoms. The prevalence of aortic impairment in GCA is estimated to occur in 10–25% of cases, though this data is based primarily on retrospective reports [7, 12, 13]. A population-based study from Olmsted County, Minnesota, found that patients with GCA were 17.3 times more likely to develop a thoracic aortic aneurysm and 2.4 times more likely to develop an abdominal aortic aneurysm compared to the age- and sex-matched population [14]. There do not appear to be any reliable predictive factors for aortic involvement in GCA; however, arterial hypertension, persistent chronic inflammatory response, and frequent relapses may be associated with increased risk for aneurysm formation [14, 15].

Diagnosis

The American College of Rheumatology has established diagnostic criteria and treatment guidelines for giant cell arteritis, and these have been adapted in the most recent

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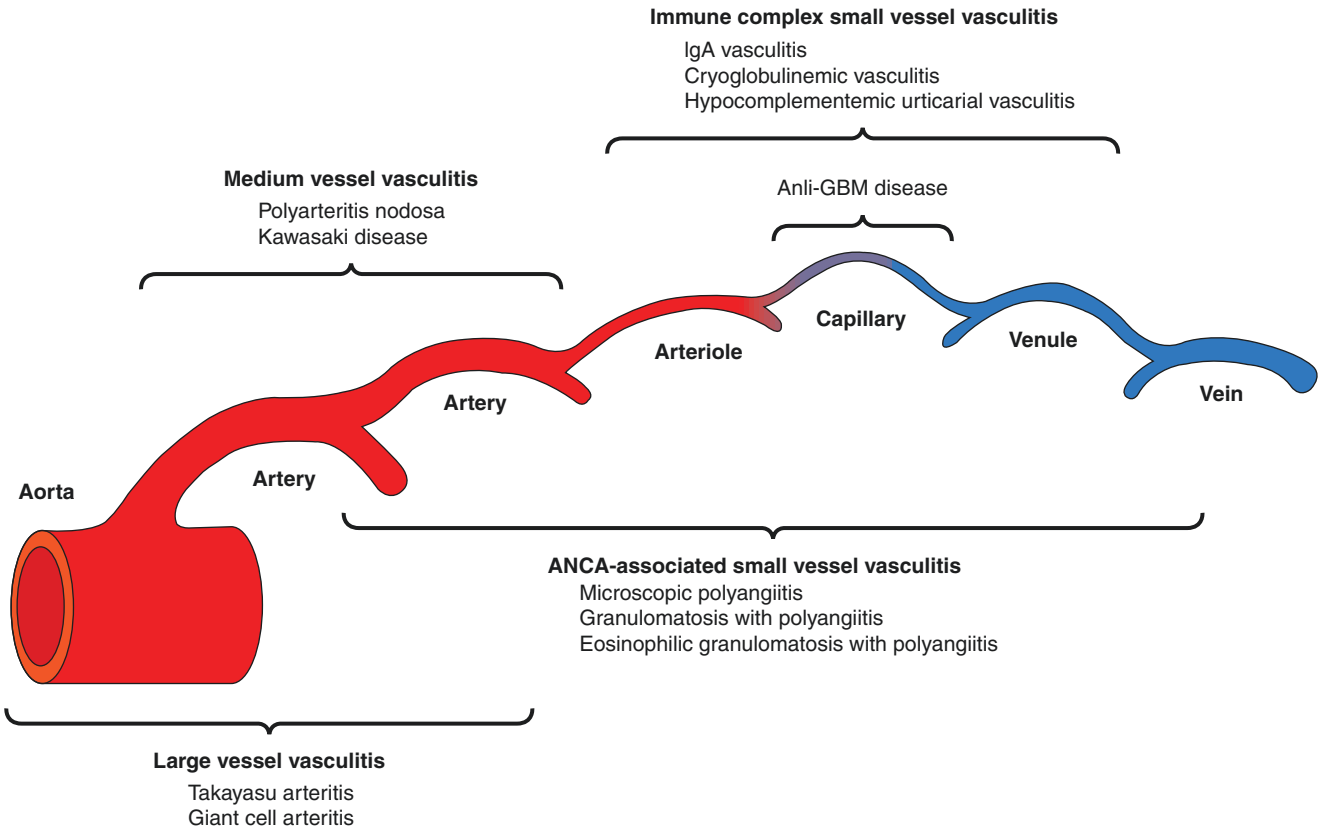

Fig. 16.1 Anatomic distribution of vessel involvement in large-, medium-, and small-vessel vasculitis. (From: Jenette et al. [5]. Reprinted with permission)

American College of Cardiology Foundation/American Heart Association guidelines for the management of thoracic aortic disease [10, 16, 17].

American College of Rheumatology Diagnostic Criteria for Giant Cell Arteritis

Must meet at least 3 criteria.

Age of disease onset ≥50 years
New-onset headache
Temporal artery with decreased pulsation or tenderness to palpation
Elevated ESR > 50 mm/hr. in the first hour of testing (Westergren method)
Biopsy evidence of vasculitis
Predominance of mononuclear cell infiltration and granulomatous inflammation, usually with multinucleated giant cells

Solomon et al. [4]

The diagnosis of GCA is considered on the basis of medical history, clinical evaluation, laboratory, and imaging studies and is confirmed based on histological findings. Three or more criteria confer a sensitivity and specificity over 90% for the disease [10].

Clinical Features

The clinical presentation of giant cell arteritis is variable and widespread, reflecting the truly systemic nature of this disease. The disease course is typically subacute, though isolated aortic disease may be asymptomatic for many months to even years. Patients may manifest with variable ischemic symptoms such as new-onset localized headache, acute ischemic optic neuropathy (resulting in blindness) and other visual changes, jaw claudication, or symptoms of upper extremity claudication; others may have a more silent and indolent course with constitutional symptoms of fever, fatigue, weight loss, and anorexia [1, 7, 10]. On physical exam, the frontal or parietal branches of the superficial temporal arteries may be thickened, nodular, and tender, and pulses may be decreased or absent [7, 8, 18].

Aortic aneurysm, dissection, and large artery stenosis of the upper extremities tend to occur late in the history of the disease but may actually be smoldering long after inflammatory markers return to baseline and therapy is tapered [12]. Aortic arch syndrome is a reported feature of severe GCA, in which arteritis spreads to the subclavian and axillary vessels [3, 19]. Bruits may be heard on auscultation over the carotid, subclavian, axillary, and brachial arteries, and pulses may be absent or diminished [8]. These features mimic the presentation of Takayasu arteritis, and further imaging studies are needed to distinguish the two diseases in the absence of typical cranial symptoms. Aortic aneurysm is often found incidentally or during workup for symptoms of chest pain, new diastolic murmur, or diastolic dysfunction. The thoracic aorta, particularly the ascending aorta, is affected more often than the abdominal aorta in GCA. Aortic dissection and/or rupture can occur during times of subclinical and clinical aortitis, and patients should be monitored even after successful completion of therapy [13].

Approximately 30–50% of patients with GCA report symptoms of PMR simultaneously or in isolation of the diagnosis of GCA [3, 7, 8]. PMR is an autoimmune syndrome that causes inflammation of the bursas and periarticular structures of the shoulder and pelvic girdle in a symmetrical distribution. Patients with PMR typically report acute onset of profound aching and morning stiffness in proximal muscle groups [4]. Patients may report symptoms of PMR before, at the time of, or after the diagnosis of GCA. Symptoms of PMR are also likely to be reported when glucocorticoid treatment for GCA is being tapered [4].

Laboratory Testing

Laboratory analysis is important in the workup of patients with suspected GCA. Infection and malignancy should be rooled out in patients presenting with fever of unknown origin, weight loss, and other nonspecific symptoms. Serum laboratory testing may show a normochromic anemia (anemia of chronic disease), decreased serum albumin, and elevated hepatic enzymes [3, 7, 20]. The characteristic laboratory findings in patients with GCA are a markedly elevated erythrocyte sedimentation rate (ESR) and concomitantly high C-reactive protein (CRP). The ESR can reach 100 mm/hour; however, a less striking elevation should not deter from the diagnosis of GCA. Response to therapy is often guided by the decrease of ESR and CRP levels, and suspicion for relapse can be monitored if these levels increase. Some studies also suggest that elevations in serum interleukin (IL)-6 concentrations correlate with clinical disease activity in GCA [21–23]. However, the clinical utility of following this biomarker has yet to be determined, and IL-6 assays are not routinely available.

Additional antibodies such as rheumatoid factor, antinuclear antibodies, and antineutrophil cytoplasmic antibodies (ANCA) are usually negative [8].

Histopathology

The temporal artery biopsy remains the gold standard diagnostic modality for GCA. Biopsy of an artery with the presence of an inflammatory infiltrate within the adventitia and media along with fragmentation of the elastic lamina, with or without giant cells, is consistent with GCA. There may also be features of panarteritis with an inflammatory infiltrate composed of lymphomononuclear cells, neutrophils, and eosinophils, but without giant cells [2]. The sensitivity of a positive temporal artery biopsy ranges from 70% to more than 90%, though it is not 100% specific [7]. Thus, the diagnosis of GCA should be made in the context of clinical and laboratory findings as well. Temporal arteries are frequently not involved in patients with predominantly large-vessel involvement, and the diagnosis should not be excluded with absent cranial features. These findings suggest that there may be two phenotypes of the same disease process [8]. As such, large-vessel biopsies are not routinely feasible, and diagnosis is made based on the presence of laboratory abnormalities and vascular imaging features. The inflammatory pattern in affected arteries is intermittent rather than continuous, thus creating an additional challenge with obtaining an affected biopsy specimen [8].

The pathogenesis of giant cell arteritis is a T cell-mediated process in which T cells enter the artery through the vasa vasorum, undergo clonal expansion, and are stimulated to produce interferon-γ, IL-17, and IL-21 [8]. Cytokine production within the arterial wall activates inflammatory and endothelial cells, vascular smooth muscle cells, and fibroblasts [4]. This process results in the formation of giant cells and ultimately granulomatous infiltrates [8, 24]. Macrophages also produce matrix metalloproteinases, vascular endothelial growth factor, and platelet-derived growth factor that promote remodeling of the arterial wall and destruction of the internal elastic lamina [4, 24]. The primary immunologic injury occurs within the adventitia of the affected segment, whereas the majority of tissue damage occurs within the media-intima junction [25]. This inflammation and remodeling result in intimal hyperplasia and obstruction of the lumen, which gives rise to the ischemic complications observed in GCA [4, 8, 24]. The mechanism is slightly different within the aorta as stenosis is not a feature. Rather, ectasia and circumferential thickening of the aortic wall are consistent with large vessel GCA [12].

It is unclear why some regions of the artery are spared and why some vascular branches are unaffected in GCA. There

appears to be a tissue tropism despite the systemic involvement of GCA. This is likely reflective of subtle differences in the microanatomy of certain regions of the arterial tree and possibly the territorial distribution of dendritic cells; however, the exact mechanism is poorly understood [19, 26]. The vessels most typically affected include the external carotid branches of the aorta, particularly the superficial temporal and occipital arteries; ophthalmic, posterior ciliary arteries; vertebral, distal subclavian, axillary arteries; as well as the thoracic aorta. Lower extremity vasculitis and involvement of the abdominal aorta is less common; intracranial, coronary, and mesenteric arteries are essentially spared [1, 3, 4, 19].

Imaging Findings

Imaging is an important component to the diagnosis and management of patients with GCA. Patients with classical cranial manifestations or biopsy-proven GCA should be screened for large-vessel disease. Likewise, aortic involvement should be considered in patients with disease relapse or persistently elevated inflammatory markers, fever of unknown origin, or upper extremity claudication symptoms. Different radiological methods have been useful in identifying the presence of aortitis and assessing response to treatment.

Magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) of the aortic arch and its branches are useful imaging techniques in the evaluation of patients with GCA (Fig. 16.2). These techniques are helpful in assessing the extent of arterial involvement in patients with biopsy-proven GCA and also to monitor vascular lesions for signs of progression [28]. Inflammatory activity is observed as delayed enhancement of the arterial wall due to leaky micro vessels. However, vessel wall edema is not always associated with disease activity or the development of new lesions and should not solely influence treatment decisions. Traditional magnetic resonance imaging (MRI) is sensitive and specific for the detection of stenosis, occlusions, dilations, and aneurysms and adds information about the presence of vessel wall thickness, edema, and mural wall abnormalities that together are suggestive of aortic wall inflammation [29].

Conventional angiography used to be the reference standard for the diagnosis of large-vessel vasculitis, though now is seldom used for diagnostic purposes due to the availability of noninvasive imaging techniques. Arteriography shows long, regular, smooth-walled stenosis in GCA, as well as occlusions and/or dilations; however, this technique is not helpful for the early diagnosis of vasculitis [28]. Aortic angiography is now reserved primarily for the planning of revascularization procedures [4].

The use of positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) has demonstrated use in the evaluation of large vessels and detection of GCA in the medium and large vessels. Increased uptake of 18F-FDG by hypermetabolic cells within blood vessels is suggestive of inflammation and can be helpful in detecting early disease before the development of structural lesions. This functional imaging technique is also useful in monitoring disease activity over time and response to treatment [30, 31]. When combined with CT, this imaging technique can demonstrate functional lesions and structure simultaneously. However, FDG is taken up by all hypermetabolic cells and currently cannot distinguish vasculitis from other inflammatory lesions such as atherosclerotic changes in vessel walls. The sensitivity and specificity of 18F-FDG PET with CT has yet to be established and is not yet a cost-effective method for diagnosing and monitoring GCA. There are several limitations of using PET and PET-CT for the long-term monitoring of patients with GCA, and further studies are needed to validate criteria for disease activity in large-vessel vasculitis.

The role of imaging studies in both short- and long-term follow-up has been insufficiently defined. Many authors suggest annual chest radiographs in patients with GCA at time of diagnosis and then for several years following remission in order to detect dilation of the thoracic aorta. Others suggest increased screening for abdominal aortic aneurysm. These recommendations are based on a proposed algorithm for the early detection of aneurysms in GCA, but remains to be validated [31, 32].

Treatment

Treatment of giant cell arteritis is currently based on European Leage Against Rheumatism (EULAR) guidelines and adapted for all large-vessel vasculidities. High-dose glucocorticoids are the mainstay treatment for inducing remission in patients with GCA and should be started at 1 mg/kg per day, maximum 60 mg oral prednisone per day. For patients with cranial GCA and visual symptoms, 3 days of pulse IV methylprednisolone is recommended in order to prevent irreversible vision loss [16]. Symptoms tend to resolve quickly once corticosteroid therapy is initiated; fever, headache, and PMR symptoms usually improve within days. Ischemic symptoms and claudication may take considerably longer to resolve. The inflammatory response usually returns to normal within 2–4 weeks, as evident by the decrease of ESR and CRP; however, the ESR and CRP are imperfect markers of disease activity in GCA and should not be used as sole predictors of response to therapy [33]. Corticosteroids should then be gradually tapered once there is clinical improvement and the ESR has returned to normal values. Treatment duration is highly variable, with majority of patients able to discontinue corticosteroid therapy within 1–2 years.

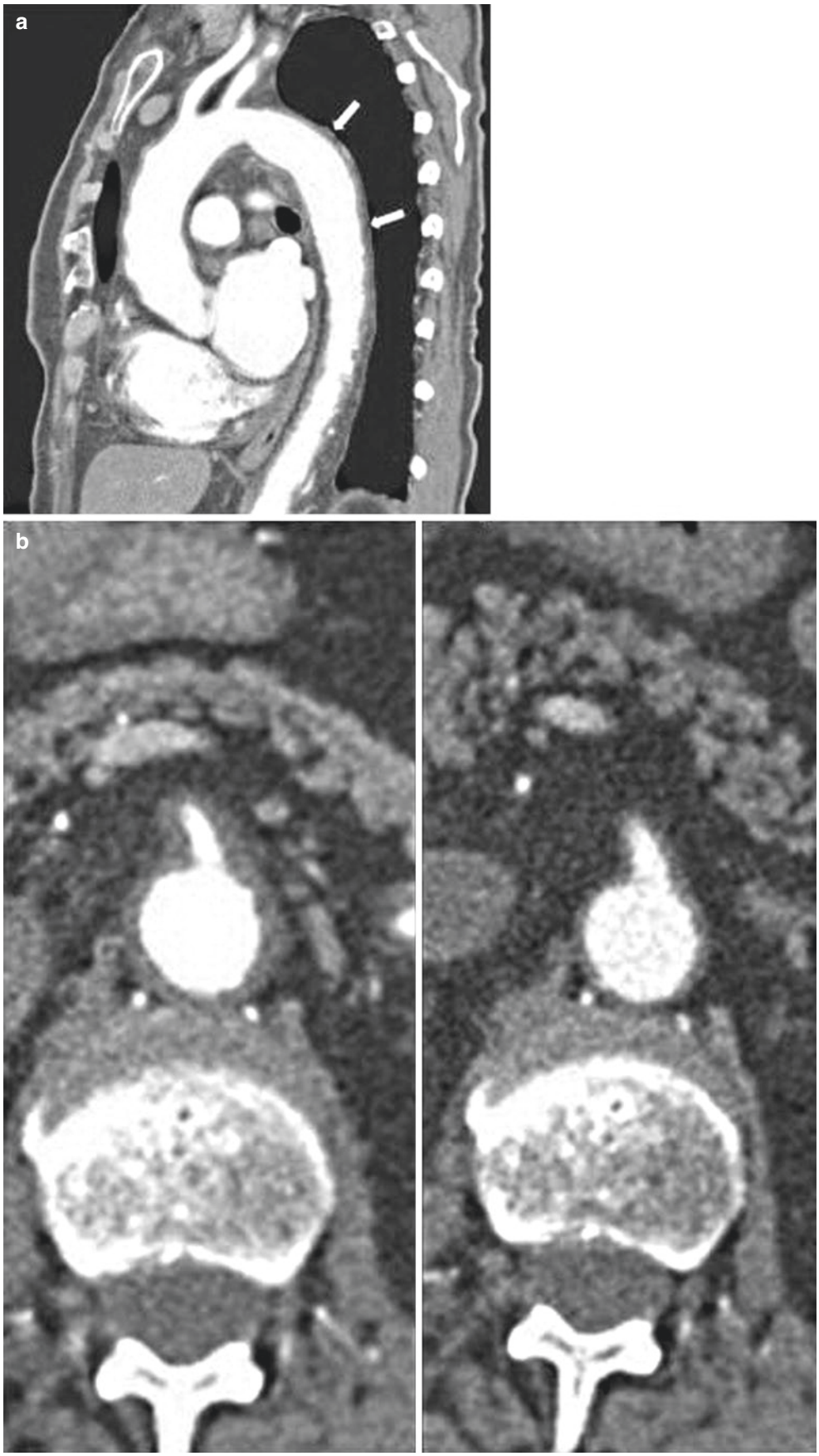

Fig. 16.2 CT angiogram of a patient with GCA and involvement of the aorta. (**a**) Sagittal image demonstrating thickened arterial walls, most prominent in the great vessels and throughout the entire descending thoracic aorta. (**b**) Arterial wall thickening extended into the upper abdominal aorta and superior mesenteric artery before (left) and after (right) treatment with corticosteroids. (From: Warrington and Cooper [27]. Reprinted with permission)

Some patients with GCA may tolerate complete discontinuation of corticosteroids and achieve remission. However, approximately 40–50% of patients experience relapse during corticosteroid tapering and require return to a higher dose. Recurrence of the disease after complete withdrawal of corticosteroid therapy is estimated to occur in 20–30% of patients and is most commonly seen within the first year after steroid discontinuation [34]. There have been several studies looking at the efficacy of methotrexate as a steroid-sparing option, though results are conflicting [34]. Tocilizumab, an IL-6 inhibitor, has recently been approved as a steroid-sparing agent and is the first biologic to be indicated for the treatment of GCA [23, 35].

There is little data on the long-term evolution of large artery involvement in GCA. Population-based studies from Minnesota and northern Spain demonstrated that median time from diagnosis of GCA to diagnosis of thoracic and abdominal aortic aneurysm was 10.9 years and 6.3 years, respectively [3, 36]. This may suggest that patients with large artery involvement may have subclinical disease that continues to smolder long after their initial disease manifestations were treated. Patients with aortic aneurysms between 3 and 5 cm in diameter which are enlarging in the context of elevated inflammatory markers (ESR and CRP) should receive high-dose glucocorticoids as well, though there is no data on the use of pulse-dose steroids [33].

The use of low-dose aspirin is recommended in patients with GCA and has been shown to reduce the risk of visual loss, transient ischemic attacks, and stroke [16, 33].

Surgical Treatment

There are no validated guidelines regarding surgical repair of aneurysms in patients with GCA; therefore, current consensus is adapted from recommendations of atherosclerosis-related aneurysms. The mortality rate in GCA patients with aortic aneurysm (excluding rupture) is similar compared to patients with aortic aneurysm unrelated to GCA [37]. Surgical intervention should be considered in cases of a symptomatic aneurysm or an ascending aorta ≥5 cm in diameter, descending aorta >6 cm, abdominal aorta >5.5 cm, and any aneurysm that has expanded >0.5 cm within a 6-month period [31]. Revascularization procedures such as stenting or bypass grafting to repair stenosis are rarely required though may be indicated in patients with subclavian artery stenosis [31]. Reports on successful revascularization for limb claudication also noted that restenosis is common, as similarly observed in patients with Takayasu arteritis [31, 38]. If required, surgical procedures should be performed during the quiescent phase of disease, so as to avoid increased complications from high doses of immunosuppression, delayed wound healing, and graft failure.

Follow-Up

The frequency for patient follow-up should be guided by their clinical manifestations and adverse events.

Takayasu Arteritis

Takayasu arteritis (TA) is a chronic vasculitis of unknown etiology that primarily affects the aorta and its main branches [39]. Takayasu arteritis has also been called pulseless disease, occlusive thromboaortopathy, and Martorell syndrome. Descriptions of this condition date back as far as 1803 in Japan and have since been reported throughout the world [40]. Women are affected in 80–90% of cases, and the age of onset is typically during the reproductive years (10–40 years old) [41]. In the United States and Europe, the estimated incidence is 2.6 per million per year, whereas in Japan, there are approximately 150 new cases each year [41].

Pathogenesis

The pathogenesis of Takayasu arteritis is poorly understood, and it is unclear how geographical differences account for the high degree of variability among the prevalence of disease. Inflammation, largely driven by mononuclear cells (predominantly lymphocytes), histiocytes, macrophages, and plasma cells, drives a process of destruction of the elastic lamina and the muscular media of the aorta and its main branches [39]. Giant cells and granulomatous inflammation occurs in the media and adventitia [39]. This destruction of the elastic lamina and media thus leads to aneurismal dilation of the affected segment. The inflammatory stage is propagated by the production of inflammatory cytokines, such as IL-6, IL-1, and RANTES. Intimal proliferation from progressive inflammation contributes to the formation of stenosis as the deposition of smooth muscle cells, mucopolysaccharides, and fibroblasts leads to fibrosis and destruction of the vessel architecture [42, 43]. Over time, dense scarring replaces the adventitia and leads to compromise of the vascular lumen [41].

The trigger that sets off the inflammatory cascade in Takayasu arteritis has yet to be determined. Inflammation is primarily localized to a portion of the thoracic or abdominal aorta, or even the entire vessel. Studies documenting early findings in Takayasu arteritis have observed that the initial vascular lesions tend to occur in the left proximal to middle subclavian artery [43]. As the disease progresses, the left common carotid, vertebral, brachiocephalic, right middle or proximal subclavian artery, right carotid, and aorta can be affected; the abdominal aorta and pulmonary arteries are involved in approximately half of cases [43].

Diagnosis

The clinical features of TA have been well described in a number of cohort studies including patients from all over the world, with a heterogeneous clinical presentation ranging from incidental physical exam findings to catastrophic neurologic events. The diagnostic criteria as outlined by the American College of Rheumatology are as follows:

American College of Rheumatology Diagnostic Criteria for Takayasu Arteritis [44]

- Disease onset ≤40 years
- Claudication
- Blood pressure difference >10 mmHg between the upper extremities
- Decreased brachial artery pressure
- Subclavian or aortic bruit
- Abnormal angiogram showing narrowing or complete occlusion not caused by arteriosclerosis or fibromuscular dysplasia

In a majority of patients, the progression of TA is thought to occur in two distinct phases. The first phase, or the "prepulseless" phase, is characterized by nonspecific constitutional symptoms such as fever, night sweats, malaise, weight loss, arthralgias, and myalgias. Vascular symptoms are rare at presentation. The second phase, or chronic "pulseless" phase, is characterized by vascular insufficiency due to dilation, narrowing, or occlusion of the proximal branches of the aorta [40]. Patients may experience claudication symptoms, chest pain, dyspnea, abdominal pain, or even neurologic symptoms from involvement of the carotid and subclavian arteries that can lead to subclavian steal syndrome [45–48]. Symptoms of congestive heart failure may also be present and indicative of aortic dilation and aortic regurgitation [41]. Due to the chronic nature of the disease, collateral circulation typically develops and can delay the onset of ischemic symptoms.

Physical exam is important in detecting TA because patients rarely look chronically ill. Obtaining blood pressure measurements of all four extremities can reveal a discordance of 10 mmHg or more when stenosis is present. Bruits may be audible over the subclavian, brachial, carotid arteries and abdominal vessels. Aortic regurgitation may also be present. Hypertension develops from stenosis of the renal artery or decreased elasticity of the aorta [45–48]. However, due to stenosis of the arteries of the upper extremities, blood pressure may be difficult to assess. Despite the variability that exists in disease presentation, roughly 20% of patients have a single, self-limited inflammatory episode, while the remaining population has a progressive and relapsing disease course [40, 45, 49].

Laboratory studies most often reveal findings consistent with inflammation, with elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). A normochromic normocytic anemia suggestive of anemia of chronic disease and hypoalbuminemia may be present. Autoantibodies associated with other forms of vasculitis, including antinuclear, antineutrophil cytoplasmic, anti-DNA, and antiphospholipid antibodies are not found in TA [42, 43].

Radiographic imaging is an important tool in establishing the diagnosis of TA because arterial biopsy is typically not practical. Historically, the mainstay of diagnosis has been invasive angiography; however, noninvasive imaging such as MRI/MRA and CTA are replacing angiography as the gold standard for diagnosis (Fig. 16.3). The aortic arch and its primary branches tend to demonstrate the most extensive involvement, and lesions appear as smooth-walled, tapered, focal areas with narrowing and dilation along the vessel when observed with contrast-enhanced techniques [50]. Beyond observing luminal stenosis, MRI/MRA and CTA offer information about vessel wall thickness, edema, and contrast enhancement, which can be diagnostic and also useful for monitoring disease activity and response to treatment. The use of 18-FDG PET can also be used to provide valuable information about cellular activity and metabolically active lesions within an inflamed vessel before morphological changes appear on other imaging studies [50]. PET scanning is limited in the ability to provide information regarding wall structure of luminal blood flow, however. At the current time, there is no single best imaging modality for the diagnosis and monitoring of disease activity in patients with Takayasu arteritis, and often, patients will require more than one imaging study to determine changes in their disease course.

Medical Treatment

The goals of medical therapy remain focused at suppressing inflammation in order to arrest the progression of existing lesions as well as prevention of new lesions. Corticosteroids are the first-line drug of choice and work quickly to decrease the acute inflammatory response that causes damage to the vasculature. In approximately 60% of patients, there is a short-term response with the decrease in ESR, improvement in peripheral pulses, and resolution of inflammatory symptoms. However, TA can remain clinically active at a subclinical level when steroids are decreased, and relapse occurs in as many as 50% of patients when steroid therapy is weaned [40, 49]. Historically, steroid-sparing agents such as cyclophospha-

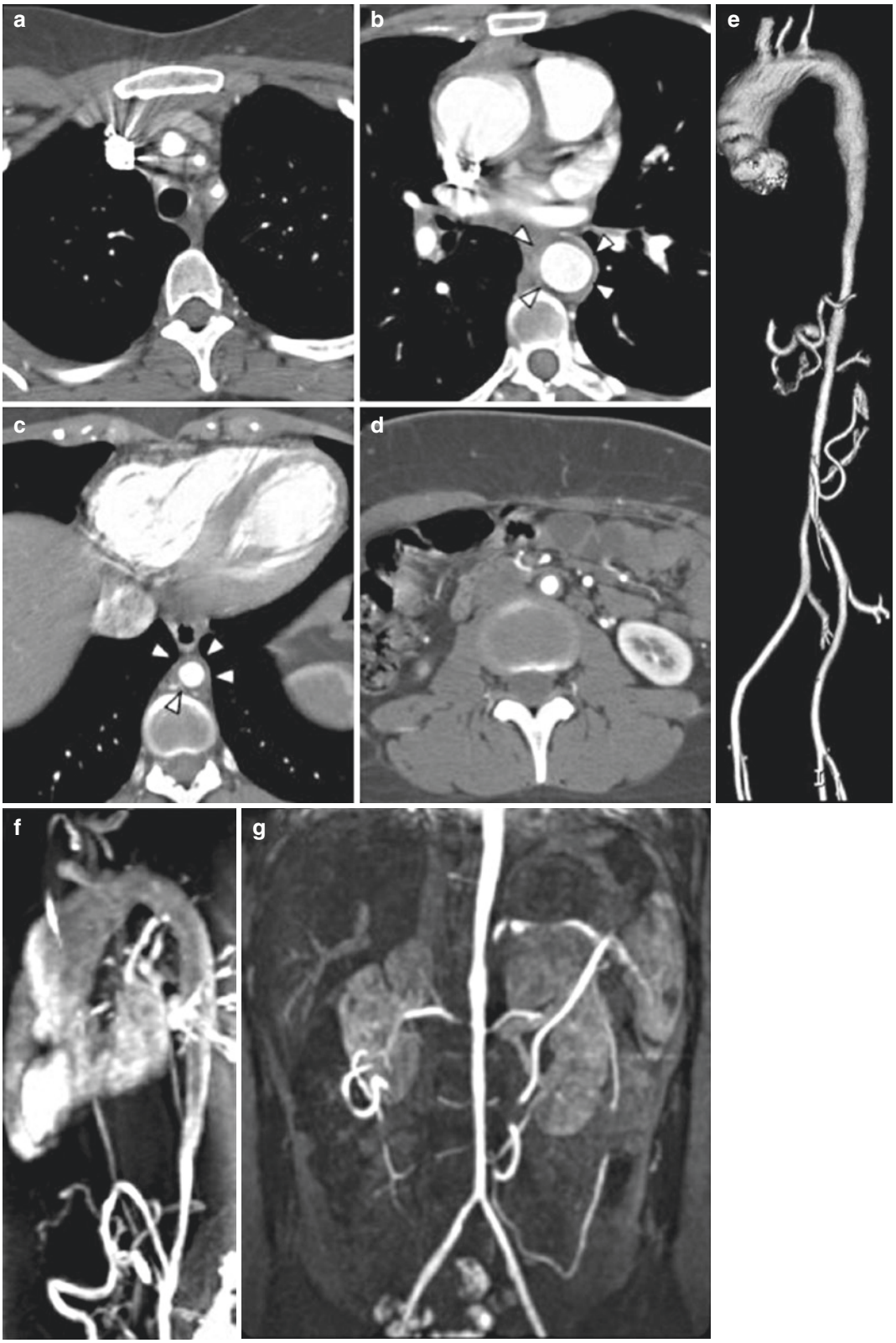

Fig. 16.3 Takayasu arteritis with involvement of the thoracoabdominal aorta and great vessels as shown on contrast-enhanced CT and MR studies, noting the narrowing of the arterial lumen and circumferential soft tissue thickening of the walls of the vessels. (**a**) Narrowing of the left common carotid and left subclavian arteries. (**b**) Mid-descending aorta. (**c**) Aorta just above the diaphragm. (**d**) Infrarenal aorta. (**e**) Volume-rendered image from CT showing the extent of involvement. (**f**) MR sagittal slices of the thoracic aorta. (**g**) MR coronal slices of the abdominal aorta (CT, computed tomographic imaging; MR, magnetic resonance imaging). (From Hiratzka et al. [18]. Reprinted with permission from Elsevier)

mide, azathioprine, methotrexate, and mycophenolate mofetil have been used for patients with disease refractory to steroid therapy; however, data supporting these alternatives has not been reinforced by large randomized controlled clinical trials. Biologic agents such antitumor necrosis factor agents (TNF-alpha inhibitors) such as etanercept and infliximab have been used with some success to achieve sustained remission in several patients once corticosteroids were weaned [51]. Tocilizumab, an interleukin (IL)-6 inhibitor, has also been used to treat patients with TA with some success [52]. There is currently no data to support the duration of treatment required for patients with a diagnosis of TA, but close symptomatic monitoring is important once stenosis is observed because fibrosis eventually replaces the inflammatory lesions and can lead to symptom onset even years after initial diagnosis and treatment.

Surgical Treatment

The diagnosis of TA is often made after stenotic and occlusive lesions have already occurred, and unfortunately, these lesions are not reversible with medical therapy. Surgical intervention to correct the stenosis for symptomatic lesions is often necessary. Surgical indications in patients with TA include secondary hypertension with critical renal artery stenosis, symptomatic claudication limiting activities of daily living, cerebrovascular ischemia or stenosis of greater than three vessels, moderate aortic insufficiency, myocardial ischemia, stenosis of the aortic arch, as well as thoracic aortic aneurysm greater than 5 cm [45, 49, 53, 54]. Surgical intervention is preferred when disease is quiescent in order to decrease the risk of early complications including restenosis, anastomotic failure, thrombosis, bleeding, and infection. There have been higher rates of restenosis observed with endarterectomy, patch angioplasty, and endovascular procedures compared with traditional bypass grafting [45, 49, 53, 54]. Bypass grafting remains the surgical treatment of choice, with an estimated 20-year rate of restenosis estimated between 20% and 30%. The 20-year rate of patients who undergo bypass grafting for TA has a 75% survival [40, 45, 49, 53, 54]. Long-term survival data in patients with TA undergoing aortic valve repair and aortic arch replacement are 76% for 15-year survival and 83% for 10-year survival, respectively [55, 56].

IgG4-Related Disease

IgG4-related disease (IgG4-RD) is an increasingly recognized immune-mediated inflammatory condition that has been shown to affect nearly every organ, including the aorta [57]. The condition is suspected to account for a large proportion of previously unidentified causes of inflammatory thoracic and abdominal aneurysms. Retroperitoneal fibrosis is also one of the major manifestations of IgG4-related disease and can present as a mass compromising the aorta and its branches. IgG4-related disease is characterized by tumefactive lesions, dense lymphoplasmacytic infiltrate with an abundance of IgG4-positive plasma cells, and storiform fibrosis (star-like whirling pattern of cellular infiltrate) [58]. Patients will often have elevated serum IgG4 levels, though this is not an essential diagnostic criterion [58].

IgG4-related disease was first described in the literature as an etiology of autoimmune pancreatitis. Patients with infiltrating pancreatic lesions who underwent biopsy were noted to have specimens that contained large numbers of IgG4-positive plasma cells without concomitant evidence of malignancy [59]. Walker et al. initially described features of inflammatory abdominal aortitis in 1972 as marked thickening of the aneurysm wall, fibrosis of the adjacent retroperitoneum, and rigid adherence of adjacent structures to the anterior aneurysm wall [60]. In 2008, these same features were again described along with an abundance of IgG4-positive plasma cells within the inflammatory infiltrate and lead to the hypothesis that IgG4-related disease could be responsible for a subset of inflammatory abdominal aneurysms [61]. Similar histopathologic features have now been described in virtually every organ system, including the meninges, lymph nodes, lungs, liver, biliary tree, salivary glands, periorbital tissues, kidneys, aorta, breast, prostate, thyroid, pericardium, skin, mediastinum, and retroperitoneum.

Epidemiology

The epidemiology of IgG4-related disease is inadequately described in the literature, and there are very few population-based studies that describe the disease in detail. There has traditionally been a lack of definition of IgG4-related disease in literature prior to the current decade, and nomenclature as well as the understanding of the disease process continues to evolve [62]. A Finnish retrospective case-control study estimated an incidence of retroperitoneal fibrosis to be 1 per 1,000,000 person-years, although this figure is likely to increase as recognition of the disease evolves [63]. The majority of patients diagnosed with IgG4-related disease are men over the age of 50 years, though disease severity appears to affect men and women similarly [62]. Recent literature suggests that approximately 2–15% of abdominal aortic aneurysms are inflammatory in nature and approximately 1–6% of those inflammatory aneurysms are estimated to be IgG4-related [64].

Diagnostic Criteria

The diagnosis of IgG4-related disease is made primarily on the basis of characteristic histopathological features and the presence of elevated IgG4-positive plasma cells within the tissue. The number of IgG4-positive plasma cells per high-power field that is consistent with a diagnosis of IgG4-related disease varies from tissue to tissue [65]. The presence of a dense lymphocytic infiltrate, storiform fibrosis, and obliterative phlebitis classically represents IgG4-related disease [65]. The formation of a mass may be the predominant feature in some patients, and in others, a plaque-like infiltrate may predominate [66]. The inflammatory infiltrate is composed of B and T lymphocytes, and plasma cells are often in abundance [58, 65]. Eosinophils and scattered macrophages are also present in the infiltrate. The storiform pattern of fibrosis mimics the spokes of a cartwheel with spindle cells that radiate from the center and is typically found within the lymphocytic infiltrate [65]. Greater than 50 IgG4-positive plasma cells in a biopsy sample of the aorta is highly suggestive of IgG4-related disease; likewise, a biopsy of a retroperitoneal mass with greater than 30 IgG4-positive plasma cells is consistent with the diagnosis [65]. IgG4-positive plasma cells should be distributed throughout the infiltrate, rather than being clustered in isolation. The inflammatory process of aortic disease predominantly appears as marked enlargement of the adventitia with inflammatory cells intermixed with irregular fibrotic areas; other features include sclerosing inflammation within the media with disruption of elastic fibers and scattered eosinophils [61, 66, 67]. Despite disruption of the media and aneurysm formation, rupture occurs less frequently than other forms of aortitis, likely due to the thickened arterial wall [68]. This pattern of inflammation differs from the erosive and exudative changes with predominant neutrophilic infiltration within the intima and media, as seen with atherosclerotic disease [61]. Necrotizing forms of arteritis are not typically seen and if present should raise suspicion for the diagnosis of IgG4-related disease [65]. Granulomatous formation is also unusual [58]. Chronic lesions may appear as dense fibrosis with little inflammatory infiltrate, which often makes the diagnosis of IgG4-related disease challenging [66]. Serum levels of IgG4 are elevated in approximately 60% of patients with biopsy-proven IgG4-related disease; however, the degree of elevation of IgG4 immunoglobulins does not correlate with disease activity [62, 65]. The presence of elevated serum IgG4 levels alone is not recommended to make a diagnosis of IgG4-related disease and monitoring serum levels can be helpful to follow in response to treatment if they are positive at time of diagnosis [62].

Clinical Presentation

IgG4-related disease typically presents subacutely, and symptoms are largely related to the organ or organ systems involved. Patients rarely have a fever or feel constitutionally ill. There may be subtle findings on laboratory evaluation, but inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often normal [62]. Along with the tumefactive lesions, many patients with IgG4-related disease have features of atopy, eczema, asthma, and low-grade eosinophilia [68]. The mass-like lesions observed with IgG4-related disease are typically discovered incidentally on radiographic studies or diagnosed via biopsy specimens. Patients may have disease that is confined to one organ; others may present with symptoms related to multiorgan dysfunction [58].

Retroperitoneal fibrosis is typically discovered as an inflammatory mass involving the abdominal aorta, the kidneys, or the ureters and may present as vague abdominal or flank pain, back pain, urinary retention with hydronephrosis, edema of the lower extremities, or lower extremity claudication symptoms [57, 58, 62, 64]. Aortic aneurysms are often discovered during routine screening or found incidentally on chest radiography. Aneurysm formation occurs frequently along the aortic arch and less likely results in dissection at this location [64, 67, 69]. Several large case series estimated that approximately 4% of aortic root replacements had histopathological features consistent with IgG4-related disease [65, 70, 71]. IgG4-related disease should be considered in patients with aortitis of unclear etiology, particularly if involvement occurs along the ascending or abdominal segments of the aorta.

Imaging findings vary considerably from one organ to another. Radiographic features are often nonspecific and do not provide reliable distinction between IgG4-related disease and malignancy. Arterial lesions are highly reflective of sclerosing inflammation located predominantly in the adventitia [67]. Image findings include homogeneous and circumferential wall thickening with enhancement in the late phases after contrast administration on contrast-enhanced computed tomography [67]. Calcification is not a typical finding and should raise suspicion for an alternative diagnosis if observed in abundance. Affected segments of the aorta vary in length. Retroperitoneal IgG4-related disease can appear as a soft tissue density infiltrating the retroperitoneal space and encasing the aorta, often leading to compression, but not invasion [67]. The mass may also encompass the ureter and contribute to hydronephrosis or appear as a fat density in the pelvis and paravertebral area with compression of the iliac arteries [67]. It is not possible to distinguish IgG4-related disease from malignancy based on radiographic features alone, and further investigation is warranted when a retroperitoneal mass is observed.

Pathophysiology

The pathogenesis of IgG4-related disease is poorly understood. Proposed mechanisms have been supported for pathways related to genetic predisposition of human leukocyte antigen (HLA) serotypes among Asian populations in particular; also, mechanisms related to molecular mimicry and response to infectious agents have been suggested [58]. Autoimmune responses are suspected as well, though there has yet to be a specific autoantigen target identified [58]. It is also not clear if the role of IgG4 antibodies is pathogenic or acts as a response to an immunogenic process. The inflammatory cascade is perpetuated by IL-4, IL-5, IL-10, and IL-13, as well as tumor-necosis factor-β (TGF-β) [59]. These cytokines become overexpressed through an immune response dominated by type 2 helper T (Th2) cells. CD4+ cytotoxic T cells are also increased in the peripheral blood and within fibrotic masses, suggesting that these cells play a dynamic role in the disease process [62]. The inflammatory response created by upregulated cytokines and continuous antigen presentation by B cells and plasmablasts leads to eosinophilia, elevated IgG4 and IgE production, and the initiation of immune-mediated destruction of the involved tissue [58, 62]. Inflammatory cells infiltrate the target organ and lead to structural damage and tumefactive enlargement at the affected site. Epithelial damage occurs as tissue infiltration progresses and leads to immune complex deposition within the vessel walls [57]. Lymphocytes and plasma cells invade the walls of the venous channel and extend into the lumen, which contributes to obliterative phlebitis [62, 66].

Treatment and Management

The optimal treatment for IgG4-RD has yet to be determined. Current literature supports the approach established in the 2015 International Consensus Guidance statement on the management and treatment of IgG4-related disease [69]. This consensus is based upon observational data, including case reports and small case series [72]. There are few case reports about the treatment of extrapancreatic IgG4-related disease, and little is known regarding follow-up and long-term management, specifically in patients with aortitis [73]. Glucocorticoids are the first-line treatment for patients with active, previously untreated IgG4-RD. Most patients respond to glucocorticoids within several weeks, with symptomatic relief, reduction in the size of masses or organ enlargement, and improvement in organ function [72]. Serum levels of IgG4 can be helpful to monitor response to therapy if quantities were elevated at time of diagnosis, though serum levels have not shown to correlate with disease severity [62, 65]. Patients with aortitis may not have a measurable clinical response and thus will need to be monitored via repeat imaging to follow treatment response. Those patients who respond poorly to glucocorticoids may have disease that has progressed toward advanced fibrosis with little active inflammatory infiltrate; however, there is not a defined method for identifying these patients [73]. Patients should be monitored closely for side effects due to glucocorticoid therapy as well, specifically hypertension and glucose intolerance, as these comorbidities can contribute to increased morbidity in patients with IgG4-related disease.

Some patients may relapse following an initial induction course of corticosteroid therapy, and retreatment with glucocorticoids is warranted. In this event, consideration to use a steroid-sparing agent for maintenance therapy is recommended [62, 72, 73]. Azathioprine, methotrexate, and mycophenolate mofetil have been used as glucocorticoid-sparing agents in an attempt to maintain remission following initial treatment with glucocorticoids, though their efficacy has not been tested in controlled clinical trials [62, 72, 73]. These disease-modifying antirheumatic drugs (DMARDs) have not been shown to be effective in inducing remission on their own, and overall length of therapy once remission is achieved is unknown. There are also several case series, including an open-label pilot study, advocating for the role of rituximab, a CD-20 monoclonal antibody that targets B cells, as treatment for IgG4-related disease [62, 73, 74]. Results are promising, but follow-up data is lacking.

Data regarding the prognosis and appropriate follow-up for patients with IgG4-related disease has yet to be defined, specifically for aortic disease. Imaging is recommended to follow aneurysm diameter and growth, as well as mass size in respect to retroperitoneal fibrosis. Untreated IgG4-related disease often progresses from an inflammatory lymphoplasmacytic infiltrate to extensive fibrosis, though the timing of this transition is not well understood [58]. The mortality rate for patients with IgG4-related disease is estimated to be similar to the general population of the same age and sex demographics; there is little data reported regarding long-term follow-up of patients with IgG4-RD [62].

Behçet's Disease

Behçet's disease is a chronic inflammatory condition characterized by recurrent oral and genital ulcers, skin lesions, and ocular disease. The gastrointestinal tract, central nervous system, and vascular system can also be involved, and patients may report symptoms of arthritis as well. Unlike other forms of vasculitis, Behçet's disease is known to affect blood vessels of all sizes including large, medium, and small arteries, as well as veins. Mucocutaneous, articular, and ocular manifestations are often more severe in the early phase of the disease and may

be presenting features that aid in the diagnosis [75, 76]. However, central nervous system and vascular features tend to present later in the disease course, even up to 10 years following diagnosis, and can contribute to significant morbidity and mortality in patients with this disease [75].

Epidemiology

Behçet's disease primarily affects young men and women between the ages 20 and 40 years. There is a higher prevalence reported in countries along the Ancient Silk Road, particularly the Mediterranean, Asia, and the Middle East [77]. The vast majority of epidemiological information is obtained from case registries and population studies conducted in Turkey and the Middle and Far East. The prevalence of Behçet's disease in Turkey is reported as 80–421 cases per 100,000 compared to 5.2 per 100,000 in the United States [77]. In areas where Behçet's is more common, the disease affects men and women equally, though it appears to be more severe in young males [78]. The onset of Behçet's disease is rare in children and the elderly [77].

Clinical Manifestations

Patients diagnosed with Behçet's disease often present initially with complaints of recurrent and painful oral and genital ulcers. Other clinical features are variable among individuals and populations and can range in severity. Patients can also have cutaneous lesions such as palpable purpura, erythema nodosum, pathergy, and constitutional symptoms including fever, malaise, and weight loss [76]. Ocular disease can vary from uveitis to retinal vasculitis and optic neuritis. Features of pulmonary, gastrointestinal, and renal disease have also been described in patients with Behçet's disease [76].

Diagnostic Criteria for Behçet's Syndrome [79]

Recurrent oral ulcerations.

- At least three aphthous or herpetiform in 12 consecutive months

And at least two of the following:

- Recurrent genital ulcerations
- Skin lesions – erythema nodosum-like lesions, papulopustular-like, pseudo folliculitis, acneiform nodules
- Eye lesions – anterior or posterior uveitis, retinal vasculitis
- Positive pathergy test

Common laboratory findings included elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and an abnormal leukocyte count. There are no specific antibodies or laboratory tests associated with Behçet's disease, and diagnosis is made on the basis of clinical findings in the absence of other systemic diseases.

Vascular involvement in Behçet's disease is one of the leading causes of morbidity and mortality, particularly involvement of the arterial circulation. Vascular complications have been reported to occur in up to one-third of patients with Behçet's disease and range in severity and degree of systemic involvement [75, 80]. The most common manifestations are thrombophlebitis, arterial and venous occlusions, aneurysms and varices [81, 82]. Vascular disease is typically more severe in younger patients and more common in males [75, 80, 83]. The majority of lesions affect the venous system, though involvement of a major artery is estimated to occur in 1.5–2.2% of patients [81, 84]. The aorta, both thoracic and abdominal, and the pulmonary, femoral, and popliteal arteries are the most frequent locations of aneurysm formation [85]. Involvement of visceral vessels and coronary arteries is rare. Atherosclerosis does not appear to occur at an accelerated rate in Behçet's disease, and plaque disruption is not noted to be a component of the thromboembolic phenomenon observed with arterial occlusions [75].

Pathogenesis

The underlying cause of Behçet's disease is unknown. Similar to other autoimmune conditions, Behçet's disease may represent abnormal immune activity triggered by exposure to an unknown agent, possibly infectious, in patients with a genetic predisposition [86]. Genetic and environmental factors are suspected to contribute to increased risk of developing the disease, although the exact contribution of influences is unknown. The most frequent genetic association is with human leukocyte antigen (HLA)-B51, which has been studied in several ethnic groups [87]. Other possible mechanisms of disease include formation of immune complexes and autoantibodies to an unknown antigen, and vascular endothelial activation and hypercoagulability [86]. Once the trigger is initiated, there is evidence of altered innate immune function, abnormal cellular immunity, and upregulation of inflammatory cytokines; antibody and immune complex formation; and neutrophil activation [78]. These mechanisms lead to a complex relapsing and remitting chronic inflammatory state.

Microscopic examination of affected vessels demonstrates an inflammatory arteritis with obliteration of the vasa vasorum [85]. This process results in dilation and unstable aneurysm formation. There is lymphocyte invasion of the media that leads to perivascular degeneration and destruction

of the elastic fibers [80, 82, 85]. As the vessel structure weakens, erythrocytes extravasate and contribute to further endothelial destruction. Fibrosis results with destruction of the intima. Life-threatening dissection can occur as a result of this inflammatory cascade and rapid destruction of the vessel wall. Aortic aneurysms are at an increased risk for rupture regardless of size in patients with Behçet's disease [80].

Endothelial damage and vascular inflammation also lead to thrombus formation and occlusion within both the venous and arterial circulation. This occurs as endothelium-dependent flow-mediated dilation is reduced and inflammatory cytokines are increased in the circulation [88, 89]. Thrombosis is more common with venous disease and has been reported to cause occlusion of the superior and inferior vena cava [76].

Management

The results of surgical management are mixed; however, endovascular repair remains the preferred management for patients with life-threatening disease. The most common complications following repair of the primary lesion are recurrent graft occlusions and pseudoaneurysm formation [80]. Patients with a primary aortic aneurysm often need repeat operations to correct anastomotic aneurysms, graft thrombosis, ulceration, or aortoenteric fistula formation [82]. Ideally, surgery would be performed following the period of acute inflammation, though this is not practical in the event of an acute rupture. Iscan et al. documented a cohort of 20 patients with Behçet's disease and aortitis was found in 14 patients in the form of ascending, thoracic, abdominal, and infrarenal aneurysms [80]. Many patients had more than one aneurysm and multiple other organ systems affected. Seventy-nine percent of patients had aneurysms occurring along the abdominal aorta, and six of those patients presented with ruptured aneurysm [80]. It is not uncommon for pseudoaneurysm formation to occur at the site of angiography puncture [80]. This creates a challenge for operative repair and also monitoring of disease burden via conventional angiography; thus, less invasive methods of imaging the vasculature is recommended. Additional complications, such as suture line dehiscence, aortoenteric fistula formation, graft occlusion, and thromboembolic events, enhance the morbidity and mortality of affected patients [80].

Medical management is also paramount in patients with Behçet's disease, as the syndrome involves systemic inflammation. Symptoms are generally recurrent and relapse is common. Consensus regarding treatment is based on small clinical trials and case reports, with very few follow-up studies available. In 2008, the European League Against Rheumatism (EULAR) published recommendations for the treatment of Behçet's disease and guidelines for each of the major organ systems involved [90]. Treatment for aortic disease has been extrapolated from reports of successful use of immunosuppressive therapy in patients with pulmonary artery aneurysms and other forms of large-vessel vasculitis [90]. The combination of cyclophosphamide and high-dose corticosteroids has improved the survival of patients with pulmonary artery disease, and a similar treatment approach is applied to large-vessel disease [91]. In a retrospective review of 25 patients with large-vessel arterial disease, glucocorticoids plus additional immunosuppression with azathioprine or cyclosporine were more effective than glucocorticoids alone for the treatment of pre- and postoperative inflammation [92]. The role of tumor necrosis factor alpha (TNF-α) inhibitors in the setting of vascular disease is not known [90]. There is general consensus that patients should be maintained on immunosuppression for several years following diagnosis given the high rate of the disease relapse [90]. The optimal duration of treatment is unclear. The use of anticoagulation to prevent thrombus formation, particularly in the postoperative period, is also controversial, as the risk of fatal bleeding is of concern following aortic aneurysm repair [90, 93].

There are no formal recommendations regarding screening patients with Behçet's disease for arterial involvement. The clinician should have high suspicion for aortic involvement in patients who present with concerning symptoms of chest pain, abdominal pain, or back pain. Most experts recommend screening patients for pseudoaneurysms with duplex ultrasound, contrast computed tomography (CTA), or magnetic resonance angiography (MRA) [93, 94]. The role of CT and MRI in evaluating and monitoring vascular changes in Behçet's disease has not been fully evaluated. There is some controversy with differentiating true and false aneurysms of the aorta and pulmonary arteries by CT scan [94]. The optimal surgical techniques are also highly variable due to an increased risk for postoperative complications resulting from the systemic vasculitis but also from concomitant glucocorticoid treatment.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory disease of the axial skeleton and is one of several diseases within the greater family of spondyloarthropathies. Ankylosing spondylitis is largely a clinical diagnosis and can vary based on specific findings present on medical history, physical exam, radiographic imaging, and laboratory evaluation. Other inflammatory conditions with similar features that also involve the axial skeleton include psoriatic arthritis, reactive arthritis, and undifferentiated spondyloarthropathy. The hallmark feature of ankylosing spondylitis is enthesitis, or inflammation around the sites of ligament insertion into

bone. This is most evident in the sacroiliac joints and spine, leading to radiographic evidence of acute sacroiliitis and potentially sclerosis [95]. Inflammation is also found within large tendons, peripheral joints, and the digits [95]. Extra-articular manifestations include anterior uveitis, cardiovascular disease, and aortitis with predilection for the ascending and abdominal aorta [95, 96]. Ankylosing spondylitis is strongly associated with the human leukocyte antigen (HLA)-B27 gene [96].

Aortitis

Aortic disease in patients with ankylosing spondylitis was first described in the 1970s when Bulkley et al. illustrated features of aortic regurgitation characterized by annulus dilatation, thickening of the aortic cusps, and inward folding of the free margins of the leaflets, that occurred in the absence of a stenotic lesion [97]. These findings are known as lone aortic regurgitation and are strongly associated with the presence of HLA-B27 [98, 99]. Aortic distensibility measurements have demonstrated less elasticity in the aortic root of patients with ankylosing spondylitis compared to healthy controls; this feature likely reflects a sclerosing inflammatory process that preferentially targets the aortic root and aortic cusps [100].

The fibrotic process that occurs at the annulus can also extend into the left atrium and lead to damage of the anterior leaflet of the mitral valve, which can induce mitral regurgitation and thus lead to conduction defects [101]. Classic histopathologic findings include proliferation of the intimal cells of the aorta, focal inflammation of the media with destruction of elastic tissue and fibrosis, and fibrous thickening of the adventitia [96, 97, 102]. This inflammatory process also contributes to narrowing of the vasa vasorum and infiltration of the vascular wall with lymphocytes and plasma cells [97]. There have been case reports of abdominal and thoracic aneurysm formation in patients with ankylosing spondylitis, though these complications are rare [103–106]. Specimens of abdominal aneurysms have shown hyalinization of the connective tissue, lymphocytic infiltrate, abundant calcification, and obliteration of elastic fibers within the vessel wall [106].

Clinical Presentation and Diagnosis

The diagnosis of ankylosing spondylitis is based on the recognition of clinical, laboratory, and radiographic image findings consistent with inflammatory sacroiliitis [107]. Current diagnostic suggestions are adapted from the 2013 Assessment of SpondyloArthritis International Society (ASAS). The modified algorithm has a sensitivity and specificity of 75–80% for axial disease among European patients with back pain longer than 3 months but less than 2 years and age of onset less than 45 years of age [108]. The algorithm includes the presence of sacroiliitis on X-ray, presence of inflammatory back pain, enthesitis, dactylitis, uveitis, positive family history, irritable bowel disease (IBD), psoriasis, asymmetrical arthritis, positive response to nonsteroidal anti-inflammatory disease, and elevated inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) [108]. Increased recognition of symptoms, early diagnosis, and the widespread use of disease-modifying antirheumatic drugs (DMARDs) and biologic therapy have led to fewer long-term complications, including aortitis and cardiovascular disease [109].

The clinical presentation of aortitis in patients with ankylosing spondylitis is variable and likely underestimated in the literature. Findings are often diagnosed incidentally, and symptoms do not become clinically significant until late in the disease course [102]. The spectrum of aortic involvement includes chronic hemodynamically stable disease with resultant fibrosis of the aortic root, to acute manifestations marked by a new diastolic murmur or symptoms of rapidly progressive diastolic dysfunction from involvement of the aortic valve [102, 110]. The exact prevalence of aortitis is unknown. The prevalence of aortic valve disease is estimated between 4% and 10%, with the latter noted in patients with disease duration greater than 30 years [110]. Epidemiological data is lacking, and limited case series reporting aortic involvement in patients with ankylosing spondylitis lack genetic and geographical diversity.

Despite reports that patients with ankylosing spondylitis are at increased risk for aortitis and aortic disease compared to age- and sex-matched healthy populations, there are no current guidelines for routine screening and monitoring of aortic involvement. The overall risk of aortic disease appears to directly correlate with increased disease duration and uncontrolled systemic inflammation. Small case series have demonstrated the use of transesophageal echocardiography as a method for detecting and monitoring ascending aortic disease in patients with ankylosing spondylitis; however, regular screening has not been standardized [102, 110]. Current recommendations from the ASAS and European League Against Rheumatism (EULAR) indicate that patients with ankylosing spondylitis should have appropriate cardiovascular screening based on national guidelines and aggressive suppression of the inflammatory process in order to decrease cardiovascular morbidity even further [111].

Management

Treatment course for patients with ankylosing spondylitis is based on the presence or absence of sacroiliac involvement (axial disease) and uveitis, as well as changes in disease course [111]. There are no specific therapeutic

recommendations or interventions for aortitis. Conventional surgical procedures for the repair of aortic aneurysms and valvular insufficiency are recommended [102]. Routime medical therapy for ankylosing spondylitis includes non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDS), tumor necrosis factor -alpha antagonists (TNF-inhibitors), and the anti-interleukin (IL)-17A monoclonal antibody secukinumab [109]. Clinical trials are currently investigating the efficacy of several other monoclonal antibodies as potential therapy for ankylosing spondylitis, and data will be emerging with respect to the use of biosimilar medications. Unfortunately, patients with severe disease, including complications involving the aorta, are excluded from clinical trial data [109].

Other Systemic Inflammatory Diseases with Involvement of the Aorta

Inflammatory aortitis should be considered in any patient who presents with acute aortic insufficiency, occlusive arterial disease, aortic aneurysm, or dissection without other associated risk factors [109]. Although aortic involvement has been reported in a number of systemic inflammatory diseases, the most common include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Cogan syndrome. These disease will be discussed briefly, as current treatment with the use of disease modifying antirhematic drugs (DMARDS) and biologic therapy has significantly altered the course of these diseases and the prevalence of vascular complications is decreasing.

Aortitis diagnosed in association with rheumatoid arthritis has been reported in a number of case series dating back to before the 1980s. The largest of these series included ten patients between the years of 1959 and 1985, in which nine patients were reported to have seropositive disease rheumatoid arthritis with severe extra-articular manifestations [113]. Seven of the patients (70%) had clinically significant rheumatoid vasculitis; three died as a direct result of aortitis; and four suffered fatal myocardial infarctions [113]. These complications are rare, though they continue to be of clinical concern because vascular disease can be potentially fatal. Patients will typically have severe, long-standing disease with high degrees of chronic systemic inflammation. Asymptomatic aortic regurgitation is far more common in patients with RA and has been reported in as high as 30% of patients with a confirmed diagnosis [114].

Systemic lupus erythematosus is associated with a number of cardiovascular complications; however, aortic involvement has rarely been reported [112]. While uncommon, patients with SLE and aortic involvement shared common risk factors of early onset of disease, long-term corticosteroid therapy, and significant arterial hypertension [115–118]. Interestingly, histopathologic examination of the arterial walls of patients with aortic involvement revealed distinct medial degeneration (similar to that seen in Marfan syndrome) rather than an inflammatory cellular infiltrate [116]. These findings suggest that long-term corticosteroid use and mechanical forces over time lead to aneurysm formation and instability within the vessel wall [115–117]. The prognosis in lupus patients with dissecting aortic aneurysm is grim, given that chronic corticosteroid use leads to weakening of distal segments of the aorta, thus making surgical repair and wound healing difficult [116]. Among the reported cases of SLE-related aortitis, there appears to be a predilection for the ascending aorta [115–118]. Echocardiography can be a reliable method for monitoring patients with SLE and the aforementioned risk factors for potential fatal aortic dissection [115–118].

Cogan syndrome is a systemic inflammatory disease that primarily affects young adults and involves the eyes and inner ear [119]. Aortitis with valvular insufficiency has been reported to occur at any time during the disease course and has an estimated prevalence of up to 10% of those diagnosed with Cogan syndrome [120, 121]. While aortic involvement is common, it is the association with ostial coronary artery disease that substantiates the recommendation for invasive coronary angiography in patients with Cogan syndrome and aortic involvement [119]. Acute aortitis may be life-threatening and often asymptomatic. Radiographic imaging of the aorta and its branches should be pursued in patients diagnosed with Cogan syndrome at the time of diagnosis and throughout the disease course [122]. Successful surgical treatment of both coronary artery disease and valvular regurgitation with conventional surgical techniques has been reported with good success [121, 123].

Marfan Syndrome

Marfan syndrome (MFS) is one of the most common inherited systemic disorders of connective tissue and results from mutations in the extracellular matrix protein fibrillin 1. Cardinal manifestations include proximal aortic aneurysm and disorders of the aortic root, dislocation of the ocular lens, and various musculoskeletal abnormalities such as excess linear growth of long bones and joint laxity [124].

The incidence of Marfan syndrome in the general population is estimated between 2 and 3 cases per 10,000 individuals [124, 125]. Marfan syndrome is most often inherited in an autosomal dominant respect with complete penetrance and variable expression. The majority of cases are caused by mutations in the FBN1 gene [123]. In as many as 25% of cases, a sporadic mutation leads to syndrome features, though the genetic history of the disorder is still being stud-

ied [126]. Other genes that have been linked to Marfanoid phenotypes include FBN2, TGFBR1, and TGFNR 2 [126].

Pathophysiology

The FBN1 gene is responsible for encoding fibrillin-1 monomers, which are an important glycoprotein component of the extracellular matrix and also function to preserve the synthesis and maintenance of elastic fibers. The production of abnormal fibrillin-1 monomers disrupts the formation of fibrillin-1 multimers and thereby the formation of structurally normal microfibrils. These microfibrils normally serve as the substrate for elastin within the aorta and other connective tissues [127]. More recently, a second genetic mutation has been identified and termed Marfan syndrome type 2 (MFS2), which is caused by a mutation in the gene that encodes the transforming growth factor beta type II receptor (TGFBR2) [128]. Mutation of this gene results in decreased and disordered incorporation of fibrillin into the connective tissue matrix [129]. Disruption of these structural protein components in the extracellular matrix leads to weakening of the vessel walls, and predisposes to dilatation and aneurysm formation. This dilatation, usually beginning at the level of the sinuses of Valsalva and extending into the ascending aorta, is thought to be secondary to the shear forces experienced by the aorta at these anatomic segments [125].

Clinical Manifestations

Marfan syndrome is known to be associated with a number of cardiovascular complications, particularly with the cardiac valves. Thickening of the atrioventricular valves can lead to prolapse and regurgitation, which may then progress to overt heart failure. This phenomenon is the leading cause of morbidity and mortality in younger individuals diagnosed with MFS. Mitral valve prolapse (MVP) is the most prevalent valvular abnormality in MFS, and is observed in 35–100% of patients [124]. Aortic insufficiency typically presents later in life in 15–44% of affected individuals, secondary to progressive dilatation of the aortic root [124]. Aortic dilatation is already present in 50% of those affected with MFS during childhood and is known to be a progressive phenomenon, in such that the severity of disease is directly proportional to the degree of dilatation and the length of the affected segment [125]. Dilatation is often greatest at the aortic root, which portends to a more favorable prognosis than if the dilation extends to involve the aortic arch [130]. Aortic aneurysm and dissection remain the most feared and life-threatening manifestations of MFS and should be ruled out in any patient with characteristic features of disease presenting with chest pain. There is an increased incidence of dissection with increasing aortic diameter and a family history of dissection, which makes lifelong monitoring for aortic disease a necessity in patients with MFS [124, 125].

Management

Routine monitoring of aortic dilation is essential for management of individuals with MFS. Current recommendations suggest baseline imaging with TTE, CT, or MRI, followed by repeat imaging within 6 months to assess rate of change (Fig. 16.4) [125, 131]. If the vessel wall is stable and less than 4.5 cm in diameter, annual screening thereafter is acceptable. TTE reliably allows for serial measurement of the proximal aorta, and CT and MRI offer the additional benefit of imaging the more distal segments of the aorta. More frequent monitoring is recommended if aortic diameter is approaching the threshold for surgical intervention (5 cm) or exhibits rapid growth (>0.5 cm per year) [125].

Beta-blocker therapy has been the cornerstone of medical therapy to decrease the rate of progression of aortic dilatation in patients with MFS, although this is not clearly defined by the small amount of data available [125, 132]. There are conflicting opinions within international societies, as the most recent American Heart Association (AHA) guidelines recommend the use of beta-blocker therapy in patients with MFS, while the European Society of Cardiology does not. Additional therapies have been investigated within the last decade, including the role of angiotensin-II receptor blockers (ARBs), for their role in inhibiting the TGF-β receptor. Brooke et al. demonstrated that the use of ARBs showed a significantly lower rate of progression of aortic dilatation once therapy was initiated in one study of a small cohort of pediatric patients [133]. The largest study to date by Lacro et al. monitored more than 600 children and young adults with MFS over a 3-year period and compared the use of losartan to atenolol and followed the rate of aortic dilation between groups. This study demonstrated no statistically significant difference between the two groups, and both groups showed a clear decrease in the aortic root Z scores [132].

Patients with Marfan syndrome should also be counseled regarding lifestyle modifications due to the increased risk for aortic dissection. Affected individuals should avoid contact sports and strenuous exercise that can lead to additional mechanical stress on the aorta. Additionally, women with MFS should be cautioned against pregnancy if the aortic diameter is greater than 4 cm, due to an increased risk for dissection [125]. Women with aortic dilation should be followed with serial TTEs and continued on beta-blocker therapy during pregnancy [125].

In terms of surgical management for patients with aortic involvement, elective repair is recommended when diameter is

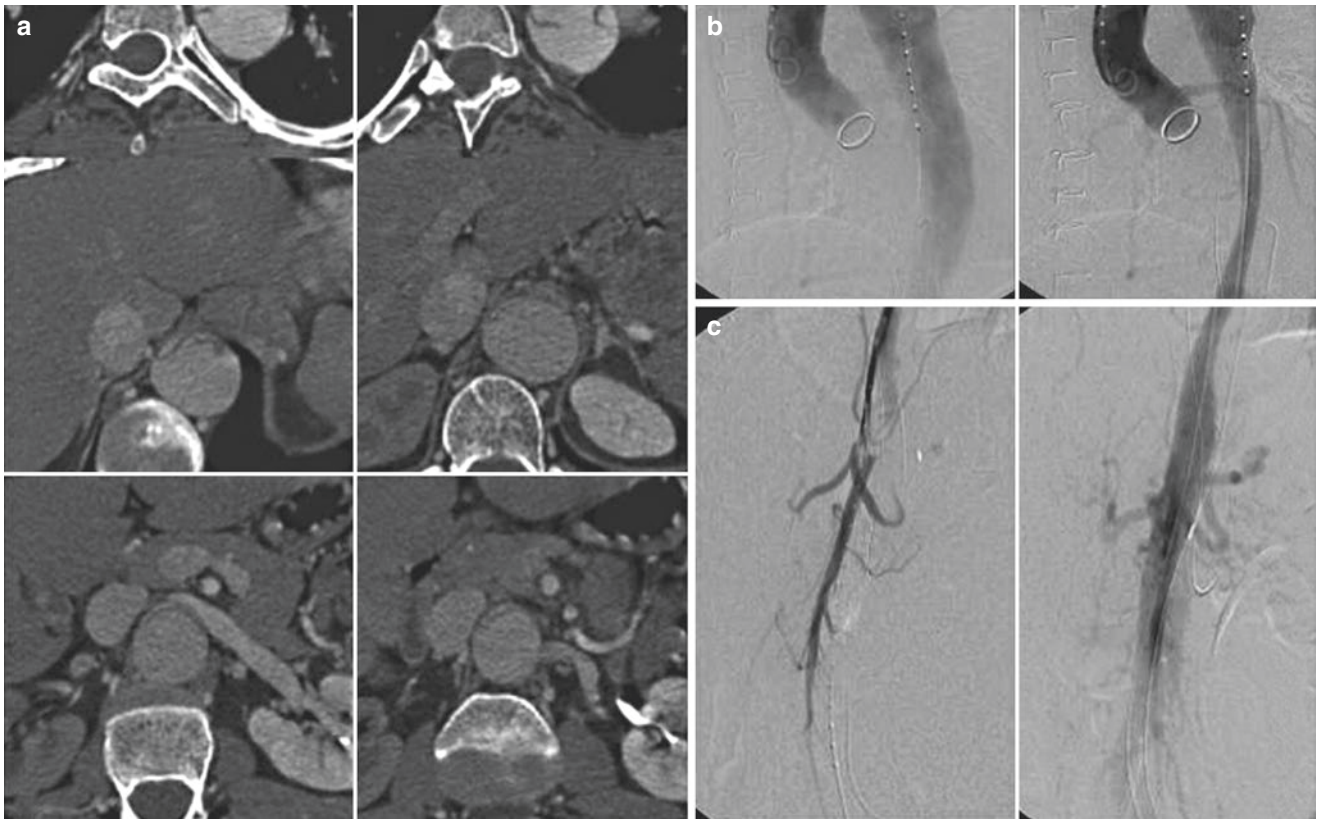

Fig. 16.4 Stent graft treatment in a 27-year-old with Marfan syndrome and newly diagnosed symptomatic type B aortic dissection. (**a**) Selected images from the CT scan showing type B dissection with a large proximal entry tear and true lumen collapse distally. True lumen is obliterated at the level of the abdominal aortic branch vessels, and the left kidney is supplied by false lumen and appears well perfused. (**b**) Aortograms before and after implantation of a stent graft. (**c**) Abdominal aortograms before and after stent graft placement. (From: Cherry and Dake [131]. Reprinted with permission from Elsevier)

≥5 cm, rate of growth is >0.5 cm per year, there is a family history of aortic dissection at a diameter <5 cm, or there is significant aortic insufficiency [125]. Gott et al. published a large case series that compared 30-day mortality rate in elective versus emergent aortic aneurysm repair and reported nearly a tenfold decrease in mortality favoring elective repair [134]. Surgical technique has evolved since first pioneered by Bentall, and currently, valve-sparing procedures are the method of choice when appropriate [135]. Valve-sparing surgery greatly decreases the risk of valve thrombosis and anticoagulation-related morbidity [135]. When compared to composite graft replacement, valve-sparing surgery demonstrated a lower mortality immediately postoperative and at 5 years, as well as decreased rates of both thrombotic and bleeding complications [134]. Despite the many advances in endovascular therapies for the treatment of vascular disease, open repair remains the treatment of choice in patients with MFS. Endovascular repair should be reserved for individuals with MFS and previous aortic replacement if complicated by distal dissection or false aneurysm, as mortality risk is estimated to be 33% with repeat open repair in this patient population [135].

Ehlers-Danlos

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders that results from mutations in the genes responsible for the formation of the extracellular matrix. These mutations create loss of structural integrity of virtually all tissues throughout the body. The syndrome is characterized by features of joint hypermobility, skin extensibility, and tissue fragility. EDS is a rare condition, with a prevalence of 1 per 10,000–20,000 births [136]. Table 16.1 lists the Villefranche classification of EDS and associated genetic mutations [136]. The vascular subtype, formerly type IV, is an autosomal dominant condition with 100% phenotype penetrance. The genetic mutation involved in vascular EDS occurs within the COL3A1 gene and results in structural defects of the pro α1 (III) chain of collagen type III. Mutations result in decreased thermal stability of the collagen network and abnormalities in procollagen production and apoptosis [138]. Type III collagen is an essential structural component of blood vessels, particularly arteries, as well as other connective tissues [139]. The abnormalities in collagen

Table 16.1 Villefranche Classification

New (former name)	Genetic defect	Protein defect	Inheritance pattern
Classical type (I and II)	COL5A1	Collagen V	Autosomal dominant
	COL5A2		
	COL1A1	Pro α(I) and pro α2(I) chains of procollagen I	Autosomal dominant
	COL1A2		Autosomal dominant or recessive
Hypermobility type (III)	TNX	Tenascin X	Autosomal dominant
Vascular type (IV)	COL3A1	Collagen III	Autosomal dominant
Ocular-scoliotic types (VIa/VIb)	PLOD1/unknown	Decreased PLOD1 enzyme activity/unknown	Autosomal recessive/unknown
Arthrochalasic types (VIIa/VIIb)	COL1A1/COL1A2	Prevent cleavage of N-propeptides	Autosomal dominant
Dermatosparactic type (VIIc)	ADAM-TS2	Deficient in procollagen I N-terminal proteinase	Autosomal recessive
Other forms			
X-linked (type V)			X-linked recessive
Periodontotic (VIII)			Autosomal dominant
Fibronectin deficient (X)	TNX	Tenascin X	Autosomal dominant
Unspecified			

From Germain and Herrera-Guzman [137]. Reprinted with permission from Elsevier

production and function can thus lead to spontaneous rupture of large- and medium-sized arteries, including the aorta. The abdominal aorta and its branches, the vessels of the aortic arch, and the large arteries of the limbs are the most vulnerable and prone to rupture [140]. Vascular EDS comprises roughly 4% of all EDS subtypes, and of those patients affected, approximately 80% of individuals are estimated to experience a vascular event by the age of 40 [138, 139, 141].

Pathogenesis

There have been 29 types of collagen identified in the human body, and each type provides unique structural support to the extracellular matrix of tissues including the skin, bones, liver, vascular system, muscles, and so on. Collagen surrounds the smooth muscle cells and the elastic lamellae, and together with elastin, create the tensile strength and stiffness of the aorta [142]. Over 90% of collagen is comprised of types I, II, III, and IV. Type I is the most abundant [142]. Type III is structurally similar to type I and contributes support to the skin, bones, and arteries. The aorta and its main branches are composed of type I and III collagen (as well as types IV, V, VI, and VII) [137]. Type III collagen specifically increases the overall flexibility of the aortic wall. Defects in the processing of procollagen III lead to vascular wall weakness and instability. In the normal aorta, type I and III collagen form the architecture of the intima, media, and adventitia layers. The concentration of type III collagen is particularly increased in the adventitia throughout the entire length of the aorta [137]. The endothelial and smooth muscle basement membranes are primarily composed of types I, III, IV, and V collagen [137]. Collagen also plays a critical role in vessel wall repair and regeneration, and the absence or altered composition of specific collage fibrils can result in impaired restoration of the vessel architecture.

The distribution of collagen is important in the flexibility and extensibility of the vascular system, and most specifically the aorta. Nonlinear elasticity is one of the most important mechanical features of the aorta and is dependent upon the ideal collagen and elastin structural motif [137]. The extracellular matrix of the aorta also varies slightly along the length of the vessel to accommodate for physiological changes in mechanical stress. The ascending aorta is dominated by type I, III, and IV collagen within the intima and media layers, whereas type I and IV collagen are distributed throughout the intima and media layers of the descending thoracic aorta [142]. The abdominal aorta is composed of type I and IV collagen within the intima and media, and type III collagen is heavily distributed in the adventitia layer [142]. The ratio of type I to type III collagen is also important in the pathophysiology of aneurysm development and vessel strength. In 1987, Menashi et al. demonstrated that a subgroup of patients with a significant family history of aortic aneurysm had decreased amounts of type III collagen in the media compared to the control group without aortic aneurysms [143]. This finding is consistent with features that are observed in patients with vascular EDS, as type III collagen is the main structural defect that contributes to abnormal wall structure of the aorta and thus increased incidence of aortic aneurysm formation.

Diagnostic Criteria for Vascular Ehlers-Danlos (Type IV) [142]

Major Criteria:

- Family history of vascular Ehlers-Danlos
- Arterial rupture
- Intestinal rupture
- Uterine rupture during pregnancy

Minor Criteria:

- Thin translucent skin
- Extensive scars and hyperpigmentation over bony prominences and skin
- Easy bruising
- Characteristic facies
- Acrogeria (aged appearance to the extremities)
- Hypermobility of small joints
- Tendon or muscle rupture
- Early-onset varicose veins
- Arteriovenous carotid-cavernous sinus fistula
- Pneumothorax or pneumohemothorax
- Mitral valve prolapse
- Club foot
- Chronic joint dislocations/subluxations
- Congenital dislocation of hips
- Gingival recession

Clinical Manifestation and Diagnosis

The diagnosis of vascular EDS is made on the basis of specific clinical criteria shown below:
The combination of two major criteria is highly specific for the condition, and the presence of one or more minor criteria supports the diagnosis of EDS [136]. Unlike other forms of EDS, skin and joint hyperextensibility is not often associated with vascular disease. Further biochemical and genetic testing to assess for abnormalities in procollagen production and the identification of the COL3A1 gene mutation are necessary to confirm the diagnosis of vascular EDS [138, 139, 141].

Individuals with vascular EDS are at risk for spontaneous vascular rupture, gastrointestinal perforation, or other organ rupture. Approximately 70% of patients with vascular EDS present with hemorrhagic shock, acute abdomen, retroperitoneal hemorrhage, or uterine rupture at the time of delivery [138]. Patients typically present with a major arterial or gastrointestinal event by the third decade of life, and the overall life expectancy of individuals with vascular EDS is 45 years old [144]. Stroke is an uncommon manifestation; however, there have been case reports of intracranial aneurysm rupture, spontaneous carotid-cavernous sinus fistulae formation, and cervical artery aneurysm [144]. Mitral valve prolapse and spontaneous coronary artery dissection in patients with EDS have also been reported but are rare events [144]. Individuals with primarily the hypermobility subtypes of EDS appear to have a higher incidence of aortic root dilatation, which is not a common feature of vascular EDS [145].

Management

There are currently no specific medical interventions shown to decrease mortality of patients with vascular EDS and no standardized protocols for monitoring patients with EDS. Morbidity can be somewhat modified by educating the affected individual about specific risk factors unique to vascular EDS. All patients should be offered genetic counseling and counseling regarding lifestyle modifications, including strict blood pressure control to avoid hypertension, avoidance of strenuous physical activity and contact sports (to limit sheering stress on the vasculature system and abdominal organs), and counseling about pregnancy and the risk of uterine rupture [139–141]. Patients are recommended to avoid GI endoscopies and should also avoid the use of antiplatelet therapy due to the increased risk of bleeding [140]. Ong et al. reported results from a multicenter, open-labeled, randomized trial in which celiprolol, a selective β1 antagonist with partial β2 agonist activity, was compared to no treatment in 53 patients with a clinical diagnosis of vascular EDS [146], results demonstrated a decreased incidence of arterial rupture and dissection in patients over a 4-year period compared to the control group [146]. Celiprolol (along with other selective β1-antagonists) has been shown to suppress the expression of transforming growth factor-β (TGF-β) in damaged vessels, which further reduces matrix remodeling [140]. Patients should be followed with noninvasive imaging to monitor for the development of asymptomatic aneurysms and dissections via echocardiogram, CT angiography (CTA), or MR angiography (MRA), and should have baseline imaging done at time of diagnosis [147] (Fig. 16.5). Patients with vascular EDS should be evaluated for cardiac valvular and vascular disease, as well as aortic dilation. Several experts recommend that patients are monitored with noninvasive imaging every 3–6 months [144, 145, 149].

Surgical procedures are challenging in patients with vascular EDS, as patients have an increased risk of complications from elective surgery and arteriography. The main concerns include life-threatening hemorrhage, anastomotic failure/disruption, poor wound healing, and wound dehiscence [140]. Surgical repair of affected vessels should be reserved for those presenting with imminent life-threatening

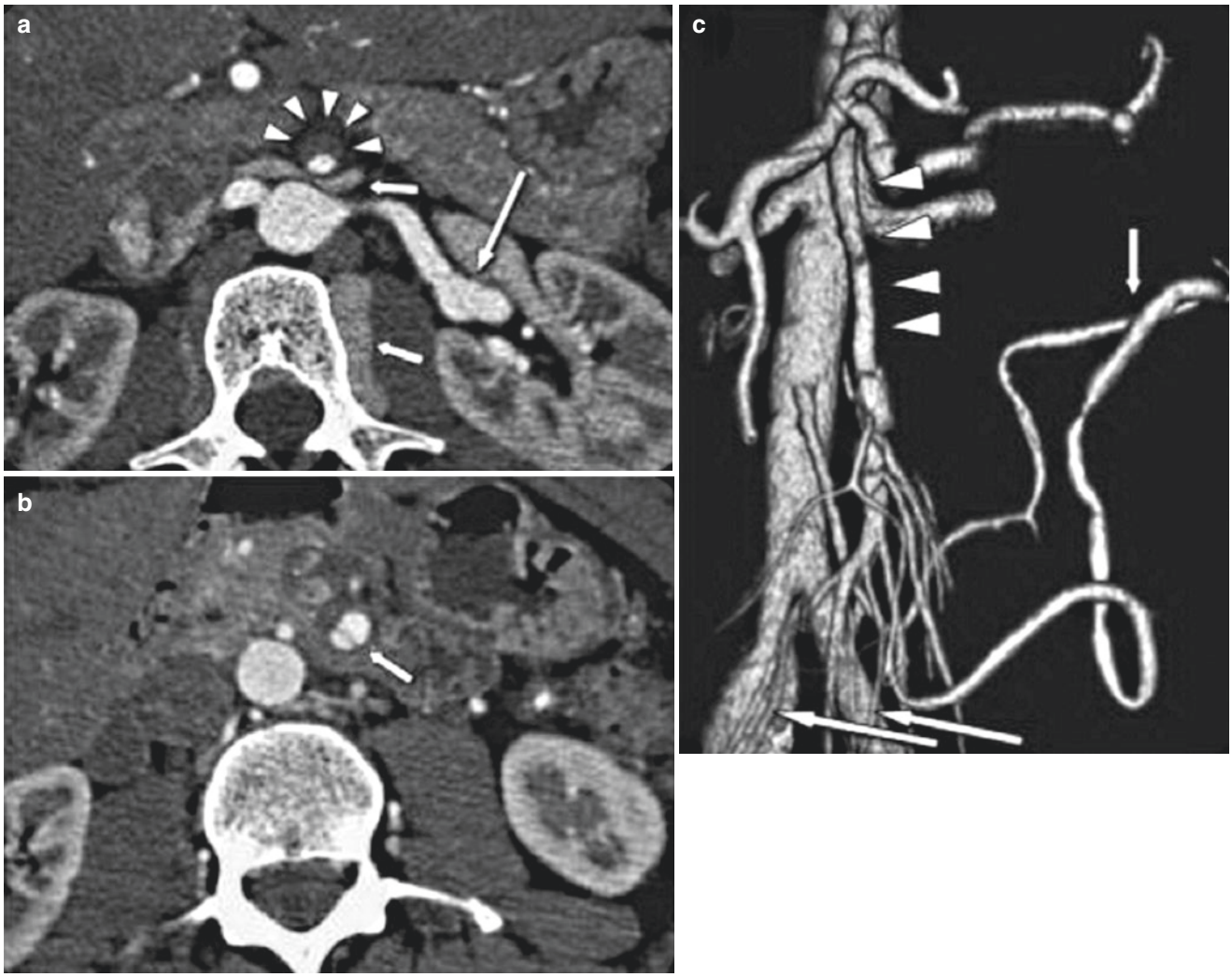

Fig. 16.5 CT angiogram revealing the dissecting aneurysm of the superior mesenteric artery (SMA) in a patient with type IV EDS. (**a**) Pictures show a thrombus occluding the false lumen of the proximal superior mesenteric artery [arrow heads], left renal artery aneurysm [long arrow], azygo-lumbar venous arch ectasia and "nutcracker" sign of the SMA (short arrows). (**b**) Intimal flap of the distal SMA aneurysm. (**c**) 3D reconstruction, straight aspect of the SMA with missing proximal branches (arrow heads), a well-developed Drummond arcade (short arrow), and bi-iliac aneurysms (long arrow). (From Nourissat et al. [148]. Reprinted with permission from Elsevier)

bleeding or vascular rupture. When surgical intervention is necessary, special consideration/attention to technique is imperative, including gentle handling of all tissues, use of balloon occlusion or of protected arterial clamps, tensionless anastomosis with pledgeted sutures, and application of Dacron or Teflon cuffs to cover the anastomosis [150]. Endovascular approaches are preferred if arterial or venous embolization is achievable [150].

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is an inherited group of connective tissue disorders that results from genetic alterations in type I collagen. The condition results in a wide range of phenotypic expression and features, most of which are inherited in an autosomal dominant manner; autosomal recessive mutations as well as de novo mutations have also been reported [151]. There are eight classic types of OI, ranging from clinically silent to mutations that are incompatible with life. All phenotypes of OI have some degree of vascular involvement, as type I collagen is a major structural protein of the aorta and its branches.

OI has an estimated incidence of approximately 1 in 20,000 births, and the severity of disease presentation depends largely on the expression of the genetic mutation [152]. Milder forms of OI lead to decreased amounts of normal type I collagen, while the more severe forms result from the complete absence of type I collagen [153]. Given this genetic variability, the clinical manifestations vary substan-

tially within families. There is variable expression of the classic features, including blue sclera, abnormal dental development (dentinogenesis imperfecta), hyperlaxity if ligaments and skin, hearing impairment, and abnormal development and structure of bones [154]. Other features involve abnormalities in the development of the respiratory system and decreased muscle tone of peripheral muscles [154].

Pathogenesis

Osteogenesis imperfecta is caused by mutations of the COL1A1 or COL1A2 genes, which leads to defects in the alpha-1 and alpha-2 chains of type I collagen. These defects are predominantly autosomal dominant [151]. Type I collagen fibers are polymers of tropocollagen molecules, each of which is a triple helix that contains portions of one alpha-2 chain and two alpha-1 polypeptide chains [151]. Type I collagen is an important structural protein, integral to the composition of bone and numerous connective tissues [151]. Elastin and collagen (types I and III) are the primary load-bearing elements in aortic tissue. Type I and III collagen make up 80–90% of the collagen present in the aorta and are the major constituents of the intimal, medial, and adventitial layers [155]. Deficiencies in both elastin and type I and III collagen have been well described in the literature, as predisposing to aneurysm formation.

While diagnosis of OI is made based on the observation of clinical signs and symptoms as previously described, there is no direct serologic test for the diagnosis of OI. Individuals may have nonspecific lab abnormalities indicative of bone and mineral metabolism, such as elevated alkaline phosphatase and hypercalciuria [156].

Little data exists on the prevalence of cardiovascular complications in patients with the varying forms of OI, and most patterns are drawn from small case series. Numerous cardiovascular complications have been reported in individuals with OI, including aneurysms or dissection that can present in nearly any vascular territory. Valvular heart disease including aortic valve insuficiency and mitral valve prolapse are common most commonly AI and MVP [157]. Patients with OI present a similar clinical challenge to those with EDS given the increased tissue friability, increased bleeding risk, and theoretical potential for late pseudoaneurysm development and should therefore be managed in a similar fashion.

Bicuspid Aortic Valve

Bicuspid aortic valve (BAV) was first described in 1844 by Paget and is now one of the most common cardiac congenital anomalies. The estimated prevalence of BAV ranges from 0.5% to 2% in the general population, with a male predominance of 3:1 [158, 159]. The exact mechanism of embryologic development that leads to bicuspid valve formation is not entirely understood. Over half of patients with BAV have additional congenital cardiovascular malformations, including anomalous coronary artery variants, atrial septal defect, ventricular septal defect, patent ductus arteriosus, supravalvular aortic stenosis (William's syndrome), obstructing left heart lesions (Shone's syndrome), and aortic wall abnormalities including coarctation (with or without Turner's syndrome), dilation, or dissection [158]. BAV is an important clinical challenge to physicians due to the significant number of associated conditions, early development of valvular lesions, and increased risk of endocarditis. Complications are common in adulthood, and therefore, the burden of disease related to BAV is more significant than any other congenital cardiac lesion.

Genetics and Pathogenesis

BAV shows a strong familial predisposition. Approximatley 10–14% of first-degree relatives will have BAV as well [158]. Inheritance is thought to follow a multifactorial and occasionally autosomal dominant pattern, with evidence of incomplete penetrance and variable expression [158, 160]. There is general consensus that individuals with BAV have an accelerated loss of the aortic media, low fibrillin content, and increased matrix metalloproteinase 2 activity, which leads to loss of elastic tissue and predisposition to aortic root dilatation [158, 160]. Interestingly, in smaller studies, the prevalence of aortic root dilatation in first-degree relatives of individuals with BAV, who have morphologically normal tricuspid aortic valves, has been reported as high as 32% [161]. In these studies, it was found that both patients with BAV and their first-degree relatives with dilated aortic roots were found to have a lower aortic distensibility and higher aortic stiffness index as compared to control subjects [161].

Clinical Presentation and Diagnosis

The diagnosis of BAV can be difficult as the majority of patients may have a normal physical exam and are clinically asymptomatic until the development of valvular disease. Symptoms of aortic stenosis, aortic insufficiency, and infectious endocarditis can incidentally lead to the identification of BAV. A systolic ejection murmur may be present on physical exam. Chest radiography may reveal cardiomegaly in the setting of chronic AI, aortic dilation, rib notching if coarctation is present, or aortic valve calcification [162].

Transthoracic echocardiography (TTE) is usually diagnostic for BAV. Chan et al. reported a sensitivity and specificity of 92% and 96%, respectively, for identifying bicuspid

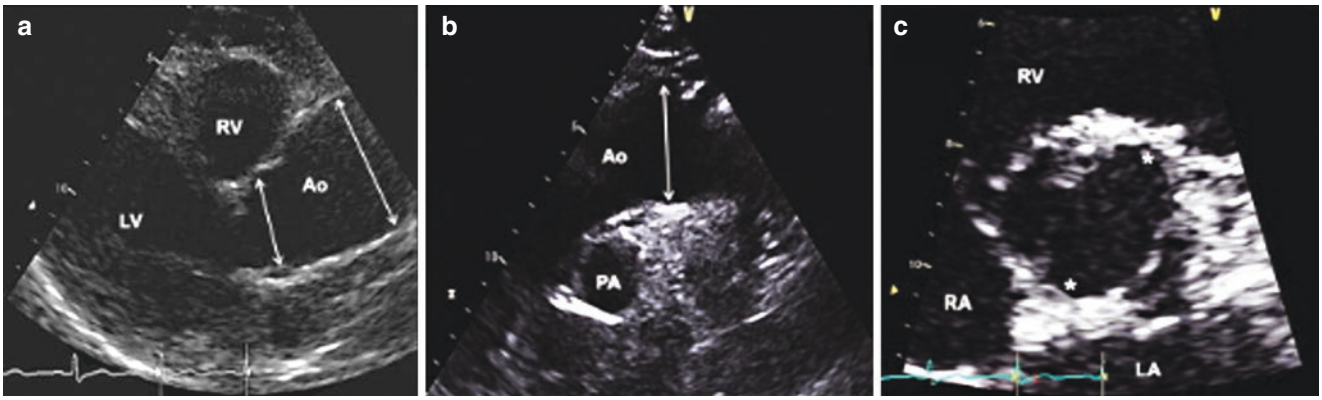

Fig. 16.6 Transthoracic echocardiogram of a 60-year-old woman with bicuspid aortic valve. Images show (**a**) parasternal long axis view showing aortic aneurysm with dilated root measuring 3.6 cm (first arrow from the left) and mid-tubular ascending aorta measuring 4.7 cm (second arrow from the left). (**b**) Suprasternal view showing mildly dilated proximal arch measuring 3.6 cm. (**c**) Parasternal short axis view through the aortic valve in systole showing two commissures (asterisks) with nonright fusion. RV right ventricle, LV left ventricle, Ao aorta, RA right atrium, LA left atrium, PA pulmonary artery. (From: Michelena et al. [165]. Reprinted with permission from Elsevier)

valve when adequate echocardiographic images are obtained [163]. Espinal et al. published a series of 710 patients and demonstrated improved diagnostic accuracy using transesophageal echocardiography (TEE), especially when using multiplane analysis. Transesophageal echocardiography is also superior for the assessment of the aortic root as well as for aortic dissection [164]. MRI and CT imaging have very high sensitivity and specificity for identifying cardiac valve structural abnormlaities and have the advantage of providing additional information about other associated anomalies as well as the extent of aortic involvement [158, 160] (Fig. 16.6).

Management

The management of bicuspid aortic valve is multifactorial and may require several important lifestyle modifications to prevent future complications. Patients should be educated regarding the risk of valvular lesion progression, the risk of infective endocarditis, as well as the potential for aortic aneurysm and dissection. Aortic stenosis in patients with BAV has been shown to progress more rapidly with a projected increase in gradient of 27 mmHg per decade and requires surgical replacement on average of 5 years earlier than individuals with normal tricuspid aortic valve stenosis [166, 167]. Aortic insufficiency secondary to BAV has been reported to be 1.5–3% and may occur in isolation or in association with aortic root dilatation, coarctation, or infective endocarditis [168–172]. BAV has been reported in as high as 25–54% of cases of aortic valve endocarditis, despite the overall decrease in cases of infective endocarditis in developed countries [173–175]. Good oral hygiene should be recommended for patients with BAV; however, current American College of Cardiology and American Heart Association guidelines do not recommend antibiotic prophylaxis for patients with BAV [176].

The most common abnormality in patients with BAV is aortic dilatation, with a prevalence of 20–84% [159]. Aortic dilatation begins in childhood in patients with BAV and increases throughout life at a higher rate than that of individuals with tricuspid aortic valves [177]. Originally thought to be secondary to long-standing effects of shear wall stress from abnormal flow dynamics, more recent investigation supports evidence of underlying structural abnormalities at the cellular level [178]. Dilatation can occur in the absence of valve dysfunction and typically involves the aortic root, ascending aorta, and occasionally the arch. The most feared complication is aortic dissection. While the exact incidence is controversial, some sources estimate that aortic dissection occurs 5–10 times more frequently in patients with BAV, and at a younger age on average, than those with structurally normal aortic valves [158, 160].

Screening and Follow-Up

The American College of Cardiology and the American Heart Association have several recommendations regarding the management of patients with bicuspid aortic valves. All first-degree relatives of patients with known BAV should undergo transthoracic echocardiography (Class 1, LOE C) [176]. Patents with known BAV should have both the aortic root and ascending thoracic aorta evaluated for evidence of aortic dilatation (Class 1, LOE: B) [176]. Serial transthoracic echocardiograms should be performed annually if there is presence of significant valve lesions or aortic root ≥40 mm; if neither abnormality is present, then patients can undergo screening every 2 years [179, 180]. Patients with BAV remain at risk for development of aortic root

dilation even after aortic valve replacement and should have continued surveillance following surgical correction [158, 160].

Treatment

The treatment approach for patients with bicuspid aortic valve should entail a combination of blood pressure control, lifestyle modification, and serial monitoring for the development of severe valvular dysfunction. In most cases, indications for aortic valve replacement are similar to those for patients with degenerative tricuspid aortic valve disease. If significant valvular disease is present during childhood or young adulthood, valvuloplasty remains the procedure of choice. In the adult patient, calcification of the valve and comorbid conditions makes valve replacement the preferred approach. Approximately 30% of adults who undergo aortic valve surgery will also require aortic root replacement secondary to ascending aortic aneurysm [181, 182]. Indications for resection of aortic aneurysm in patients with BAV are shown below. Surgical options include replacement of the supracoronary ascending aorta with a graft, replacement of the root and ascending aorta with reimplantation of the coronary arteries (Bentall procedure), and valve-sparing replacement. The Bentall procedure has the advantage of avoiding re-operation and lower rate of aortic complications, which make this technique the ideal procedure for young patients [158, 160].

Indications for Resection of Aneurysm Involving the Ascending Aorta in Patients with BAV [158, 160]

- Aortic diameter >5.0–5.5 cm
- Aortic ratio >1.5 or 1.4 in women planning to become pregnant
- Annual growth rate >3–5 mm
- Symptomatic aneurysm
- Large sinus of Valsalva aneurysm
- Patients undergoing valvular surgery for BAV with aortic diameter >4–5 cm or ration >1.4

Special Considerations

Women with BAV should be counseled regarding the risk of physiological and hemodynamic changes that occur during pregnancy which can lead to deterioration and rapid symptoms of congestive heart failure. Females with BAV and significant dilation >45 mm should be counseled against pregnancy [179].

Exercise restrictions for individuals with severe AS or AI and dilated aortic root with BAV are no different than those for patients with structurally normal aortic valves and thoracic aortic disease, with some caveats [176]. Patients with aortic diseases, in general, should be counseled on exercise. Aerobic exercise is typically encouraged. Some have advocated a treadmill exercise stress test to evaluate the blood pressure response to aerobic exercise. Heavy lifting or those activities resulting in significant strain or use of the Valsalva maneuver should be avoided. Isometric activities can cause an increase in the mean arterial pressure, and consequently a significant rise in central aortic pressure with a theoretical increased risk for aortic dissection or rupture. This phenomenon is observed with the Valsalva maneuver also. Therefore, strenuous labor and routine heavy lifting should be avoided in those with an ascending aortic aneurysm [176].

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Aortic Infection: Pathophysiology, Bacteriology, and Management

17

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Introduction

Infections of the aorta remain a challenging problem for the vascular surgeon. The deceptively simple surgical caveat of "source control" with removal of all infected material requires sophisticated strategies to maintain perfusion to the viscera and lower extremities. Exposure of the vasculature in an inflamed or infected field may be associated with injury to surrounding critical structures. The type of conduit chosen for repair is a complex decision depending on patient factors, microbiology of the infection, need for sufficient size of the replacement conduit and immediate availability. The question as to which types of infection may be managed with less aggressive debridement continues to evolve. For some of these patients, endovascular options may exist in the presence of a severe inflammatory response but may not be appropriate in settings of frank purulence or with aggressive types of infection. Fortunately, aortic infections are rare.

Types of Aortic Infection and Incidence

Aortic infections can be described by anatomic location (arch, thoracic, suprarenal, infrarenal), by type of organism (gram positive, gram negative, polymicrobial, fungal, treponemal, polyresistant), and by etiology or mechanism (primary or secondary which also includes postinstrumentation and postsurgical). Primary aortic infections are the rarest of all infections described and include primary aortitis, infected atherosclerotic ulcer, and infected aortic aneurysm [1]. Historically, infectious aortitis has also been referred to as bacterial, microbial, mycotic, and cryptogenic aortitis [2]. Analysis of surgical specimens removed at time of abdominal aortic aneurysm repair found a 4.3% prevalence of asymptomatic aortitis in one case series [3]. A true incidence of primary microbial aortitis, infection of the aorta from bacteremia or from an infected contiguous structure, is not known as many of these patients may die from overwhelming sepsis or die from unknown causes while being treated for overwhelming infection.

Pathophysiology

Several mechanisms have been proposed to explain infections of the aorta. Septic emboli from endocarditis may infect the aorta by lodging in the vasa vasorum. This may lead to relative ischemia of the wall and cause full-thickness degeneration and aneurysm formation. Historically, this caused the majority of infected aneurysms and the organisms most often were streptococcus [4]. Atherosclerotic irregularities of the wall or areas of ulceration may also be prone to infection during episodes of bacteremia and may harbor septic emboli with the same result [2, 5]. These atherosclerotic lesions are most often suprarenal, and infections in this location are more difficult to treat [5]. A case report from the author's institution (Case #1) documented the development of an infected aortic ulceration in a period of 2 weeks in a patient with recent trauma and bacteremia with serial CT scan examinations [6] (Fig. 17.1). Contamination of the thrombus in an already existing aortic aneurysm may also occur and most frequently occurs in the infrarenal position since this is the most common site of aortic aneurysms [7, 8]. Direct contamination from inadvertent self-inflicted arterial punctures (instances of drug abuse) or in cases of therapeutic endovascular intervention or diagnostic arteriography is also possible [4].

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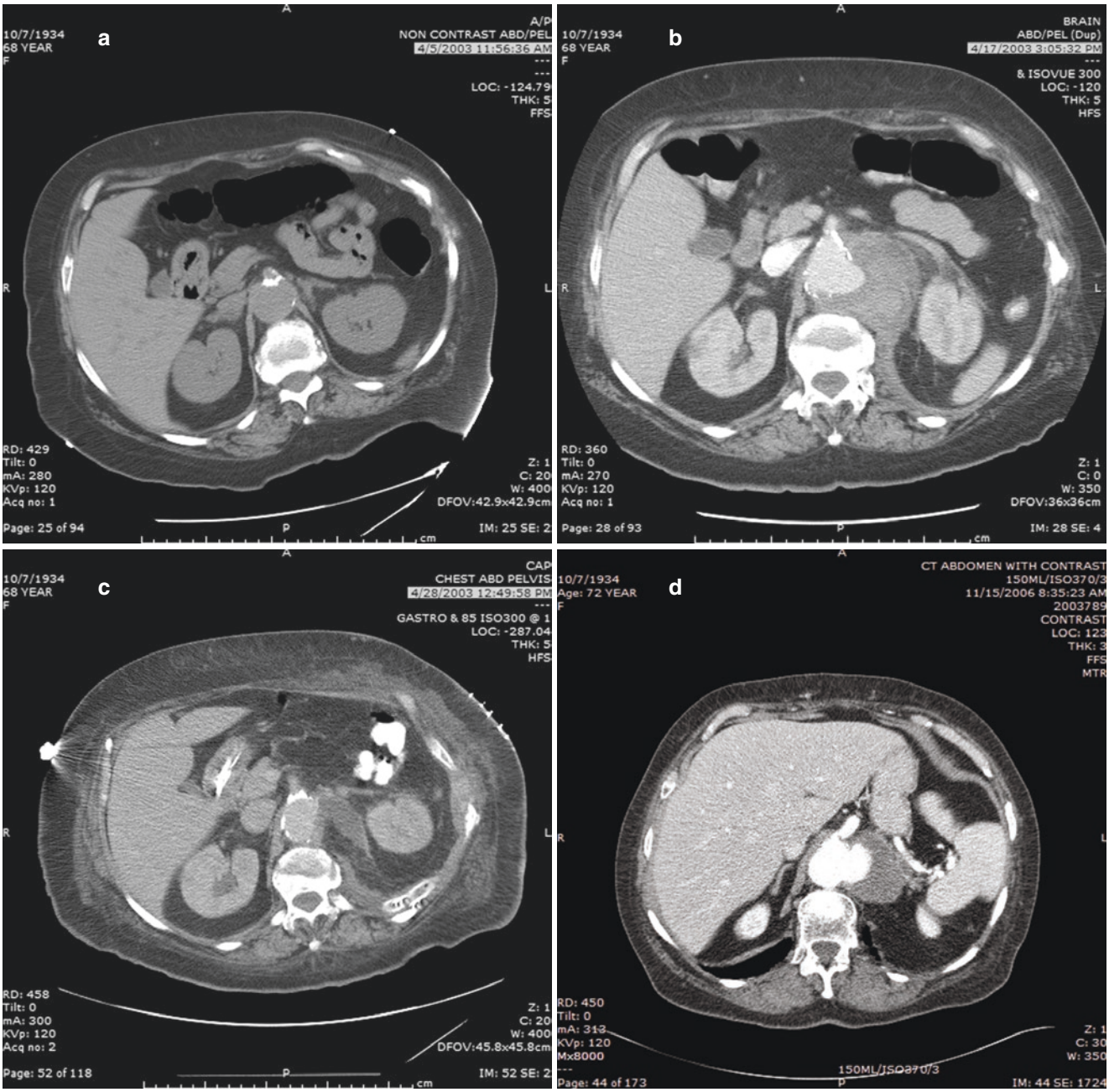

Fig. 17.1 Case #1. A 68-year-old woman presented with back pain and a nondisplaced L1 fracture on CT (**a**). She was managed with bracing. Two weeks later, she was readmitted with a left lower lobe pneumonia and worsening back pain. CT scan showed an aneurysmal segment of the aorta (**b**). Blood cultures were positive for methicillin-sensitive *Staphylococcus aureus*, and echocardiogram demonstrated an aortic vegetation. Emergent operation found a penetration of an atherosclerotic ulcer. Debridement of the infected tissue and primary repair was performed with a good result as shown on CT 2 weeks after discharge (**c**). She was treated with 6 weeks of intravenous antibiotics and then oral suppressive therapy. She subsequently developed recurrent aneurysmal dilation at the site 3 years later (**d**). She remained asymptomatic and with negative blood cultures. She declined any further intervention and expired at home 5 years later. (**a**) CT 4/5/2003. (**b**) CT 4/17/2003. (**c**) Post-operative CT 4/28/2003. (**d**) CT 11/6/2006

Bacteriology

Series have documented up to 60% of bacterial aortic infections are gram positive and are most often staphylococcal species, *Enterococcus*, or *Streptococcus pneumoniae* [2]. Gram-negative infections still occur with the majority being *Pseudomonas aeruginosa* and *Salmonella* [9, 10]. Results may vary by institution and geographic location [11]. Salmonella infections, occurring more frequently in Asia, are known to adhere well to vascular endothelium and

atherosclerotic lesions making the aorta a frequent site of infection [12]. Most mycotic aneurysms are caused by a nontyphoidal species which have a recognized tendency to dilate the aorta rapidly and rupture. Modern antibiotics appear to be highly effective against these species, however, and may have a markedly positive impact on the long-term success of the procedures performed in these patients [13]. In contrast to the previous bacteriologic profile, more recent Western series have documented gram-positive bacteria in 41% of aortic infections, salmonella in only 15%, pseudomonas in 3%, other gram-negative bacteria in 13%, and anaerobic bacteria in 2%. Negative cultures are reported in up to 25% of patients with obvious inflammatory changes and may reflect prior antibiotic treatment or failure to identify anaerobic pathogens [14]. Conversely, the presence of bacteria in the aortic wall without overt signs of infection or illness may be much more common and well tolerated than is commonly thought. One series of aortic wall cultures performed during routine aneurysm repair in patients with no systemic signs of infection recorded positive cultures in 15% with 81% being gram-positive organisms and 19% gram negative [15]. Subsequently, it has not been recommended to routinely culture the aortic wall during aortic surgery or treat those patients should one of those cultures be positive without signs or symptoms of systemic illness [16].

Historically, *Treponema pallidum* infections were the most common cause of thoracic aortic aneurysms showing a predilection for the ascending aorta (50%) and arch (35%). Unlike the other infections described, *Treponema pallidum* directly invades the aortic wall causing an endarteritis which results in necrosis of the elastic fibers with wall necrosis and eventual rupture [17, 18]. With appropriate antibiotic therapy currently available, these infections are reported only rarely. *Mycobacterium tuberculosis* infection of the aorta is more common in countries where pulmonary infection is endemic and may occur from direct extension of the infection from the surrounding lung to the thoracic aorta [19]. Aneurysms from this infection occur rarely [20]. Pathology typically reveals granulomatous changes and noncaseating lesions. Acid-fast bacillus may be identified on Ziehl–Neelsen staining [21]. Atypical pathogens, such as fungus, are also rare but may occur in those patients with chronic immunosuppression [22].

Clinical Presentation

The clinical presentation is also determined by the location, the type of organism responsible for the infection, and the presence of an aneurysm [23]. Nearly all patients present with nonspecific symptoms of fever and chills. Patients may present with life-threatening hemorrhage from aortoesophageal, aortobronchial, or aortoduodenal fistulae as the initial presentation. Those with aneurysms previously present or rapidly enlarging may have symptoms of back or abdominal pain as well. Some patients with rapidly enlarging aortic segments may experience compressive symptoms on surrounding structures such as hoarseness, cough, and dysphagia or note a palpable pulsatile mass [19]. Some may present with arterial thrombosis or distal embolization of septic thrombi. More common, however, are the patients with very nonspecific symptoms of generalized pain in a setting of bacteremia which may have been attributed to a pneumonia or urinary tract infection. Physical examination may be benign in these patients [24]. It has been reported that 40% of infected abdominal aortic aneurysms may not be palpable and remain unrecognized until rupture [25]. A history of spinal osteomyelitis, retroperitoneal abscess, chronic immunosuppression, or steroid use in a patient with nonspecific symptoms should alert the physician to the possibility of an aortic infection. Other conditions associated with aortic infections such as malnutrition, diabetes mellitus, and chronic renal failure occur so frequently in the general population to be of little aid in diagnosis.

Diagnosis

Routine laboratory evaluation in these patients most often shows an elevated white blood cell count (65–85%), erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) (75–80%) [26, 27]. Blood cultures may or may not be positive at the time of presentation. Positive blood cultures are present in 50–70% of patients with infected aneurysms. As mentioned previously, a negative blood culture does not exclude the diagnosis [28, 29]. CT scanning with contrast provides the most rapid, most specific, and least invasive means of confirming the diagnosis. Characteristic features of aortic wall infection include wall thickening, presence of gas within the wall, surround adventitial edema, increased soft tissue mass around the aorta, and enhancement of the aortic wall. In cases of preexisting aneurysms, gas within the thrombus or aortic wall and surrounding inflammation suggest the diagnosis. For aneurysmal degeneration, which occurs in the setting of aortic wall infection, the aneurysms are eccentric, localized, saccular, multiloculated, and most often occur in atypical locations. Radiographically these can be visualized with disruption of calcium in the aortic wall. Most frequently the aorta above and below the infected aneurysm appears entirely normal [11, 30, 31]. Routine confirmation with arteriography is no longer necessary for the diagnosis but may add important definition of critical branches in the visceral segment. Rapid growth in a matter of days or weeks in patients with serial CT examinations is also suggestive of infection [6]. Contiguous abscess or osteomyelitis can also alert the physician to the possibility of aortic infection.

Other imaging modalities have been utilized. Radioisotope-tagged leukocyte scans have been utilized but are not specific for aortic infection [32]. MRI can be considered when contrast CT is contraindicated but also carries the risk of nephrogenic systemic fibrosis (NSF) from the administration of intravenous gadolinium in dialysis-dependent patients or in those with an estimated glomerular filtration rate (GFR) less than 30. MR images typically show a low-intensity signal surrounding the aorta on T1-weighted images and a "halo" of hyperintense signal on T2-weighted images [33, 34]. Positron-emission tomography (PET)-CT scan has been reported to demonstrate increased fluorodeoxyglucose (FDG) uptake in inflamed aortic walls and correlate with aneurysm wall instability and symptoms [35].

Preprocedure Management

Culture-directed antibiotic therapy at the time of initial diagnosis is ideal. Unfortunately, as many as 50% of patients will have a negative initial blood culture [28, 29]. Other adjacent sites of infection such as vertebral osteomyelitis or psoas abscess may be biopsied and used to guide therapy. If cultures are negative, most advocate broad-spectrum antibiotic coverage for both gram-positive and gram-negative bacteria and anaerobes. Unless the patient has unique characteristics such as a previous diagnosis of syphilis, travels to areas where tuberculous infections are endemic, or is immunosuppressed, coverage for atypical infections is not initially recommended [22]. Antibiotic coverage should be narrowed as soon as the type of infection has been confirmed.

Surgical planning is critical but should be done expeditiously since even aneurysms of a smaller size frequently rupture in this setting. Strategies should consider the type of organism. Polyresistant and gram-negative infections are more virulent and require more extensive resection and debridement in comparison to pan-sensitive gram-positive infections which may be managed with less aggressive treatment. Patient anatomy also dictates requirements for the type of operation and may be modified by pre-existing comorbid risk factors. Some severely impaired patients with less virulent infections may be candidates for more limited procedures with lifelong antibiotic suppression compared to younger individuals where a more extensive but durable procedures may offer the best chance for long-term survival. Despite these admonitions, aortic infection remains a lethal disease with hospital mortality rates ranging from 16% to 44% [36–38].

Procedural Options

Any strategy should achieve the dual goals of control of infection and maintenance of perfusion to critical organs. Antibiotic therapy alone without surgical excision has been attempted with poor patient outcomes [40, 41]. Generally, removal of all infected portions of the aorta has been the standard of care. Any surrounding infection in the retroperitoneum should also be removed at the time of the initial operation. Debridement back to healthy aortic tissue is necessary even in cases of extra-anatomic reconstruction in order to close the aortic stump adequately or to perform a durable anastomosis. Stump closures should be performed with a two-suture line technique consisting of a proximal row of horizontal mattress sutures followed by an independent simple closure of the cut aortic edge. This closure is then reinforced with prevertebral fascia whenever possible [42]. Surgical options for the restoration of perfusion included extra-anatomic bypass (axillary to bifemoral), or in situ reconstruction with PTFE, antibiotic-impregnated Dacron graft, cryopreserved cadaver homograft, or bypass with a patient's own native deep femoral veins (NAIS procedure). The retroperitoneal space, aortic stump, or new aortic suture line should also be covered with omentum whenever possible to isolate the suture line from direct contact with the bowel. Endovascular options covering infected segments of the aorta have been previously utilized as a temporizing measure until definitive excision of all infected material can be performed. Currently, there appear to be some select circumstances where endovascular therapy may provide a durable option with a low morbidity and mortality. Antibiotics should be maintained for the perioperative period regardless of the type of reconstruction. There is, however, no consensus for the duration of antibiotic therapy. Most clinicians recommend 6 weeks of culture-directed intravenous antibiotics and lifelong suppression with an oral antibiotic such as sulfamethoxazole/trimethoprim thereafter [30, 37, 43].

Nonoperative management with continued antibiotic therapy is not recommended for definitive care and has been associated with an in-hospital mortality of 50% with an event-free survival of 32% at 1 year [40]. A recent series of patients with primarily salmonella (60%) infections confirmed an in-hospital mortality of 58% for those managed with antibiotics alone versus 12% for those managed with surgical intervention [44]. The authors also commented in this retrospective review that patients in the medically managed group were a self-selected group due to their prohibitive comorbid illnesses where survival was not likely regardless of the treatment offered.

Early reports of in situ reconstruction with synthetic graft materials were plagued with both a high reoperation rate for graft infection (23–63%) and later recurrent infection (7%) with concerns for later aneurysmal degeneration of the graft in the setting of infection [1]. Others noted improved results with the use of rifampin-soaked graft material [45] or silver-impregnated grafts in infected fields [46]. Perioperative mortality rates were still high (25% in one series) and recurrent infections were still frequent occurring in 15%. Silver was

subsequently found in animal models not to inhibit bacterial growth [47] while further study demonstrated good adherence of rifampin solutions (up to 10 mg rifampin/liter of saline soaking for 15–25 min) [48] to commercially available off-the-shelf collagen-impregnated Dacron grafts [49]. As this strategy became more commonly adopted, more authors noted that infections of low virulence without antibiotic-resistant bacterial strains and, more specifically, low-grade staphylococcal infections were best treated in this manner [23]. Operative mortality was noted to be much lower in stable patients (2.3%) [50], and recurrent infections occurred more rarely ranging from 0% to 8% in multiple small series [51–53].

For patients with aggressive or extensive infection, extra-anatomic constructs were the only option for revascularization for many years. These were lengthy procedures (often 8–12 h) requiring careful attention to performing the "clean" portions of the procedure without contamination from the "dirty" excisional portion. In a retrospective series of infected aneurysms, a 13% perioperative mortality due to continued sepsis was reported for extra-anatomic revascularization which compared favorably to the 32% mortality for those patients with in situ reconstruction [14]. Later authors attempted to decrease the morbidity and mortality from this lengthy procedure by performing the reconstruction first, allowing the patient (and surgeon) time to recover. This strategy was first employed in patients with aortic graft infection with improved patient survival [54]. A 10-year retrospective review of aortic excision and extra-anatomic reconstruction found perioperative mortality relatively stable at 11% (four patients out of 36) with two additional late deaths from bypass graft failure and aortic stump disruption. This series also noted the high incidence (25%) of axillobifemoral graft failure (thrombosis) requiring re-intervention [55].

In an attempt to minimize both the risk of recurrent infection and reoperation for graft failure, autologous reconstruction was offered as a durable alternative for good risk patients. The Neoaortoiliac System (NAIS) harvests the femoropopliteal vein and uses it in place of synthetic graft (Figs. 17.2, 17.3 and 17.4). The dissection can be time consuming and technically demanding, and a thorough review of the anatomy is recommended prior to attempting the procedure [56, 57]. Additionally, venous duplex is required prior to procedure to identify veins <6 mm or veins with signs of chronic occlusive disease as not being suitable for use as conduit. Procedure length for experienced surgeons remains at 8–10 h. 30-day mortality has been reported to be <10% with 5-year mortality rates ranging from 30% to 50%. Anticoagulation and long-term antibiotics are not recommended for these patients with extensive debridement of infection and autologous anatomic reconstruction. Reinfection rates have been reported to be extremely low (<2%), and limb salvage rates have been high at 89–96% with this strategy. Interestingly, venous morbidity was also

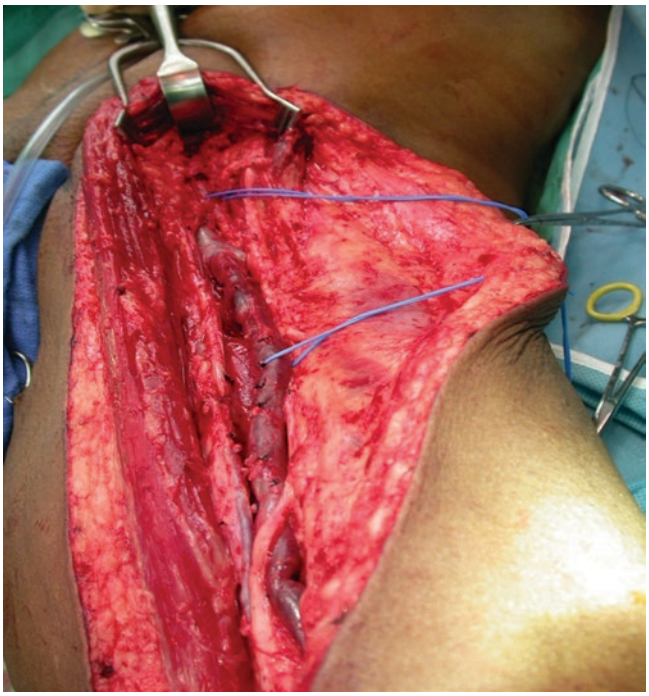

Fig. 17.2 Intraoperative photo demonstrating dissection of superficial femoral vein. (Image courtesy of Ahsan Ali MD)

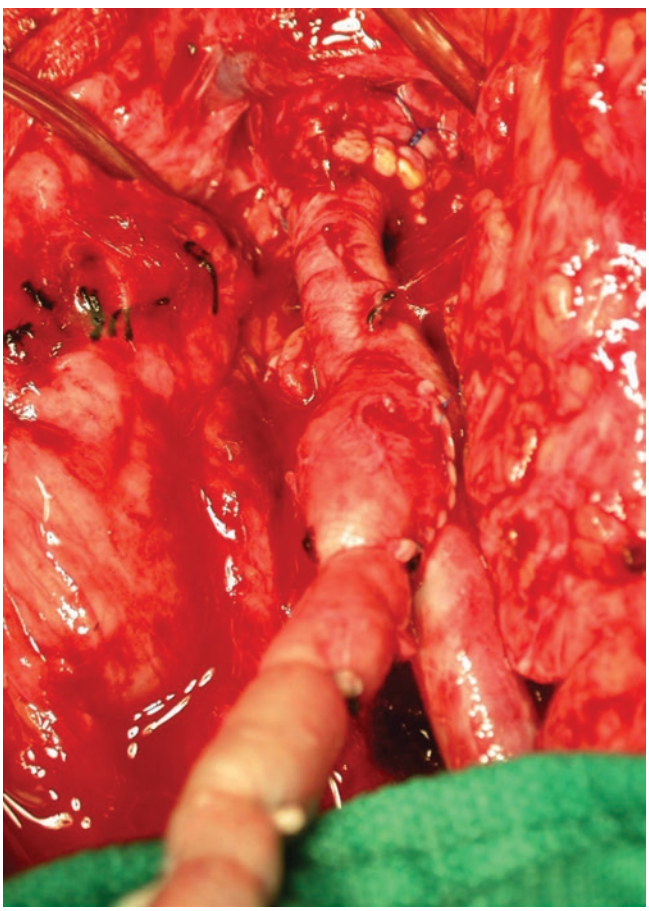

Fig. 17.3 Aorta and iliac reconstruction with native superficial femoral vein. (Image courtesy of Ahsan Ali MD)

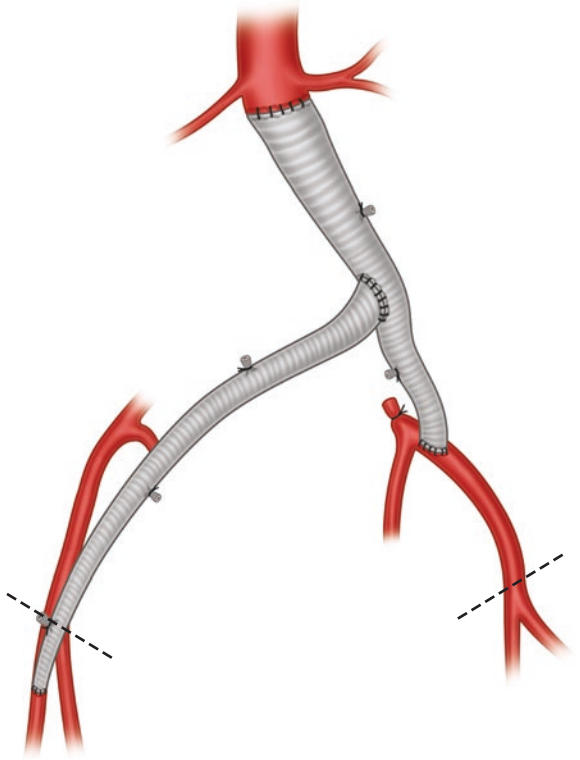

Fig. 17.4 Diagram of NAIS reconstruction with aorto-profunda femoris and aorto-external iliac anastomoses. (Drawing courtesy of Ahsan Ali MD)

reported to be extremely low with only 12% of patients requiring fasciotomy and 15% experiencing long-term venous insufficiency [56]. In a more recent series of 56 severely ill patients where 21 had aortoenteric fistulae as the presenting symptom, 30-day mortality was 13% with seven subsequent anastomotic ruptures from reinfection and a 4% major amputation rate. Primary graft patency rates remained high, and 5-year survival was 63% [58]. Risk factors identified in both series for poor patient outcome with recurrent infection and death included the presence of aortoenteric fistula, positive perioperative cultures, fungus identified as the infecting organism, and the need for femoral anastomoses [56, 58].

The use of allografts in this setting has enormous appeal with a decrease in patient morbidity when compared to extra-anatomic reconstruction, an overall decrease in operative time when compared to the NAIS procedure, and a theoretical resistance to infection when compared to synthetic grafts. Additionally, large-sized grafts are available for more proximal aortic reconstruction just as with synthetic grafts. Allografts were originally used in the 1950s, but results were disappointing with rejection and late aneurysm formation occurring frequently [59]. Currently, these grafts are cryopreserved within 24 h of harvest and selected to be ABO compatible. Cryopreservation has been shown to maintain structural integrity while decreasing antigenicity [60, 61]. More recently, however, it has been noted that some immunogenic properties of the vessel are maintained in the allograft [62]. Differing degrees of rejection reaction have been postulated to occur long term, and the necessity for ABO and HLA matching is no longer certain [61, 63].

Multiple case reports have documented reasonable operative times with acceptable perioperative morbidity and mortality (6%) throughout the 1990s with use of these grafts [64]. Distinct technical challenges were recognized as more experience was gained. The thawing procedure for these grafts is somewhat lengthy (30–60 min) but maintains durability and should be timed accordingly for graft availability during the procedure. Rapid thawing or mechanically removing ice from the material increases the risk of micro-fracture of cryopreserved material. Additionally, these grafts should not be clamped for the same reason. If absolutely necessary, the portion of the graft that will later be excised is recommended as a clamp site. Consideration of the angle of the iliac limbs and performance of a tension-free anastomosis are important factors to maintain long-term patency and to avoid anastomotic aneurysms. Side branches should be carefully searched for and suture ligated since late blow out or erosion into surrounding viscera has been reported. Use of an allograft does not eliminate the need for aggressive debridement or drainage of the area. Aggressive, difficult-to-treat infections may require prolonged intravenous therapy for up to 3 months, but use of an allograft does not appear to increase the risk of complications. With these factors recognized, 30-day mortality has decreased to 2.6% in one series [65]. These results have been confirmed in more recent series (8%), and more data is being accumulated on long-term complications. In a retrospective review of 25 patients treated over a 10-year interval, late mortality occurred in 20% with graft complications occurring in 12%. These included one case of thrombotic occlusion of the graft, one aneurysmal degeneration, and one case of aortoenteric fistula. Seventy-four percent of patients survived 3 years in this series with an event-free survival of 58% [63]. It has been observed that in series with more patients with aortoenteric fistula, mortality rates are higher (39%) [66]. Additional patient factors such as the cause of infection (primary versus graft related), co-existing comorbidities, type of organism, completeness of debridement, anatomic location (thoracic versus visceral segment versus infrarenal) and emergent nature of procedure impact patient outcome as well. Observations gained from multiple case reports and retrospective small series have found that patients who tolerate this procedure with less morbidity and risk of mortality are generally those younger than age 65 with a native aortic infection in an infrarenal position from a pan-sensitive gram-positive organism without obvious purulence at operation. A sufficient length of

omentum to cover the new allograft and anatomy not requiring a femoral anastomosis also impact favorably on the outcome [63–69].

Given the risk to the patient and the complexity of the procedures described, the appeal of endovascular options to treat these aortic infections is apparent. In discussing current experience and recommendations, there are distinct anatomic differences with many initially advocating TEVAR as the treatment of choice for all ruptured mycotic thoracic aneurysms and most of the intact ones [13]. One-year survival is 76% with this strategy [70]. Others have noted no perioperative mortality and a 30% later conversion to an open procedure in a small series of patients treated with TEVAR which included a patient with aortoesophageal fistula and one with an aortobronchial fistula [71]. In contrast, EVAR was more often seen as a bridge to definitive therapy in patients with infrarenal aortic infection. A recent European multicenter collaboration is the largest series of 123 patients studied. One-month survival was 91% with 5- and 10-year survival rates of 76% and 66%, respectively [13]. Twenty-seven percent of the patients included in this study had an infectious complication with one-third occurring within the first 30 days and 82% by the end of the first year. Patients with non-*Salmonella*-positive blood cultures were more likely to have late infectious complications associated with mortality. The authors noted that this compared very favorably to the results obtained with the previously described procedures especially considering that this European series had a majority of patients with severe comorbidities, hostile anatomy, ongoing sepsis, or rupture. The current results also seem exceedingly positive when compared to the large Swedish study of 946 patients undergoing routine elective EVAR for noninfected abdominal aortic aneurysm where the 5-year survival rate was 65% [72]. The authors also noted that even with this largest series of patients, the mortality is indisputably low, but risk factor analysis may be plagued by type II statistical error due to the small sample size.

Postoperative Management and Outcome

After any of these types of procedures, patients are extremely ill and most often requiring prolonged ICU stays. Little is written in textbooks of vascular surgery about this important phase of these patients' care. Ventilatory support is often required for at least the first 24–48 h. While patients may already be receiving intravenous broad-spectrum antibiotics, often they appear septic perioperatively from the debridement of the infected tissue. In addition, there are further fluid shifts ("third spacing") with prolonged clamp times during aortic excision and reconstruction. As a result, patients appear volume depleted with ongoing fluid requirements. They may appear tachycardic (heart rate > 90), tachypneic (>20 breaths/min or $PaCO_2$ < 32), febrile (core temperature > 38 °C), or hypothermic (core temperature < 36 °C) and have either a high or low white blood cell count (>12 × 10^9/l or <4 × 10^9/l) [73]. Key points in management during this phase are in keeping with the Surviving Sepsis Guidelines and include use of crystalloids for initial resuscitation, consideration for albumin use with large volume requirements, norepinephrine for persistent hypotension despite adequate volume resuscitation with the addition of epinephrine or vasopressin as indicated, and consideration for systemic corticosteroids only for those patients who remain unstable despite all of the above measures [74]. Abdominal compartment syndrome should be checked for with ongoing resuscitation by measurement of bladder pressures through the Foley catheter [75, 76] and lower extremity compartment syndrome considered in patients after a NAIS procedure.

Debrided infected material should be sent from the operating room for gram stain and culture (including fungal) regardless of the presence of positive blood cultures. Antibiotic therapy should be directed based on culture results and appropriate follow-up arranged with infectious disease specialists for monitoring drug levels and side effects. Most recommend a minimum of 6 weeks of intravenous antibiotics [77]. Frequent physical examinations with white blood cell count, sedimentation rate, and C-reactive protein levels are frequently checked during this period to monitor for signs of worsening infection, poor response to therapy, or abscess. The role of suppressive antibiotics after this treatment is debated. Because of the concerns of recurrent infection in the space on in newly place graft material in difficult to access areas, most recommend lifelong antibiotics [23, 38, 51, 63]. The role of routine postoperative radiologic imaging is also debated since early postoperative images (within the first month) will undoubtedly have retained fluid and gas at the site of infection. Once a patient is beyond the immediate postoperative period, the role for routine imaging becomes even less clear since few would advocate surgical intervention in an asymptomatic patient who had already received a definitive high-risk procedure to address the infection.

Complications from primary aortic infections can present at time of diagnosis as aneurysmal degeneration, septic emboli, or thrombosis or can occur as a result of treatment. Subsequent graft thrombosis can also occur acutely as a result of these processes or occur late with the highest incidence occurring in those patients with extra-anatomic reconstructions. Limb loss is not infrequent in these patients with some series reporting subsequent amputation rates greater than 20% [78]. Abscesses in adjacent structures such as the psoas muscle and vertebral body can further complicate management and mandate further debridement [79].

Recommendations

The AHA has published guidelines on the best operative strategies for patients with these complex infections [80]. The involvement of experts in radiology, cardiology, infectious disease, and vascular surgery is key to management. Antibiotics are recommended for a minimum of 6 weeks and as long as 6 months in select cases. Lifelong suppression should also be considered for patients who have prohibitive operative risk for a repeat intervention or for those with extensive or aggressive infection. Antibiotics alone are recommended only for those patients are not fit for surgery or who refuse intervention. For the majority of patients, excision of the infected aneurysm and surrounding tissue is the treatment of choice with in situ revascularization. Extra-anatomic reconstruction as part of a staged management strategy is recommended for those with gross purulence in the operative filed, retroperitoneal or psoas abscess, adjacent vertebral osteomyelitis, inadequate response to preoperative antibiotics, or in cases of aortoenteric fistula. Endovascular management may be considered as a bridge to definitive therapy for ruptured infected aneurysms, cases of aortoenteric fistula, or for those who are unfit for open procedures. This strategy allows for later removal of the endograft, excision of surrounding infected material, and reconstruction when the patient has been stabilized.

Aortic Graft Infections

Incidence and Risk Factors

Literature on infections of the aorta needs to be reviewed closely since many series discuss primary aortic infections in conjunction with aortic graft infections when discussing operative results and long-term outcomes. Graft infections are a distinct separate entity with a reported incidence of 0.5–2% [81]. In a large retrospective study of 12,626 patients with abdominal aortic aneurysm surgery from 1987 to 2005, the 2-year incidence of graft infection was extremely low at 0.19% [82]. Others have noted an incidence as high as 6% with groin incisions [39, 83–87]. Factors identified making patients susceptible to graft infection were surgical site infections and episodes of bacteremia during the index hospitalization. Other risk factors include recent hospitalization, MRSA colonization, failed arterial reconstruction, femoral anastomosis, and history of smoking and diabetes mellitus. With CDC and NSQIP data documenting skin and superficial surgical site infections for aorto-bifemoral bypass surgeries as high as 10–15%, long-term follow-up with a high index of suspicion is needed [88]. Aortic endografts are also not immune to infectious complications with a reported incidence of 0.5–0.7% [89]. Aortic graft infections remain a serious concern even in this era of modern antibiotics.

Classification

Aortic graft infections are characteristically categorized based on time of graft implantation and severity of infection. Early graft infections occur within 4 months and late graft infections occur after 4 months of graft implantation. The oldest classification is the Szilagyi classification of graft infections, outlined in 1972. Grade I is phlegmon, grade II is subcutaneous tissue infection, and grade III is graft infection. Samson's classification is very similar and also clinically relevant: class I is superficial infection involving the skin and/or subcutaneous tissue but no deeper than the dermis, class II is deep incisional infection involving deep soft tissues such as fascia and muscles but without involvement of the graft, class III is infection of the graft but without anastomotic site involvement, class IV is infection with anastomotic involvement, and class V is infection with anastomotic disruption and/or sepsis [90–92].

Bacteriology

While several factors exist that increase the risk of a graft infection, the majority of graft infections are the result of contamination during surgery at the time of implantation. Additional risk factors to consider include wound healing capabilities of the patient which are affected by medical comorbidities such as diabetes mellitus, obesity, and malnutrition, as well as use of immunosuppressive medications. End-stage renal disease is a well-known risk factor for graft infection as uremia acts to depress the immune system and dialysis patients are more commonly colonized with methicillin-resistant *Staphylococcus aureus* [89]. Elective placement of an aortic graft is by definition a clean procedure with an expected infection rate of <3% predicted by the CDC [93]. Placement of a foreign material (aortic graft) provides an environment for bacterial adhesion and biofilm. Intraoperative factors including hypothermia, hypotension, excessive blood loss, hypoxia, simultaneous infections of extremities, prolonged procedures, concomitant additional procedures, and emergent procedures are all common with extensive aortic surgery and have also been associated with increased risk of infection [94, 95]. Surgical incisions with extensive dissection in poorly perfused areas during arterial clamping combined with lymphatic disruption and later hematoma formation are also common with aortic surgery and provide an ideal environment for the development of infections.

Unlike primary aortic infections, the vast majority of aortic graft infections are gram positive. While important to obtain, blood cultures are still negative in 25–50% of patients [96]. The most common microorganisms cultured from aortic graft infections are *Staphylococcus aureus* (30–36%) and coagulase-negative *Staphylococcus* species (21–47%) [96, 97]. Methicillin-resistant *Staphylococcus aureus* has been reported in some series as being the most prevalent at 75% [98]. Other series, with high numbers of aortoenteric fistula at presentation, have found greater numbers of gram-negative and anaerobic infections (46%) [99]. *Pseudomonas* infections are most commonly associated with graft disruption and hemorrhage [95]. *Proteus* species are also highly virulent, secreting potent proteases that cause tissue disruption and can result in dramatic clinical manifestations such as anastomotic disruption and frank hemorrhage. Laboratory markers such as white blood cell counts and ESR and CRP levels are frequently elevated but are neither sensitive nor specific for aortic graft infection. Late infections (>1 month) with no history of prior wound infection are more often *Staphylococcus epidermidis* and are most frequently indolent infections [45].

Presentation

Similar to primary aortic infections, aortic graft infections can present as acute or chronic. Early graft infections present more commonly with systemic signs of infection with high fever, sepsis, abdominal and back pain, and leukocytosis. They are more commonly caused by highly virulent organisms. These are the infections most commonly associated with groin-related complications such as hematoma, seroma, and incisional dehiscence with subsequent soft tissue infection. Late graft infections tend to be more subtle with less systemic symptoms, generalized malaise, weakness, weight loss, and often lack a febrile response. Infrainguinal infections presenting as cellulitis, soft tissue infection, draining sinus tracts, or pseudoaneurysm can alert the clinician to a possible graft infection. Intraabdominal graft infections can present more dramatically as overwhelming sepsis or herald gastrointestinal bleeding or appear to be very nonspecific with symptoms of ileus and abdominal distention with or without abdominal tenderness [95].

Diagnosis

A complete assessment of the graft and adjacent anatomy is achieved with CT imaging. The evidence of infection on imaging may range from subtle signs of perigraft inflammation to large perigraft inflammatory masses with adjacent gas. CT diagnostic criteria for graft infection include perigraft fluid, perigraft soft-tissue attenuation, perigraft gas, pseudoaneurysm, and focal bowel wall thickening. The challenge in imaging-based diagnosis is the timing from graft implantation as perigraft fluid and gas may be visualized in the postoperative period for up to 1 week in patients without infection. These same findings are considered abnormal, however, and diagnostic of graft infection when present 4–7 weeks postoperatively [100].

Other radiologic modalities can be used to detect aortic graft infection. Duplex ultrasound (DUS) is noninvasive, more cost effective, but highly operator dependent, and its usefulness may be limited by anatomic location. DUS is most useful for infrainguinal evaluation and diagnosis of pseudoaneurysm, peri-prosthetic air, or fluid collections and can distinguish hematoma from abscess [95]. For Central aortic graft infection, the diagnostic ability is very limited with DUS due to overlying bowel gas and body habitus of patients. The sensitivity and specificity is thus quite low, and DUS is not as useful for definitive diagnosis of aortic graft infections [101]. MRI can be equally as challenging to decipher as CT imaging in the early postoperative period but is superior, however, in differentiating small perigraft fluid collections from inflammatory changes. As is seen in primary aortic infections, a low-density signal on T1 images and hyperintense signal on T2 images is consistent with infection. MRI has the advantage of being noninvasive with comparable sensitivity and specificity rates as CT in diagnosis [102, 103]. FDG-PET-CT is based on metabolically active cells' uptake of radioactive-labeled glucose. This imaging method can detect even subtle graft infections and document the extent. A focal uptake of FGD can be observed in 93% of graft infections, and in the absence of uptake, infection may be able to be excluded in 97% of cases [104]. Indium white blood cell scanning can provide useful information as to the extent of graft infection [105]. Suspicions of aortic enteric fistula should be evaluated with careful endoscopy in a setting prepared for immediate exploration and repair of the fistula. In the largest series of aortic graft infections, the majority of these patients were diagnosed based on signs of systemic infection including fever, chills, or septic shock or signs of infection including elevated white blood cell count or C-reactive protein. Radiologic findings were more obvious than with primary aortic infections and include air, fluid, or abscess around the graft [99]. In an attempt to establish evidence-based guidelines, a set of major and minor criteria has been established to diagnose aortic graft infections. Aortic graft infection is *suspected* in a patient with any isolated major criterion or minor criteria from two of the three categories: clinical/surgical, radiological, or laboratory. Aortic graft infection is *diagnosed* in the presence of a single major criterion, plus any other criterion (major or minor) from another category [106] (see MAGIC table Fig. 17.5).

	Clinical / Surgical	Radiology	Laboratory
Major criteria	• Pus (confirmed by microscopy) around graft or in aneurysm sac at surgery • Open wound with exposed graft or communicating sinus • Fistula development e.g. aorta-enteric or aorto-bronchial • Graft insertion in an infected site e.g. fistula, mycotic aneurysm or infected pseudoaneurysm	• Peri-graft fluid on CT scan ≥ 3 months after insertion • Peri-graft gas on CT scan ≥ 7 weeks after insertion • Increase in peri-graft gas volume demonstrated on serial imaging	• Organisms recovered from an explanted graft • Organisms recovered from an intra-operative specimen • Organisms recovered from a percutaneous, radiologically-guided aspirate of peri-graft fluid
Minor criteria	• Localized clinical features of AGI e.g. erythema, warmth, swelling, purulent discharge, pain • Fever ≥38°C with AGI as most likely cause	• Other e.g. suspicious peri-graft gas/fluid/soft tissue inflammation; aneurysm expansion; pseudoaneurysm formation; focal bowel wall thickening; discitis/osteomyelitis; suspicious metabolic activity on FDG PET/CT; radiolabelled leukocyte uptake	• Blood culture(s) positive and no apparent source except AGI • Abnormally elevated inflammatory markers with AGI as most likely cause e.g. ESR, CRP, white cell count

Fig. 17.5 Criterion for diagnosis of aortic graft infection. (From: Lyons et al. [106]. Reprinted with permission from Elsevier)

Endograft Infections

While less invasive, aortic stent graft infections do occur despite the increasing number being performed percutaneously. Previous reports have described an incidence of 0.43–0.69% [107, 108]. A recent review of patients treated in Ireland over an 8-year period documented an incidence of graft-related sepsis occurring in 6 of 509 patients (433 elective and 76 emergent) [109]. The majority of the infections in these series have presented within 2–5 years after implantation [110]. The identified technical risk factors associated with the development of subsequent graft infection included subsequent interventions for endoleak, aortoenteric fistula, and systemic infections temporally related to the time of graft implantation [107, 108]. Presentation of aortic endograft infections appears to have been slightly different as well with one-third presenting with symptoms of chronic infection, one-third with acute sepsis, and remaining one-third as aortoenteric fistulae [107, 108, 111, 112].

Debate still exists as to which procedure, open or endovascular, poses less infectious risk to the patient. Proponents for open procedures note the increased bacterial adherence and less resistance to infection found with endografts [112, 113]. There is, however, good data documenting similar rates of infection between the two procedures [82, 113]. Endovascular proponents note the sterile delivery system, but those advantages may unfortunately be offset by the decreased sterility noted in many radiology suites when compared to traditional operating rooms [107]. All agree, however, that any type of graft is subject to bacterial seeding and that determining the cause of infection in many patients is difficult since most are referred to tertiary care referral centers where the details of their care may not be available [108].

Prevention

Current recommendations for prevention include intravenous antibiotics 30–60 min prior to incision to address both gram-positive and gram-negative bacteria. For patients with known MRSA colonization, vancomycin should be administered 60–120 min prior to incision (due to its slower distribution) with an additional antibiotic for gram-negative organisms. Antibiotics should be continued for 24 h. Preprocedure, patients should have careful inspection of the groins even if groin incisions are not planned. Incisions through areas where excoriation or rash are present should not be done for elective procedures. Hair on the abdomen and in the groins should be clipped and not shaved due to the increased risk of skin trauma with razor use. Preprocedure shower with antimicrobial soap is recommended for both hospitalized and same-day admission patients. Antimicrobial incisional drapes are routinely recommended. Dressings should remain intact for the first 24–48 h unless significant drainage is present [94]. Any signs of superficial wound infection or breakdown should be aggressively treated.

Management of Aortic Graft Infections

The management of graft infections is similar to the management of primary aortic infections, and is based upon the principles of source control of the infection and restoration of perfusion to critical organs. Initial drainage procedures should be considered if the patient is hemodynamically stable and without anastomotic disruption. Antibiotics should be initially broad spectrum and narrowed based on culture results. The surgical options for reconstruction are the same

as for primary aortic infections although there appears to be an increasing trend toward in situ reconstructions with homograft due to the emergent nature of many of these infections with either anastomotic disruption or aortoenteric fistula [87, 99]. Elimination of the dead space and coverage of all new graft material and stump closures should be a planned part of the procedure. Others have also emphasized the difference between the Samson classifications of aortic graft infections and tailored treatment accordingly. This strategy led to excision of only 10/34 infected grafts in the original series published by Samson with only 11 graft infections ultimately requiring total removal, 2 deaths (6% mortality), and limb loss in 8 patients (24%) [114]. Some have advocated treatment algorithms based on blood culture results with in situ reconstruction being recommended only for patients with negative cultures [108]. The additional benefit of in situ reconstruction is in cases where there is the late development of pseudoaneurysm, calcification, or aneurysmal dilation, and endovascular options for subsequent repair exist and may be far less morbid (see Case #1 – Fig. 17.1). For cases of extra-anatomic reconstruction with aortic stump closure, the risk of aortic stump blowout remains high at 30% and reinfection occurs in 5–15% [87, 115, 116].

Aortic graft infections remain a lethal condition with series reporting mortality ranging from 8% to over 50% with morbidity rates of 60% and higher [46, 117]. Some have noted that this wide range is more consistent with the patient's concomitant illnesses rather than the type of surgical procedure with increasing mortality observed in patients with coronary disease, chronic obstructive pulmonary disease, and diabetes [99]. One series identified those patients greater than 70 years of age, CRP >5.0 mg/dl, and serum creatinine >1.2 mg/dl as having a mortality of greater than 90% for in situ reconstruction with allograft [99]. Consequently, it is appealing to attempt to restrict the surgical approach to something more limited in patients with increased risk of mortality. Conservative management with intravenous antibiotics and drainage has been done with generally poor patient outcomes. The exception to this appears to be in cases of isolated graft infection in the groin (for those patients treated with aortobifemoral grafts) where there is a growing trend toward preservation of the graft with long-term antibiotics and sartorius muscle flap coverage with adjunctive negative pressure wound therapy with good patency and long-term survival [118, 119]. Conservative management in cases where the aortic portion of the graft is involved is not routinely recommended for patients since mortality frequently occurs within 2 years [120–122]. Rare survivors have been reported with this strategy [40, 107, 109]. Consequently, to be considered for this option, a patient should have prohibitive comorbidities, infection limited to the body of the graft (without extensive surrounding tissue infection), and a culture of an indolent gram-positive organism. Other options for conservative therapy include intravenous antibiotics with percutaneous drainage [123], irrigation and perigraft debridement [78, 124], and muscle and/or omental flaps [118, 125]. Some have advocated a combined approach with suppressive antibiotic therapy and drainage for high-risk patients as long as cultures do not show invasive gram-negative infections such as *Pseudomonas* or *Salmonella*. Drainage of the perigraft space can be done percutaneously or with laparotomy with the goal of continual irrigation of the space until the cultures are negative. Long-term survivors have also been reported with this management [122]. There is a growing experience in using endovascular techniques to temporize and stabilize the critically ill patients with graft infections, particularly those who present with aortoenteric [126] or aortobronchial fistulae [127]. The obvious concern in these patients is that the remaining hole in the airway or viscera is untreated and remains a continual source of bacterial contamination. This has led to the recognition that this treatment is a bridge to definitive therapy and not as adequate treatment [27].

Case report

A 65-year-old patient with a history of an aortic tube graft has recurrent GI bleeding. CT imaging and radionucleotide imaging failed to identify infection (Case #2 – Fig. 17.6). Endovascular therapy with aortic cuff placed at the proximal anastomosis was performed. Six months later, CT reveals air around the stent graft (Fig. 17.6a). At the time of exploration, periaortic phlegmon was encountered (Fig. 17.6b) and aortic reconstruction was performed with cryopreserved graft and omental wrap. The graft was intact at explantation (Fig. 17.6c).

Surgical options previously described for the treatment of primary aortic infections remain the gold standard for treatment of aortic graft or endograft infections. Suprarenal fixation with some aortic endografts can make excision of these graft materials even more challenging than simple excision of an infrarenal graft, but the reconstructive options remain the same. Given the complexity of these patients, advocating for a specific treatment algorithm for each type of procedure is difficult. Some observations can be made, however, based on the existing literature [107]. In situ reconstructions can be performed with rifampin-impregnated Dacron [45] or homograft [128] for patients with indolent infections. Risk factors for mortality have been identified in previous studies and include age >70, creatinine >1.2 mg/dl and C-reactive protein >5.0. Patients with only one risk factor have been documented to have an in-hospital mortality rate of 7.7% and mortality >90% when two or more are present. There has been no statistically significant difference found with the duration of aortic clamping, transfusion requirements, or use of vasopressors between survivors and nonsurvivors [99]. The strategy of excision and in situ reconstruction does not appear to be as durable for patients with aggressive gram-negative infections, extensive surrounding necrosis or contamination, or those with fungal

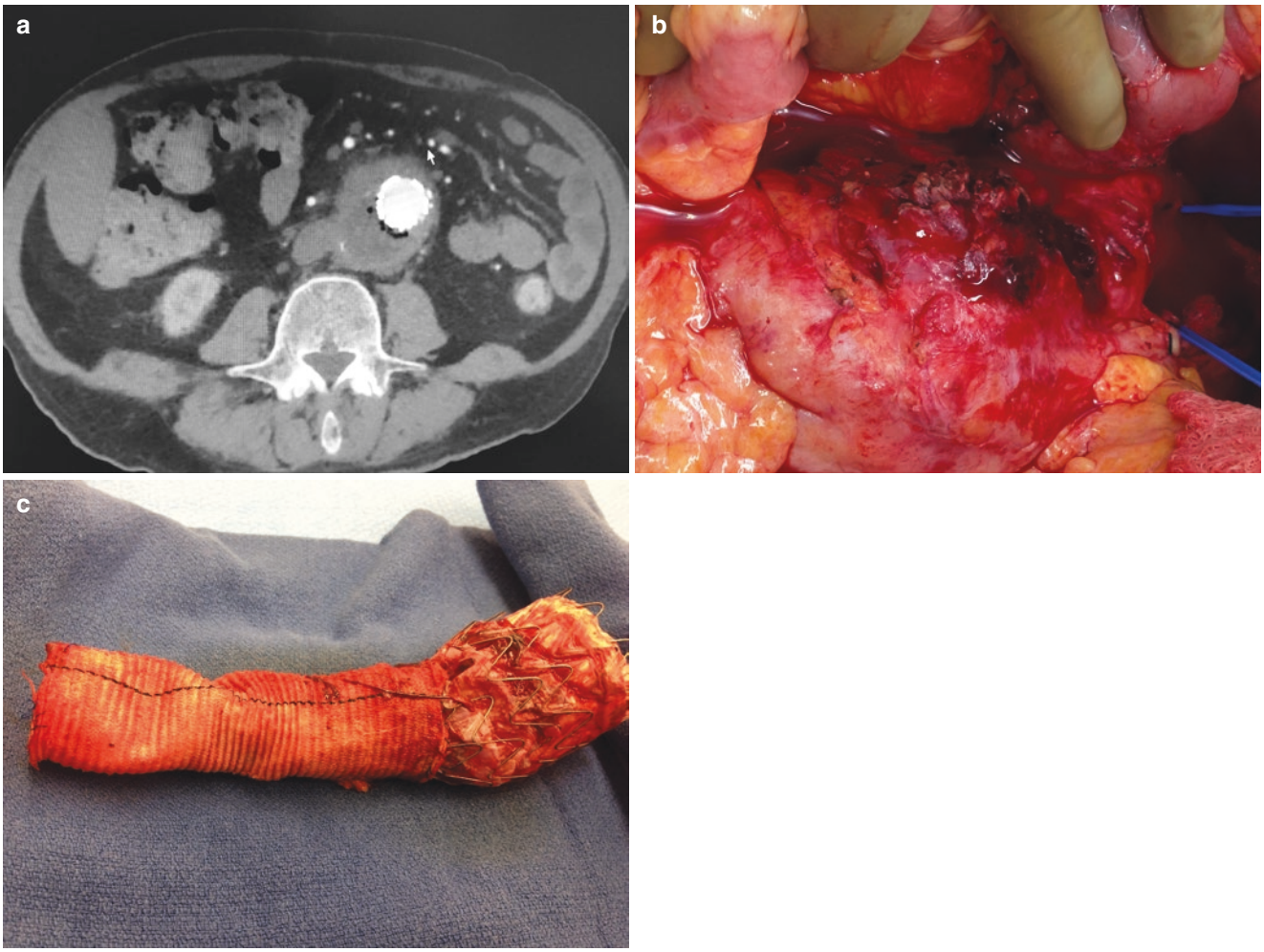

Fig. 17.6 Case #2. (**a**) CT scan showing air around existing graft. (**b**) Intraoperative appearance of retroperitoneum. Iliac arteries at top of image. (**c**) Aortic tube graft and endovascular extension cuff after explantation. Note minimal tissue incorporation around graft. (Images courtesy of Raghu Motaganahalli, MD)

infections with subsequent infectious complications occurring 5 times more frequently in these patients [45]. For well-selected patients, in situ reconstruction with allograft affords a durable repair with survival of 82% at 2 years [129]. Long-term degeneration of the graft remains a concern, but accumulated data has shown an extremely low incidence [130]. Staged procedures with extra-anatomic reconstruction being performed through clean fields with subsequent aortic graft excision at a later surgery appear to afford the surgeon an easier operation with improved patient survival (13%) when compared to a single-stage procedure (26%) [54, 55, 129]. The long-term patency of these constructs is not as robust with 3-year primary patency rates reported as low as 43% and amputation rates ranging from 6% to 25% with most authors reporting a 10% rate of limb loss at 5 years [26, 55, 131]. These patients also have the risk of rupture of the aortic stump closure [84, 87]. The NAIS procedure appears to be a durable reconstruction that is resistant to subsequent infection but remains as a long, technically demanding procedure [56, 132]. In a meta-analysis comparing the different surgical options of extra-anatomic bypass, rifampin-bonded synthetic grafts, cryopreserved allografts, and autogenous venous grafts, statistically significant differences were observed. Extra-anatomic bypass procedures had higher mortality and amputation rates than reconstruction with rifampin-bonded grafts, higher rates of thrombosis compared to cryopreserved grafts, and higher infection rates than autogenous vein grafts. Overall, the complication rates, reinfection rates, and mortality were higher than with another other reconstructive procedures [87]. Caution is urged when interpreting such data, however, as the data may be seriously impacted by the inclusion criterion, higher number of patients with Samson class V infections, and referral bias from individual studies [80].

Patients who present with aortoenteric fistula require a clear understanding of the management strategy for both control of hemorrhage and infection. Most present with

symptoms of an upper gastrointestinal bleed. If hemodynamically stable, CT scanning can alert the clinician to the proximity of the bowel to the graft. While endoscopy is useful to demonstrate the area of erosion, this should only be attempted in a surgical environment where large bore intravenous access has been established and there is an immediate ability to proceed with emergent laparotomy to control hemorrhage. Temporary supra celiac control may be achieved with an endovascular balloon or by direct surgical exposure. Control of the iliac arteries should proceed expeditiously. Aggressive efforts should be made to dissect the bowel free and enable an infrarenal clamp to be placed whenever possible. In some patients, there may not be enough aortic neck to allow this and the next critical step in management is over sewing of the aortic stump as previously discussed. Once control of hemorrhage is obtained, definitive excision should be performed and reconstructive options may be considered. Previously, the "gold standard" was extra-anatomic reconstruction with high rates of complications and mortality [26, 54, 85, 133–139]. For patients with less aggressive infections, in situ reconstruction with allograft or native vein is a durable option associated with less morbidity and mortality [50, 87, 129, 140–143]. Unfortunately, for the majority of these patients, the type of infection is not known at time of emergent operation and the decision as to which procedure is best is left to the discretion of the surgeon. Postoperatively, parenteral antibiotics for 6 weeks is recommended (AHA) with most recommending 3–6 months of oral antibiotic therapy and a consideration for lifelong oral antibiotic suppression for patients with extensive or aggressive infections [80].

Current Recommendations for Treatment

The AHA has published guidelines to aid the clinician when confronted with these challenging patients. For patients with Samson class I or II infections, surgical debridement and 2–4 weeks of antibiotic therapy is an appropriate choice. For Samson class III or IV patients, initial therapy of 4–6 weeks may be extended up to 6 months. For those patients presenting as class V, 4–6 weeks of parenteral antibiotic therapy is recommended with an additional 6 months of suppressive antibiotic therapy. These current recommendations also emphasize the difference in treatment for aggressive pathogens with MRSA, pseudomonas, multidrug-resistant organisms, and fungal infections with a recommendation for long-term suppressive therapy. Patient factors such as multiple prior procedures, in situ reconstructions, or those who are poor candidates for surgical procedures may also be considered for long-term antibiotic therapy [80].

When considering surgical options for these patients, the AHA has also offered some recommendations. For early (<2 months) Samson class III infections, graft preservation can be considered with appropriate antibiotic therapy and follow-up. Late (>2 months) Samson class III infections should be considered for graft excision and reconstruction instead of preservation. For class III or IV infections with aggressive infections as previously discussed, extra-anatomic reconstruction with graft excision is the treatment of choice. Class V patients should be treated with prompt extra-anatomic revascularization followed by graft excision. The guidelines also emphasize ultrasound imaging as a routine part of follow-up every 3 months for the first 2 years followed by ultrasound examination every 6–12 months thereafter. What makes these guidelines difficult to apply globally is that there is no standard surgical option and no specific recommended operation for each type of infection as individual patient factors, surgeon experience and available resources will impact management.

Conclusion

Evaluating the literature for primary aortic infections, infectious aneurysms, aortic graft infections, and endovascular graft infections is difficult. Most publications include case reports or small numbers of patients and are retrospective analyses of operations performed at the discretion of the surgeon caring for the patient. Often, "aortic infections" are grouped in these studies to include both primary infections and graft infections and complications, and mortality rates are reported as a composite endpoint for the total group. Long-term follow-up is frequently limited. In addition, the bacteriologic profile of aortic infections has changed in recent years as well as the baseline characteristics of patients with a significantly higher proportion of patients having extensive cardiac and pulmonary disease [144]. The comparison of newer types of reconstruction to older procedures in historical series may be inherently biased by modern anesthesia and postoperative critical care which may affect both morbidity and patient survival. Despite these issues, the principle of treating aortic infections remains consistent. Management of these patients involves a multidisciplinary team composed of experts in infectious disease, cardiology, radiology, and surgery. Intravenous broad-spectrum antibiotics should be administered when infection is suspected and, as a general rule, all infected material should be removed and perfusion restored to critical organs and the extremities. 4–6 weeks of parenteral antibiotics are recommended as a minimum with consideration for 6 months, or lifelong suppression should be considered in cases of extensive infection or infections with aggressive organisms. Significant postoperative complications depend on the type of reconstruction with increased risk of graft thrombosis and amputation occurring in extra-anatomic grafts, increased risks of infection with synthetic grafts, and increasing durability with

native vein constructs and allografts. Sound knowledge of the types of reconstruction can help the vascular surgeon decide the appropriate treatment for these patients with this highly lethal disease.

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Surgical Treatment of the Thoracic Aorta

18

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Perfusion Techniques for Proximal Aortic Aneurysms

Cardiopulmonary bypass (CPB) (Fig. 18.1) is utilized for providing circulatory support in ascending aortic aneurysms (aortic annulus to innominate artery). If the involvement is restricted to the aortic root or ascending aorta alone, then CPB is sufficient. When aneurysmal disease involves the arch, or arch repair is anticipated, circulatory arrest is generally required. There are multiple approaches to circulatory arrest including deep hypothermia without cerebral perfusion and varying degrees of hypothermia with cerebral perfusion. The best strategy for cerebral protection is currently under debate and is a focus of active investigation. Options include deep hypothermia (18–22 °C), moderate hypothermia (22–26 °C), and mild hypothermia (26–30 °C). Cannulation for arch disease depends on the cerebral perfusion strategy. Direct aortic cannulation with dual-stage right atrial cannula can be used in selective antegrade cerebral circulation via direct arch vessel ostia once circulatory arrest is initiated (Fig. 18.2). Multiple techniques are available in clinical practice for cerebral perfusion: (1) retrograde cerebral perfusion, (2) selective unilateral antegrade cerebral perfusion via right axillary perfusion, and (3) direct bilateral antegrade cerebral perfusion via ostia of the arch vessels (Fig. 18.2). When comparing antegrade versus retrograde cerebral perfusions during deep hypothermic circulatory arrest, there is no difference in 30-day mortality or stroke in the postoperative period [1]. When comparing deep hypothermic circulatory arrest to moderate hypothermic arrest, there are shorter cross clamp times, shorter cardiopulmonary bypass times, and fewer transfusion requirements during moderate hypothermic circulatory arrest [2]. Some studies have shown moderate hypothermic arrest is also associated with fewer neurologic sequelae compared to deep hypothermic arrest and lower 30-day mortality; however, no randomized data exist [3].

Surgical Technique

The patient is positioned supine and a roll is placed between the scapulae to allow greater exposure to the sternum and mediastinum. The neck should be extended which is particularly helpful for patients with large body habitus. The arms are tucked to the side. Body hair is clipped, and the patient is prepped from the angle of the mandible to feet. Care is taken to stay midline while performing the sternotomy. The sternal periosteal vessels are coagulated, and vancomycin paste is applied to the sternal edges. Although the utility of vancomycin applied to sternal edges is highly debated, several studies have found significant reduction in superficial and deep wound infections [4–7]. A sternal retractor is used to expose the anterior mediastinum. The thymus is separated midline up to the innominate vein. The pericardium is opened from the diaphragmatic pericardium up to the superior pericardial reflection and transversely at the superior and inferior portion of the pericardium. If the arch is uninvolved, there is minimal dissection needed onto the arch of the aorta. Circumferential dissection of the aorta is carried out in preparation for replacement with graft.

Repair of Aortic Root and Ascending Aortic Aneurysms

Root repair can be performed in many fashions, with composite replacements being more common compared to valve-sparing procedure. Composite mechanical prosthesis is generally chosen for younger patients with few comorbidities.

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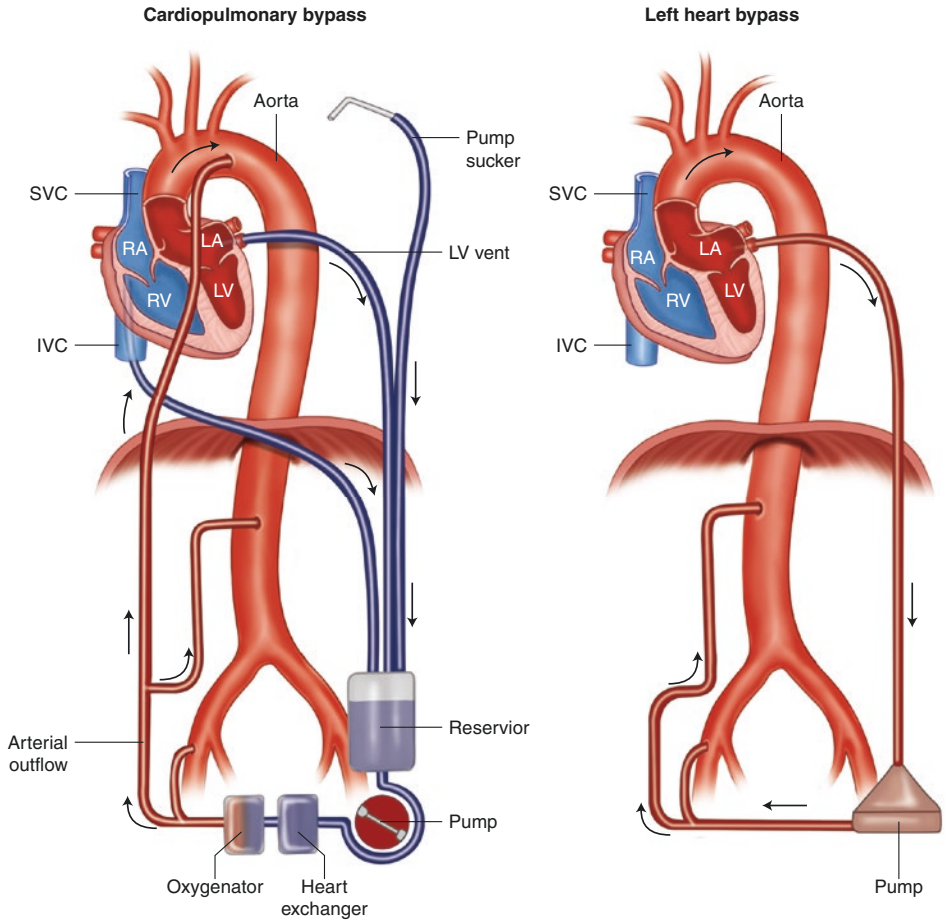


Fig. 18.1 Partial cardiopulmonary bypass versus left heart bypass for open TAAA repair

Biologic composites are often reserved for those in advanced age who could not tolerate anticoagulation. Bioprosthetic valves additionally offer patients many benefits such as freedom from anticoagulation and potential for transcatheter replacement if structural degeneration occurs.

All patients undergo intraoperative transesophageal echocardiography (TEE) to evaluate for aortic valve insufficiency or other aortic pathology which may alter the therapeutic approach. For ascending aorta replacement alone, cannulation of the aorta should be distal enough to allow cross clamp and anastomosis to healthy aorta. If the diseased segment extends to the level of the innominate artery, this may require circulatory arrest to achieve adequate aortic replacement. If circulatory arrest is contemplated because the aneurysm approaches zone 1 of the aorta, then the cannulation site need not be distal on the aortic arch. The atrium is then cannulated with a dual-stage cannula. A ventricular vent catheter is strongly recommended in all aortic root procedures, as manipulation of the aorta may cause aortic insufficiency. When the integrity of the proximal arch is in question, hypothermic circulatory arrest is used to allow for complete inspection of the arch.

Prior to cannulation, the patient is given heparin (400 units/kg), and cardiopulmonary bypass is instituted at an activation clotting time (ACT) of greater than 480 s. The patient is cooled to 22–28 °C. While cooling, any further dissection is completed prior to cross clamping. The cross clamp is applied, and cardioplegia is administered. A transverse aortotomy is performed at the sinotubular junction. The distal segment of aorta the ascending aorta is then removed. For aortic root replacement, the right and left coronary buttons are fashioned by sharp excision leaving enough aorta around the ostia to allow for a safe anastomosis to the graft/tissue. The aortic root is completely mobilized using a combination of sharp and cautery dissection.

The aortic root anastomosis is completed with composite conduit with 2–0 polyester suture pledgeted horizontal mattress sutures. The suture line is dried and Bioglue may be applied to the suture line particularly in friable tissues. The right and left coronary buttons are sized and location on the conduit chosen for the anastomoses. It is imperative to have sufficient mobility on both coronary buttons to ensure a tension-free anastomosis. The ostial sites are then opened with a high-temperature cautery pen. If a biologic conduit is being used such as homograft or xenograft root, a 4 mm punch is used to create the ostial sites. The left coronary button is first anastomosed followed by the right coronary button.

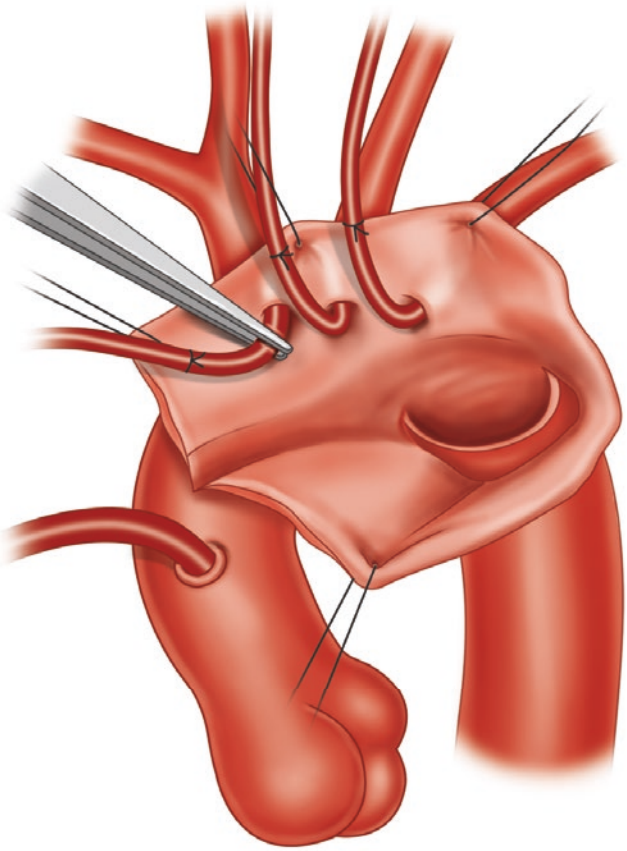


Fig. 18.2 Selective antegrade cerebral perfusion vial ostia of arch vessels

The distal anastomosis is performed proximal to the aortic clamp with a 4-0 polypropylene suture in a running fashion. If the aorta is thin or of poor quality, then a felt strip is used to bolster the anastomosis. Bioglue can be applied to the distal anastomosis, and the aorta is deaired prior to removing the cross clamp (Fig. 18.3).

Ascending Aortic Aneurysms

Supravalvular aortic aneurysms are treated with tube graft replacement of the ascending aorta. Aortic arch or innominate artery cannulation is performed, which allows for innocuous manipulation of the proximal aorta during anastomosis. Venous cannulation is performed with a dual-stage cannula. Prior to initiating cardiopulmonary bypass, the ascending aorta is evaluated for the cross-clamp site. For isolated tube graft replacement of the ascending aorta, mild hypothermia is used unless prolonged bypass is anticipated, as in cases where concomitant cardiac procedures are performed.

Once cardiopulmonary bypass is initiated, the ascending aorta is resected distal to the sinotubular junction to distal disease-free margin of the distal ascending aorta. 4-0 polypropylene suture is used to create a running anastomosis. Bioglue can be administered to the aortic anastomosis (Fig. 18.4). If the proximal aortic arch is involved, moderate hypothermia is utilized, and a brief period of circulatory arrest is used with selective antegrade cerebral perfusion.

Aortic Arch Disease

Aortic arch disease involves a unique set of challenges. When considering treatment options for patients with arch disease, one must take into consideration the extent of the disease and assess the need for descending aorta repair. These issues will direct the optimal cannulation strategy. Preferentially, right axillary antegrade flow which allows selective unilateral antegrade cerebral perfusion or direct aortic cannulation with ostial cerebral perfusion while on circulatory arrest is chosen over retrograde cerebral perfusion or no cerebral perfusion. In the context of a patient with cerebral vascular disease or circle of Willis that is not in continuity or diseased, direct cannulation and perfusion of the arch vessels is a better alternative once on circulatory arrest. Venous cannulation is performed with dual-stage cannula. Options for arch replacement are tube graft to the distal aortic arch with an end-to-side anastomosis of the arch island as a patch. A triple-branch arch graft with a side arm to re-establish perfusion through the graft once the distal and arch vessel anastomosis are complete is the preferred graft choice because it avoids the risk of subsequent patch aneurysm formation.

Once cardiopulmonary bypass is initiated, the patient is cooled to 22 °C. The extent of the aortic aneurysmal disease is inspected. Antegrade cardioplegia is administered, and then diseased aorta is resected. The innominate artery is clamped proximal to the right axillary artery and carotid bifurcation. Selective antegrade flow is set at 10 cc/kg/min of flow, and distal perfusion is ceased. To ensure antegrade perfusion is functioning, we visualize flow through the left common carotid and left subclavian arteries. Bilateral cerebral oximetry and electroencephalography are important monitoring adjuncts to ensure adequate cerebral protection. If there are concerns during unilateral antegrade cerebral perfusion, direct ostial cannulation of the left carotid is implemented for cerebral protection. Another alternative is retrograde cerebral perfusion, but this modality is preferred for shorter circulatory arrest times such as hemiarch replacement only.

The anastomoses are started distal to proximal. The first anastomosis is to the descending aorta. This is completed in a similar fashion as the distal ascending arch repair, generally using a 3–0 polypropylene and felt strip, with Bioglue around the anastomosis. The subclavian artery anastomosis is typically performed under circulatory arrest to assist with visualization, using a 4–0 polypropylene suture (Fig. 18.5). The side branch of the graft can be recannulated and cardiopulmonary bypass re-established to achieve distal organ perfusion. The left carotid and innominate artery anastomoses are then sequentially performed, taking care to de-air each of

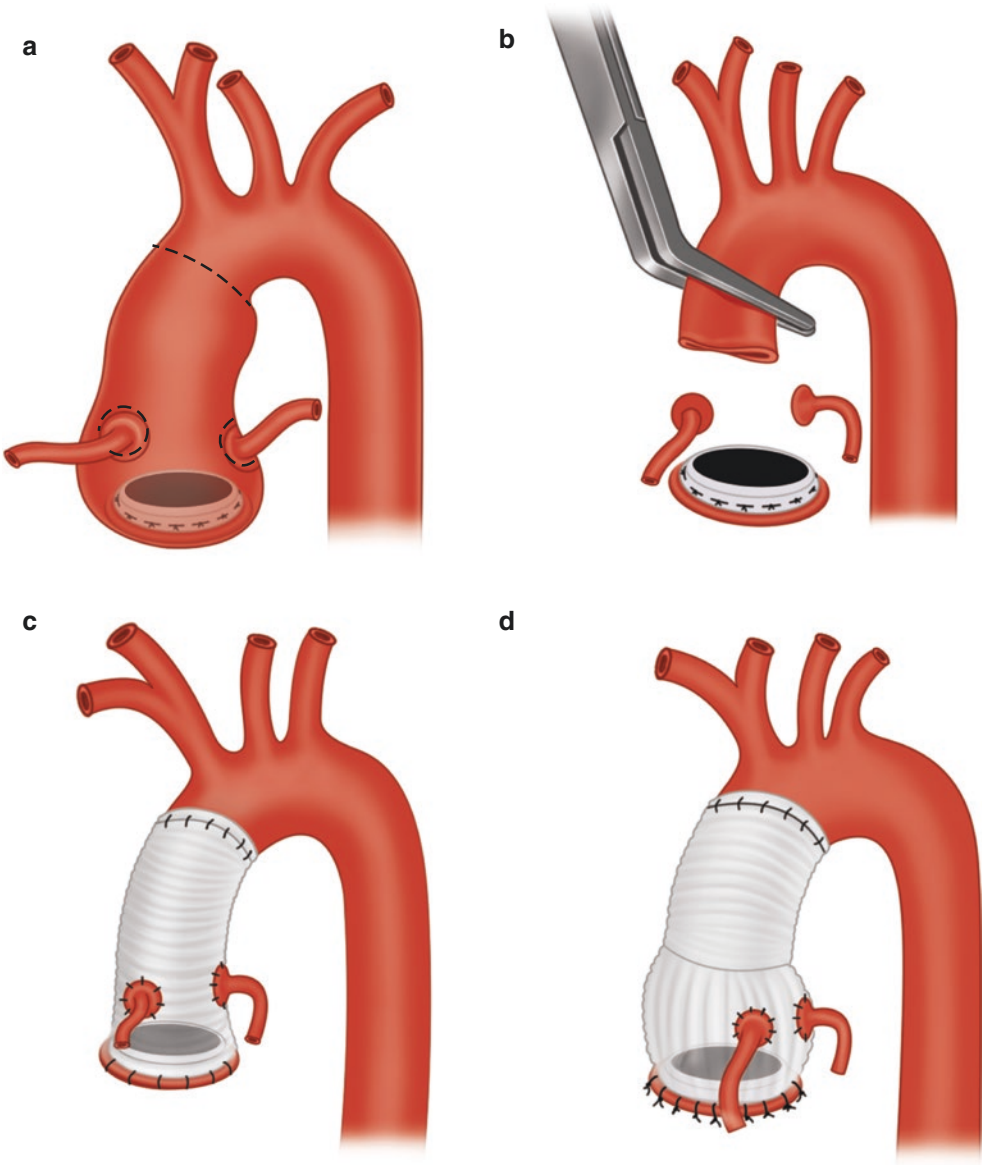


Fig. 18.3 (**a**–**d**). The complete Bentall procedure

these anastomoses prior to re-establishing antegrade flow. The proximal anastomosis is performed in the same manner as above. De-airing maneuvers are performed, and the clamp is released while the patient is rewarmed.

Outcomes and Complications

Mortality

Survival from proximal aorta and arch aneurysms is variable. Elective replacement of the proximal aorta carries a mortality rate of 1–3.4%, whereas it is up to 15.4% for nonelective cases [8, 9]. There are many factors that contribute to mortality including urgency of the case, age, ventricular function, arch surgery, concomitant coronary surgery, pulmonary disease, nonsinus rhythm, female sex, NYHA >II, and renal dysfunction [10]. The risk of mortality increases with renal injury up to 10% depending on the degree of renal dysfunction [9]. Hospital volume contributes to surgical outcomes in proximal aortic disease as well. Centers with high volume have a mortality rate of 1–3.4% compared to 5.8% in low-volume centers [9, 11].

Complications

Elective proximal aortic surgery can be accomplished relatively safely with good outcomes. However, the commonly encountered complications include cerebrovascular accident, temporary neurologic dysfunction, hemorrhage, and pulmonary and renal dysfunction. The occurrence of a complication contributes not only to length of stay but mortality.

Coagulopathy is caused by many interacting factors: hypothermia, inflammation, and anticoagulation. Preoperative

disseminated intravascular coagulation has been described in aortic aneurysms [12]. Ultimately, abnormalities in the clotting cascade lead to increased transfusions. Cardiopulmonary bypass induces a proinflammatory state. Its utilization, particularly with prolonged bypass times, can lead to end-organ damage along with coagulopathy. Visceral injury from cardiopulmonary bypass can be caused by hypoperfusion [13].

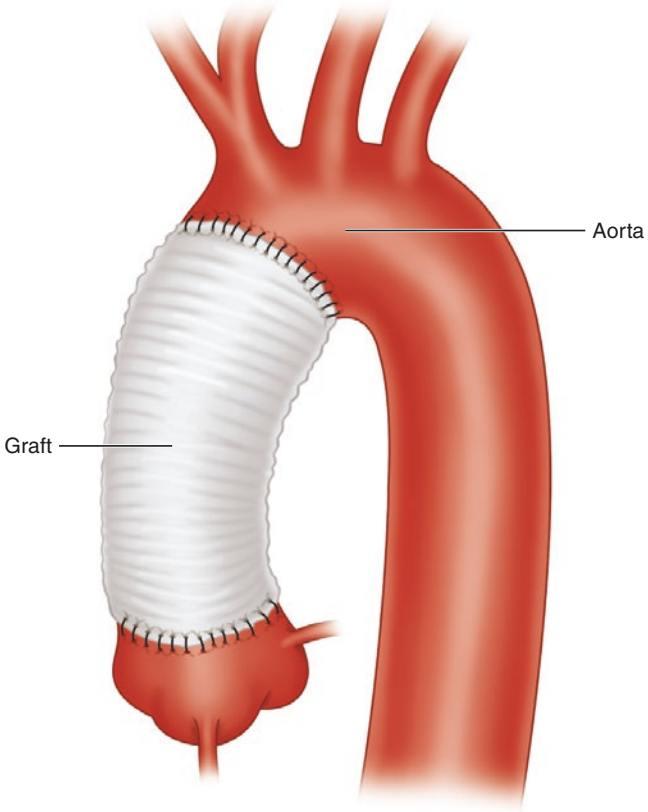


Fig. 18.4 Completed ascending aortic aneurysm repair

It is difficult to quantify these conditions as surgical approach, length of surgery, length of cardiopulmonary bypass, length of circulatory arrest, and volume of surgical interventions vary from surgeon to surgeon.

Stroke is a complication of aortic surgery and varies depending on urgency of the intervention. The majority of strokes are embolic [14]. The length of cerebral ischemia is correlated to increased rates of stroke. There have been decreased rates of stroke with the combination of hypothermia, cannulation strategies, and antegrade cerebral perfusion.

Long-Term Survival

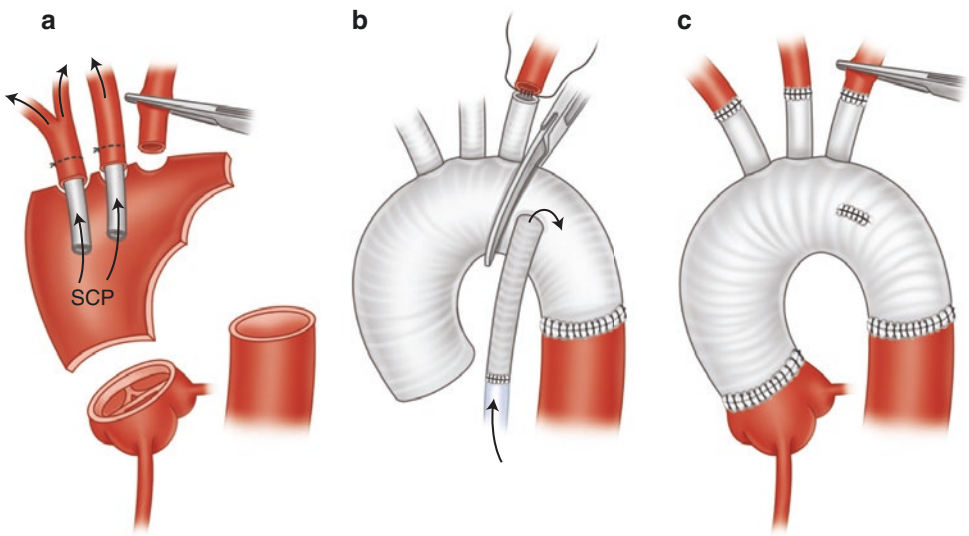
As surgical techniques continue to evolve, long-term survival has improved. Long-term mortality decreased from 16.7% to 11.6% from 1992 to 2004 at 60 days and varies between 32% and 57% at 10 years when evaluating dissections and aneurysms [15–17]. Most commonly, mortality is associated with cardiac or aortic correlating to the age of the patient [15, 18]. Age greater than 60 is independently associated with long-term mortality [18]. Five percent of patients at 5 years will have reoperations and at 10 years nearly 8% [18].

Surgical Treatment of Descending Thoracic and Thoracoabdominal Aneurysms

Introduction

While open repair of descending thoracic aortic aneurysms (TAAs) and thoracoabdominal aortic aneurysms (TAAAs) remains the gold standard for the treatment of these complex disease processes, it involves some of the most challenging preoperative planning, intraoperative decision making, and postoperative care that surgeons encounter. Successful

Fig. 18.5 (**a**–**c**) Completion of aortic arch repair



outcomes not only require appropriate patient selection and meticulous execution of chosen repair but have also evolved to include adjuncts for end-organ and spinal cord protection and protocol-driven postoperative care to limit morbidity related to spinal cord ischemia (SCI) and renal failure.

Intraoperative Considerations

Anesthesia

The usual setup for DTAA or TAAA repairs includes a double-lumen endotracheal tube, central lines, a pulmonary artery catheter (for hemodynamic monitoring), a transesophageal echocardiogram (TEE) probe (to optimize cardiac function and to guide cannula placement if using CPB), and arterial lines (in both the upper and lower extremities to monitor both proximal and distal perfusion during aortic clamping). Lumbar cerebrospinal fluid (CSF) drains are used routinely for Crawford extent I and II repairs [19]. The target CSF pressure is typically 7–10 mm Hg with drainage over the chosen pressure. Cranial and peripheral electrodes are placed for monitoring of somatosensory or motor evoked potentials to assess intraoperative spinal cord protection and perfusion [20]. Mannitol and sodium bicarbonate infusion are commonly administered to protect the kidneys while the aorta is occluded [21]. Blood counts are checked frequently throughout the operation and cell saver, packed red blood cells, and fresh frozen plasma are transfused as necessary. If vasodilators are needed, nitroprusside and hydralazine should be avoided due to their potential detrimental effects on ischemic tolerance of the spinal cord [22].

Perfusion Techniques

Regarding circulatory support for TAAA repair, most groups advocate either left heart bypass (LHB) or partial cardiopulmonary bypass (Fig. 18.1) [19, 23]. With LHB, oxygenated blood from the heart is delivered to a centrifugal pump via a cannula inserted into the left atrium or the left inferior pulmonary vein. The pump then delivers the blood to the distal aorta including its visceral and pelvic branches through a cannula that is inserted directly into the femoral or iliac artery, or into an 8 mm Dacron conduit that has been sewn to the left common femoral artery. This technique is beneficial as it reduces cardiac strain despite the proximal aortic clamping and decreases the incidence of ischemia-associated complications such as metabolic acidosis, acute renal failure, and paraplegia. Also, it avoids the inflammatory insult associated with the use of a membrane oxygenator [24].

Alternatively, some groups prefer partial cardiopulmonary bypass achieved through femoral arterial cannulation (either direct cannulation or through an 8 mm Dacron graft) and bicaval venous cannula inserted through the left femoral vein and positioned in the center of the right atrium under TEE guidance to allow for blood return to the oxygenator. By monitoring radial and femoral arterial lines, the blood pressure proximal and distal to the aortic cross-clamps can be manipulated by adjusting the pump flow and venous drainage. This technique reduces strain on the right side of the heart despite the proximal aortic clamping and is beneficial in patients with poor pulmonary function who may not tolerate single lung ventilation [25, 26]. In cases where a proximal clamp site is not feasible, circulatory arrest is mandatory for construction of the proximal anastomosis [27]. The same cannulation strategy can be used but in conjunction with deep hypothermic circulatory arrest (DHCA) and subsequent total body retrograde perfusion, enabling a uniform strategy for all TAAA repairs [28].

Spinal Cord Protection

Numerous strategies have been implemented to reduce the risk of spinal cord ischemia associated with TAA and TAAA repair.

Spinal Cord Protection Strategy During Descending and Thoracoabdominal Aortic Aneurysm Repair

Anatomical

- Motor evoked potential monitoring to identify critical segmental arteries to reattach
- Sequential aortic clamping when possible

Physiological

- Moderate heparinization (1 mg/kg)
- Permissive mild hypothermia (32–34 °C, nasopharyngeal)
- Cerebrospinal fluid drainage
- Left heart bypass during proximal anastomosis

Naturally, the risk of spinal cord injury (SCI) increases when fewer radicular arteries are patent after TAAA, which varies by the underlying aortic pathology as well as the extent of aortic replacement. This concept led surgeons to selectively or nonselectively reimplant intercostal arteries [29, 30], but this strategy seems to have limited benefit in those with aneurysmal disease and an almost negligible role in those with acute dissection [31, 32]. Jacobs and colleagues elegantly demonstrated that intraoperative neurologic monitoring with motor evoked potentials (MEPs) can be used to help identify critical intercostal arteries for revascularization and augment hemodynamics in order to reverse SCI [20]. A sudden drop in MEP amplitude following sequential clamping prompts an increase in distal perfusion pressures; if MEPs do not rebound, then intercostal vessels in the involved

segment are reimplanted with an inclusion button. Patients with extensive Type II TAAAs derive the most benefit from the use of MEPs with targeted intercostal reimplantation as opposed to those with less extensive TAAAs [32].

Additionally, there are several physiologic maneuvers that have been shown to diminish the risk of SCI. These include hypothermia, decreasing spinal pressure via CSF drainage, increasing mean arterial pressure (MAP), maintaining oxygen delivery to tissues by avoiding anemia and hypoxia, and neurochemical protection with naloxone, steroids, and burst suppression [33, 34]. In fact, sophisticated work by Acher and colleagues has shown that these physiologic parameters account for 80% of paraplegia risk, whereas intercostal blood flow is responsible for 20% of risk [32].

Moderate hypothermia (32 °C) has been shown in animal models to confer SCI protection for up to 50 min [35]. Some studies suggest that DHCA (15–20°C) may offer even greater spinal cord protection with TAAA repair [36]. The systemic temperature goal is typically achieved actively with the use of a heat exchanger within a CPB circuit. Using CPB allows for active rewarming of the patient but with risk of coagulopathic bleeding, pulmonary dysfunction, and cardiac arrhythmias, all of which are more profound if deep hypothermia is utilized [27]. In contrast to active cooling, passive systemic cooling can be accomplished through the administration of cold intravenous fluids and avoidance of external warming mechanisms. An alternative option is regional hypothermia whereby an epidural infusion system is used to instill iced saline into the watershed zone of the spinal cord, taking care to avoid increasing CSF pressure [37].

CSF drainage effectively acts to increase spinal perfusion pressure by decreasing CSF pressure to 8 mm Hg intraoperatively and 10 mm Hg postoperatively. Two randomized trials from the same center have shown conflicting results with CSF drainage [38, 39]. Nonetheless, most agree that CSF drainage remains central to a spinal cord protection protocol.

Additional physiologic adjuncts can include the administration of steroids methylprednisolone (30 mg/kg) and mannitol (12.5 g) during anesthesia induction to reduce ischemia-reperfusion injury. Mannitol not only decreases CSF pressure and preserves urine flow after renal ischemia but also acts as a free radical scavenger [21]. Acher and colleagues also utilize a naloxone infusion (1 mcg/kg/hr) because it has been shown to decrease excitatory neurotransmitters from ischemic neurons [40]. Finally, MAP is typically maintained above 100 mm Hg while the aorta is clamped, and hemoglobin concentrations should be kept ≥10 g/dL to help preserve spinal cord oxygen delivery. The importance of maintaining goal arterial pressure cannot be overemphasized, as most causes of delayed SCI likely arise from brief periods of postoperative hypotension [41].

Visceral Organ Protection

Some of the methods used for spinal cord protection additionally aid in preventing ischemic injury of the abdominal viscera. These include permissive hypothermia and sequential aortic clamping in the repair of any TAAA. Additionally, cold crystalloid selective renal perfusion and selective perfusion of the celiac and superior mesenteric axes are frequently employed in extent I and II TAAA repairs [42]. This is accomplished utilizing balloon-tipped catheters and a separate arterial inflow circuit from the bypass pump to perfuse the celiac and superior mesenteric vascular beds with oxygenated blood, particularly during the reattachment of proximal thoracic aortic segmental arteries.

Surgical Approach

Surgical Positioning and Exposure

The patient is placed in a modified right lateral decubitus position with padding of all pressure points and a right axillary roll to protect the axillary nerve (Fig. 18.6). The hips are rotated obliquely to the left to allow access to the right groin, if necessary. The right knee is flexed, and the left kept straight, with padding between the legs to avoid stretch on the left femoral nerve. A beanbag is used to maintain this position and the table is flexed just above the iliac crest. The field is prepped to include the left chest including the axilla superiorly and the spine posteriorly. The entire abdomen and both groins are prepped.

An incision along the fifth or sixth intercostal space is adequate for most Type I and Type II TAAAs. Type III TAAAs are approached through the seventh or eighth intercostal space and Type IV TAAAs through the ninth interspace. The incision is extended down along the abdominal wall onto the left lower quadrant, staying lateral to the left rectus muscle. The costal margin is divided connecting the retroperitoneum to the chest cavity. The retroperitoneal plane is developed deep to the transversus abdominus muscle taking care to not violate the peritoneum, which can be quite thin medially. Care should be taken upon entering the abdomen to clearly identify the external and internal oblique layers, as their identification aids in closure later in the case. After the costal margin is divided, the diaphragm is incised circumferentially taking care to avoid injury to the phrenic nerve but leaving enough diaphragmatic cuff on the chest wall to facilitate closure. The left kidney and viscera are reflected medially, exposing the aorta from the hiatus to the iliac bifurcation. At this point, single-lung ventilation can be used, and a self-retaining retractor system should be placed to maintain exposure.

The left inferior pulmonary ligament is divided, and the lung is mobilized from the aneurysm. The extent of proximal exposure again depends on the location of aortic disease.

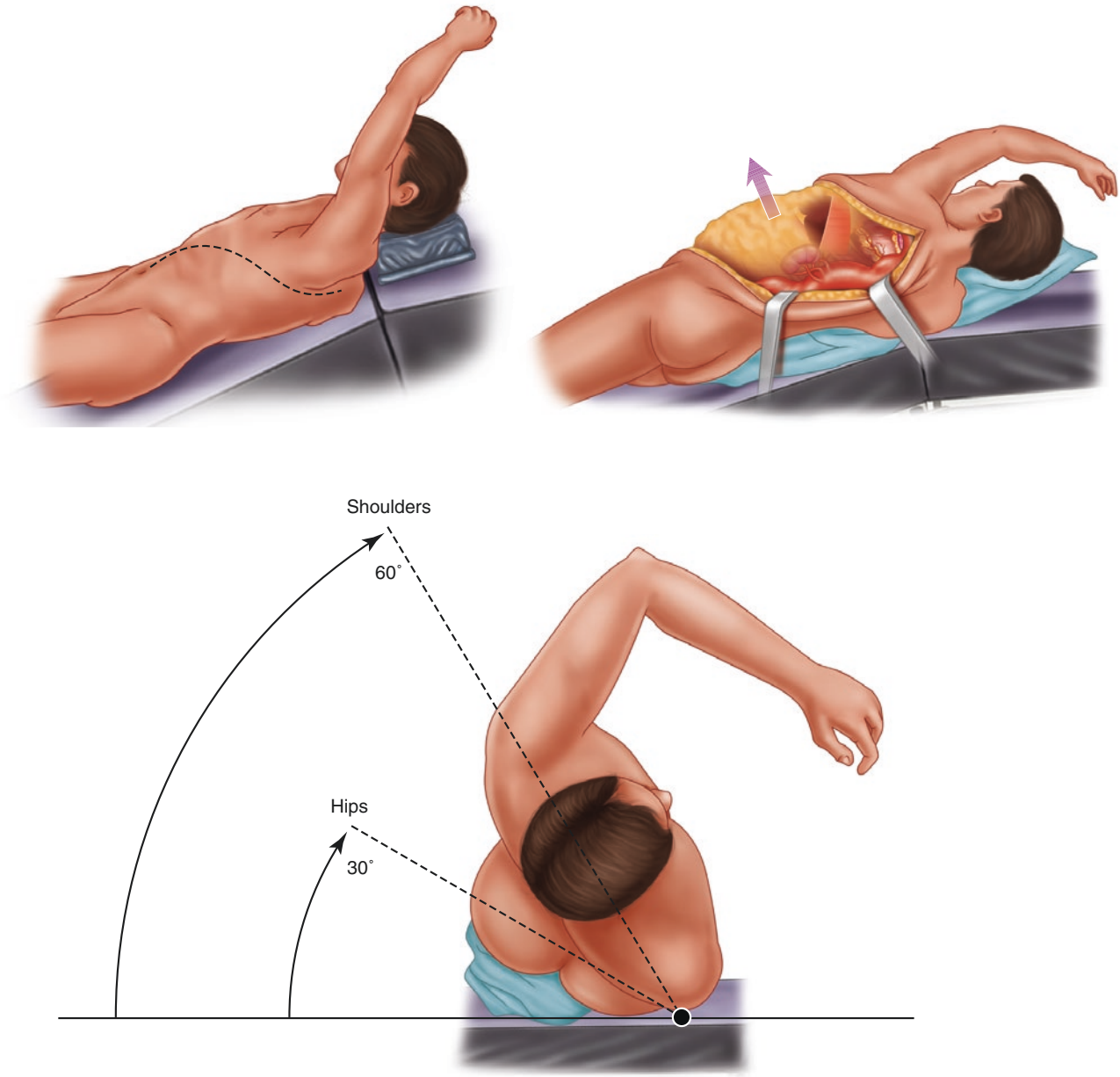


Fig. 18.6 Patient positioning. For repair of the descending thoracic aorta, the patient is positioned in modified right lateral decubitus position. The surgical incision extends from the left scapula through the fifth to seventh intercostal space across the costal margin and toward the left periumbilical region to allow the surgeon to enter the retroperitoneal space

Care should be taken to identify and avoid injury to the phrenic, vagus, and recurrent laryngeal nerves, which are encountered during the dissection of the proximal thoracic aorta. If repairing a TAAA, the abdominal aortic branches are now exposed dissecting free the celiac artery (CA), superior mesenteric artery (SMA), and left renal artery (LRA). Sufficient exposure of the SMA and CA to allow clamp placement will prevent unnecessary blood loss from back bleeding upon opening the aneurysm sac.

Repair of the Descending Thoracic Aorta Segment

After sufficient exposure, the sequence and method of aortic reconstruction can proceed in a variety of ways depending on surgeon preference. The basic principles are to facilitate the completion of the reconstruction, prevent spinal cord injury, and allow perfusion of the branch vessels/lower extremities for as long as possible through each step to avoid ischemia/reperfusion injury of the end organs.

The selected perfusion technique is initiated (LHB or partial CPB), heparin (150 units/kg) is administered, and the patient is passively cooled to 32–34 °C prior to clamp placement. Additionally, prior to clamp placement, MAP is increased and maintained at 100 mm Hg.

The proximal aortic clamp is placed either between the left common carotid and subclavian artery origins or distal to the subclavian artery depending on the extent of the proximal involvement of the aneurysm. The distal clamp is placed such that the pump provides blood flow to the lower body/visceral segment as the proximal reconstruction is performed (usually at T4–T6) (Fig. 18.7). The aorta is opened longitudinally between the two clamps and freed from the surrounding structure including the esophagus. A cuff of the proximal descending thoracic aorta about 2–3 cm distal to the proximal aortic clamp is cut transversely and sewn to a woven Dacron tubular graft using a running 3–0 polypropylene suture (Fig. 18.8).

Elephant Trunk Repairs

A staged elephant trunk repair is used when the aneurysm involves both the aortic arch and the descending thoracic aorta. It involves replacing aortic arch with a synthetic graft leaving a short segment of the graft floating in the descending aorta (hence the name elephant trunk) to facilitate the subsequent open replacement of the descending aorta in the second stage. During the second stage, the aorta is opened and the graft trunk is retrieved and anastomosed to the graft used for the DTAA or TAAA repair [43].

If the DTAA or TAAA are much larger than proximal arch or ascending aneurysms or causing symptoms (back pain or rupture), the descending thoracic part is addressed first. During the reversed elephant trunk procedure, proximal end of the graft is inverted into the lumen to facilitate the arch repair during the second stage [44].

Intercostal Patch Anastomosis

Should the surgeon choose to reimplant the intercostal arteries, this can be done with a side biting clamp and a Carrell patch or an independent bypass to a patch of aorta including the intercostal arteries, performed end-to-end or with a "loop" graft using a Dacron tube sewn proximally and distally to the Dacron aortic tube graft (Fig. 18.9). The latter methods create an easy method of exclusion with TEVAR should the involved aorta at the site of the intercostal arteries degenerate and become aneurysmal over time. If ligation of the intercostal arteries is planned, this should be done quickly at the time of opening the aorta to avoid a pressure sink from back bleeding into the open aorta, which can contribute to spinal cord ischemia.

Following the intercostal artery anastomoses, the graft clamp is moved distally to allow perfusion of the newly anastomosed intercostal arteries. Then the infrarenal portion of the abdominal aorta is then clamped and opened. The four visceral arteries are perfused using 8-Fr size balloon-tipped catheters via single roller pump at arterial flows of 150–200 mL/min (Fig. 18.10).

Visceral Branch Vessel Anastomosis

After completion of the proximal anastomosis, the abdominal segment is clamped 2–3 cm below the proposed distal anastomotic site and the aorta is opened longitudinally posterior to the origin of the left renal artery. The origins of the CA, SMA, and LRA are identified and endarterectomies are performed if necessary. These visceral arteries are anastomosed to the graft either independently or with a visceral patch (Fig. 18.11). The visceral patch including the CA, SMA, and RRA is fashioned and sewn to the graft using 4–0 polypropylene suture. The LRA requires a separate branch graft anastomosis as well. When a multibranched graft with independent bypasses to the visceral/renal vessels is utilized, the CA, SMA, and LRA can often be taken off the aorta one at a time, allowing continuous perfusion from the pump to the rest of the distal aorta/lower extremities as each anastomosis is completed. Creating independent visceral/renal/intercostal arterial bypasses rather than using a Carrell patch is recommended in patients with known or suspected connective tissue disorders due to the risk of future aortic

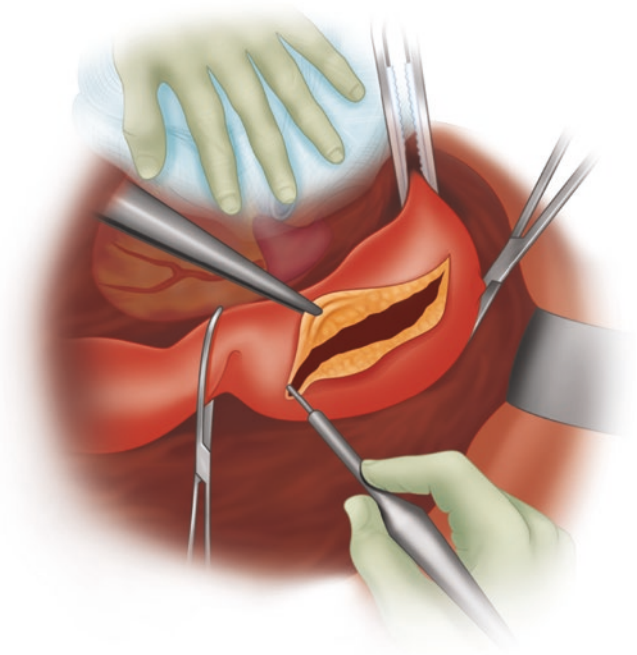


Fig. 18.7 Clamp placement. Demonstration of the clamp placement and transection of the aorta in preparation for proximal end-to-end anastomosis. In this case, the proximal clamp is placed across the arch of the aorta between the left carotid and left subclavian arteries with the distal clamp on the descending aorta and a third clamp on the takeoff of the left subclavian artery

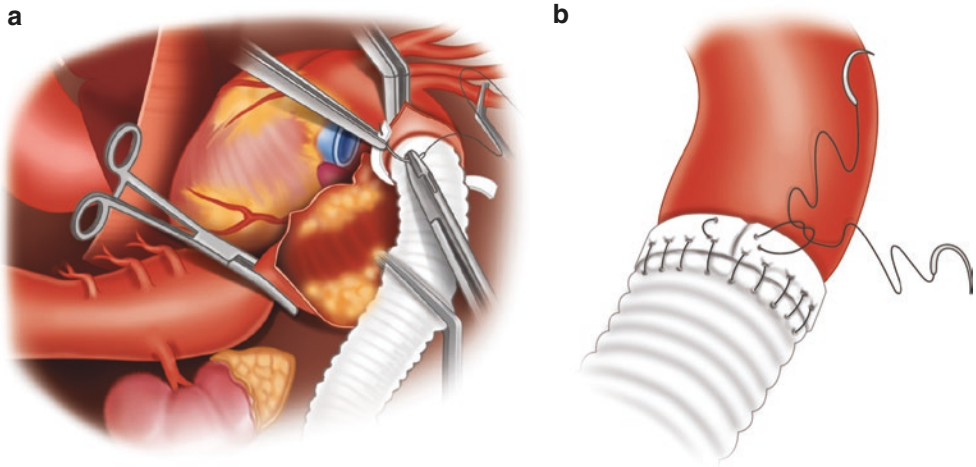


Fig. 18.8 (**a**, **b**) Proximal anastomosis. The proximal anastomosis from native healthy aorta to the graft is performed with a running 3–0 monofilament suture with Teflon strip reinforcement

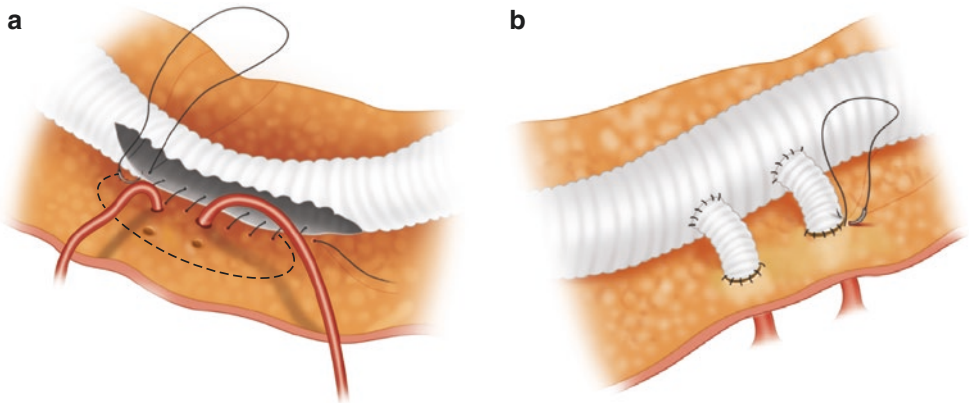


Fig. 18.9 Options for intercostal artery reimplantation. (**a**) Patent orifices of no more than two pairs of intercostal arteries can be anastomosed to a side hole in the graft as an aortic patch using an inclusion technique with a 4–0 monofilament suture. (**b**) Alternatively, the intercostal arteries can be attached using graft interposition, with several small grafts connected to the orifices of the intercostal arteries

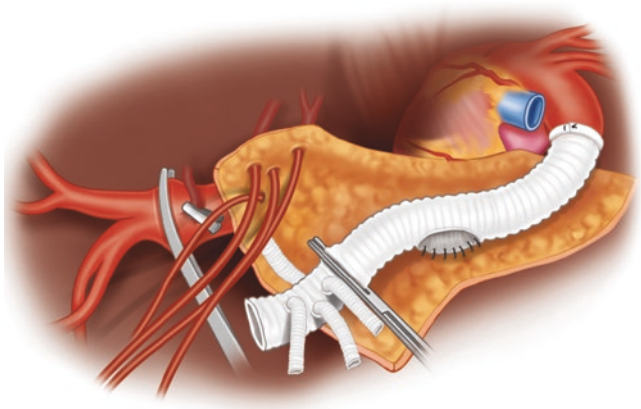


Fig. 18.10 Visceral artery perfusion. Following completion of the intercostal artery anastomoses, the distal clamp is moved distal to the visceral vessels to allow intercostal perfusion. The infrarenal aorta is the clamped and opened. Size 8-Fr balloon-tipped catheters are inserted into the four visceral arteries (celiac artery, SMA, left and right renal arteries) to allow selective perfusion with a single roller pump using arterial flows of between 150 and 200 ml/min

patch degeneration. Similarly, if a Carrell patch be utilized, the patch should be kept as small as possible to avoid future patch aneurysm. If prolonged visceral/renal ischemia time is anticipated, selective perfusion of these vessels can be performed. Mesenteric and renal ischemia time is typically less than 60 min, and thus, directed perfusion of these vessels is generally not necessary. It is worth mentioning that extent I aneurysms can be repaired with a beveled anastomosis to the abdominal aorta just above the visceral segment, and extent V aneurysms can be repaired in a similar fashion with a beveled anastomosis including the bilateral renal arteries.

Distal Aortic Anastomosis and Closure

The graft is anastomosed to the distal aorta below the aneurysm or in patients with iliac artery aneurysms, and a bifurcation graft is sewn onto the end of the straight graft and anastomosed to the common iliac, external iliac, or common femoral artery, depending on the extent of the disease (Fig. 18.12).

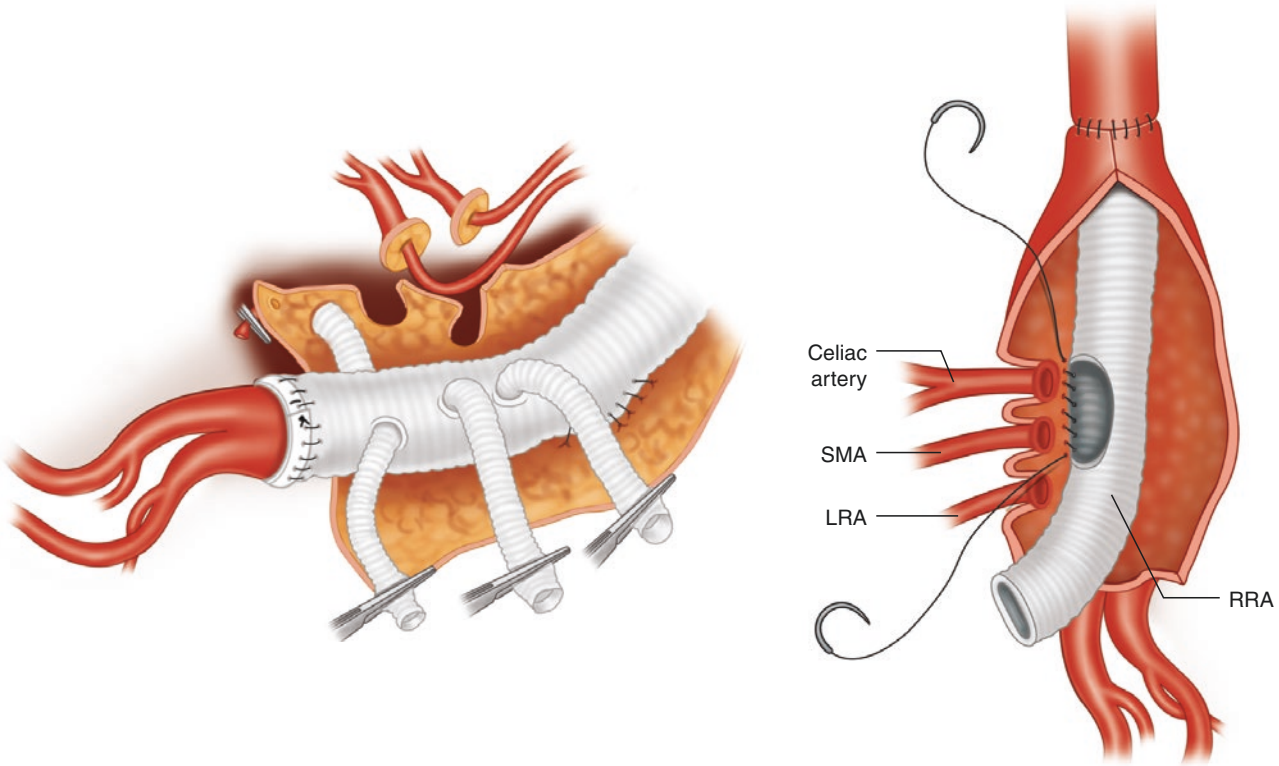


Fig. 18.11 Visceral artery anastomoses. Similar to the intercostal arterial anastomoses, the visceral arteries can be anastomosed to the graft with small individual grafts coming off the main graft (*left*) or through a common visceral patch for the CA, SMA, and right renal artery with a separate branch graft anastomosis for the left renal artery (*right*)

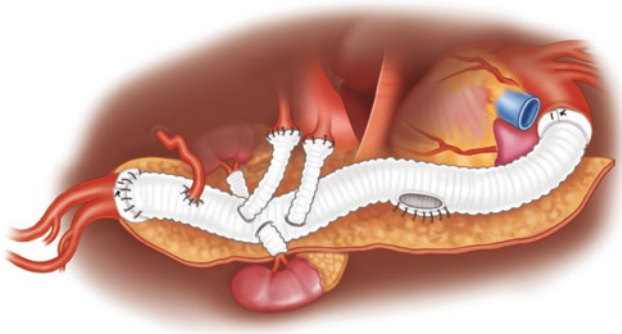


Fig. 18.12 Completion of repair. The newly implanted graft with proximal, distal, intercostal, and visceral anastomoses is shown above. Following completion of anastomoses, the patient is weaned from cardiopulmonary bypass and hemostasis is achieved following protamine administration

After distal anastomosis and clamp removal, heparin is reversed with protamine sulfate and hemostasis is achieved both surgically and by administering blood products as necessary. To assess adequate renal function, blue dye is administered intravenously, and transit time to urine output is measured. The bowel, spleen, and liver are all assessed for adequacy of perfusion. The spleen is examined for capsular injury; if a splenic hematoma is present, the spleen is removed to avoid postoperative bleeding and hypotension. The aneurysm wall is then loosely wrapped around the aortic graft. Two large bore thoracic drains are posteriorly located, and a closed-suction retroperitoneal drain is placed before closure. The diaphragm is closed with continuous polypropylene suture, and the wound is closed in layers in the usual fashion.

A word of caution regarding open repair of TAAAs in the setting of chronic dissection, the true and false lumens can be difficult to distinguish from one another. Transection of the aorta proximally is helpful in discerning the true from the false lumen. Both lumens should be opened along their entire course by excising the dissection septum to allow full visualization of the intercostal arteries and visceral/renal branch vessels that arise from each lumen.

Follow-Up After Open Repair

Typical follow-up of patients following open TAAA repair varies by center but frequently includes computed tomography angiography and office checkups at 3 and 12 months postoperatively and yearly afterward [45]. Postoperative CTs

are obtained to check for not only the integrity of the repair and possible recurrence but also for visceral vessel patency, which is a crucial benchmark in comparing open and endovascular approaches to repair [45].

Outcomes and Complications

Operative and In-Hospital Mortality

When performed in centers of excellence, TAA and TAAA repairs have good outcomes, with 30-day mortality rates of 2.8–15.9% reported in large institutional studies compared to closer to 20% when examining state-wide or national data [45–48]. Multiple factors have been linked to higher perioperative mortality including advanced patient age, surgeon/hospital volume, presence of rupture/emergency procedure, incidence of postoperative spinal cord ischemia, postoperative renal dysfunction, and Crawford extent type with Types II and III carrying the highest mortality risk [46, 48]. Patients under 50 years old, while making up a small minority of patients undergoing open TAAA repair, have been shown to have lower rates of operative death 3.2% vs. 8.2% and fewer adverse events 5.2% vs. 15.9% in institutional series [49]. Despite advanced age being considered a risk factor for higher mortality, Karimi et al. demonstrated favorable outcomes of octogenarians undergoing open thoracic aorta operations with in-hospital mortality of 13% for open repair and only 28% of patients suffering a major adverse event [50].

Complications

Open TAA/TAAA repair is a significantly morbid procedure, with nearly 50% of patients sustaining a major pulmonary event, 15% sustaining a cardiac complication, and several other operation-specific concerns including the potential for postoperative renal dysfunction and spinal cord ischemia [51]. Bowel ischemia is uncommon but can occur usually secondary to embolization from clamp manipulation or intraoperative hypotension. Finally, graft-related complications can arise leading to life-threatening conditions such as aorto-bronchial or aorto-esophageal fistulae.

Risk factors for pulmonary complications include underlying COPD, history of tobacco use, and concurrent cardiac or renal complications [52, 53]. Girardi et al., in their series of 726 patients, demonstrated that an FEV1 < 50% is strongly predictive of increased respiratory failure, tracheostomy, and operative mortality in patients undergoing open TAA/TAAA repair [52]. Dolapoglu et al. found in a large institutional series that postoperative cardiac arrhythmia was common after TAAA repair, occurring in 26.5% of patients, with older patients and patients who underwent visceral perfusion being at increased risk [53].

Renal dysfunction, which is linked to increased risk of early death following open TAA/TAAA repair, occurs in up to 25% of patients, with 10% progressing to require hemodialysis [51]. Further, postoperative renal failure following open TAA/TAAA repair has been linked to up to seven times higher operative mortality as well as an increased risk of major adverse events and significantly worse 5-year survival [54]. In a large series of the 5.7% of patients who progressed to permanent renal failure, more than half died in the hospital [47].

Although numerous perioperative complications have the potential to arise following TAA and TAAA repair, spinal cord ischemia (SCI) receives increased focus due to its devastating consequences: spinal cord ischemia may result in paraparesis or paraplegia of variable length. Large series estimate the risk of paraparesis/paraplegia to be 2.9–8.1% for TAA/TAAA [45–47, 55]. In a review of 3309 TAAA repairs performed between 1986 and 2014, Coselli and colleagues report incidences of 2.9% for paraplegia and 2.4% for paraparesis [47]. To combat spinal cord ischemia and other end-organ damage, intraoperative adjuncts, specifically distal aortic perfusion (DAP) and cerebrospinal fluid drainage (CSFD), have been widely explored at major centers and in the literature [46, 56]. Although exact practices vary between institutions and surgeons, one such large review advocates leaving the CSF drain in place for 3 days postoperatively, maintaining pressure at less than 10 mm Hg but limiting drainage to 15 mL/h with a neurologically intact patient or—should a neuro deficit occur—to allow free CSF drainage to maintain a CSF pressure < 5 mm Hg [46]. In recent years, automated devices for controlled and continuous CSF drainage have been developed and implemented in small series [57].

Reducing readmissions following TAA/TAAA repair is another metric worthy of attention and are not well studied [58, 59]. A series published by Wu et al. showed an 11% readmission rate after open TAAA repair and identified risk factors, including renal dysfunction, sleep apnea, and postoperative infection [59]. Unfortunately, state-wide data suggests that early readmissions may be more frequent: a study by Glebova et al. found that of 115 Maryland residents undergoing TAA/TAAA repair in an 11-year period, early readmissions occurred in 29% of patients, and of the readmitted patients, 79% were not readmitted to the index hospital where their operation was performed [58].

Long-Term Survival

Long-term survival after TAA/TAAA repair is not well-reported except for by a few, high-volume centers [47]. Coselli et al., in a review of 3309 open repairs, found survival rates of 83.5% at 1 year, 63.6% at 5 years, and 36.8% at 10 years [47]. In their cohort of 1896 repairs, Estrera et al. reported similar survival rates of 57.7% at 5 years and 42.9% at 10 years [46]. While survival is low compared to the healthy population, the natural history of an unrepaired TAAA carries a 76% mortality at 2 years and upward of 95% mortality at 5 years [48, 60]. The decision to undertake these

complex and morbid operations should include a complete discussion of the risks and benefits involved, especially considering a patient's postoperative quality of life and function. Unfortunately, postoperative quality of life often goes overlooked; one small study assessing 134 long-term survivors after TAAA repair showed composite physical and mental health scores significantly lower than an age-adjusted reference population [61]. A further study by Rectenwald et al. showed that only 50% of patients reported a "good" outcome at 1-year post-TAAAA repair, based on their ability to ambulate or be residing at home or a rehabilitation center [62].

Special Considerations: Redo Operations and Mycotic Aneurysms

Because aortic disease is a chronic, progressive illness that may require multiple interventions throughout a patient's lifetime, it is common for patients with TAA and TAAA to undergo redo procedures [63–65]. Large series examining TAA/TAAA repair have shown 10–15% of open TAA/TAAA repairs to be redo operations [63, 64]. One such series showed indications for redo operation include extension of disease 86.8%, intercostal patch expansion 6.8%, visceral patch expansion 10.9%, infection 4.5%, anastomotic pseudoaneurysm 8.3%, and previous endovascular aortic repair complications 6.4% [64]. In one series, redo operations had a higher early mortality rate of 22.9% and lower long-term survival of 46.6% at 5-years compared to 58.1% for nonredos [64]. In another series, early mortality was comparable, 8.7% vs 5.3% for primary, and there was no difference in 5-year survival, 57.6% for redos and 58% for primary [63].

Mycotic TAA and TAAA are an unusual variant, while they make up less than 1% of all aortic aneurysms that are very lethal, with a high incidence of fatal rupture without surgical intervention [66, 67]. Data on outcomes of open repair of this unique pathology are limited to small series and case reports: a series of 14 patients published by Lau et al. showed 1 in-hospital death, and actuarial 5-year survival of 71%, suggesting that open repair with aggressive debridement and appropriate antibiotic coverage including lifelong antibiotic suppression therapy remain the gold standard for treatment of mycotic TAA/TAAA [66].

Pseudoaneurysm

An aortic pseudoaneurysm is a disruption in the artery wall with direct communication to a cavity contained by adjacent mediastinal tissue. The causes of aortic pseudoaneurysm vary from traumatic, infection, or iatrogenic from previous cardiac procedures. Traumatic causes can be focal aortic transection from penetrating trauma (gunshot or stab wounds) or from acceleration-deceleration injuries (motor vehicle accidents or falls) [68]. They characteristically occur along the undersurface of the aortic isthmus at or near the site of the ductus arteriosus [68]. They also occur from nontraumatic pathologies such as penetrating atherosclerotic ulcers [69]. Pseudoaneurysms can be a rare complication of cardiac surgery related to aortic anastomoses, saphenous vein conduits during coronary artery bypass grafting, and prior aortic cannulation sites [70]. The most common location of pseudoaneurysm is the ascending aorta. Chest pain and congestive heart failure symptoms are the most common clinical presentations [71]. Many pseudoaneurysms may be detected incidentally on surveillance CT imaging. If persistent fever, chills, and leukocytosis are present, the patient should be suspected of having a mycotic pseudoaneurysm.

Treatment and surgical approach for pseudoaneurysms vary according to the site and the pathologic features. Operations can be technically challenging, especially in the presence of infection, previous cardiac surgery, or aortic valve regurgitation. The ascending aorta often requires axillary cannulation or femoral artery cannulation. If the pseudoaneurysm cavity abuts the sternum in the reoperative setting, it is prudent to establish cardiopulmonary bypass via the femoral vessels prior to sternal division. If the pseudoaneurysm is entered during sternal re-entry, temporary manual pressure should be performed while cooling the patient on cardiopulmonary bypass for hypothermic circulatory arrest [71]. In this scenario, it is important to be prepared to effectively vent the left ventricle as the patient will experience ventricular fibrillation due to hypothermia. If adhesions preclude safe access to the right superior pulmonary vein, a small left anterior thoracotomy can provide exposure to the left ventricular apex for direct venting.

Descending thoracic aortic pseudoaneurysms can be treated either by endovascular or open replacement. If the pseudoaneurysm is mycotic in origin, then excision and replacement of the aorta are indicated and are usually treated with lifelong antibiotics [72]. Left heart bypass can be utilized during surgical replacement of the aorta with interposition tube graft. Pseudoaneurysms caused by trauma are often distal to the left subclavian and can be managed with endovascular stenting [73].

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Surgical Treatment of the Abdominal Aorta

19

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Abbreviations

AAA	Abdominal aortic aneurysm
AIOD	Aortoiliac occlusive disease
ePTFE	Expanded polytetrafluoroethylene
IMA	Inferior mesenteric artery
PFA	Profunda femoral artery
rAAA	Ruptured abdominal aortic aneurysm
SFA	Superficial femoral artery

Aortic Aneurysm

Background

The modern era of surgical treatment of AAA (abdominal aortic aneurysm) began with Dubost's successful repair using homograft in 1951. Since that time, techniques of open repair and perioperative care of the surgical patient have been refined and outcomes today remain excellent. Mortality rates for elective repair approach 1% in experienced hands [1]. The incidence of these lesions is 1.5–3.0% based on autopsy series; however, this figure rises in selected populations. Hypertension, atherosclerotic disease, and known aneurysmal disease of other vessels are risk factors. The natural history of all aneurysms is for progressive increase in size over time; thus, the risk of rupture-specific death rises with age. The intent of repair is to prevent late death related to aneurysm rupture. Although the advent of endovascular treatment options has revolutionized the treatment of AAA, thorough knowledge of the techniques for traditional open surgery remains an essential element of the modern vascular surgeon's armamentarium. Here, we will focus on considerations for open surgical repair.

AAA is a permanent localized dilatation of the intra-abdominal aorta greater than 30 mm in diameter, and this generally accepted definition has been used as the basis for the population-based studies which clarified the natural history of small infrarenal aneurysms [2].

By far, the most common location of abdominal aneurysms is infrarenal. These involve only the segment caudad to the renal arteries, with a portion of normal aorta between the most inferior renal orifice and the abnormal arterial tissue sufficient to allow for open reconstruction while maintaining renal perfusion throughout the repair. Pararenal aneurysms are more proximal lesions in which repair will more directly involve the renal arteries. Juxtarenal aneurysms are pararenal aneurysms with normal tissue at the orifices but inadequate space for an infrarenal aortic clamp. Repair of these lesions requires intraoperative interruption of renal perfusion by cross-clamping proximal to either or both renal arteries; the reconstruction itself remains limited to the infrarenal aorta. Suprarenal aneurysms are those pararenal aneurysms for which both cross-clamp and reconstruction must start superior to the renal arteries, dictating both interruption of renal blood flow and subsequent revascularization during the same procedure. Any aneurysmal involvement of the paravisceral segment of the abdominal aorta is considered a thoracoabdominal aneurysm, requiring a much more complex

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reconstruction with supraceliac clamping and revascularization of the mesenteric circulation.

As the purpose of repair is to prevent rupture-specific death, indications for surgical repair must balance the increasing risk of mortality posed by aneurysm growth with the risks associated with any procedure undertaken for repair. The results of population-based cohort studies on the natural history of AAA suggest an aortic diameter threshold of 5.5 cm for elective repair. This represents a consensus view of the point of equipoise between the risks of intervention and the risks of continued observation [3]. This number should however be considered in the context of each patient individually. Younger patients who otherwise represent a lower surgical risk may be candidates for elective surgery at a diameter of 5.0 cm given that such aneurysms nearly always progress to the 5.5 cm threshold with time. Smaller aneurysms that demonstrate rapid growth of more than 5 mm within a surveillance period of 6 months should also be considered for repair, as these lesions are considered a higher rupture risk. Female patients have long been to known to have higher risk for rupture and death at smaller diameters than their male counterparts. A threshold of 5.0 cm diameter has been proposed for AAA in women; however, high-quality data are lacking [4]. Conversely, patients with a life expectancy of less than 2 years are unlikely to benefit from elective repair. Patients whose comorbidities create prohibitive operative risk require circumspect judgment regarding the timing or feasibility of elective repair, although as the aneurysm becomes larger than 5.5–6.0 cm the risk of rupture-related death usually outweighs perceived operative risk. In the special case of a symptomatic or ruptured aneurysm, the risk of death is so great that very few contraindications exist for surgical intervention so long as such intervention is consistent with the patient's goals of care.

Any decision to perform elective open surgical treatment of AAA must be accompanied by an evaluation of the patient's overall health and any other coexisting health conditions. An assessment of the patient's ability to benefit from the procedure is mandatory. As the objective of AAA repair is to prolong life, risk factors for both perioperative and late morbidity and mortality must be carefully considered against the risk of late rupture of an untreated aneurysm [5]. The most challenging cases are typically those of older, chronically ill patients with large aneurysms. Advanced age, significant cardiopulmonary disease, or dialysis-dependent renal failure all represent increased risk for perioperative complications. These patients are often best served by endovascular treatment. At a minimum, any preoperative assessment should include a thorough review of the patient's medical and surgical history, paying particular attention to any evidence for unreconstructed coronary disease, congestive heart failure, parenchymal lung disease, diabetes mellitus, or chronic renal failure [6]. These conditions should be optimized prior to surgery. The most common cause of death at the time of surgery and following repair is coronary artery disease. A resting 12-lead EKG should be obtained in any patient under consideration for AAA repair as the incidence of coronary artery disease in this population is high [7]. In addition, preoperative cardiac stress testing should be considered for those patients with risk factors for occult coronary disease. Abdominal imaging using computed tomography angiography should almost always be obtained for preoperative planning. Recent research has also suggested that both surgeon and hospital volume play a role in outcomes for elective AAA repair, with higher volumes giving improved results [8].

The first consideration in open operative technique for aneurysm repair is to determine the necessary extent of the reconstruction. As discussed above, the anatomy of the AAA with regard to the renal and mesenteric vessels will dictate the crucial steps of the surgery. The general rule is to exclude all abnormal aortic tissue, replacing it with a graft material, which is sutured to normal aorta in order to restore arterial blood flow distally. In all cases, the surgeon will need to make a determination about the location of the proximal and distal anastomoses; this should be planned prior to the operating room based on the available preoperative imaging. In the case of infrarenal aneurysm, the reconstruction should include the entire infrarenal aorta up to the renal artery orifices in order to prevent recurrent aneurysmal degeneration in any normal-appearing tissue left behind. Pararenal aneurysms will require some period of ischemia to one or both kidneys due to the necessary suprarenal cross-clamp position. Repair of suprarenal AAA will by definition require reimplantation of at least one major aortic branch vessel, and the time necessary for this revascularization lengthens the ischemic period. To prevent postoperative renal insufficiency, this ischemia time must be kept to a minimum. Meticulous intraoperative planning is the key to avoiding this complication; principles of minimizing ischemia time include completion of the proximal anastomosis immediately after clamp placement, followed by repositioning of the clamp onto the graft distal to the renal arteries, thus restoring renal perfusion as the distal portion of the reconstruction proceeds. The position of the cross-clamp must also be considered as a potential cause for embolization of intramural cholesterol crystals or chronic thrombus; preoperative imaging can be very helpful in this regard.

In some cases, the repair can be accomplished with only two anastomoses: proximally as dictated by the extent of disease around the renal arteries and distally at the very furthest

portion of the aorta. This is known as a tube graft repair for the shape of the graft used. Otherwise, the distal reconstruction will require a bifurcated graft, with the point of anastomosis on each side determined by the condition of the iliac arteries. These repairs are referred to as aortobiiliac or aortobifemoral depending on the final position of the distal reconstruction (Fig. 19.1).

Graft Material

Synthetic grafts are available in one of two materials: polyester, available as a knitted or woven graft, and expanded polytetrafluoroethylene (ePTFE). Knitted polyester grafts are typically impregnated with collagen or gelatin to reduce porosity. Woven polyester is stronger than the knitted variety,

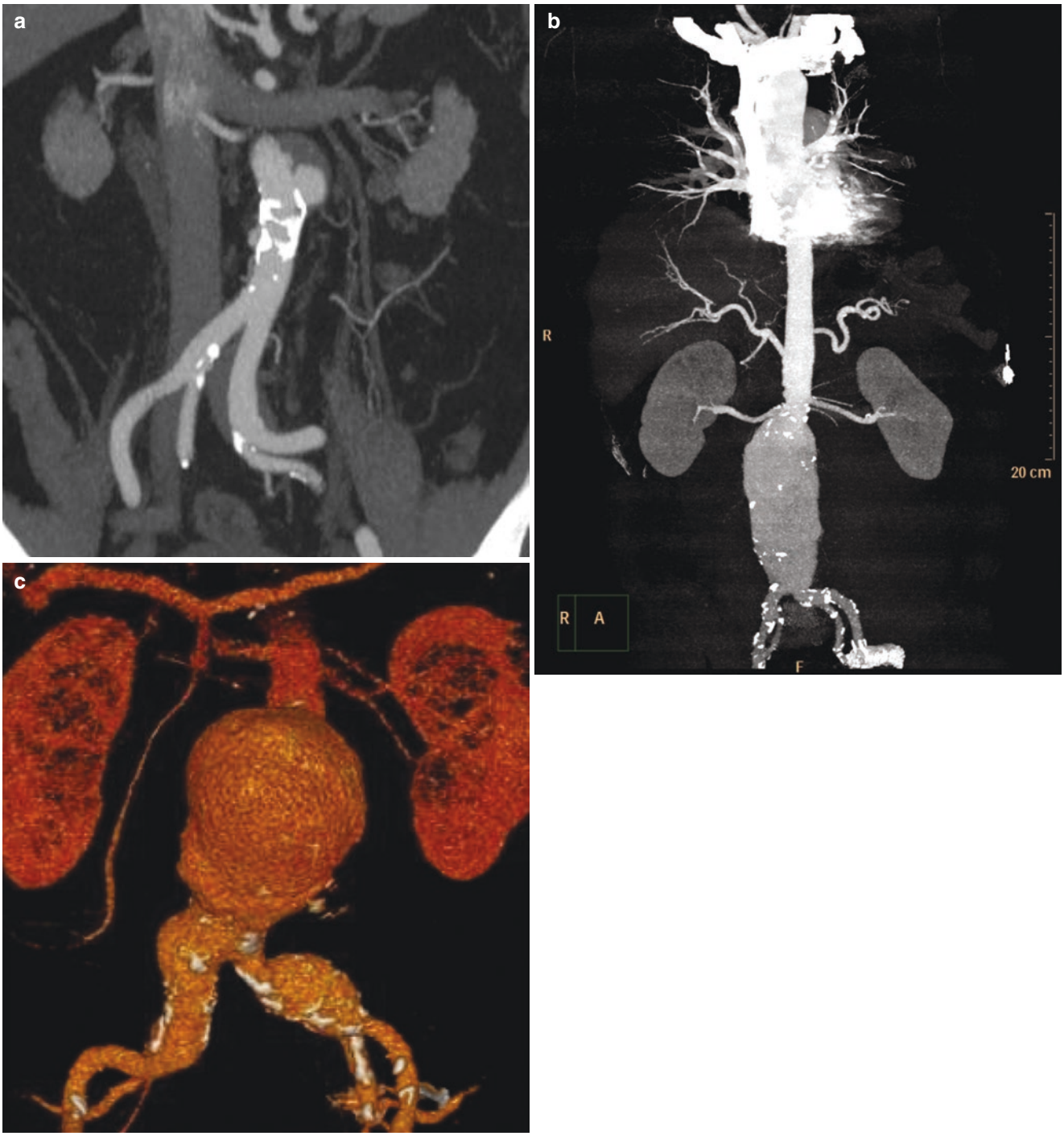

Fig. 19.1 (**a**) Isolated infrarenal aneurysm suitable to tube graft repair. (**b**) Infrarenal aortic aneurysm extending to aortic bifurcation suitable for aortobiiliac repair. (**c**) Infrarenal aortic aneurysm with aneurysmal bilateral iliac arteries suitable for aortobifemoral repair

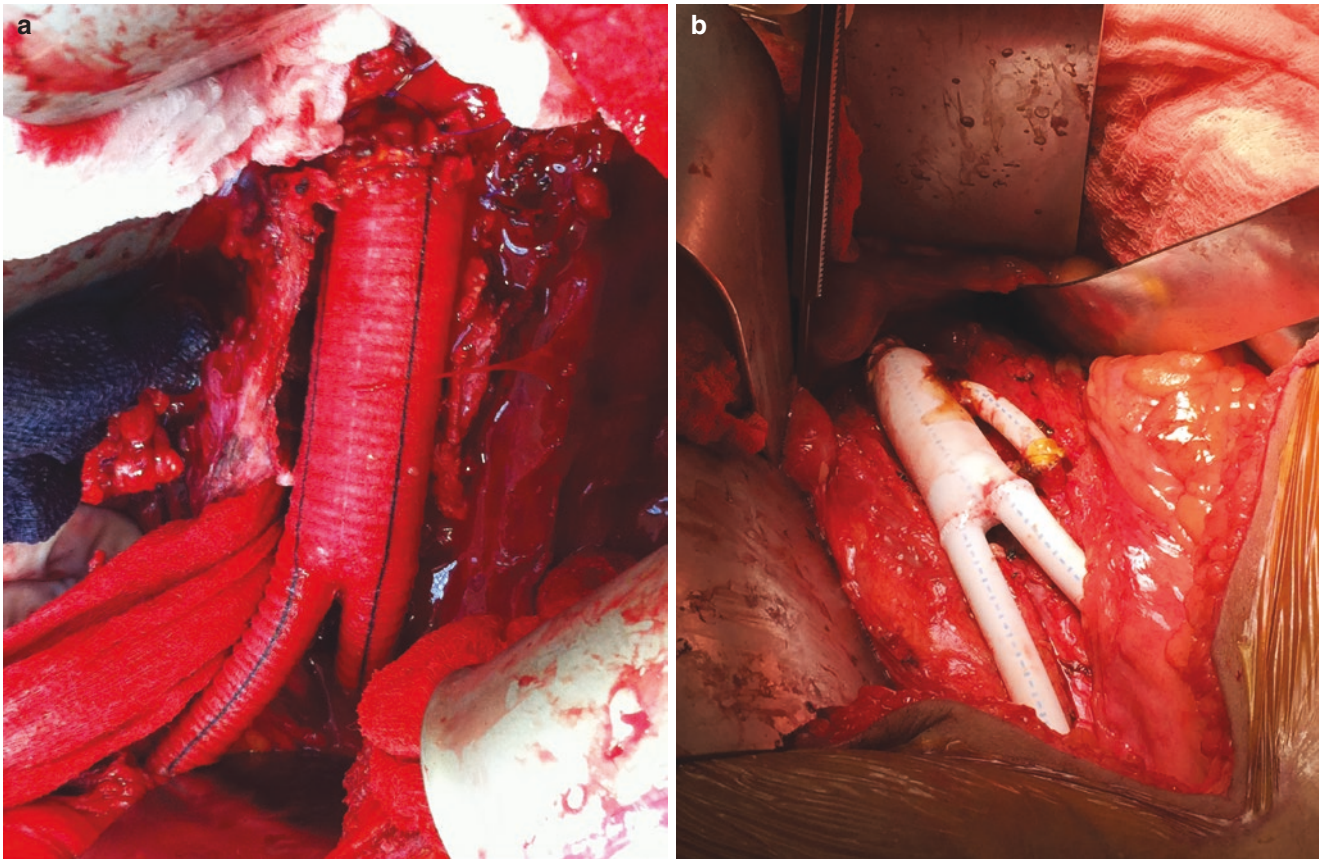

Fig. 19.2 (**a**) Polyester fabric aortic aneurysm repair. (**b**) ePTFE aortic aneurysm repair

but is more difficult to handle. The two materials have been shown to be equivalent for purposes of aortic reconstruction, and the choice is primarily one of surgeon preference based on personal experience and handling characteristics [9] (Fig. 19.2).

Operative Technique

The classic operative exposure for exposing the aneurysmal abdominal aorta is the midline incision. This is made starting from the tip of the xiphoid process and is extended distally to the pubic bone. This allows for transperitoneal exposure of the entire abdominal aortoiliac system if necessary, as well as for comprehensive inspection of the peritoneal contents. A disadvantage of this approach is suboptimal exposure of pararenal aneurysms, depending on the position of the left renal vein. This vessel is usually found immediately anterior to the aorta and can be mobilized or ligated, but with concomitant increased risk of bleeding which can prove difficult to control [10]. Once the abdomen is entered via the midline incision, the transverse colon is mobilized superiorly and the small bowel mobilized to the right side of the abdomen after releasing the ligament of Treitz. These maneuvers provide access to the retroperitoneum. If wider exposure is required to expose the paravisceral aorta, a medial visceral rotation can be performed. This involves mobilization of the descending colon, pancreas, and spleen.

Proximal control of the aorta is established by circumferential dissection of the vessel at the transition point to normal aortic tissue. This may involve some dissection of retroperitoneal lymphatic tissue, which should be ligated to prevent leakage. Control of renal or mesenteric vessels may be required depending upon the extent of the aneurysm; this is accomplished with silastic vessel loops placed under tension. The left renal vein is identified and kept safely out of harm's way. If the left renal vein is divided, its collaterals from the adrenal glands and the pelvis must be preserved. A retroaortic vein should be suspected if none is noted anteriorly; failure to do so can lead to vein injury and dangerous bleeding upon aortic dissection and clamping. Lumbar veins can also sometimes be located immediately behind the aorta, leading to similar bleeding problems if the surgeon does not think to anticipate them (Fig. 19.3).

Distal control is obtained in a similar manner over the iliac vessels, with attention given to identifying and protect-

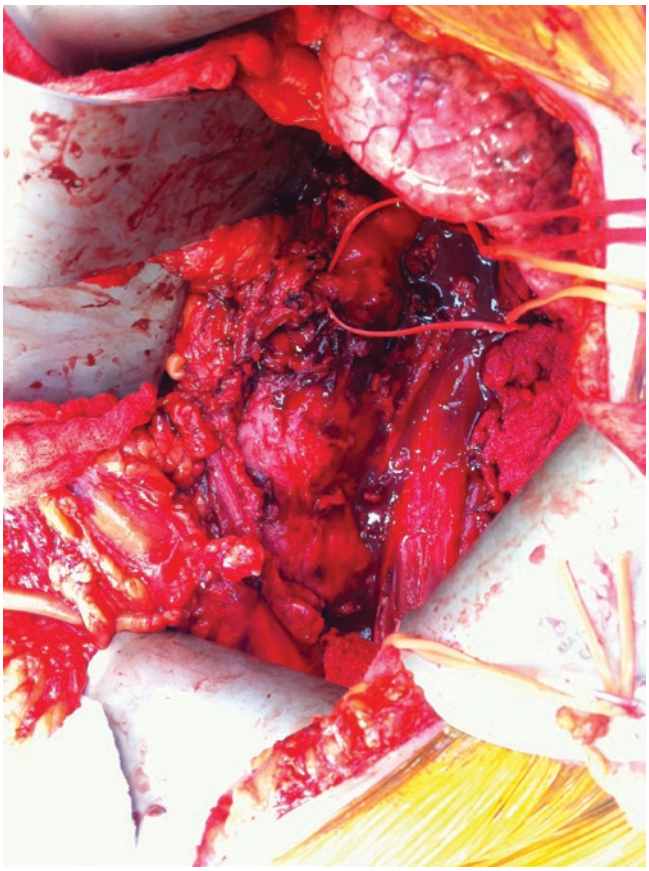

Fig. 19.3 Retroperitoneal exposure of infrarenal AAA with silastic vessel loop around the left renal artery

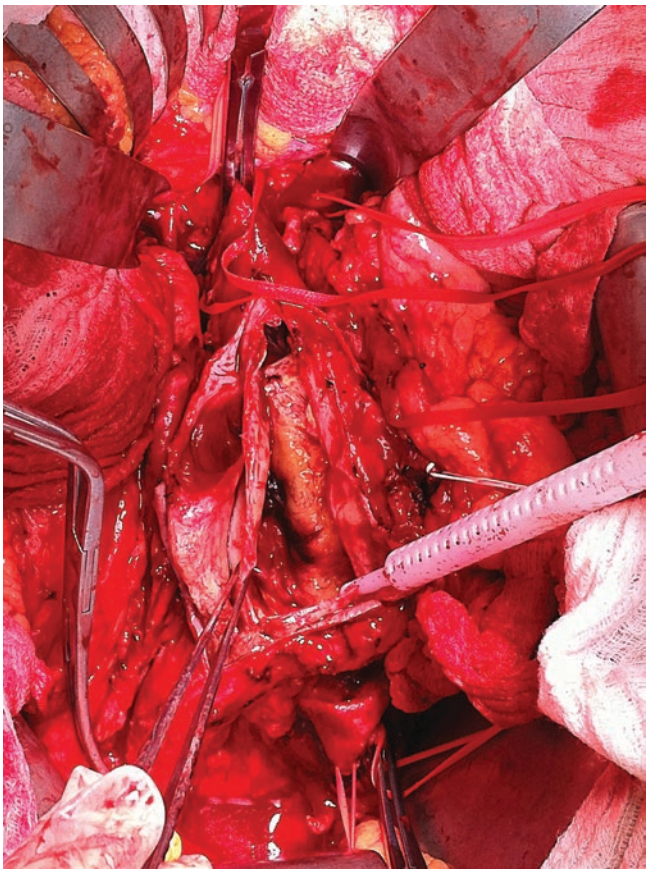

Fig. 19.4 AAA sac is opened and thrombus removed

ing the ureters and iliac veins. Typically, there is no need to pursue dissection on the common iliac arteries much past the aortic bifurcation. The graft anastomosis must be completed using healthy tissue however, and exposure distally should adhere to this concept, as in the case of concomitant aortoiliac aneurysm. When possible, care should be taken in male patients to preserve the autonomic nerve plexus that overlies the left common iliac artery. Sacrificing this structure will not affect the repair but is associated with postoperative sexual dysfunction. With proximal and distal blood flow to the aneurysm sac interrupted by placement of aortic clamps, intravenous heparin is given for prevention of arterial thrombosis. Meticulous attention must be paid to the precise position of the clamps, as a heavily calcified aorta may in fact continue to bleed or be damaged by application of the clamp. This bleeding can be very difficult to control.

The aneurysm sac is entered via longitudinal incision (Fig. 19.4). Intraluminal debris and chronic thrombus are removed, and any back-bleeding lumbar vessels are oversewn. The proximal anastomosis is then completed, followed by the distal anastomoses, using a continuous monofilament polypropylene suture. This is a permanent synthetic suture material with a history of durability in this context. Prior to removing the aortic clamps, the iliac arteries are back-bled and the graft flushed with heparinized saline to prevent distal embolization of thrombus that may have formed during the reconstruction. Unclamping is done in a deliberate manner and in particularly close communication with the anesthesiology team. Profound hemodynamic changes can occur at this time as blood flow is restored. At the conclusion of the reconstruction, the aneurysm sac is closed over the graft with sutures to reduce the likelihood of future aortoenteric fistula. The peritoneal contents are inspected and replaced into the abdomen, and the abdominal wall is closed.

With regard to smaller branches of the aortoiliac system, the inferior mesenteric artery (IMA) and hypogastric arteries deserve special attention. The IMA should be evaluated for the presence of pulsatile back bleeding. If this is the case, then the IMA can be safely ligated. Good flow suggests adequate arterial collateralization to the hindgut. The surgeon should have a low threshold for reimplantation of this vessel if there is concern about this collateral flow, as the consequences of perioperative bowel ischemia can be catastrophic. Similarly, antegrade flow should be preserved to at least one hypogastric artery to limit the likelihood for postoperative

pelvic or bowel ischemia, buttock claudication, or sexual dysfunction. If the distal anastomosis is proximal to the iliac bifurcation, anatomic flow is maintained. Otherwise, an end-to-side anastomosis to the external iliac artery should provide retrograde flow to the origin of the ipsilateral hypogastric artery.

Alternative Exposure

The retroperitoneal exposure via an oblique incision is an alternative to the midline transperitoneal approach. The standard incision is made on the patient's left flank from the 10th or 11th intracostal space to the lateral edge of the rectus abdominis muscle in the area of the umbilicus [11]. The incision can be extended caudad for better iliac exposure or cephalad and into the pleural space if control to the visceral or supraceliac aorta is needed. Partial rib resection can also be undertaken to allow more visualization. This approach is preferred by many surgeons for the generous access it provides to aorta for most of its length. The retroperitoneal approach is also said to decrease rates of postoperative ileus and respiratory failure, to reduce resuscitation requirements, and to reduce length of hospital stay. The peritoneal cavity is more difficult to explore from this approach (if necessary); however, this may be a worthwhile trade-off in the case of a reoperative abdomen. No clear advantage has been shown for one approach over the other [12]. The choice of incision should consider individual patient characteristics but typically remains at the discretion of the surgeon.

Special Consideration: The Ruptured AAA

Considerations for repair of ruptured or symptomatic aneurysms (rAAA) differ markedly from those of elective repair. Perioperative management is essentially that of a critically injured trauma patient – one of advanced age and often with multiple chronic illnesses. Preoperative resuscitation should pursue a strategy of permissive hypotension, but should not delay moving the patient to the operating room as the definitive treatment is surgical. Although many rAAA are today treated with endovascular techniques, many centers are not yet equipped to provide this intervention and many patients prove too unstable for transfer. Furthermore, a large proportion of rAAA have anatomy hostile to endovascular therapy (Fig. 19.5).

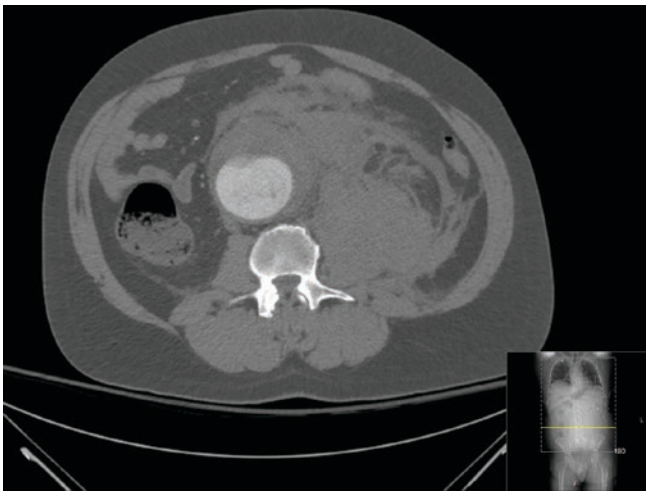

Fig. 19.5 Ruptured infrarenal abdominal aortic aneurysm with retroperitoneal hemorrhage and stranding around aneurysm

Operative Technique

The preferred open approach in most cases of ruptured AAA, particularly infrarenal, is transperitoneal via the midline incision as described above. The initial phase of the operation must focus on control of hemorrhage. This is done by first obtaining supraceliac control with an aortic cross-clamp. Manual aortic compression at the base of the diaphragm can also be utilized if free intraperitoneal hematoma prevents straightforward initial access to the clamp site. Another alternative is the deployment of an endoluminal aortic occlusion balloon. Indeed, some surgeons will place a balloon initially as a temporizing measure, followed by clamp placement once possible. Care must be taken during exploration and clamping not to damage any of the larger veins, as this will worsen hemorrhagic shock and prolong operative time. Once proximal and distal control is obtained, hematoma is removed to facilitate access to the aneurysm sac. The duration of supraceliac clamping should be minimized to shorten ischemia time to the viscera and kidneys. The clamp site should be moved down onto the graft once the proximal anastomosis is complete; however, this is not always possible in the case of pararenal aneurysm. Heparin is not used, as these patients are in shock and all have some degree of coagulopathy. Close coordination with the anesthesia team is necessary to effectively manage the abrupt hemodynamic shifts that occur around the times of clamping and unclamping. Once hemostasis is assured, the patient must be aggressively resuscitated; many will meet the requirements for a massive transfusion protocol [13]. Acidosis, coagulopathy, and hypothermia (the so-called "lethal triad") will contribute to perioperative mortality and morbidity if not recognized and treated rapidly. In spite of these efforts, the mortality rate for rAAA remains stubbornly high. Most patients who tolerate the initial insult relatively well will survive with surgical treatment, but the vast majority of those with persistent hemodynamic instability and end-organ failure will die.

Outcomes

As noted above, the perioperative mortality percentage rate for elective AAA repair lies in the low single digits when performed at centers of excellence. This is most commonly due to acute coronary events; the high prevalence of ischemic heart disease in AAA patients mandates an adequate preoperative cardiac risk assessment. Hypotension during the operation or in the acute postoperative period must raise suspicion for hemorrhage. Venous injuries in particular can be very challenging to manage, emphasizing the importance of a careful approach to dissection. If hypotension is due to bleeding after surgery, a return to the operating room is mandatory. The strategy once there is not unlike the approach to a ruptured aneurysm. Hypotension can also lead to end-organ ischemia, which can affect any organ in the body, most notably the heart, kidneys, bowel, liver, and brain.

Acute postoperative renal insufficiency following AAA repair can be due to ischemia, embolization, or iodinated contrast injury. Chronic kidney disease predisposes patients to worsening kidney function postoperatively. This complication has been linked to a higher incidence of progressive chronic renal failure and late mortality and is an ominous sign in postoperative rAAA patients [14, 15]. While the rate of acute kidney injury is approximately 10% in elective open infrarenal AAA repair, it is higher in those operations requiring renal ischemia time or revascularization [16]. Surgical technique must encompass steps to minimize the possibility for kidney injury in all operations undertaken for AAA repair.

While some degree of ileus is universal following transperitoneal repair, bowel ischemia is a less likely (2%) but far more serious complication [17]. Full-thickness colonic ischemia carries a high mortality rate even when diagnosed early. Diarrhea within the early postoperative phase is always suspicious for this problem and mandates immediate endoscopic investigation. There is no straightforward method to guaranteeing adequate bowel perfusion while in the operating room. However, the techniques mentioned above for IMA reimplantation, antegrade hypogastric flow, and assessment of the bowel prior to closure are crucial to minimizing the chances for a poor outcome. Intraoperative injury to the bowel or ureters can create a range of complications, ranging from prolonged ileus to chronic renal insufficiency, graft infection, or peritonitis. These injuries are best mitigated when recognized and managed at the time of surgery.

While coronary disease remains the leading cause of mortality in the postoperative period, pulmonary complications are the most common. Most patients will be liberated from the ventilator within 48 hours of the completion of surgery; however, postoperative pain and pre-existing lung disease contribute to respiratory failure, reintubation, and pneumonia. Respiratory complications also have a direct negative effect on late survival [18].

The long-term survival of patients undergoing AAA repair is 49–75% at 5 years [19]. This is worse than these patients' age-matched cohorts without AAA, but this is to be expected given this population's higher rates of medical comorbidities. Significant late complications of open AAA repair include incisional hernia, bowel obstruction, graft thrombosis, graft failure, aortoenteric fistula, and graft infection. The combined incidence of these problems is low, but they can prove extremely challenging to manage [20]. Any of these can present years after the index operation, and all providers involved with the patient's care should be vigilant in watching for them.

Hybrid Repair

Background

Although open repair remains the surgical standard of care for pararenal AAA and aneurysmal disease involving the visceral aorta, many patients are considered too high-risk to successfully undergo this physiologically challenging procedure. It was with this consideration in mind that endovascular treatment of aneurysmal disease was first attempted. The indications for fully endovascular repair of these complex lesions continue to expand as the limits of the available technology grow. For some patients, however, the anatomy of the disease is not suitable to treatment with currently available endograft devices and the severity of their comorbidities precludes traditional open repair. When intervention is indicated in these patients, techniques for combined surgical and endovascular repair ("hybrid") can prove very useful. Hybrid procedures combine the most appealing aspects of each method for aneurysm repair: the durability of open revascularization and the improved perioperative survival of endovascular intervention.

Operative Technique

Any endovascular stent-grafting procedure for aneurysmal disease must include adequate landing zones for the proximal and distal ends of the device; this ensures proper apposition of the device to the aortic wall for exclusion of the aneurysm sac. In hybrid repair, these landing zones can be created surgically using aortic reconstruction techniques. If stent-graft coverage of the renal or mesenteric arterial origins is required, the aorta can be debranched by surgical bypass [21]. These vessels should then be surgically ligated or endoluminally coiled proximal to the bypass anastomosis to prevent endoleak.

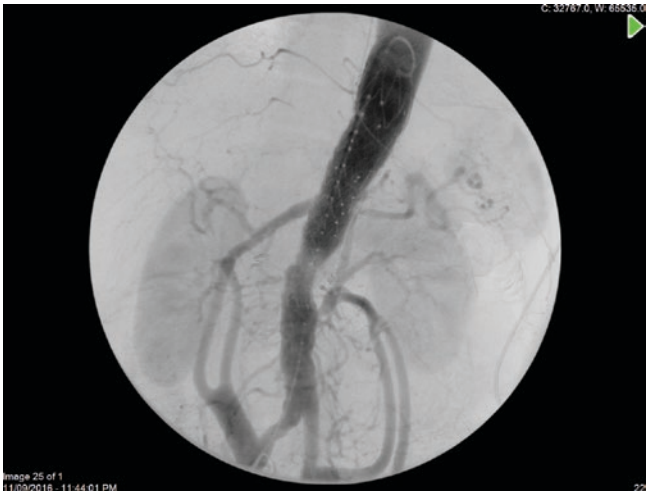

Fig. 19.6 Thoracoabdominal aneurysm hybrid repair post four-vessel debranching and stent graft placement. Bifurcated grafts off of each common iliac artery supply the bilateral renal arteries, SMA, and hepatic arteries

The inflow for the bypass grafts may come from any normal segment of the aorta or common iliac arteries. Bypasses may also be originated from an infrarenal aortic reconstruction or an existing aortobifemoral bypass graft (Fig. 19.6).

Hybrid repair of abdominal aneurysm is typically undertaken as a staged procedure. Debranching and any necessary open aortic grafting is completed as one stage, followed by aortic stent-grafting at a later date once the patient has had time to recover. This minimizes the physiologic insult of ischemia time and allows recovery of renal function prior to the contrast administration necessary for endovascular intervention. At some centers, both procedures are performed during the same admission to reduce the chance for interval aneurysm rupture [22].

Perioperative care for hybrid procedures is much the same as for each procedure when done individually. The dreaded complication of hybrid repair is neurologic deficit due to spinal cord ischemia following long-segment aortic coverage with stent-grafting. For this reason, the endovascular procedure itself is sometimes staged when possible, and spinal drainage is routinely used [23]. With careful patient selection, near-term results are comparable to traditional open repair [21, 24].

Aortic Dissection

Background

Recent advances in medical and endovascular therapies have rendered open surgical technique for management of descending aortic dissection all but obsolete. Although acute Stanford type B dissection remains a complex condition with a high mortality rate when untreated, most patients can be treated to excellent outcomes without the need for open repair. This preference for alternative modalities is in large part due to the great perils associated with open surgery for this condition. Even modern series report operative mortality exceeding 20%, with higher risk for older patients and those presenting in shock [25]. Postoperative rates of stroke, spinal cord ischemia, and end-stage renal failure are also significant.

Preoperative Management

The first-line treatment for stable type B dissection is medical management with strict blood pressure control in an intensive care setting. Complicated dissection is characterized by the presence of any of the following: aortic rupture, end-organ malperfusion, expansion of the false lumen or the dissection plane, or uncontrolled pain [26]. Complicated dissection suggests futility or failure of medical management and represents an indication for urgent intervention. No high-quality studies have been done to compare open and endovascular techniques in this setting. Nevertheless, the daunting risks associated with open repair favor a first-line endovascular approach. Although relatively little is known about the long-term results of endovascular treatment with stent-grafting or fenestration of complicated type B dissection, it has become the preferred management (Fig. 19.7). Open surgical repair, although it represents the historical standard, has therefore become the option of last resort.

Operative Technique

The objectives of open surgical management mirror those of endovascular treatment. The proximal entry tear is closed, and the aortic wall is reconstructed at the distal anastomosis. This eradicates antegrade flow pressurizing the false lumen, improves flow to the true lumen, and preserves distal perfusion. The exposure is made via left posterolateral thoracotomy; this can be extended distally for retroperitoneal access to the distal aorta if revascularization of important branch vessels is required. No firm recommendation for cardiopulmonary bypass exists, and the decision to use it should be individualized based on the risk posed by expected cross-clamp time and surgeon preference. The portion of aorta reconstructed should be kept to a minimum, as the incidence of devastating neurologic complications due to spinal cord ischemia is directly related to the extent of aortic resection [27]. The most common location for the entry tear is just distal to the origin of the left subclavian artery, often necessitating cross-clamping between the subclavian and left common carotid arteries. The dissected aortic wall is invariably quite friable and should be reinforced with polytetrafluoroethylene

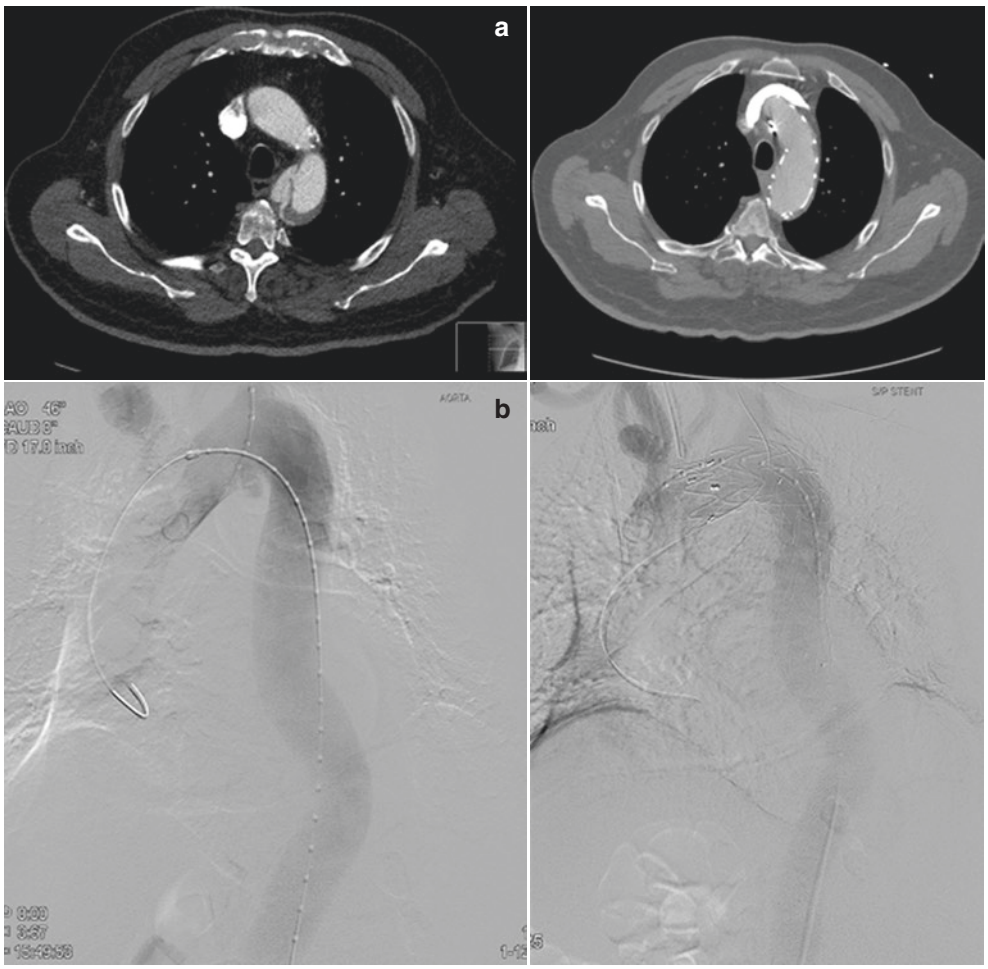

Fig. 19.7 (**a**) Type B dissection with entry tear just distal to left subclavian artery origin before and after stent graft coverage. (**b**) Intraoperative angiogram with stent graft deployment over entry tear

felt or glue aortoplasty prior to reconstruction with a woven polyester graft. The false lumen is closed by reapproximating the aortic wall and incorporating it into the distal anastomosis [28]. If proximal reconstruction does not correct downstream malperfusion, the procedure may include exposure of the distal aorta as described above. The aortic clamp is moved distally to the supraceliac position, and control of the major branches is obtained as in open thoracoabdominal aneurysm repair. The visceral aorta is opened via longitudinal aortotomy, and the intraluminal septum is divided; this fenestrates the dissection plane and usually restores blood flow to aortic branches compromised by the false lumen. However, direct revascularization of the threatened organs and/or distal aortic reconstruction may be necessary.

Aortoiliac Occlusive Disease

Background

Patients with aortoiliac occlusive disease (AIOD) represent a group of patients with peripheral vascular disease whose disease typically concentrates in the infrarenal aorta, iliac arteries, and femoral arteries. There is a trend toward endovascular-first treatments for these patients, as well as a multitude of hybrid repairs (Fig. 19.8). While selecting treatments for AIOD, patient factors such as medical comorbidities, age, life expectancy, previous abdominal surgeries, acute versus chronic presentation, and the patient's preference come into play. The extent of this typical multilevel disease directs the treatment as well. In either case, the operator needs to have expertise in both open and endovascular techniques.

AIOD initially manifests with intermittent claudication, with symptoms involving the thigh, buttock, and calf muscles. Male patients may also complain of erectile dysfunction due to inadequate perfusion of the internal pudendal arteries. Leriche syndrome classically manifests with the triad of claudication of thigh and buttock muscles, impotence, and limb claudication in the absence of femoral pulses [29]. AIOD may progress to rest pain or limb gangrene typically when combined with multilevel disease of the femoropopliteal system. Risk factors for AIOD are the same for general atherosclerosis, including smoking, hypertension, hyperlipidemia, and diabetes [30, 31].

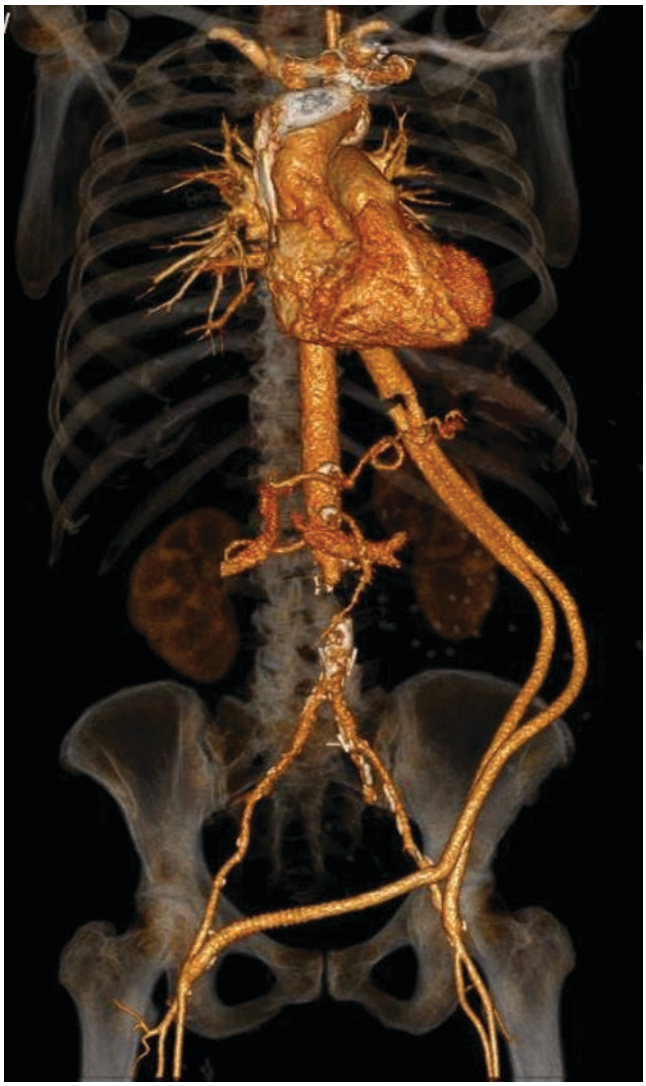

Fig. 19.8 Thoracobifemoral bypass after failure of bilateral iliac artery stents, aortobiiliac bypass for occlusive disease

The most common location for aortoiliac occlusive disease is at the terminal aorta and proximal common iliac arteries. The lesions typically then progress both proximally and distally over time. Over time, the aortic disease can progress and lead to occlusion of the distal aorta, with thrombus propagation up to the level of the renal arteries (Fig. 19.9). Starrett and Stoney observed in studies that over 30% of patients with aortic occlusion will progress to renal artery thrombosis over a 5- to 10-year period. In contrast, other studies have shown the renal arteries remain patent [32, 33].

Aortobifemoral Bypass Reconstruction

Aortobifemoral bypass grafting is regarded by many as the gold standard for the surgical management of atherosclerotic AIOD confined to infrarenal aorta and extending to the femoral artery bilaterally. This procedure is the choice for most patients who are fairly free of serious comorbidities. The procedure can be done via transabdominal or retroperitoneal approach, similar to aortic reconstruction for aneurysmal disease.

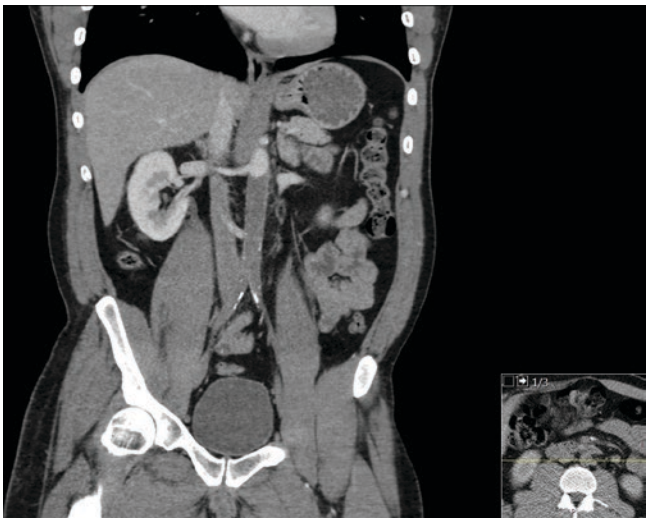

Fig. 19.9 Thrombus flush with renal arteries

The patient is given broad-spectrum antibiotics intravenously prior to incision. General anesthesia is utilized, and patients should have arterial line for continuous blood pressure monitoring, Foley catheter, and either large-bore IV access or central line access. Operative field extends from the xyphoid process to the bilateral knees.

The infrarenal abdominal aorta is exposed by either transabdominal or retroperitoneal approach. The advantages of both approaches mirror those described previously for abdominal aortic aneurysm repair. The patent pararenal aorta is dissected out and typically Silastic vessel loops placed around the renal artery origins if a suprarenal clamp is to be placed. This is determined by the level of AIOD in the infrarenal aorta. Dissection around the aorta at the planned proximal clamp site is undertaken with sharp and blunt finger dissection to the level of the anterior spine to ensure circumferential dissection. The aorta is also felt at this level to determine the level of calcification to ensure an adequate clamp, as a circumferentially calcified aorta may be impossible to clamp and require intraluminal balloon control or a more proximal clamp. The IMA is identified and encircled with vessel loop for either ligation or reimplantation. The distal clamp site may be either bilateral common iliac arteries or the distal aorta.

Bilateral groin incisions are made to expose the femoral vessels. Incisions can be oblique and 1 cm above the inguinal crease or vertical, depending on the condition and extent of disease of the femoral vessels. Crossing lymphatics and veins are clipped or suture ligated and divided to minimize any possible hematoma or lymphatic leak, which risks a

postoperative graft infection. The common femoral artery is circumferentially dissected out at the level of the inguinal ligament, and the inguinal ligament can be partially divided at its posterior attachments to ensure no kinking of the graft in the tunnel. Crossing veins under the inguinal ligament are ligated and divided. Dissection is carried distally to beyond the femoral artery bifurcation, and superficial and deep femoral artery branches are encircled with silastic vessel loops. If preoperative imaging has shown superficial femoral artery (SFA) occlusion or significant profunda femoral artery (PFA) disease, the dissection is carried another 2–3 cm further along the PFA to ensure adequate distal endpoint for the graft. This typically involves ligation of the first branch of the profunda femoral vein to allow for further dissection.

Prior to systemic heparinization, the retroperitoneal tunnels between the aortic and femoral fields are created. The tunnels are made with blunt dissection, and a long instrument can be utilized with care as well. The tunnel should lie in the avascular plane directly anterior to the iliac vessels and posterior to the ureter. Umbilical tape, Foley catheter, or vessel loop is left in the tunnel for later passage of the graft.

The aorta is clamped proximally either above the level of the renal arteries or just below, depending on the extent of thrombus and disease. In the event of pararenal thrombus, the vessel loops around renal arteries are pulled up prior to clamping to avoid thrombus propagation into the renal arteries. Once offending pararenal thrombus is cleaned out, the proximal clamp can be moved to infrarenal location to avoid prolonged renal ischemia time.

Proximally, the bypass can be done in an end-to-side or end-to-end fashion. The end-to-end style is preferred by many surgeons as it has several advantages. There is no competitive flow through the native aortoiliac system, and in theory, it has more superior hemodynamics. Less turbulent flow results in less development of clot or atheroma and eventual graft thrombosis [34]. In addition, an end-to-end anastomosis lies flat in the native vessel configuration, with less impingement on the retroperitoneal covering, reducing the chance of a devastating graft-enteric fistula.

The end-to-side anastomosis does have advantage in certain anatomic configurations, primarily with the interest in maintaining pelvic flow through a large inferior mesenteric artery or maintaining flow to the hypogastric arteries in patients with external iliac artery occlusive disease. In these patients, retrograde flow is impossible through the external iliac arteries, and thus, with an end-to-end configuration, they are more at risk for colonic ischemia, impotence in males, and even neurological compromise [34].

Regardless of the proximal anastomosis type, the proximal aorta is transected (end-to-end) or arteriotomy made (end-to-side) after the proximal aorta is cross-clamped. If the distal aorta is patent or common iliac arteries are patent, distal clamps will be utilized to prevent back bleeding prior to proximal aortic clamping. If a suprarenal clamp is placed and there is pararenal thrombus, the renal arteries are controlled with silastic vessel loops to avoid thrombus propagation with clamping. The aorta is cleaned out and thrombus removed with large forceps and irrigated copiously with heparinized saline. Once clear of thrombus, the clamp can then be moved to infrarenal location. The proximal graft is then beveled to match the transected aorta or arteriotomy and anastomosed in standard fashion. If the quality of the aorta requires extensive endarterectomy, felt pledget cuff may be incorporated. In order to perform the end-to-end anastomosis, a small amount of the diseased aorta is excised to allow room for the new graft to lie. In addition, the distal aorta is typically endarterectomized in a limited fashion to allow for oversewing of this region.

One graft limb is then controlled with vascular clamp and heparinized saline flushed through the other limb to test the anastomosis. Once hemostatic, this limb is clamped as well and proximal aortic clamp released. In an infrarenal clamp location, at this point, there should be little to no change in hemodynamics of the patient. Systolic blood pressure is monitored to avoid hypertension and avoid tension on the fresh anastomosis.

The limbs of the graft are then pulled fully distended through the previously created retroperitoneal tunnels to each groin. One technique commonly utilized is to lift the previously placed umbilical tape and utilize it to guide a long, blunt-tipped aortic clamp to pass the graft through the tunnel, thus minimizing trauma or inadvertent injury to surrounding structures. Care is taken to confirm the graft lies nicely under the inguinal ligament, without any external compression.

The femoral anastomosis location depends on the condition of the outflow vessel branches. In the event of common femoral or profundae disease, local endarterectomy with tacking suture of distal endpoints is crucial. If the superficial femoral artery and profunda are both patent on preoperative imaging, the distal anastomosis can be a standard beveled anastomosis on the common femoral artery. In the event of SFA disease or occlusion, it is recommended to perform profundaplasty with hood of the distal graft onto the PFA to ensure long-term patency. Profundaplasty can be achieved with vein patch angioplasty, or with the hood of the graft itself. After distal anastomoses are completed and hemostasis obtained, the retroperitoneum is closed over the graft and all incisions closed in multilayered fashion (Fig. 19.10).

Excellent early and late term results of aortobifemoral bypasses are noted in several large series. With a carefully chosen patient population for these surgeries, the graft patency at 5 years is estimated at 85–90% and 70–75% at 10 years [35]. Perioperative mortality at tertiary care facilities is single digits at well under 5%. In addition, it should be noted that patients with focal distal aortoiliac atherosclerotic disease are expected to be lower than that of patients with more multilevel disease, thought to be due to concomitant

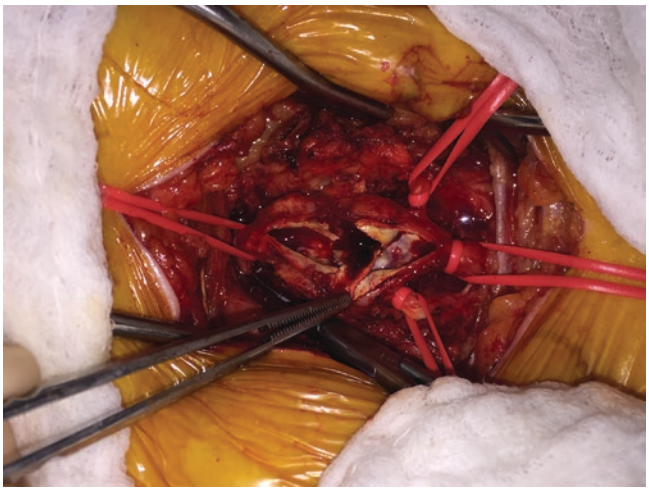

Fig. 19.10 Femoral dissection showing diseased common femoral artery requiring endarterectomy prior to distal anastomosis. The hood of the graft can be used for patch angioplasty

coronary and visceral occlusive disease. Sadly, graft patency exceeds life expectancy in this population on average, with a mortality rate of 35–40% at 5 years and 50–60% at 10 years postoperatively, the majority thought to be from occlusive coronary disease [35].

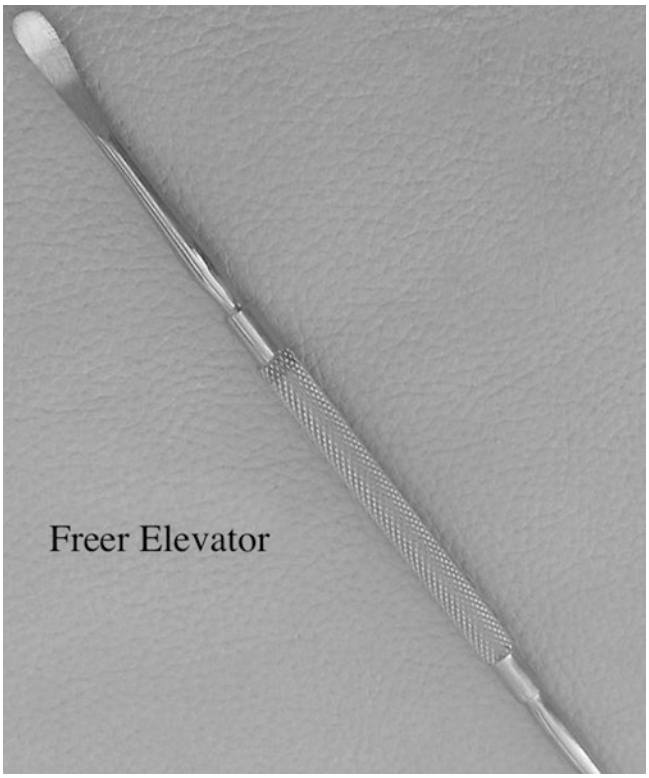

Fig. 19.11 Freer Elevator device utilized for arterial endarterectomy

Aortoiliac Endarterectomy

Open aortoiliac endarterectomy was historically utilized in patients who now would undergo an aortobifemoral bypass. Wylie performed the first successful procedure in the USA in 1951 [36]. This procedure is still utilized for patients whose disease is confined to the distal abdominal aorta and common iliac vessels. An advantage to this procedure over traditional aortobiiliac or aortobifemoral bypass is that it does not involve synthetic material and thus is not at risk for graft infection. For similar reasons, it is more advantageous in an infected operative field. The procedure should not be utilized in the presence of an aneurysmal aorta.

The patient is supine, and exposure is obtained via the standard midline abdominal incision. Transverse colon is reflected upward and the bowel mobilized to the patient's right. Retroperitoneal space is entered over the aorta and incision carried down along the bilateral iliac arteries. Care is taken to avoid the nerves overlying the left common iliac artery. The infrarenal aorta is carefully dissected out in the avascular plane, as well as lumbar branches and the inferior mesenteric artery origin. The origin of the hypogastric arteries is typically encircled with vessel loop, and external iliac arteries are dissected free for clamping. After heparinization, vascular clamps are placed on the external iliac arteries and infrarenal aorta. The lumbar arteries, IMA, and hypogastric arteries are controlled for back bleeding. The aorta is incised longitudinally down to the level of the aortic bifurcation. Standard endarterectomy is then performed by identifying the disease and deep media plane. Aortic wall is pushed away from disease to further the dissection plane along. Proximally, the diseased intima is transected to endpoint, and tacking sutures may be utilized. More important is the distal endpoint. A small transverse incision is made in bilateral common iliac arteries just proximal to the bifurcation of the iliac artery. The diseased intima is transected, and deep medial plane is extended proximally utilizing Freer elevator or Beaver blade until the specimen is completely mobilized and can be removed (Fig. 19.11). Tacking sutures are utilized to stabilize the distal plaque endpoint to avoid dissection. Disease at the origin of the hypogastric artery can be removed with eversion endarterectomy. The arteriotomies are copiously irrigated to ensure no remaining debris, iliac arteries back bled, and the aorta forward-flushed, and the aortotomy is typically closed with running prolene suture and iliac arteriotomy closed with interrupted sutures. Typically, the hypogastric artery is flushed forward first, so that any clamp debris can be directed toward the pelvis instead of the legs via the external iliac arteries.

The 5-year patency rates after aortoiliac endarterectomy approach 90% in literature [37]. Aneurysmal degeneration of the aorta, although a concern with the deep medial endarter-

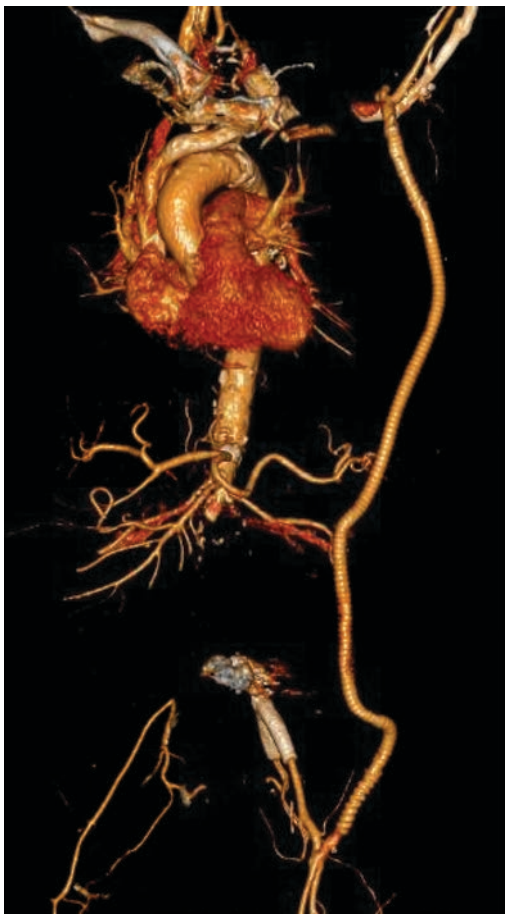

Fig. 19.12 3D reconstruction of patient with left axillofemoral bypass

ectomy plane, has not been seen during long-term follow-up, and if recurrent stenosis or occlusion occurs, this can be managed by the other techniques described above.

Axillofemoral Reconstruction

In patients whose comorbidities make them a poor candidate for anatomic reconstruction, extra-anatomic bypass may be the only option. This is typically done by axillofemoral reconstruction, which was first utilized in the 1960s for patients with high cardiopulmonary risk for aortic reconstruction [38, 39]. Preoperatively, blood pressure measurements with demonstration of triphasic Doppler waveform in the brachial artery confirm the absence of disease in the subclavian or axillary artery.

The operation is performed with the patient supine under general anesthesia. The donor arm is typically abducted to some degree. The donor axillary artery is exposed utilizing a transverse incision typically two finger widths below the middle of the clavicle, and the pectoralis major muscles are split and deep fascia divided. Crossing veins and lymphatics are ligated, and care is taken to avoid the adjacent brachial plexus and vein. Control of the axillary artery is obtained. The proximal graft anastomosis is medial to the pectoralis minor muscles, and care is taken to leave enough laxity on the graft with a gentle curve to avoid the dangerous complication of axillary pullout syndrome, which occurs when abduction of the arm results in disruption of the proximal anastomosis. The tunnel between axillary artery and femoral artery should be as close to the fascia as possible and anterior to the anterior superior iliac spine to avoid graft compression. Proximally, the graft can be tunneled anterior to the pectoralis minor or posteriorly. A counter incision can be utilized to assist with tunneling. Typically, a graft of 6–8 mm diameter is utilized, depending on inflow artery size.

The femoral dissection and anastomosis are similar to that for aortofemoral reconstruction. A bifurcated graft can be utilized from the axillary artery to bilateral femoral arteries, or a single axillary artery to ipsilateral femoral artery bypass is performed, with a femoral-femoral bypass then performed with the anastomosis between the distal end of the axillofemoral bypass to the contralateral femoral artery (Fig. 19.12).

Axillobifemoral bypass is associated with approximately 50% 5-year primary patency and 75% secondary patency. 30-day mortality for the procedure in patients with occlusive disease was 10%, significantly higher than aortobifemoral reconstruction. Patency is also significantly lower, with studies showing primary patency at 1, 3, and 5 years was 68%, 53% and 53%, while secondary patency at the same intervals was 83%, 73%, and 73%. Survival at 5 years was 70%, and limb salvage rates approach 96% [40].

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Endovascular Repair of the Ascending Aorta and Aortic Arch

20

Adam Iddriss, Jota Nakano, and S. Chris Malaisrie

Introduction

Surgical pathologies of the ascending aorta and aortic arch are currently managed using an open approach in suitable candidates, with a mortality rate of 3% for the ascending aorta [1–5], 4–10% for the aortic arch [6, 7], and approximately 25% for acute type A dissections [8, 9]. Open surgery requires sternotomy, cardiopulmonary bypass, and cerebral protection. Patients with advanced frailty, multiple comorbidities, or unfavorable anatomic features are often considered prohibitive risk for open repair of the ascending aorta and aortic arch due to increased morbidity and mortality. Endovascular repair has emerged as a viable option for patients considered high risk for an open surgery. While the endovascular approach, devices, and technique have been well described for the descending and infrarenal aorta, endovascular repair of the ascending aorta and aortic arch is in its relative infancy, available only in an off-label fashion using devices approved for the descending and abdominal aorta. Here, we review the current knowledge on the indications, approach, techniques, and outcomes of endovascular repair of the ascending aorta and aortic arch.

Preoperative Diagnostic Imaging

Imaging the ascending aorta and aortic arch is essential in the evaluation and treatment of aortic pathology. Several imaging modalities including computed tomography angiography (CTA) and magnetic resonance angiography (MRA) have been successfully used to identify pathology of the ascending aorta and aortic arch. Multidetector CT can be used to determine operative candidacy, during preoperative planning, and in the postoperative surveillance of patients undergoing aortic surgery [10]. Images can be converted into three-dimensional reconstructions which enable angiographic evaluation of the ascending aorta, aortic arch, supra-aortic trunks, and access vessels. Motion artifacts can be reduced with electrocardiographic (ECG) gating, which can also be used to assess the coronary vasculature. Transesophageal echocardiography (TEE) can be used to assess cardiac hemodynamics and aortic valve pathology associated with thoracic aneurysm and left ventricular thrombus [11]. TEE is also useful for monitoring complications following graft deployment such as aortic regurgitation (AR) and coronary obstruction.

Intraoperative Monitoring

Intravascular ultrasound (IVUS) has emerged as one of the key instruments for performing endovascular repair in the ascending aorta and aortic arch, serving as the most accurate method of measuring intraluminal diameter [12]. IVUS provides real-time dynamic images that can be used to establish graft landing zones and graft selection, visualize thrombi or plaques, and inspect branch vessel anatomy.

Fusion imaging integrates preoperative CT images with intraoperative fluoroscopy and provides a nuanced method for developing a strategy for proximal aortic repair. This process has been used in complex aortic procedures including fenestrated branched endovascular repair and has been shown to increase the accuracy of endovascular graft placement and decrease the contrast load. Fusion imaging is also associated with lower operative and fluoroscopy times. Moreover, confirmation of postprocedural success using fusion imaging is comparable to multidetector CT (MDCT) [13].

Instrumentation of the ascending aorta and aortic arch increases the risk for developing neurologic complications due to the proximity of the supra-aortic vessels and atheroma burden of the aortic arch. Moreover, graft placement can

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involve several wire manipulations which may generate and propagate thrombi. Several modalities have been developed for intraoperative neurologic monitoring. Transcranial Doppler can be used intraoperatively to provide real-time detection of cerebral microemboli and changes in cerebral blood flow [14]. Variations in cerebral flow velocities can be monitored as endografts are deployed through the ascending aorta and aortic arch. Near-infrared spectroscopy can also be used to assess cerebral oxygenation during endovascular repair of the aorta [15, 16].

Indications and Contraindications

Traditional indications for thoracic endovascular aortic repair (TEVAR) have included asymptomatic thoracic aortic aneurysms larger than 5.5 cm, symptomatic thoracic aortic aneurysms (TAAs) or those with expansion greater than 5 mm over 6 months [17, 18], type B aortic dissection [19, 20], penetrating aortic ulcers, intramural hematomas [21], and traumatic aortic injury [22]. Several case reports and series have contributed to a growing body of literature seeking to expand TEVAR indications to include patients with type A dissections [23, 24] or those deemed prohibitive risk for surgery [25]. The primary contraindication to TEVAR is unfavorable anatomy. Patients with inadequate access vessels (heavily calcified vessels or iliac diameter <7 mm, unable to accommodate 22F or 24F sheaths), inadequate proximal or distal seal zones (<10 mm in length or at extremes of diameter [<16 mm or > 42 mm]), extensive aortic tortuosity, or an actively infected field may not qualify for endovascular repair. TEVAR is also generally avoided in patients with connective tissue disorders unless used as a salvage procedure before definitive open surgical management.

Ascending Aorta

Endovascular intervention in the ascending aorta has traditionally been limited by several inherent anatomic features including its angulation, short length, complex spatial geometry, hemodynamic throughput, large diameter fixation sites, and proximity to the aortic valve and coronary vessels. Thus, the endovascular approach to the ascending aorta has usually been reserved for patients at prohibitive risk for open intervention. Initial reports described the use of ascending TEVAR for type A dissections, pseudoaneurysms, and penetrating atherosclerotic ulcers [26, 27].

The anatomical considerations for ascending TEVAR are listed in Table 20.1. Access for endovascular repair of both the ascending aorta and aortic arch is most commonly achieved with a transfemoral approach using commercially available endografts designed for the descending thoracic aorta. Transapical, transseptal, transaxillary, and carotid approaches have also been described for patients in whom femoral access is not possible [11, 29, 30] or when using aortic extension endografts designed to reach the abdominal aorta (and too short to the thoracic aorta).

Table 20.1 Anatomical requirements for ascending aortic TEVAR [28]

Proximal/distal landing zones	Length > 10 mm
	Diameter >16 mm and <42 mm
	No significant difference between proximal and distal landing zones (<10%)
	Absence of calcification or thrombotic material
In aortic dissection	Intimal tear > 10 mm above the sinotubular junction
	Intimal tear > 5 mm proximal to the innominate artery
	No aortic regurgitation
Access vessels	Diameter of the common/external iliac artery > 7 mm

From Muehle et al. [28]. Reprinted with permission from Wolters Kluwer Health, Inc
TEVAR Thoracic endovascular aortic repair

Several reports have described the ascending TEVAR with the use of thoracic stent grafts that have been modified for the ascending aorta, usually with proximal extensions of thoracic endografts [31–33]. We have used the extension cuff from an abdominal aortic stent graft to perform an aortic reconstruction for an ascending aortic pseudoaneurysm in a patient deemed prohibitive risk for open surgery. Kolvenbach described the use of stent grafting the ascending aorta in 11 patients [27]. Technical success was achieved in 91% of the cohort with one endoleak, one cerebrovascular accident, and one death due to left ventricular perforation by a wire. Li recently reported the long-term outcomes of a series of 15 patients who had undergone endovascular repair of ascending aortic dissections [34]. Although no deaths occurred in the median 72 months of follow-up, there were eight major complications and four reinterventions. One patient developed a new dissection in the aortic arch distal to the endograft at 3 months and was treated with a branched stent graft. Another patient experienced a retrograde type A aortic dissection 29 months following endografting and underwent replacement of the ascending aorta and proximal arch. There was also one endoleak which occurred at 71 months which was managed conservatively. At 12 months, significant decreases in false lumens and total aortic diameter were observed along with an increase in the true lumen. These changes in aortic remodeling remained stable over 3 years, thereby demonstrating the sustained effect of endovascular exclusion.

Devices for the Ascending Aorta

The Zenith Ascend TAA endovascular graft (Cook Medical) is a single-component tubular endograft which consists of polyester fabric sewn onto self-expanding nitinol stents (Fig. 20.1). Both the proximal and distal ends of the graft contain uncovered stents which can be used to improve graft deployment and subsequent apposition in the aorta. It is 65 mm long and comes in diameters ranging from 28 to 46 mm. Endograft deployment is performed using a 100-cm pre-curved introducer using sequential deployment which enables a staged release. Using either a transfemoral or transapical approach, the device can then be deployed under rapid ventricular pacing, adenosine-induced cardiac arrest, or vena cava occlusion technique.

Metcalf reported the first successful clinical implantation of a dedicated ascending aortic endograft in a patient with a type A dissection [36]. Tsilimparis later reported

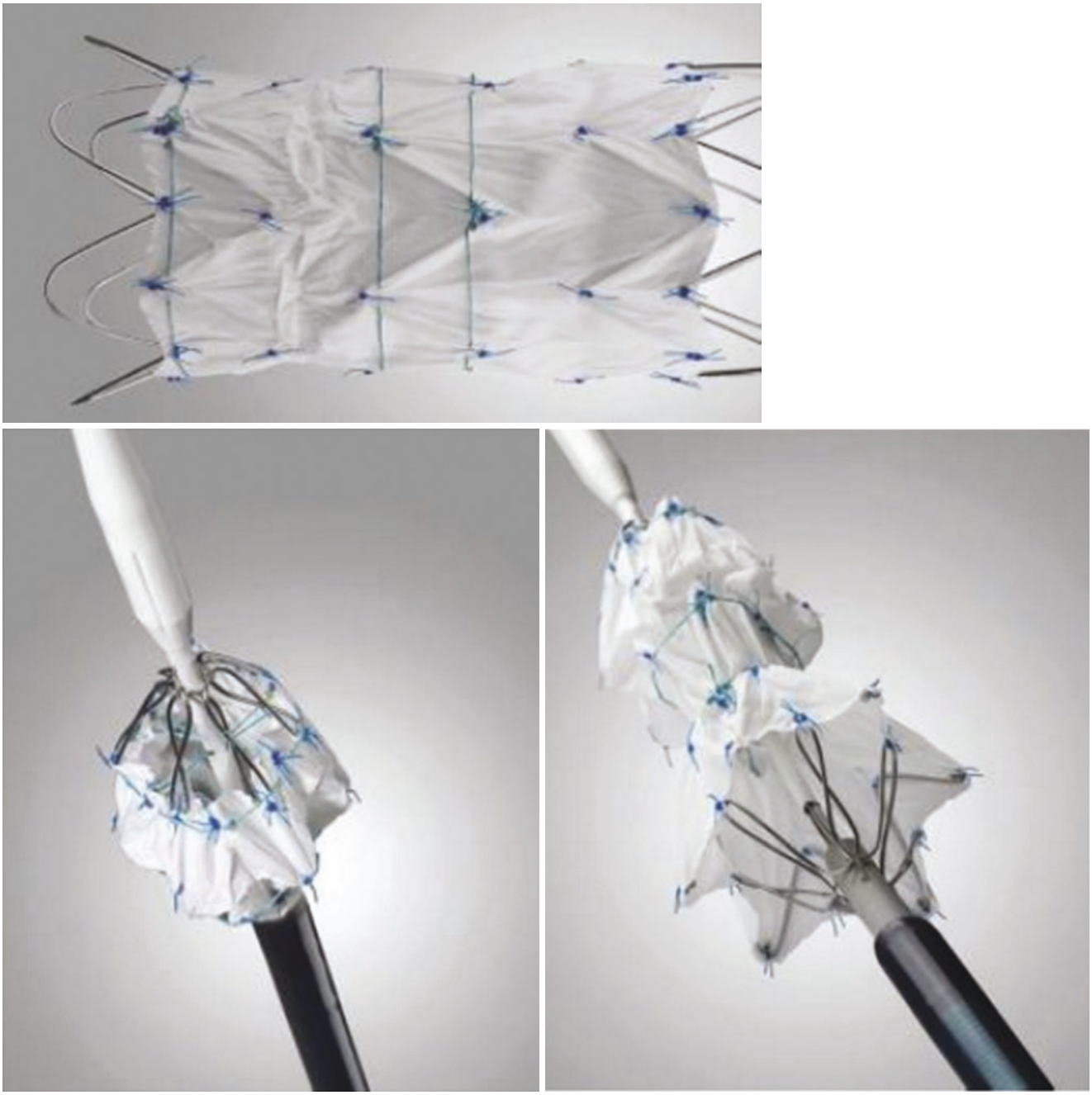

Fig. 20.1 Cook Medical Zenith Ascend TAA endovascular graft. (From Tsilimparis et al. [35]. Reprinted with permission from Elsevier)

outcomes using a modified version of this graft in a series of 10 patients with ascending aortic pathology deemed unsuitable for open surgery [35]. There was one perioperative death which occurred in a patient who developed a persistent type Ia endoleak after undergoing ascending aortic grafting for an intraoperative aortic valve implantation dissection in the setting of transcatheter aortic valve replacement (TAVR). Late outcomes included three additional deaths and two graft replacements for endoleaks.

The Valiant PS-IDE was available in two configurations, one with a proximal closed-web design with distal stent and a second one with proximal FreeFlo stent (Fig. 20.2). The device comes in 5-, 7-, and 9-cm lengths with diameters ranging from 28 to 44 mm. Bilateral femoral arterial and venous access is established for IVUS, device delivery, and ventricular pacing, respectively. Khoynezhad reported the early results of a feasibility study using the Valiant Captiva (Medtronic, Inc.) in a series of six patients who received investigational device exemption [37]. There were no perioperative deaths, but one patient died 4 months after undergoing ascending aorta repair for de novo ulceration in the mid-aortic arch which required a total arch replacement and frozen elephant repair. One patient developed a lacunar infarct and type I endoleak and an additional patient experienced wire perforation of the left ventricle with resultant pericardial effusion which resolved with conservative management.

Aortic Arch

The aorta is divided into five landing zones from 0 to 4 (Fig. 20.3). Placement of endografts into the aortic arch (Zones 0 through 2) results in occlusion of the aortic arch branches and requires additional techniques for branch revascularization. Endovascular repair of the aortic arch can be achieved with hybrid arch repair, chimney stent grafting, fenestrated stent grafting, or branched stent grafting. In the hybrid approach, endovascular techniques are combined with anatomic and extra-anatomic surgical revascularization of the arch vessels to extend the proximal seal zone.

Hybrid Repair

Hybrid repair combines supra-aortic artery debranching to create a proximal landing zone (Fig. 20.4). In its simplest

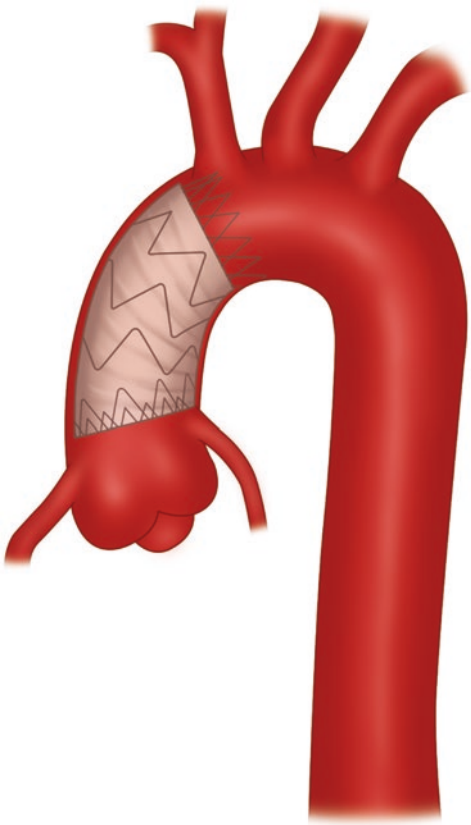

Fig. 20.2 Medtronic Valiant PS-IDE. (From Khoynezhad et al. [37]. Reprinted with permission from Elsevier)

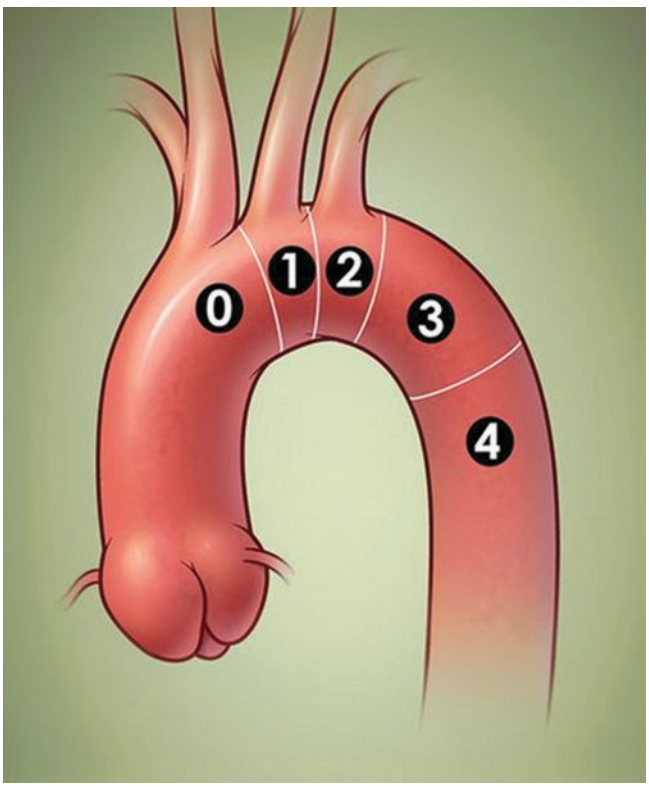

Fig. 20.3 Zones of the aorta [38]. (From Azizzadeh et al. [38]. Reprinted with permission from Elsevier España)

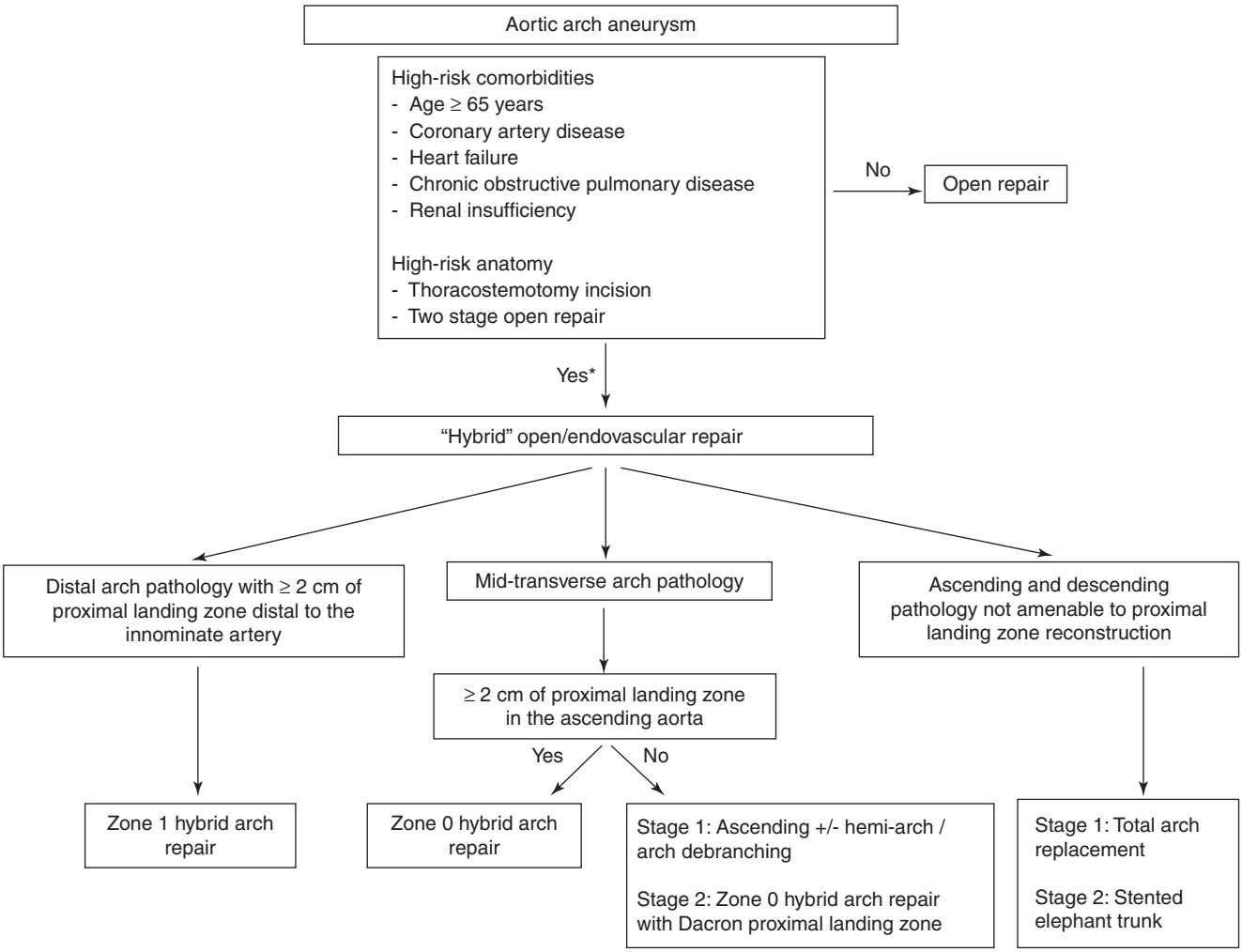

Fig. 20.4 Algorithm for hybrid aortic arch repair. *Note that these criteria are relative factors in the decision-making process but not absolute indications/contraindications. Ideally, the decision for conventional versus hybrid repair should be made by a surgical team with expertise in both techniques. Institutional results with each approach should further influence the decision-making process. (From Andersen et al. [39]. Reprinted with permission from Elsevier)

form, the left subclavian artery (LSA) artery may be revascularized by either carotid–subclavian transposition or carotid–subclavian bypass for Zone 2 TEVAR. The transposition technique requires more extensive dissection in order to gain access proximal to the vertebral artery and has also been associated with a higher rate of complications [40]. The bypass technique, on the other hand, requires a bypass graft and an additional procedure to occlude the proximal portion of the subclavian artery. In its most complex form, the entire arch can be debranched and revascularized using a combination of anatomic and extra-anatomic configurations (Fig. 20.5).

Moulakakis et al. conducted a systematic review of hybrid arch replacement techniques including 26 studies with 956 patients who underwent debranching procedures and 20 studies with 1316 patients who underwent elephant trunk procedures [42]. Perioperative mortality was estimated at 11.9% in the debranching group and 9.5% in the elephant trunk group. Pooled rates of cerebrovascular complications were 7.6% and 6.2% in the arch debranching group and elephant trunk group, respectively.

Miao recently published an analysis comparing hybrid arch repair to open surgical approach [43]. Their work combined the results from seven studies with 727 patients, 269 of whom underwent hybrid arch repair and 458 who underwent open surgical repair. Although hybrid arch repair was associated with decreased ICU lengths of stay and overall hospital stay, there was a trend toward increased late mortality at 2 years compared to an open approach (OR 3.41; 95% CI 0.83–14.03; $p = 0.09$). Operative mortality (OR 0.75; 95% CI 0.41–1.30; $p = 0.37$), neurological complications (OR 1.24; 95% CI 0.73–2.13; $p = 0.42$), and renal failure (OR 0.80; 95% CI 0.40–1.61; $p = 0.53$) were comparable between the groups. Importantly, patients undergoing open repair had decreased

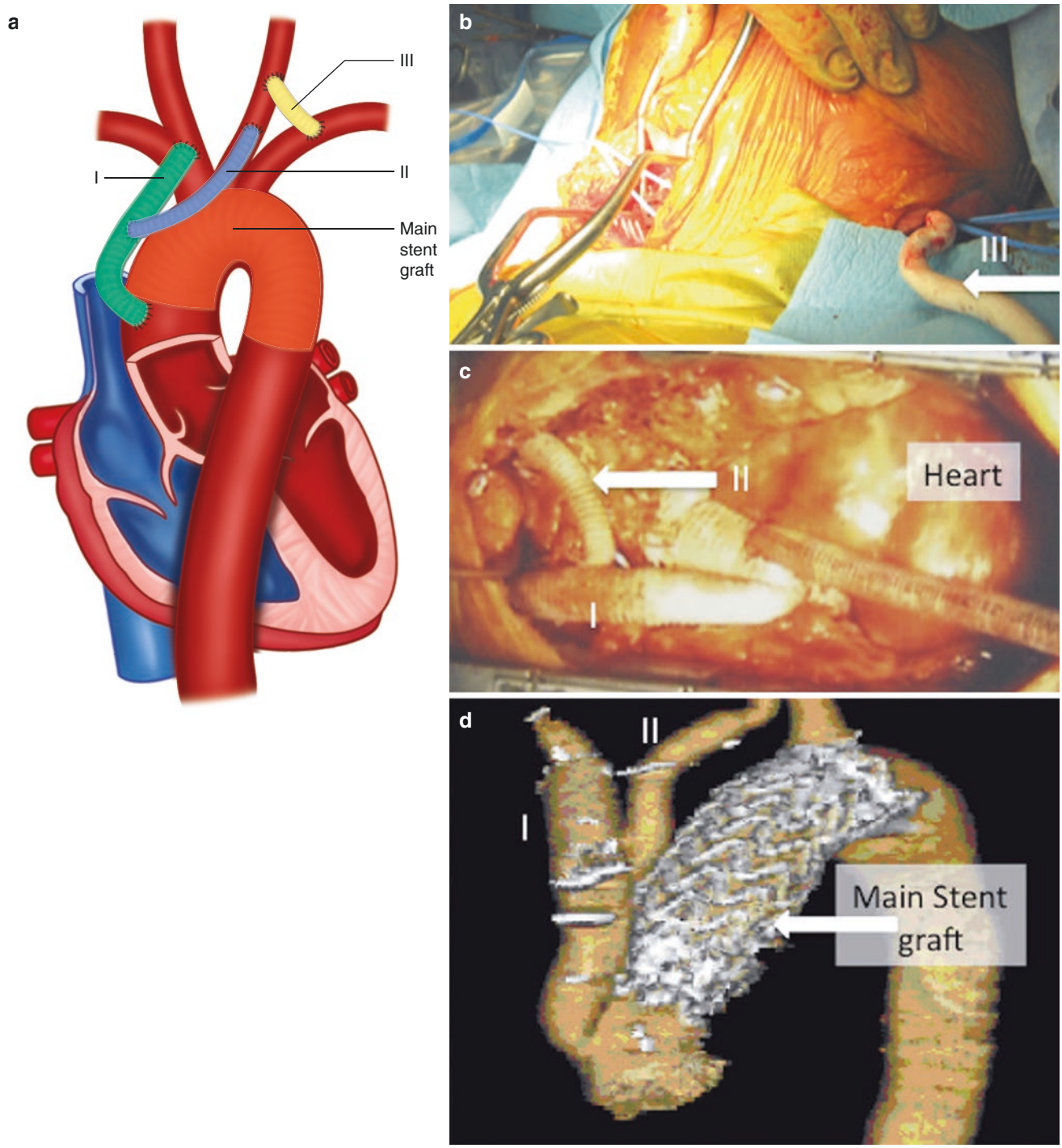

Fig. 20.5 Hybrid aortic arch repair. (**a**) Scheme of the operative approach (I: aorto-brachiocephalic bypass; II: bypass side branch to the left common carotid artery; III: carotid–subclavian bypass). (**b**) Carotid–subclavian bypass (III). (**c**) Bypass to the brachiocephalic artery (I) and to the left common carotid artery (II) in the open aortic surgery. (**d**) Reconstructed, contrast-enhanced computed tomography scan with the main stent graft in the ascending aorta and aortic arch, covering the ostia of the brachiocephalic and the left common carotid artery (I: aorto-brachiocephalic bypass; II: bypass side branch to the left common carotid artery). (From Shah et al. [41]. Reprinted with permission from Ali Khoynezhad, Long Beach Medical Center)

need for reintervention compared to those undergoing hybrid arch repair (OR 3.43; 95% CI 1.72–6.84; $p = 0.0005$).

The cause of increased reinterventions in the hybrid arch group was likely the increased rate of type I endoleaks with continued growth of the aneurysm which could increase the risk of rupture. Type I endoleaks usually result from propagation of a pathological lesion, inadequate proximal or distal seal, or technical difficulties associated with the device.

Lower rates of endoleak and reintervention were observed in patients undergoing hybrid arch repair in Zone 0 [43]. Type I endoleak may therefore be theoretically reduced with the use of an additional stent graft, which is extended to Zone 0. The increased reinterventions and late mortality associated with hybrid arch repair may also result from the increased risk associated with patients undergoing hybrid repair who often have multiple comorbidities which may preclude them from undergoing an open repair.

Chimney Stent Grafting

With chimney stent grating, multiple stent grafts are placed in the aortic arch branches in the same seal zone, entering the aorta parallel to the main aortic stent graft (Figs. 20.6 and 20.7). Although chimney stenting does not lengthen the seal zone, it does increase the available space for proximal fixation of the stent graft. It also enables blood to be simultaneously directed through the main aortic stent and chimney graft to provide both aortic and branch vessel perfusion. Greenberg et al. first described chimney stent grafting as a method of renal artery preservation in the management of abdominal aortic aneurysms with short proximal necks [44]. This technique was then adapted by Criado in a bailout operation following left common carotid artery coverage by a TEVAR graft [45]. The current indications for chimney stent grafting include poor candidacy for open surgery or hybrid procedures, insufficient landing zones for traditional TEVAR, and bailout revascularization following inadvertent overstenting during endovascular operations.

Unfortunately, the process inherently creates gutters between the parallel chimney graft and the main aortic stent graft, which may lead to type Ia endoleaks [46]. Oversizing by at least 20% enhances wall apposition, facilitates the formation of channels lateral to the graft, and decreases gutter development [47]. Adequate sealing and fixation can be brought about by using aortic neck lengths > 10 mm and ensuring appropriate stent-graft overlapping. The chimney stent graft provides a degree of interference along the endograft which enables the aortic length distal to the chimney graft to be available for preventing type Ia endoleak. The degree of overlap between the chimney graft and the thoracic endograft should be between 3 and 7 cm [48, 49].

Chimney stents are available in balloon expandable or self-expanding stent forms. The balloon expandable stents create strong radial force and are associated with more accurate positioning. Self-expanding chimney stents are better able to conform complex geometry of aortic anatomy. Mangialardi et al. reported outcomes of 26 patients who underwent chimney stenting with TEVAR for various aortic pathologies including thoracic aortic aneurysm, complicated type B dissection, type I endoleak following prior TEVAR, and penetrating ulcer [50]. They reported a technical success rate of 100% with one perioperative death from a cerebral hemorrhage. At 18 months, chimney graft patency was 89.3%, and 23% of patients developed type I endoleaks. A recent analysis by Mangialardi et al. reviewed 182 patients who underwent 217 chimney graft implantations including 91 to the LCCA, 89 to the LSA, and 36 to the brachiocephalic artery [51]. They reported a technical success rate of 98%, a stroke rate of 5.3%, and endoleak rate of 18.4%.

Fenestrated Stent Grafting

Fenestrated stent grafts, or those which feature openings along the fabric to enable blood flow into branch vessels, have been used successfully in the management of distal aortic pathology. Newer devices have been developed in an attempt to apply fenestrated technology to the aortic arch. Kawaguchi described the results of the first generation of the Japan's Najuta system (Kawasumi Laboratories, Tokyo, Japan), a preformed, stainless steel stent attached to PTFE [52]. From 1995 to 2008, approximately 1100 endovascular repairs were performed including 435 in the distal aortic arch, of which 288 involved the fenestrated endograft. The initial technical success rate (absence of type I or III endoleak) was 95.2% with a stroke rate of 5.5% in the cohort managed with the fenestrated endograft. The Najuta graft used in this trial required patients to have a proximal landing zone greater than 20 mm. The device was subsequently modified to allow placement in patients with proximal landing zones greater than 10 mm. Azuma et al. reported their experience in aortic arch reconstruction in 393 patients using 19 types of curved stent skeletons and eight types of graft fenestrations [53]. Technical success was achieved in 99.2% of patients, while hospital mortality rate was 1.5%, and 1.7% of patients experienced a cerebrovascular accident (CVA). The modified endograft therefore proved efficacious in cases with short landing zones.

Fenestrated graft deployment often requires substantial catheter manipulation to achieve accurate positioning, which can increase the risk of cerebrovascular complications and arterial embolization. By creating fenestrations directly in the graft across from the corresponding vessels, the in situ technique reduces the need for catheter manipulation and can be readily applied to off-the-shelf stent grafts. Retrograde fenestration is achieved from the common carotid approach using laser, radiofrequency, or a needle [54].

Branched Stent Grafting

In 1999, Inoue et al. described the use of branched stent grafts in 15 patients with aortic arch aneurysms [55]. Two

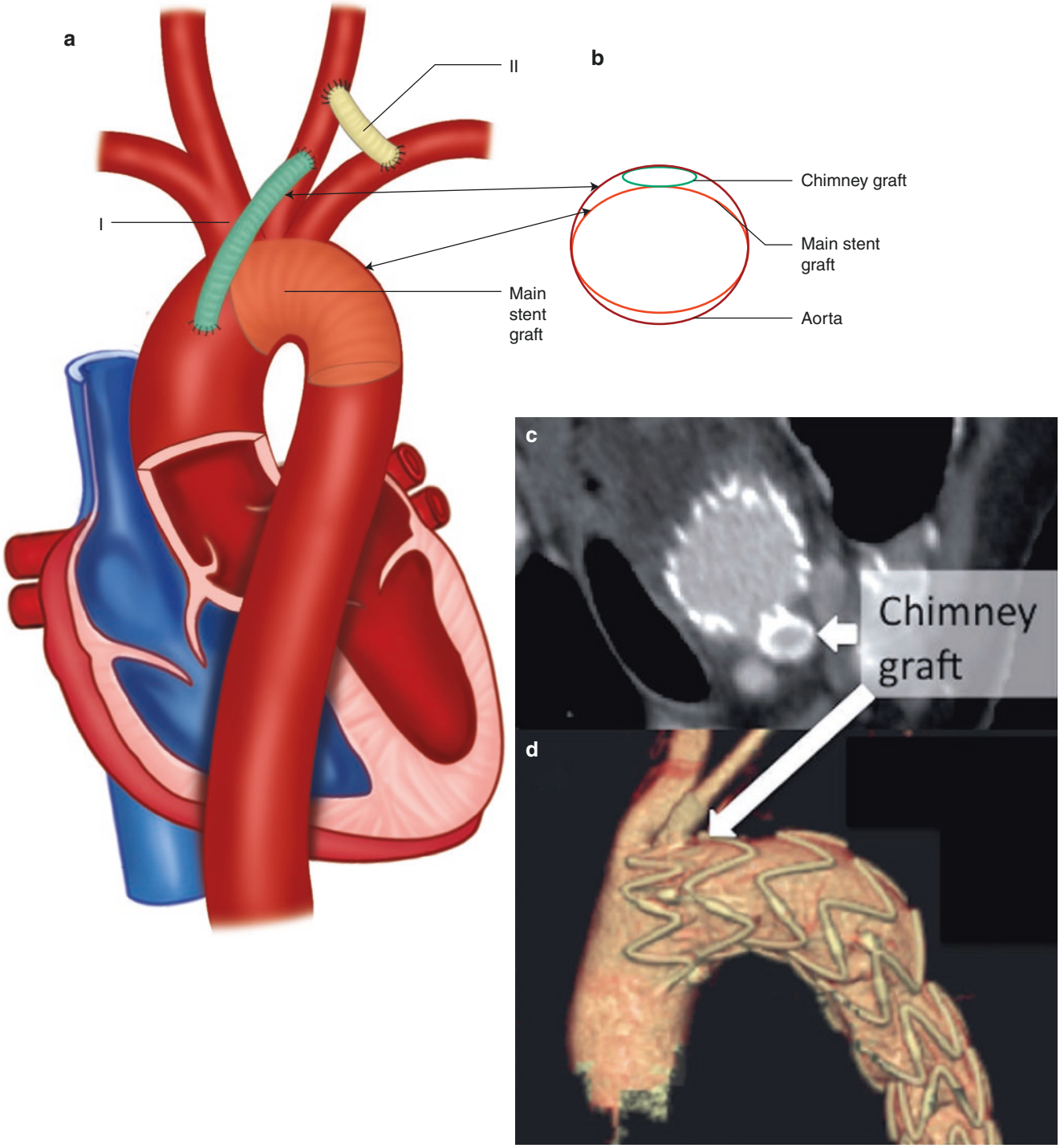

Fig. 20.6 Chimney technology. (**a**) Illustration of the chimney stent graft technology. The "chimney" stent graft (I) supplies the left common carotid artery and is located alongside the main stent graft. A carotid–subclavian bypass will ensure the perfusion of the left subclavian artery (II). (**b**) Scheme of the arrangement of the stent grafts in the aorta in the transversal section view. (**c**) Transverse computed tomography (CT) scan section with the chimney graft and main stent graft (arrow indicates the chimney stent graft). (**d**) Reconstructed CT angiogram with the chimney stent graft in the left common carotid artery (arrow). (From Shah et al. [41]. Reprinted with permission from Ali Khoynezhad, Long Beach Medical Center)

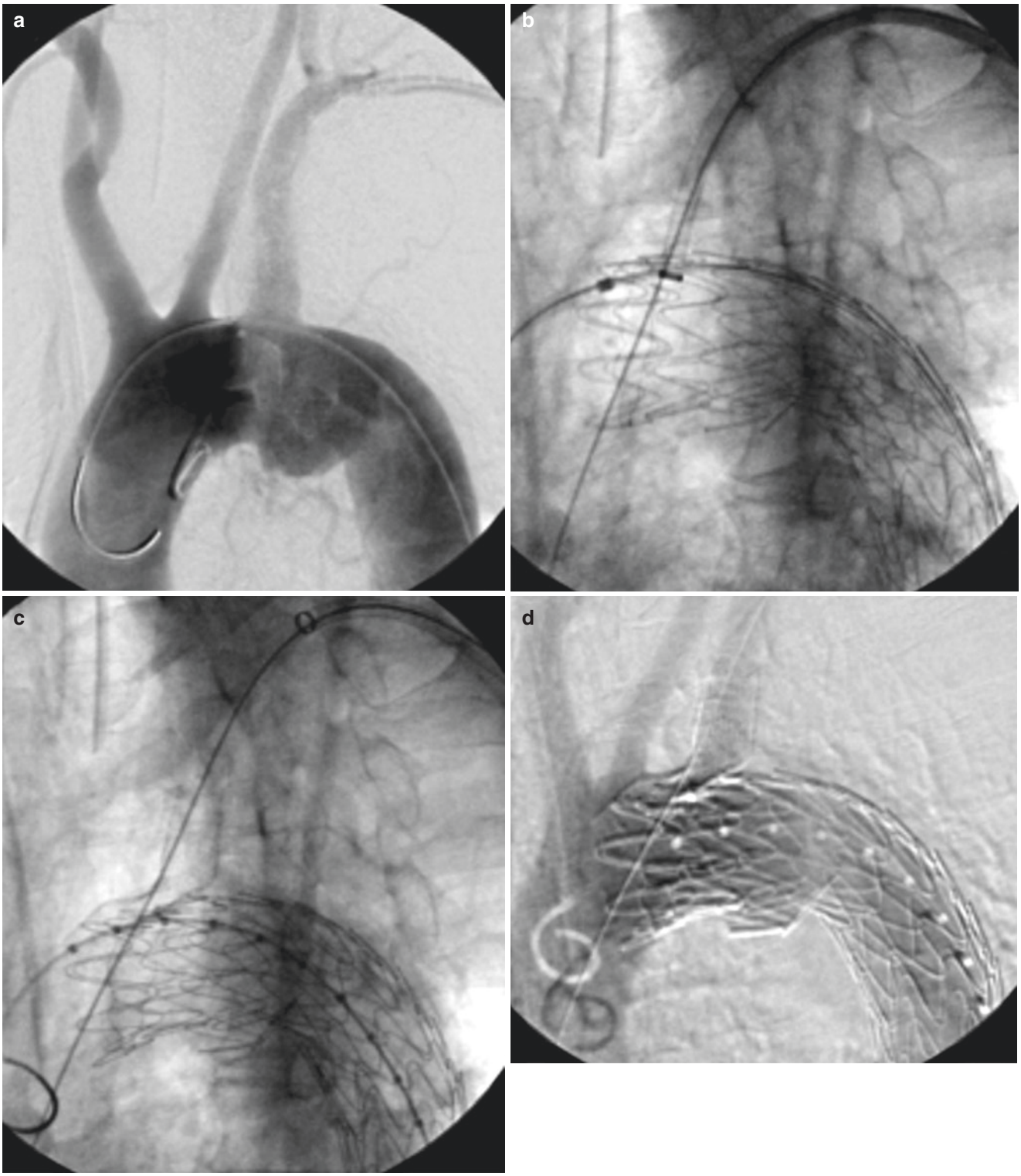

Fig. 20.7 Chimney procedure. (**a**) Preoperative angiogram demonstrating aortic pseudoaneurysm on the lesser curve of the aortic arch at the origin of the left subclavian artery (LSA). (**b**) Fluoroscopic image demonstrating the chimney sheath protruding into the aortic arch adjacent to the deployed aortic stent graft. (**c**) Fully deployed aortic stent graft and LSA chimney stent graft. (**d**) Completion angiogram revealing successfully excluded aortic pseudoaneurysm with patent LSA stent graft and no endoleak. (From Shah et al. [41]. Reprinted with permission from Ali Khoynezhad, Long Beach Medical Center)

failures were noted in which the stent graft did not pass through the 22F sheath due to increased tortuosity and small iliac artery diameter. Ultimately, complete aneurysm thrombosis was achieved in 11 (73%) patients. In the Chuter method, two stent grafts are inserted following CC and LCA-SA bypass creation to repair wide-necked aortic arch pseudoaneurysms (Fig. 20.8). The branched stent graft is positioned proximally in the ascending aorta and distally in the innominate artery and descending thoracic aorta. The technique, however, proved to be technically challenging and associated with high rates of morbidity and mortality. There was also a risk of modular disconnection. Modern devices for branched and fenestrated stent grafting are available as part of investigational device studies. Once approved, these devices have the potential to decrease the need for debranching techniques, chimney stent grafting, and ultimately open aortic arch repair.

Single-Branched Endografts

Reconstruction of the distal aortic arch may require endograft occlusion of the left subclavian artery, following subclavian revascularization, to achieve an adequate proximal landing zone. Single-branched endografts were designed to maintain LSA patency, thereby obviating the need for revascularization during stent graft deployment in thoracic aortic aneurysms. The custom-made Inoue system features a Dacron stent graft, a detachable carrying wire, a balloon catheter, an introducer wire, and two detachable traction wires. After the graft is positioned using the carrying wire and traction wire, the aortic and branched sections are deployed using balloon dilation. Saito described the successful deployment of the Inoue system in 17 patients with thoracic aortic aneurysms with 3 patients developing endoleaks, 1 patient developing spinal ischemia, and no device-related mortality over the course of

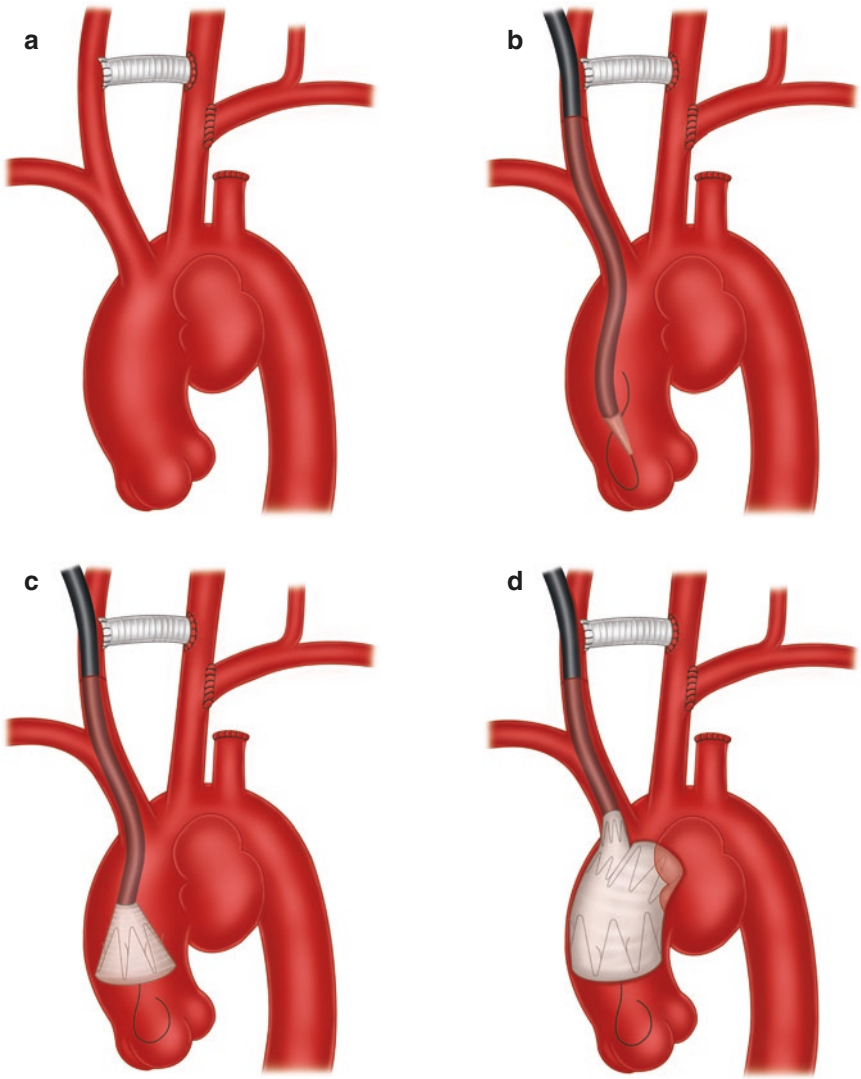

Fig. 20.8 Chuter branched stent technique. (From Chuter et al. [56]. Reprinted with permission from Elsevier) (**a**) Carotid-carotid bypass and subclavian-carotid reimplantation (**b**) Insertion of first sheath (**c**) Deployment of proximal stent (**d**) Deployment of short aortic limb

28 months [57]. The Valiant Mona LSA system (Medtronic Inc., Santa Rosa, CA, USA) features a nitinol-containing main and branch stent grafts which are delivered separately (Fig. 20.9). Roselli reported the early feasibility results of the system in nine patients with four endoleaks, four minor CVAs, and no mortality was observed in nearly 6 months of follow-up [58]. The Gore Thoracic Branch Endoprosthesis (TBE) (W.L. Gore, Flagstaff, AZ, USA) is nitinol-based expanded polytetrafluoroethylene stent graft with an internal portal that accommodates a tapered, heparin-coated, stent graft oriented in a retrograde manner (Fig. 20.10). Patel reported early feasibility results of the system in 22 patients demonstrating no mortality, stroke, paraplegia, or type 1 endoleaks at 30 days and 1 patient with paraparesis [59]. The Gore TBE device is also currently being studied in Zone 2 TEVAR (NCT02777593) and Zone 0/1 TEVAR (NCT02777528) using a hybrid approach (Fig. 20.11).

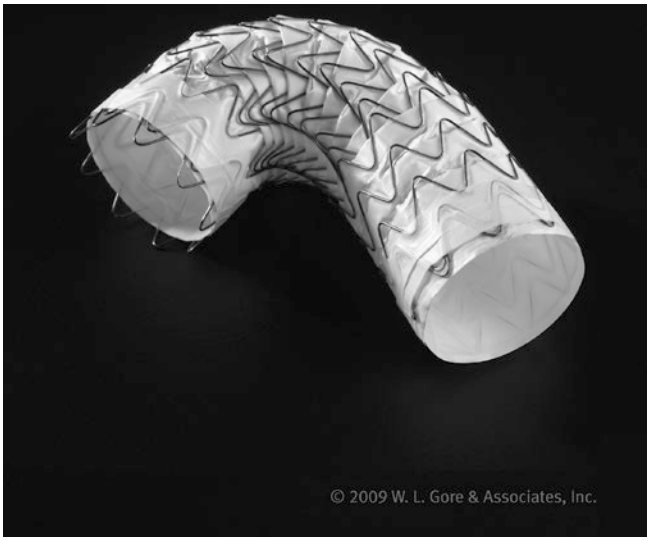

Fig. 20.10 Conformable Gore® TAG® thoracic branch endoprosthesis (TBE). (Image provided courtesy of W. L. Gore & Associates)

Fig. 20.9 Medtronic Valiant Mona LSA. (From Roselli et al. [58]. Reprinted with permission from Elsevier)

Double-Branched Endografts

The custom-made Cook arch branched system (Cook Medical Inc., Denmark) features a curved body endograft with two side branches (Fig. 20.12). Using a 22 or 24 Fr delivery system, the device is designed for a Zone 0 landing with a diameter $\leq$ 38 mm. The main graft is delivered through femoral access, while the left axillary and right common carotid arteries are cannulated to obtain access to the left common carotid and innominate arteries, respectively. Haulon et al. reported the outcomes of a multicenter study involving 38 patients who underwent endovascular exclusion of arch aneurysms using a branched endograft with two inner branches [60]. Perioperative mortality was 13.2%, and technical success was achieved in 84.2% of patients. Cerebrovascular complications were noted in 6 (15.8%) patients, while endoleaks were noted in 11 (28.8%) patients. The authors also reported a learning curve of ten operations, after which reductions in perioperative mortality (two vs. three; $p = 0.066$), intraoperative complications (three vs. four; $p = 0.04$), secondary procedures for endoleak (zero vs. three; $p = 0.014$), and operative time (248 vs. 320 min; $p = 0.03$) were achieved. Ascending aorta diameters $\geq$ 38 mm were associated with an increased risk of combined early mortality and cerebrovascular events ($p = 0.026$). The authors reasoned the increased risk was due to the less accurate endograft deployment in a large ascending aorta which itself could represent a less stable sealing zone.

The Double Branch Arch system (Bolton Medical, Sunrise, FL, USA) includes a fixed branch configuration with a large opening for two nitinol internal branches inside the main endograft (Fig. 20.13). Locking barbs in both internal tunnels help to prevent component migration and disconnection.

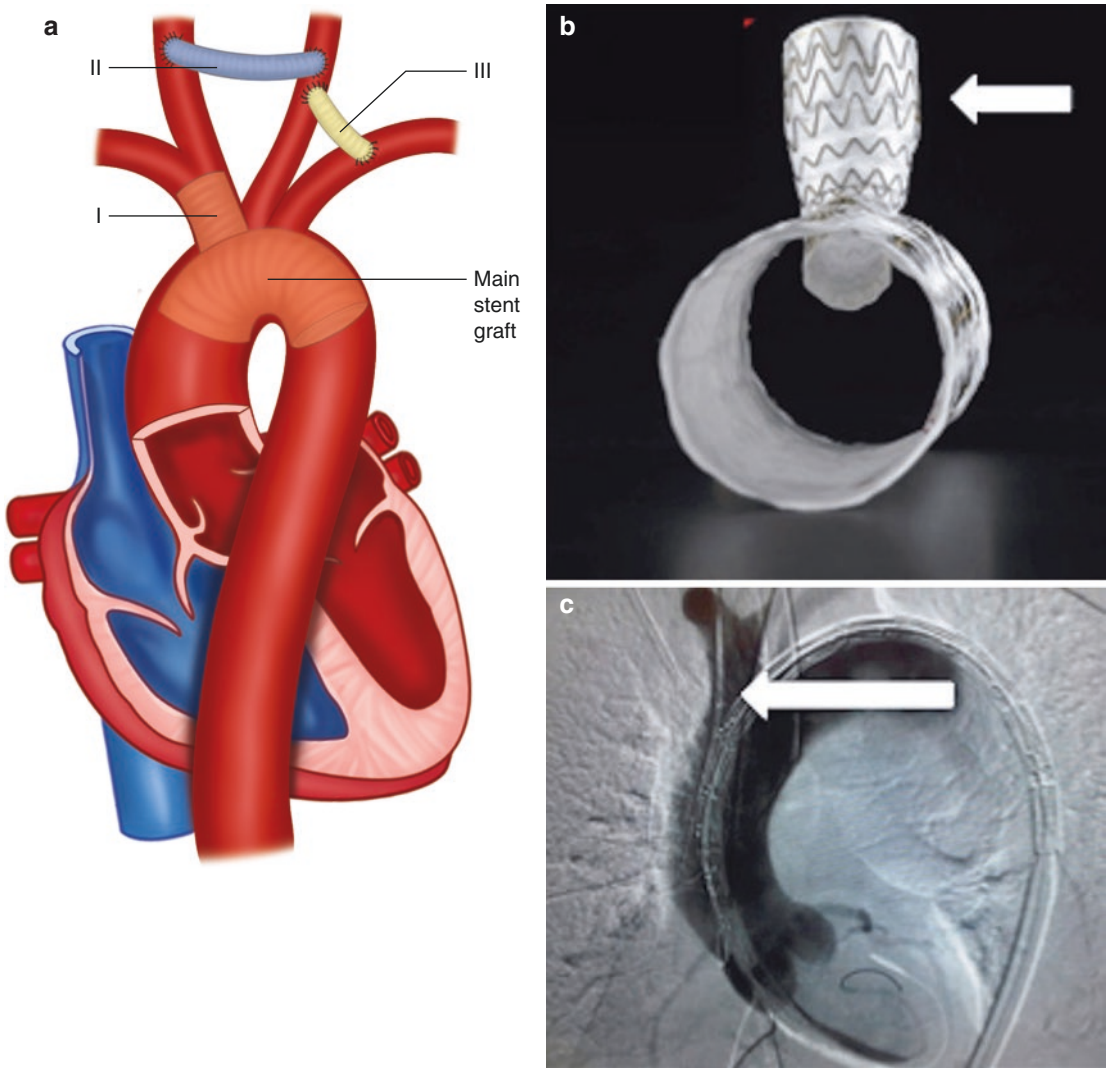

Fig. 20.11 Branched/fenestrated thoracic endovascular aortic repair. (**a**) Illustration of a branched stent graft (I) from the main stent graft supplying the brachiocephalic artery (red). To ensure sufficient blood supply for the covered brachiocephalic vessels, a carotid–carotid bypass (II) and a carotid–subclavian bypass (III) can be performed. (**b**) Branched stent graft (Gore TBE). The arrow indicates the stent graft that will be deployed into the brachiocephalic vessel. (**c**) Fluoroscopy of a branched brachiocephalic trunk (arrow). (From Shah et al. [41]. Reprinted with permission from Ali Khoynezhad, Long Beach Medical Center)

Riambiau recently reported the early results of 26 patients undergoing treatment with the double-branched endograft for thoracic aortic aneurysm or dissection [61]. In this cohort, there were three endoleaks, one stroke (which resulted in death), and a perioperative mortality of 7.7%.

Triple-Branched Endograft

Triple-branched stenting was developed as part of a hybrid technique in which the transverse arch and proximal descending aorta are repaired in an open approach. Chen et al. described the successful repair of the ascending aorta and aortic arch and 3 arch vessels simultaneously with an open placement of a triple-branched stent graft combined with graft replacement of the ascending aorta as part of the primary repair in 30 patients with acute type A dissection [62]. This technique was successfully applied in a cohort of 121 patients with selective antegrade perfusion with excellent results [63]. Perioperative mortality was 3.3%, and although neurovascular complications were noted in 13 patients, no permanent dysfunction was identified.

Surveillance Imaging Following Endovascular Repair

Patients undergoing endovascular interventions of the ascending aorta and aortic arch should be followed closely in the first year after intervention. Scheduled exams should occur at

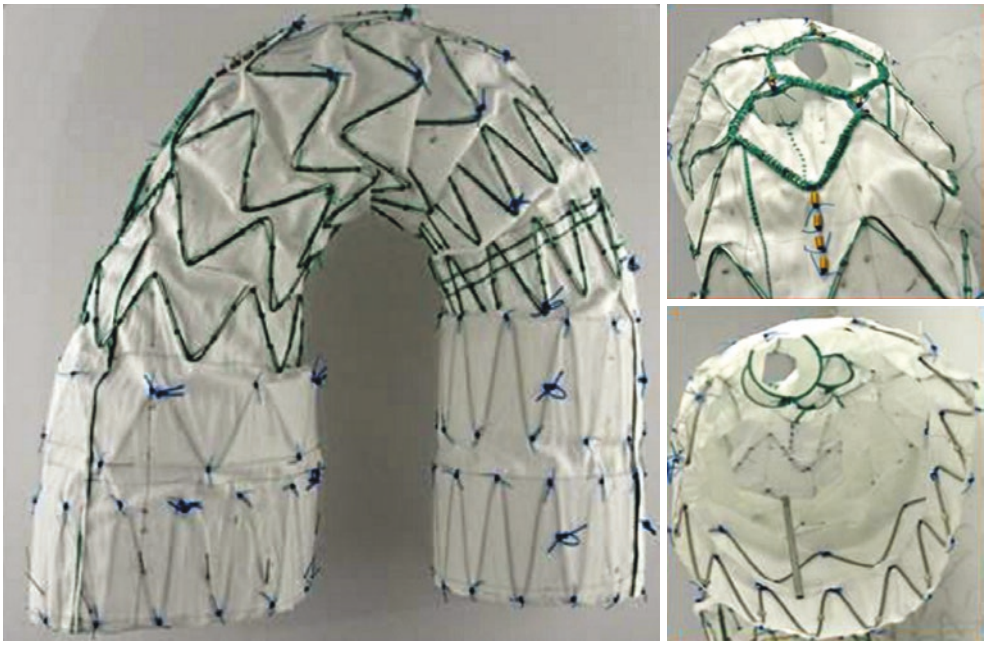

Fig. 20.12 Cook arch branched system. (Image courtesy of Cook Medical)

Fig. 20.13 Bolton Medical double branch arch graft. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved)

1 month of treatment followed by surveillance visits at 6 months, 12 months, and then yearly. Clinical evaluation should focus on blood pressure management and detection of complications, which may present subtly. CT is presently the first-line imaging modality in surveillance following TEVAR (Level IC; [64]). Although the principal disadvantage of CT is the amount of radiation delivered during scans, several device innovations such as prospective gating, low tube voltage, and dose reduction protocols have been developed to mitigate the risks [65, 66]. MRI has also been successfully used in the surveillance of nitinol stent grafts [67]. Endografts containing stainless steel components may generate artifacts on MRI which may limit its clinical applicability [17]. In patients with contraindications to CT or MRI, a combination of TEE and chest radiography can be used for postoperative surveillance.

Conclusions and Future Directions

The ascending aorta and aortic arch remain the last frontier of endovascular aortic intervention. Innovations in endovascular technology for the ascending aorta and aortic arch continue to rapidly evolve with direct applications for treating aortic pathology. In the USA, surgeons have modified the preexisting technology for thoracic/abdominal EVAR to create solutions for the ascending aorta and aortic arch. Newer devices are needed which can conform to the unique anatomical constraints of the ascending aorta and aortic arch with low profile delivery systems. Approval of devices specifically designed for the ascending aorta and aortic arch will expand the armamentarium for managing patients at advanced surgical risk. Long-term outcomes and device durability remain prominent concerns of the new devices. As the technical considerations and complications are minimized, endovascular repair of the ascending aorta and aortic arch may prove a viable option for lower risk surgical patients. Until then, open surgery remains the standard of care for diseases of the ascending aorta and aortic arch.

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Endovascular Repair of the Thoracic Aorta

21

Alexandra H. Fairchild and Robert A. Hieb

Introduction

Thoracic endovascular aortic repair (TEVAR) is an attractive alternative to open aortic repair and has continued to grow since its first published use in 1991 [1]. Initially approved for repair of thoracic aortic aneurysms, TEVAR indications have expanded to include traumatic aortic injury, complicated type B dissections, and penetrating aortic ulcer. Benefits of the endovascular approach over the traditional open surgical approach include avoidance of a thoracotomy or sternotomy and avoidance of aortic cross-clamping.

Aortic Pathology

Management of descending thoracic aortic pathology is largely dictated by the patient's health as well as the type of pathology with which he or she presents. Broadly, aortic pathology can be divided into traumatic and atraumatic pathology. Atraumatic entities include aortic aneurysm, type B dissection, penetrating aortic ulcer, and intramural hematoma.

Blunt Traumatic Aortic Injury

Thoracic aortic injury is the second leading cause of death after head injury among blunt trauma patients [2]. Most victims die in the field, and the few who survived to the hospital were, until recently, taken for early operative repair due to perceived high risk of impending rupture [2]. Computed tomographic angiography (CTA) now allows for rapid screening, injury classification, and intervention planning [2, 3].

The Society of Vascular Surgery has a four-tiered classification scheme for blunt aortic injury (BAI) (Table 21.1). This system was created based on retrospective review of BAI in patients presenting to Harborview Medical Center in Seattle, WA, between 1999 and 2008 [4]. Patients presenting with grade 1 intimal tear alone may be managed medically with heart rate and blood pressure control alone. Grade 2, grade 3, and grade 4 injuries require repair. In patients who are hemodynamically stable without free rupture, aortic repair is delayed until other injuries are addressed as appropriate and associated with improved mortality [5].

Aortic Aneurysm

TEVAR was first approved by the FDA for repair of thoracic aneurysm following the results of the Gore TAG trial in 2005 [6]. Typically, a thoracic aortic diameter greater than 6–6.5 cm is considered the threshold where the risk of repair is outweighed by the risk of rupture [7]. Aneurysms with a rapid growth rate of greater than 1 cm per year or presenting with symptoms should also be repaired [8].

Type B Dissection

Type B dissection complicated by rupture or malperfusion warrants repair. In the case of malperfusion, coverage of the entry tear with an endograft allows for the re-expansion of the true lumen and improved organ perfusion [9].

Uncomplicated type B dissection has classically been treated with antihypertensives targeted to reduce left ventricular ejection fraction and titrated to maintain a systolic blood pressure less than 120 mmHg [10]. A short-acting beta-blocker is the initial drug of choice [10]. This approach was supported by the results of the INvestigation of STEnt grafts in patients with acute type B Aortic Dissection (INSTEAD) trial, which compared medical management to TEVAR and found no difference in all-cause mortality at

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Table 21.1 Classification of blunt aortic injury

Injury grade	Type of aortic injury	Definition
1	Intimal tear	Normal external aortic contour: tear and/or associated thrombus is <10 mm
2	Large intimal flap	Normal external aortic contour: tear and/or associated thrombus >10 mm
3	Pseudoaneurysm	Disruption of the external aortic contour: contained
4	Rupture	Disruption of the external aortic contour: not contained, free rupture

1 year [11]. However, subsequent 5-year follow-up data from the INSTEAD-XL trial suggests a long-term benefit to TEVAR with decreased aortic specific mortality and disease progression compared to medical management alone [12]. It is hypothesized that the endograft promotes thrombosis of the false lumen and favorable aortic remodeling, thus reducing the risk of aneurysmal degeneration of the aorta in this population [12].

Penetrating Aortic Ulcer and Intramural Hematoma

Penetrating aortic ulcers (PAUs) and intramural hematomas (IMHs) represent more focal aortic pathology on the dissection spectrum. A PAU is characterized by an ulceration of an atheromatous plaque that disrupts the internal elastic lamina allowing hematoma to extend into the media [13]. An IMH is hemorrhage within the aortic wall without clear evidence of intimal disruption. Notably, a PAU may cause an IMH which can then progress to dissection. Indications for treatment of a PAU include a depth greater than 10 mm or diameter greater than 20 mm, as these lesions are at high risk for progression [14]. Of patients presenting with IMH alone, 34% show regression, 16–47% of patients will progress to develop aortic dissection, and 20–45% will develop aortic rupture if left untreated [15].

Imaging

Initial imaging for most patents presenting with suspected thoracic aortic pathology is a chest radiograph. While the sensitivity of a chest radiograph can vary widely between 12.4% and 81%, it can serve as a tool to quickly evaluate for and potentially rule out other plausible causes for a patient's symptoms [16–18]. Ultimately, more definitive imaging is required for accurate diagnosis and procedure planning.

Computed tomographic angiography (CTA) is now the "gold standard" for evaluating the aorta. In addition to diagnosing the pathologic process with a sensitivity and specificity above 95%, these images provide the needed information [19, 20]. The preoperative CTA should include the chest (including the aortic arch), abdomen, and pelvis. Inclusive in the preprocedural planning is an understanding of the great vessel anatomy off the aortic arch as well as the vertebral artery location to minimize cerebral ischemic complications when proximal extension of the graft is necessary. Imaging of the abdomen and pelvis is critical to understand the extent of aortic involvement of any process as well as determine the feasibility and appropriate route for the delivery of the endograft.

Modern 64-slice computed tomography (CT) scanners allow for high definition with extremely fast scan times. Coronal and sagittal reformats in addition to maximum intensity projections and three-dimensional volume rendering can aid in understanding the relationship of vessels and angles of the aorta. Commercially available software including Vitrea (Vital Images, Minnetonka, MN, USA), M2S (M2S, West Lebanon, NH, USA), and Aquarius (TeraRecon, San Mateo, CA, USA) allow for additional manipulation of images such as centerline reconstructions such that the true diameter of a vessel can be measured.

Devices

All thoracic endografts are a combination of metal stents (nitinol or stainless steel) and fabric (Dacron or expanded polytetrafluoroethylene). Each differs in their stent size availability, shape, radial force, conformability, delivery sheath size, ease, and precision of deployment. A difference in clinical efficacy between the currently approved stent grafts has not been clearly shown. Preferences for stent grafts often depend on the user preference and experience as well as specific characteristics of the patient's anatomy [21]. Understanding currently available devices will allow for optimal graft selection for each case. Table 21.2 provides a summary of the available thoracic endografts.

Bolton Relay

Bolton Medical currently has three thoracic endograft options on the market, the Relay Plus (Fig. 21.1), the Relay NBS Plus, and a custom stent option; however, only the Relay Plus has received FDA approval in the United States. Both the Relay NBS Plus and the Relay custom program are currently on trial devices. The Relay Plus first received approval in the European Union in April 2005 and has been available in the United States since September 2012. The Relay stent grafts are composed of self-expanding nitinol sinusoidal stents sutured to a polyester vascular graft. A curved nitinol wire sutured along the length of the graft fabric provides additional longitudinal support. The Relay Plus

Table 21.2 Thoracic endografts

Approval status	Company	Endograft	Stent	Graft material	Proximal stent	Distal stent	Graft diameters	Aortic diameters	Endoprosthesis lengths	Body shapes	Delivery system OD	Pathology
FDA approved	Bolton Medical	Relay Plus	Nitinol sinusoidal stent	Dacron	Bare metal	Covered	22–46 mm (2-mm steps)	19–42 mm	100–250 mm (50-mm steps)	Straight and tapered	22–26 French (current trials for 19–22 French systems)	Aneurysms, PAU of the descending thoracic aorta
On Trial in the USA, approved outside the USA	Bolton Medical	Relay NBS Plus	Nitinol sinusoidal stent	Dacron	Covered	Covered	24–46 mm (2 mm steps)	19–42 mm	100–250 mm (50-mm steps)	Straight and tapered	19–22 French	Aneurysms, PAU of the descending thoracic aorta
On Trial in the USA, approved outside the USA	Bolton Medical	Custom	Nitinol sinusoidal stent	Dacron	Bare metal	Covered	22–46 mm (2 mm steps)	19–42 mm	100–250 mm (5-mm steps)	Straight, tapered, reverse taper	19–22 French	Aneurysms, PAU of the descending thoracic aorta
FDA approved	Cook	Zenith TX2	Nitinol Z-stent exoskeleton	Dacron	Proximal component: covered with bare-metal barbs. Distal component: covered without barbs	Covered. Proximal component, bare metal. Distal components	28–42 mm	24–38 mm	120–216 mm	Straight and tapered	20–22 French	Aneurysms, PAU of the descending thoracic aorta

(continued)

Table 21.2 (continued)

Approval status	Company	Endograft	Stent	Graft material	Proximal stent	Distal stent	Graft diameters	Aortic diameters	Endoprosthesis lengths	Body shapes	Delivery system OD	Pathology
FDA approved	Cook	Zenith Alpha	Nitinol Z-stent	Dacron	Proximal component: bare-metal, barbed. Distal component: covered	Proximal component: covered. Distal component: bare-metal barbed	18–46 mm	15–42 mm	105–233 mm	Straight and tapered	16–20 French	Aneurysms, PAU, or blunt injury of the descending thoracic aorta
FDA approved	Gore	Conformable TAG	External, nitinol stent	Expanded polytetrafluoroethylene (ePTFE)	Partially covered	Covered	21–45 mm	16–42 mm	100–200 mm	Straight and tapered	Requires introducer sheath 18–24 French	Aneurysms, traumatic transections, acute and chronic type B dissection
FDA approved	Medtronic	Valiant	Series of sinusoidal-shaped stents	Dacron	Covered or bare metal	Covered or bare metal	22–46 mm	18–44 mm	100–212 mm	Straight and tapered	22–24 French	Aneurysms, traumatic transections, acute and chronic type B dissection

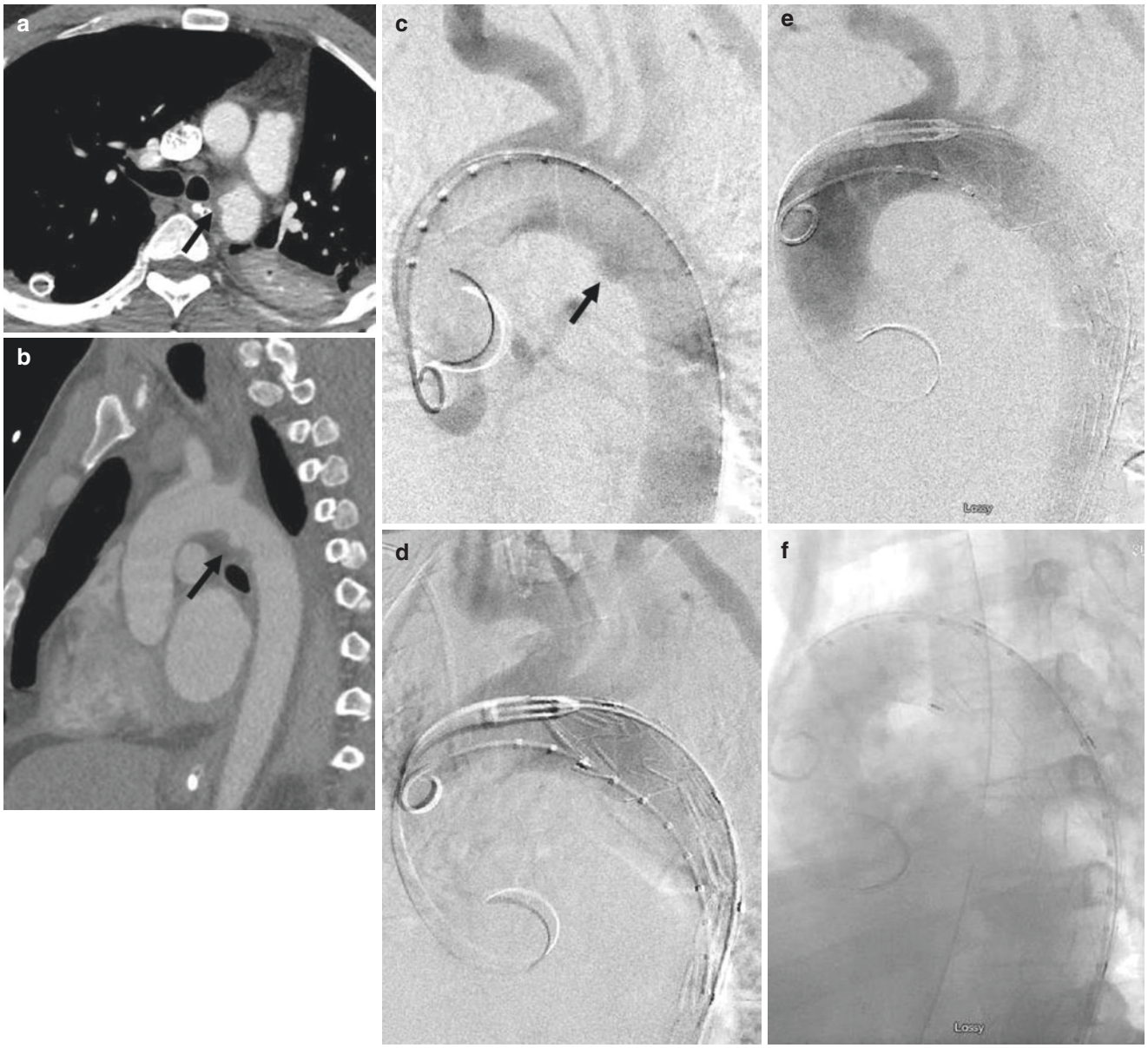

Fig. 21.1 Axial (**a**) and sagittal (**b**) contrast-enhanced CT images of the thoracic aorta demonstrating a diverticulum of Kommerell (arrow). Sequential DSA images of the thoracic aorta demonstrating the diverticulum of Kommerell (arrow) (**c**), the partially deployed Bolton Relay endograft (**d**), and the fully deployed endograft with bare metal proximal fixation devices still restrained (**e**). Final angiogram of the thoracic aorta (**f**) after successful deployment of the endograft. Note the left subclavian artery was intentionally covered due to the proximity of the diverticulum

has proximal bare-metal stents which are designed specifically for improved, stable deployment at the arch and does not have significant radial force. In contrast, the Relay NBS Plus system is completely covered. The custom option allows for an increased range of diameters (20–50 mm), increased taper options, including reverse taper grafts, and custom graft lengths. Custom grafts require approximately 3 weeks to manufacture and deliver.

Modifications of the original delivery account for the "Plus" nomenclature of the currently available stents. The Plus Delivery System has modifications from the original design to facilitate deployment of the stent graft around a smaller radius of curvature. The inferior apices are left unclasped from the delivery system catheter to allow the inferior portion of the graft to expand at the beginning of the deployment. Two heat-shaped nitinol "support wires" of the delivery system help to ensure proper apposition of the graft to the inner curvature of the aorta. Additionally, the leading end of the constraining sleeve was enlarged to allow longitudinal adjustments of the graft in its partially expanded state [22].

The grafts have diameters ranging from 24 to 46 mm in 2 mm steps accommodating vessel diameters of 19–42 mm.

Graft lengths range from 100 to 250 mm in 50 mm steps. Both straight and tapered configurations are available. Current delivery systems have an outer diameter (O.D.) of 22–26 French. Current modifications are underway for the development of the next generation of the Bolton Relay (Relay Pro) thoracic endografts which, if approved, will have a reduced profile by 4 French across stents (19–22 French O.D.).

Funovics et al. evaluated the safety and efficacy of the Relay thoracic stent graft in 22 patients between 2005 and 2007. Patients were treated for aneurysms ($n = 13$), PAU ($n = 7$), and dissections ($n = 2$). Primary technical success was achieved in 20 of 22 patients, with one persistent type I endoleak and one asymptomatic type II endoleak. No additional endoleaks were observed in follow-up. One patient died 3 days post stent placement secondary to malignant arrhythmia. One additional patient died of nonaortic cause during follow-up [23].

Cook Zenith Thoracic Graft

Cook Medical has two thoracic endografts currently on the market, the Zenith TX2 and the Zenith Alpha (Fig. 21.2). The Zenith TX2 endograft platform received FDA approval in 2008 for treatment of aneurysms or ulcers of the descending thoracic aorta with nonaneurysmal aortic segments (fixation sites) proximal and distal to the aneurysm or ulcer of at least 25 mm. The grafts have diameters of 28–42 mm to treat aortic diameters of 18–38 mm (measured outer wall to outer wall).

The graft is composed of a Dacron graft with a nitinol Z-stent exoskeleton. Active fixation with barbs is present on the proximal bare stents. The distal stent above the visceral vessels is also bare. A modification from the prior generations is the addition of ProForm to allow greater conformability at the arch, limiting the "bird-beak" effect.

A prospective, nonrandomized comparison of 160 TEVAR patients treated with the Cook Zenith TX2 and 70 open surgical repair patients found similar mortality rates of 37% for both groups [24].

In 2008, American Association for Surgery of Trauma (AAST) called for a "major and urgent need for improvement of available endovascular devices" for the treatment of blunt thoracic aortic injury. Blunt traumatic aortic injury is seen as the result of motor vehicle collisions and falls. As such, the patient population is younger than the typical patient requiring aortic endograft repair. On average, these patients have smaller iliac access vessels, smaller aortic diameters, and narrower aortic arch curvatures. In response to this need, Cook Medical designed the Zenith Alpha.

The Zenith Alpha stent graft is constructed of self-expanding nitinol stents sewn to a tightly woven Dacron. The device has a lower profile introduction system than its predecessor the Zenith TX2 (16F–20F compared to 20F–24F), can accommodate smaller and larger aortic diameters (18 to 46 mm), and accommodates an aortic arch with a radius of curvature of 20 mm. Unlike the fully covered Zenith TX2, the proximal stent of the Alpha is bare. The cannula of the delivery system is precurved to assist with proximal arch conformability.

The TRANSFIX trial is a prospective, nonrandomized, noncomparative, single-arm, multicenter clinical trial conducted to assess the safety and efficacy of the Zenith Alpha thoracic endograft [4, 25]. Recent mid-term follow-up reported a mean follow-up of 21 months (range 18–1050 days). One patient died within 30 days; however, it was not aortic injury related. Four patients died after 30 days, of which one was related to aortic injury. Two cases of stroke occurred within 30 days, and no strokes were reported beyond 30 days. One patient required surgical conversion after failed reintervention for a proximal type I endoleak. Of the 31 patients with available imaging 1-year postintervention, aortic injury healing was confirmed in 96.8% (30/31) of patients. No type I or type III endoleak or device migration was observed [4].

Gore Conformable TAG

The Gore TAG endoprosthesis was the first thoracic endograft approved by the FDA in March 2005. The current Conformable TAG (cTAG) endoprosthesis (Fig. 21.3) is the third-generation iteration of this device and was approved in 2011. In 2012, the cTAG also became the first stent graft approved for traumatic transection. In 2013, the cTAG gained FDA approval for aneurysms, transections, and acute and chronic Type B dissections.

The device is made up of an expanded polytetrafluoroethylene (ePTFE) tube with an external nickel-titanium (nitinol) self-expanding stents adhered to the ePTFE. A partially uncovered, barbless stent is present proximally with the remainder of the graft completely covered. A circumferential PTFE sealing cuff is present at each end. The device is constrained by ePTFE, which when deployed opens the graft from the middle toward each end. This design is meant to minimize the windsock effect that might otherwise be seen if the graft were to open from the ends, toward the middle.

Evaluation of the newer cTAG's deployment accuracy was compared to the prior generation TAG device by Ito et al. They found deployment accuracy at the time of implantation was significantly better for the cTAG device as compared to the TAG device (2.2 ± 1.7 mm vs. 4.4 ± 3.0 mm, $p < 0.05$). Additionally, fewer cases of bird-beaking were seen with the cTAG (1 in 12 cases vs. 8 of 20 cases) [26].

Devices are available in diameters of 21–45 mm and in lengths of 10, 15, and 20 cm. In addition, grafts are available in a range of tapered sizes. The graft is engineered for 6–33% oversizing.

Medtronic Valiant

The Medtronic Valiant stent graft (Fig. 21.4) was initially approved in April 2011 for the endovascular repair of fusiform aneurysms, saccular aneurysms, and penetrating ulcers of the descending thoracic aorta. In November 2012, the FDA expanded its approval to include all descending thoracic aortic lesions, with the exception of dissections. However, the Valiant was subsequently approved for complicated type B dissections in January 2014.

There must be at least 20 mm of nonaneurysmal aorta with a diameter range of 18–42 mm proximal and distal to the aneurysm in patients being treated for aneurysms or penetrating ulcers. Nonaneurysmal aortic diameters of 18–44 mm are approved for treatment of blunt traumatic aortic injuries and 20–44 mm for the treatment of dissections.

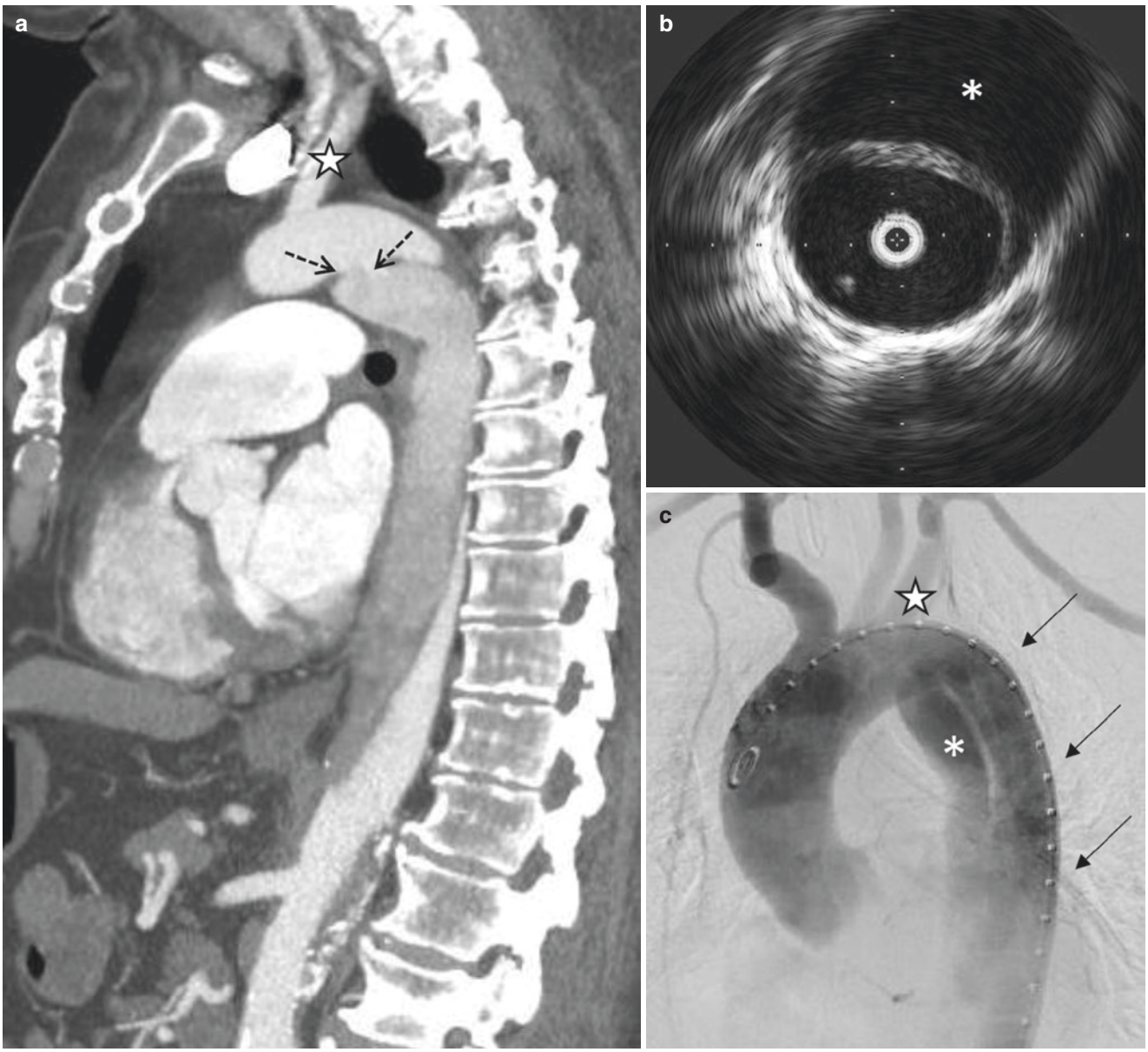

Fig. 21.2 Sagittal contrast-enhanced CT image (**a**) of the thoracic aorta demonstrating a complicated dissection. The entry tear (dashed arrows) is immediately distal to the left subclavian artery (star). Intraprocedural IVUS image (**b**) demonstrates the IVUS catheter within the true lumen and the false lumen marked by an asterisk. Initial intraprocedure digital subtracted angiogram (DSA) of the thoracic aorta (**c**) with a multimarker pigtail flush catheter (solid arrows) within the true lumen. DSA of the thoracic aorta (**d**) after the delivery of the Cook Zenith Alpha endograft into the thoracic aorta prior to deployment to assist with appropriate placement. Repeat DSA (**e**) after deployment of the first two stents of the graft. This allows for final small adjustments to the endograft positioning prior to complete deployment. Final DSA (**f**) of the thoracic aorta after successful deployment of the endograft. The left subclavian artery (star) was intentionally covered due to its proximity to the dissection entry tear

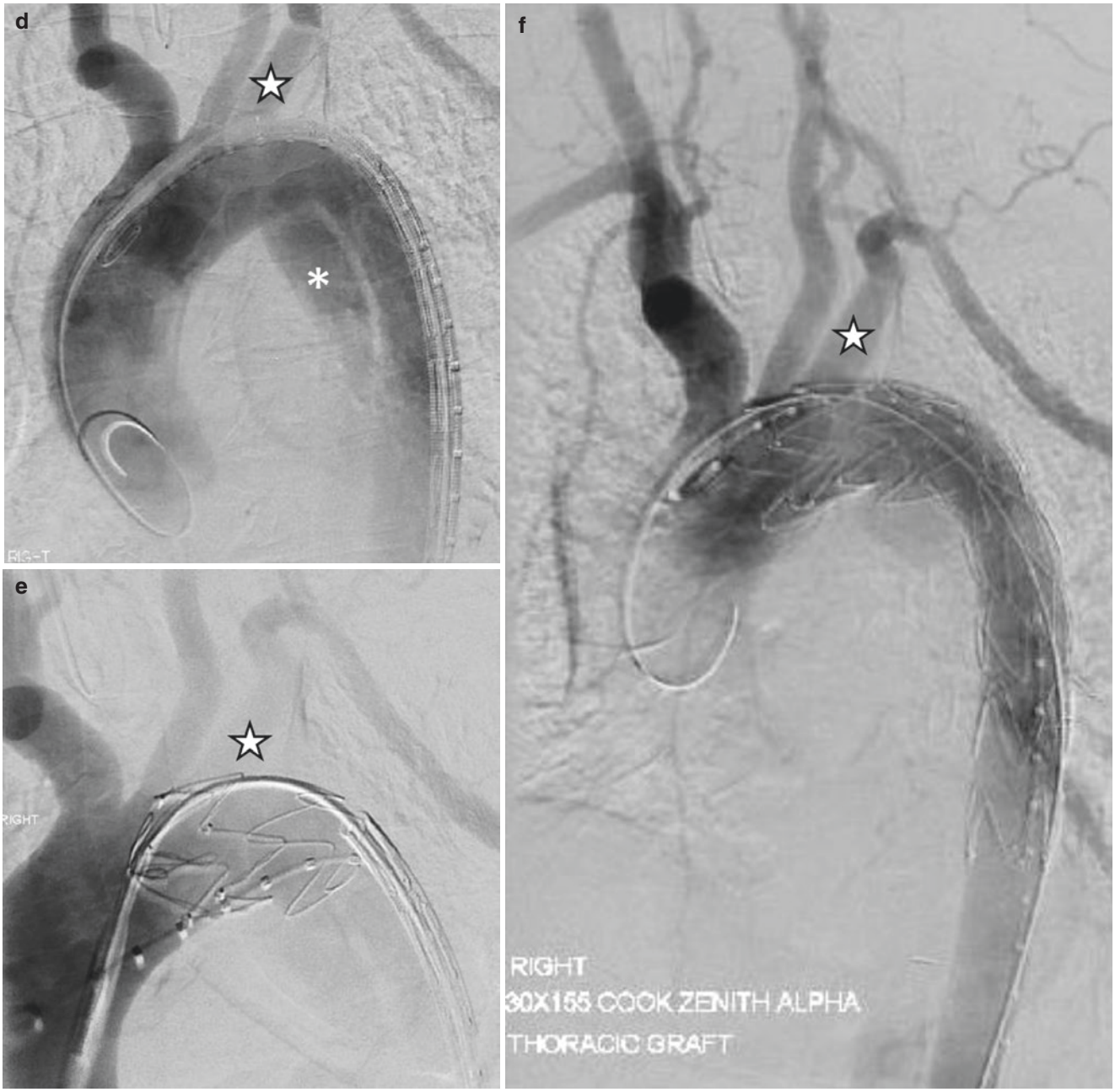

Fig. 21.2 (continued)

When treating dissections, there must be >20 mm of landing zone proximal to the entry tear, and the proximal extent of the landing zone must not be dissected.

The graft is constructed of Dacron graft attached to a series of sinusoidal-shaped, nitinol springs. There is no stiff longitudinal bar, allowing for flexibility and kink resistance of the graft. The proximal graft consists of a partially uncovered eight-peak stent to assist in even distribution of the radial force at the proximal seal. The outer diameter crossing profile of the Medtronic Valiant is 24F and does not require a sheath for delivery.

The VALOR II (Evaluation of the Clinical Performance of the Valiant Thoracic Stent Graft System in the Treatment of Descending Thoracic Aneurysms of Degenerative Etiology in Subjects Who Are Candidates for Endovascular Repair) was a prospective, nonrandomized, pivotal trial enrolling 160 patients in 24 US sites between December 2006 and September 2009. The 30-day and 12-month data

was reported in 2012 [27]. Primary success with stent graft deployment was achieved in 154 patients (96.3%). Perioperative mortality at 30 days was 3.1%. Aneurysm-related mortality was 4.0% at 12 months. Stent graft migration was 2.9%, and rate of endoleak was 13.0% at 12 months. Through 12 months, there were no ruptures, conversions to open surgery, secondary procedures due to endoleak >30 days, or loss of stent graft patency [27].

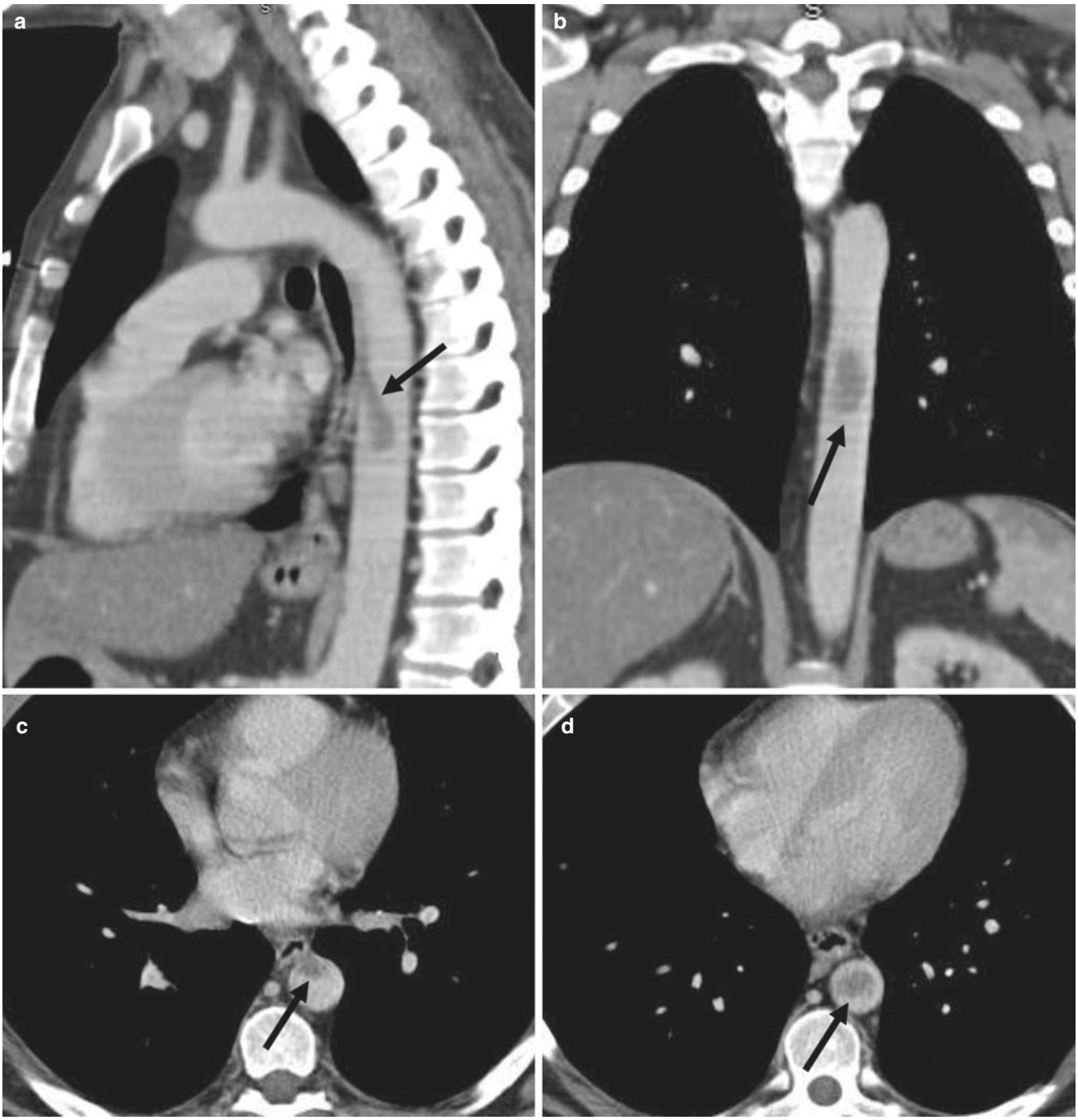

Fig. 21.3 Sagittal (**a**), coronal (**b**), and axial (**c**, **d**) contrast-enhanced CT images demonstrating a mobile thrombus (arrow) of the mid-descending thoracic aorta. DSA (**e**) and native (**f**) images of the descending thoracic aorta after deployment of the Gore Conformable TAG endograft covering the mobile thrombus

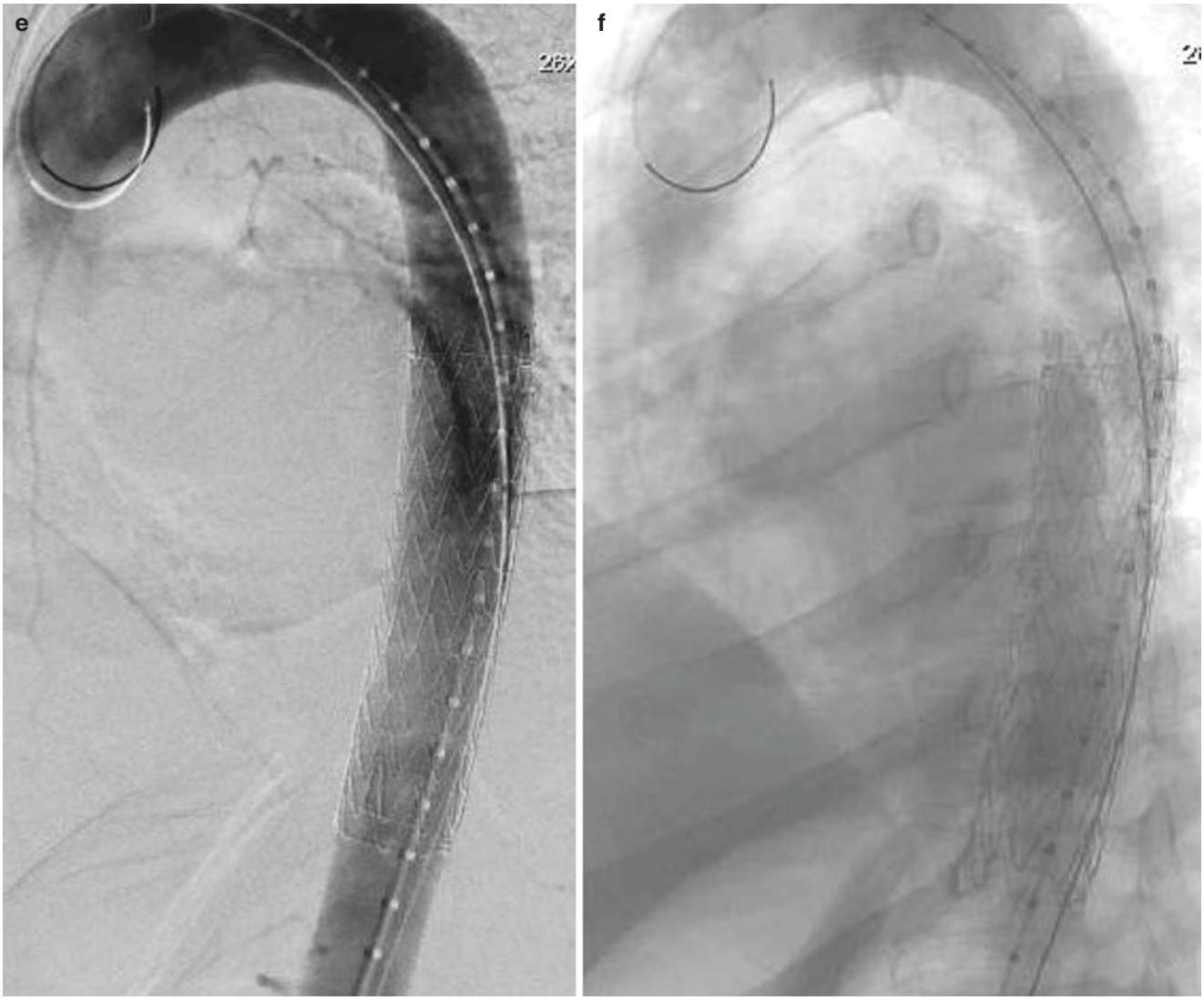

Fig. 21.3 (continued)

Preprocedural Considerations

Access

The most frequently encountered complication during thoracic stent graft trials has been access-related complications. Iliac artery morphology is essential to delivering the device percutaneously into the aorta. Factors important to the successful delivery of the stent without damage to the iliac artery include arterial tortuosity, intraluminal diameter, and calcifications [28, 29]. The issue of iliac diameter becomes particularly important in female patients, who have significantly smaller iliac arteries than men and more frequently require an iliac conduit for access [30]. Iliac artery injuries are more commonly seen in TEVAR than EVAR due to the larger delivery systems and higher percentage of women treated [31].

No absolute cut-offs or specific predictors for tortuosity, calcification, or diminished caliber exist; however, several authors have evaluated these parameters in reviews of their iliac rupture experience during endograft placement. Fernandez et al. reported a series of 369 EVARs and 67 TEVARs with 18 ruptured iliac arteries in 17 patients [32]. Patients with rupture in this series had greater calcification of the common iliac artery (66% vs. 26.5%), greater aortoiliac angulation (45° vs. 32°), and smaller external iliac caliber (8.0 vs. 8.9 mm). All ruptures occurred with the use of a delivery system of 20 French or greater [32].

Importantly, patients with intraprocedure iliac rupture have longer length of stay postprocedure and a higher procedure-related mortality. One study reported a procedure-related mortality of 11.8% in patients who sustained an iliac rupture compared to 9.8% in patients who

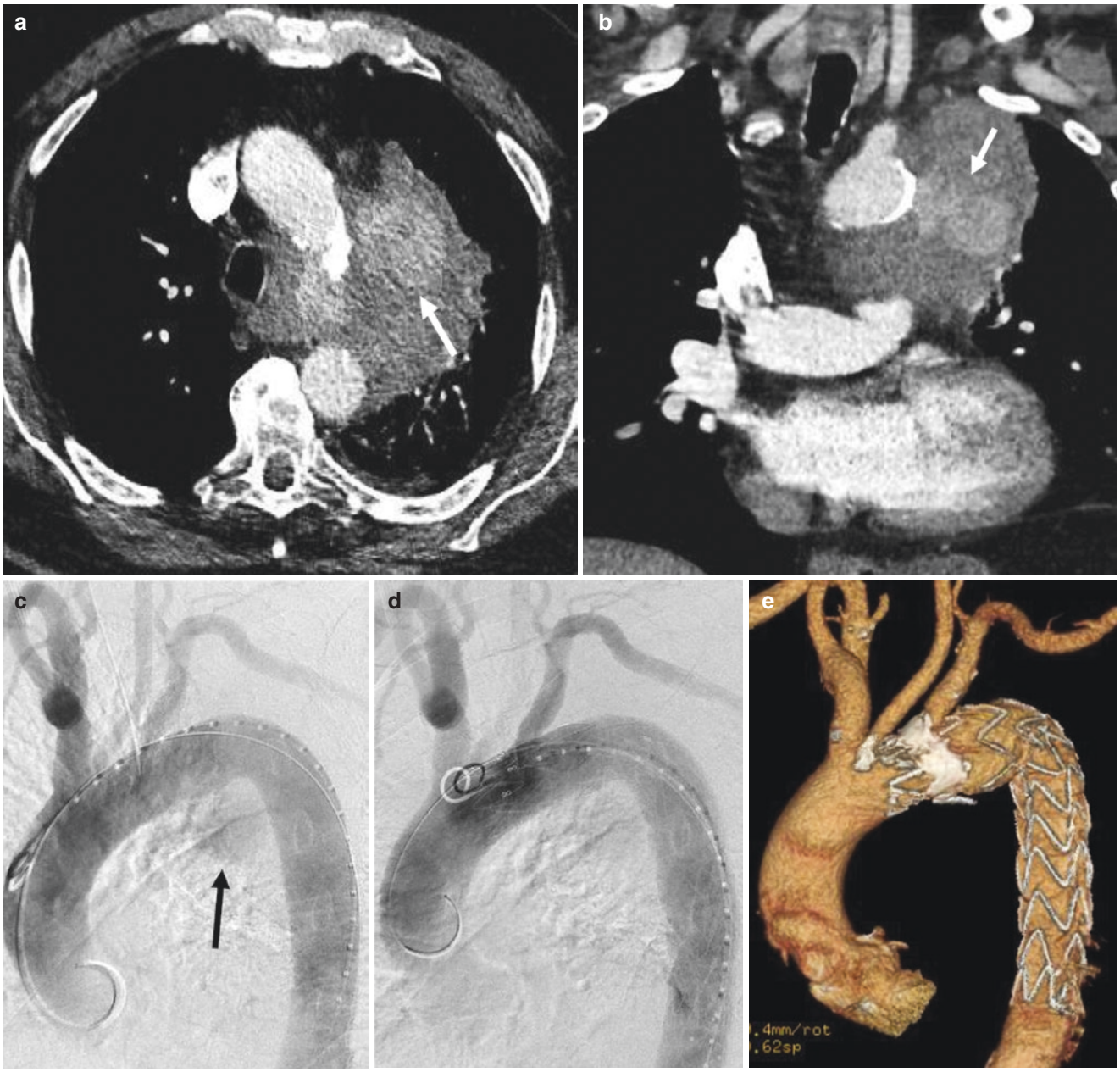

Fig. 21.4 A 71-year-old male patient presenting with chest pain and shortness of breath. Axial (**a**) and coronal (**b**) contrast-enhanced CT images of the thoracic aorta demonstrating a multilobed pseudoaneurysm (arrow) of the proximal descending aorta surrounded by the left upper lobe mass/infiltrate. DSA (**c**) of the thoracic aorta demonstrating contrast filling the pseudoaneurysm (arrow). DSA (**d**) immediately following the deployment of a Medtronic Valiant stent graft and a subsequent volume-rendered CT image (**e**) of the thoracic aorta demonstrating exclusion of the pseudoaneurysm

did not sustain an iliac rupture [32]. No intraprocedure deaths were reported [32].

Conversion to an open aortic and iliac repair has been associated with mortality rates as high as 22% [32, 33]. For this reason, endovascular iliac repair is preferred when feasible. Availability of the appropriate covered stents for iliac repair is an important preparatory step in endovascular aortic repair.

Identification of Landing Zones

The Society for Vascular Surgery published reporting standards for TEVAR, in which it identified 11 landing zones for management of aortic disease (Fig. 21.5) [34]. Using this standardization assists in evaluating the complexity of a procedure as well as the length of aorta needed to be covered.

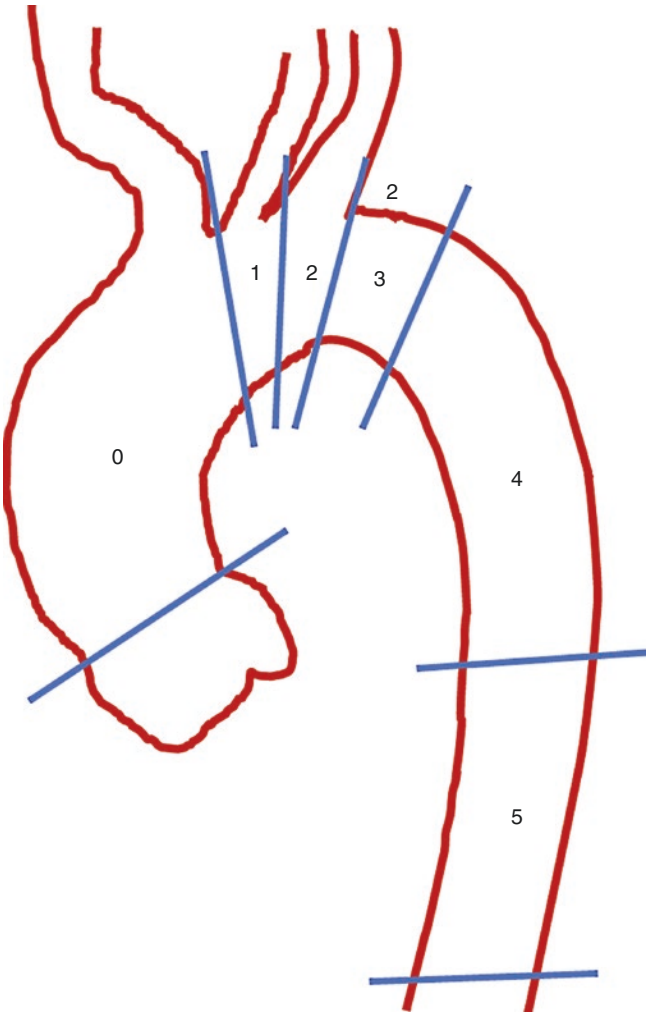

Fig. 21.5 Landing zones of the thoracic aorta. Zone 0: Proximal to innominate artery. Zone 1: Proximal to the left common carotid artery. Zone 2: Proximal to the origin of the left subclavian artery. Zone 3: The proximal descending thoracic aorta (<2 cm from the left SCA). Zone 4: Two centimeter distal to the SCA and extends to the proximal half of the descending thoracic aorta (approximately T6). Zone 5: Distal half of the thoracic aorta to celiac artery

Importantly, not all aortic pathology should be treated the same. While a device's recommended seal zone is 2–3 cm is adequate for some aortic pathology, a longer seal zone may be preferable, for example, when the graft would otherwise end in a particularly angulated segment of aorta or in the case of an atherosclerotic aneurysm. While a segment of aorta immediately abutting the aneurysm may appear normal, it is usually involved in the same degenerative process as the aneurysm itself. Later degeneration of the landing zone aorta can lead to stent graft failure. However, the desire to cover more aorta needs to be balanced with the risk of spinal cord ischemia with excessive coverage.

Device Sizing

Accurate measurements of the aortic diameter and length are imperative for appropriate device sizing. This is facilitated by a high-quality CTA with multiplanar reformats but may require additional reconstructions on a 3D workstation for precise measurements. Sobocinski et al. compared outcomes of patients who underwent endograft placement based on measurements from axial images versus those measured using a 3D workstation with multiplanar reformats and centerline analysis. After a 2-year follow-up period, the type 1 endoleak rate for grafts sized with axial images was 8.7% and 1.4% ($p = 0.004$) for grafts sized with 3D workstation assistance [35].

While each manufacturer has specific guidelines, in general, a stent graft should be oversized by approximately 20%. Too little oversizing can result in a type I endoleak and/or migration of the endograft from its intended location. Too much oversizing can result in graft infolding.

Spinal Cord Ischemia

Endovascular repair of descending thoracic aortic pathologies has grown primarily due to lower rates in periprocedural major complications including spinal cord ischemia (SCI) [36]. However, SCI rates still range between 2% and 7% for TEVAR [36, 37]. Risk factors for SCI after TEVAR are multifactorial and include length of aortic coverage, prior abdominal aortic aneurysm repair, hypotension, iliac artery injury, renal failure, and left subclavian artery coverage [38].

There are several important aspects of spinal perfusion unique to the endovascular repair of the aorta not seen in open surgery. First, there is permanent loss of intercostal perfusion as they are not reimplanted as in open surgical repair. Second, while intraprocedural hemodynamic changes and prolonged hypotension are less severe during endovascular repair, low blood pressure may be beneficial in precise device landing in difficult anatomy [39]. Finally, guidewire and catheter manipulation increases the risk of embolic insult during endovascular thoracic repair.

Preoperative placement of a lumbar cerebrospinal fluid (CSF) drain is standard in open thoracic aortic repair; however, their use is less well defined in the setting of TEVAR [40]. Current guidelines from multiple societies advocate drainage in the case of long-segment descending thoracic aortic coverage or in patients with prior abdominal aortic repair [41]. This data is based on open surgical experience, with little available data demonstrating a reduction in SCI in patients after TEVAR [40]. As a result, institutions vary greatly in the implementation of these recommendations.

While the potential benefit of drain placement can be huge, the placement of these drains is not free of complications. Subdural hematomas occur in approximately 3.5% of patients after thoracic aortic aneurysm repair with CSF drainage with associated mortality up to 67% [42]. Other complications include spinal headache, bleeding, CSF leak, meningitis, intracranial hemorrhage, nerve injury, and epidural hematoma [40]. In patients at low risk for SCI, the placement of a drain may outweigh the risk of drain placement, as only 1 in 300 (0.3%) patients without a drain sustain permanent SCI [40].

Importantly, SCI can present immediately or in a delayed fashion. While some patients have symptoms at the time of device implantation, one third of patients will have onset of symptoms hours, days, weeks, or months later [43]. Evaluation of 67 consecutive patients who underwent endovascular repair of descending thoracic aortic lesions reported 5 (7.5%) patients who developed SCI. Three (60%) of these patients presented with delayed symptoms [44]. It is postulated that delayed symptoms may be due to thrombosis of a spinal cord artery or compromise of a marginal existing blood supply [45].

Left Subclavian Artery Coverage

The left subclavian artery (LSA) is typically the most distal of the arch vessels. It gives rise to the left thyrocervical trunk, left internal mammary artery, and the left vertebral artery. Occlusion of the proximal LSA will result in reversal of flow in the left vertebral artery which becomes the dominant blood supply to the subclavian artery. The posterior cerebral circulation then relies on an intact circle of Willis. Complications following acute occlusion of the LSA include ischemia of the left upper extremity, stroke, spinal cord ischemia, endoleak, and myocardial ischemia. A meta-analysis of 51 studies found the risk of arm ischemia to be 6%, spinal cord ischemia 4%, vertebrobasilar ischemia 2%, anterior circulation stroke 5%, and death 6% when the LSA is covered during TEVAR [46].

Upper Extremity Ischemia

The physical manifestations of acute left subclavian artery occlusion during TEVAR range from asymptomatic diminution of the left arm blood pressure to left upper extremity rest pain [47]. All patients undergoing LSA coverage should be instructed to have blood pressures taken in the right arm as the left arm will provide falsely low readings. The magnitude of this pressure reduction does not, however, correlate with the development of symptoms [48].

When patients do present with symptoms, rest pain is rare. More commonly, patients may note a cool sensation of the left hand, temperature sensitivity, or exercise-induced claudication [47]. A meta-analysis of 20 studies found 51 of 498 patients (10%) developed symptoms of upper extremity ischemia [49]. Only 20 (4%) patients required subsequent revascularization due to the severity of their symptoms [49].

Klocker et al. evaluated left arm function and quality of life after TEVAR with and without LSA coverage in 138 patients. Seventy-three (52.9%) patients had LSA coverage and a single patient required left carotid to subclavian bypass postprocedure for ischemic symptoms with subsequent resolution of symptoms. All patients were evaluated based on the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire and the 12-item Short Form Health Survey. Patients were followed up for a mean of 4.1 years (±3.7). Patients with and without LSA coverage had similar Physical Component Summary and Mental Component Summary health scores (12-Item Short Form Health Survey) as well as DASH scores [50].

Gombert et al. assessed upper extremity pain and dysfunction using the DASH questionnaire in a cohort of 46 patients suffering blunt aortic injury treated with TEVAR. The results of the DASH questionnaire were available for 30 of the 46 patients (65.2%), of which 22 (73.3%) received LSA coverage at the time of their procedure. The patients responded a mean of 5.1 years (range 0.5–14.9) after their trauma. Comparison of the groups with and without LSA coverage revealed no significant difference (two-sided p-value: 0.3513) [51].

An anomalous right subclavian artery, where the right subclavian artery arises distal to the left subclavian artery, is the most common aortic arch anatomic variation occurring in up to 2% of the population [52]. Published experience with anomalous right subclavian artery coverage is limited but demonstrates similar sequelae as coverage of the left subclavian artery [47, 53].

Stroke

Stroke may result from several mechanisms during endovascular repair of the thoracic aorta. Most are the result of aortic wall atheroemboli dislodged during wire and device manipulation during the procedure [54]. Alternatively, stroke can occur in the setting of a low flow state such as hypotension. There is debate on whether ischemia in the left vertebral artery distribution occurs after coverage of the left subclavian artery (LSA) during TEVAR as much of the available data is derived from single institutional series [55].

A meta-analysis of 25 series directly comparing coverage of the LSA versus more distal deployment found an overall stroke rate of 7.4% (87 of 1177) following LSA coverage during TEVAR. The overall stroke rate for stent grafts with zone 3 or 4 deployment was 4.0% (107 of 2661, $p < 0.0001$) [55].

An evaluation of 27 series providing data on LSA revascularization prior to coverage of the LSA found an overall

stroke rate for TEVAR following LSA coverage of 4.8% (59 of 1237). When the LSA was covered without revascularization, the stroke rate was 5.6% (46 of 824) compared to 3.1% (13 of 413, $p = 0.0657$) who underwent revascularization with carotid-subclavian bypass or subclavian-carotid transposition prior to LSA coverage [55]. Adding to this, a review of 606 patients in the European Collaborators on Stent/Graft Techniques for Aortic Aneurysm Repair (EUROSTAR) registry found coverage of the LSA without revascularization resulted in a significantly higher incidence of spinal cord ischemia or stroke when compared to patients undergoing LSA revascularization prior to TEVAR (8.4% vs. 0%; $p = 0.049$) [56].

Several authors have demonstrated that coverage of the LSA is an independent risk factor for posterior stroke. Rizvi et al. presented a meta-analysis demonstrating LSA coverage was associated with increased risk for vertebrobasilar ischemia with an odds ratio of 10.8 [46]. Similarly, Ullery et al. presented a series of 530 patients where LSA coverage was an independent risk factor for posterior stroke with an odds ratio of 6.11 [57].

As a result of these reports, the Society of Vascular Surgery now recommends preprocedural LSA revascularization prior to all elective TEVAR cases despite the low-quality evidence available (GRADE 2, level C) and consideration for preprocedural LSA revascularization in the setting of acute aortic syndromes [58].

Importantly, not all strokes seen after LSA coverage are posterior strokes. A meta-analysis of 12 series describing the location of strokes after LSA coverage reported 42 strokes in 543 patients (7.7%). Eleven of the 42 strokes (26.2%) were posterior strokes. The remaining 31 strokes (73.8%) were anterior embolic or diffuse embolic strokes [55]. As previously mentioned, it is postulated that wire and graft manipulation in the aortic arch results in embolic stroke by dislodging debris [54], rather than coverage of the LSA itself.

Spinal Cord Ischemia

Coverage of the LSA increases the risk of spinal cord ischemia. Please refer to the above discussion of spinal cord ischemia for a detailed discussion.

Endoleak

Coverage of the LSA with an endograft often acts as a "flush occlusion" of the artery at its origin. The LSA will frequently thrombose to its first branch, typically the vertebral artery, by 1 month [47]. The LSA can however be a source of endoleak. This is generally seen in cases where the LSA is involved in the aortic lesion or where a left carotid-subclavian artery bypass is present without proximal occlusion of the LSA [47]. In a retrospective review of 200 patients undergoing TEVAR, the presence of a carotid-subclavian artery bypass graft performed in cases of LSA coverage was associated with the presence of an endoleak ($p = 0.0001$) [59].

Myocardial Ischemia

An important consideration for patients undergoing TEVAR is prior surgical history. The left internal mammary artery is a frequent autogenous arterial conduit used to the left anterior descending during coronary artery bypass surgery. Subsequent acute occlusion of the LSA can result in a coronary steal like entity and life-threatening myocardial ischemia [47].

Celiac Artery

In some instances, the distal landing zone is inadequate without coverage of the celiac artery. In a patient with adequate collateral circulation between the celiac axis and the superior mesenteric artery (SMA), the celiac artery can be covered safely during TEVAR [60, 61]. Adequate collateral circulation should be assessed with formal angiogram of the celiac and SMA. In patients without adequate collateral circulation, either open revascularization or endovascular placement of a periscope graft is a means of extending the distal seal zone while preserving visceral perfusion [62].

Intraprocedural Considerations

Intravascular Ultrasound

Intravascular ultrasound (IVUS) is an imaging tool which provides real-time intraluminal assessment and can allow for more accurate diameter measurements. This is a particularly useful tool in the setting of blunt aortic injury (BAI). As a whole, patients presenting with BAI are young with nonatherosclerotic, compliant aortas. As a result, the aortic diameter can vary greatly during the cardiac cycle [63]. Additionally, the patients often undergo marked hemodynamic changes during resuscitation which can also impact aortic diameter [64].

Shi et al. reviewed 41 patients undergoing TEVAR for BAI. IVUS was used in 13 cases, and as a result of the IVUS measurements, the implanted graft was changed in 6. Of note, the greatest difference between CT and IVUS measurements was noted in the proximal aorta in cases where the LSA was covered [65].

IVUS has additional utility in the treatment of aortic dissections. Koschyk et al. evaluated the utility of IVUS in 26 patients with Stanford type B dissections. They found that IVUS differentiate between true and false lumen intraprocedure as well as the location of the entry tear. This proved

helpful in navigating wire positioning and ensuring appropriate stent placement in the aorta [66].

Intraoperative Anticoagulation

A concern in blunt thoracic aortic injury or cases of rupture is the timing, if any, for anticoagulation. In routine TEVAR, systemic anticoagulation with heparin is standard once the CFA is successfully accessed either percutaneously or via surgical exposure. Anticoagulation is important to prevent lower extremity thrombosis given the large caliber delivery systems required. Additionally, full anticoagulation minimizes the incidence of thromboembolic events with wire and catheter manipulation across the aortic arch.

It is not uncommon for patients presenting with BAI to have multiple injuries including closed-head injuries. Full systemic anticoagulation in these cases can lead to devastating hemorrhagic complications. In these settings, discussion with other consulting services, particularly neurosurgery, is critical for best patient outcome. Generally, when anticoagulation may still be used, a lower dose may be considered. Some centers have reported successful outcomes of TEVAR for BAI without the use of systemic heparinization [67].

Deployment

Once access is obtained, aortography is performed in the left anterior oblique projection. This allows for identification of the aortic branch vessels and landmarks for appropriate endograft deployment. Additionally, it can serve as a check to confirm the estimated length of endograft needed.

Each endograft has specific directions for accurate deployment. These should be reviewed carefully prior to any procedure. There are, however, a few general "pearls" for successful endograft deployment. In patients where more than one endograft will need to be used, deployment of the smaller diameter graft should precede the larger graft. This will decrease the risk of subsequent type III endoleak. Temporary reduction of the mean arterial pressure during deployment can reduce the windsock effect. This is particularly important for endografts such as the Medtronic Valiant, where the graft opens one stent at a time from proximal to distal. Maintaining forward pressure on the graft and avoiding excessively slow deployment can also assist with target landing.

Completion angiogram is performed to assess placement of the endograft and evaluate for endoleaks. Type I or type III endoleaks should be addressed during the initial procedure with additional ballooning or extension with an additional endograft. Type II endoleaks usually result from flow from the intercostal arteries and can often be managed conservatively with monitoring on follow-up imaging. Type IV endoleaks usually resolve once the procedural anticoagulation has been reversed.

Postprocedure

Immediately postprocedure, patients are sent to the ICU for close monitoring of their hemodynamics and neurologic status. Most patients can be transferred to the floor within 2–3 days of the procedure and discharged home within a week.

Immediate postprocedure imaging is generally not needed unless there is a technical concern during the procedure. Scheduled follow-up imaging is recommended at 1 month, 6 months, and annually with CTA. Ideally, the CT should have a noncontrast, arterial, and delayed phase to appropriately assess for endoleak.

Clinical Outcome

Randomized comparison of TEVAR versus open surgical repair of the thoracic aorta has never been done. While a large body of literature exists on both procedures, the patients treated with TEVAR are often higher risk than those undergoing surgery, making direct comparison difficult [36, 68].

TEVAR has excellent technical success rate, quoted up to 98% [36]. Early experience with TEVAR in high-surgical-risk individuals reported 30-day mortality of 9–12% [69, 70]. More recent data report 30-day mortality significantly lower at 2% [24]. Mid-term outcomes demonstrate an advantage for TEVAR in aneurysm-related survival with a reported 95% at 1 year versus 89% for open repair [24].

Conclusion

TEVAR has become the preferred approach to thoracic aortic pathology in patients with appropriate anatomy. Careful preprocedural planning including appropriate diagnostic imaging, proper device sizing, appropriate access planning, and evaluation for appropriate landing zones is key to a technically successful procedure. Patient management with preprocedural consideration of potential complications including spinal cord ischemia and stroke and early recognition of these complications are key to the best patient outcomes. Endografts continue to improve, expanding the patient population eligible for this treatment modality.

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Aortocaval Fistula

22

Kristine Clodfelter Orion and James H. Black III

Introduction

Aortocaval fistulas are a life-threatening and difficult problem to address surgically. Description of the first major abdominal AVF was reported by Syme in 1831. Although aortocaval fistulas are rarely encountered during the career of a vascular surgeon, there are several viable management strategies. While the most common etiology may be attributed to penetrating trauma or iatrogenic injury, this chapter will focus on the aortocaval fistulas in the setting of aortic aneurysmal disease.

Epidemiology

Aortocaval fistulas occur in <1% of all abdominal or iliac aneurysms. However, among ruptured abdominal aortic aneurysms, aortocaval fistulas are appreciated at a higher incidence of 2–7%. To gender, they are more common in men with an average age of 65 years.

Historically, the mortality of this disease ranged from 16% to 66% [1, 2]. The higher estimates may have been driven by operative intervention and postsurgical cares because until the turn of the last century, most aortocaval fistulas were repaired with open surgery and limited appreciation of the cardiac effects. Improved outcomes of both open and endovascular techniques will be reviewed.

Anatomy

An aortocaval fistula is an unnatural connection between the aorta and, most often, the infrarenal vena cava. Fistulization can also occur between the aorta and the iliac veins, the iliac veins and iliac arteries, and most uncommonly the aorta and renal veins (Fig. 22.1). This phenomenon is a result of spontaneous erosion of an expanding arterial aneurysm into the neighboring venous structures. The slow necrosis of the aortic wall involves adventitial inflammation and resultant adherence to adjacent veins. Calcification of the arterial wall may not be protective from fistula development.

Physiology

Multiple studies have evaluated arteriovenous fistula physiology [3, 4] demonstrating a relationship between flow and size of the fistula.

If the cross-sectional area of the fistula is less than 1.5 times the diameter of the artery, flow in the proximal artery increases fivefold, and the direction of arterial flow distal to the fistula is maintained. As the area of the connection approaches three times that of the artery diameter, the proximal arterial flow can increase by a factor of 8, whereas the distal arterial flow can be diminished or reversed. In the setting of an aortocaval fistula, compensatory increases in cardiac output are required to maintain blood pressure.

Pathophysiology

Physiological changes to the body are many, and understanding them is essential to prompt diagnosis and selection of therapy. The initial effect of a central AVF is the decrease in peripheral vascular resistance and a marked increase in cardiac output. Increased cardiac output is both a result of increased venous return and an attempt to maintain peripheral perfusion via fluid retention by the kidneys; significant

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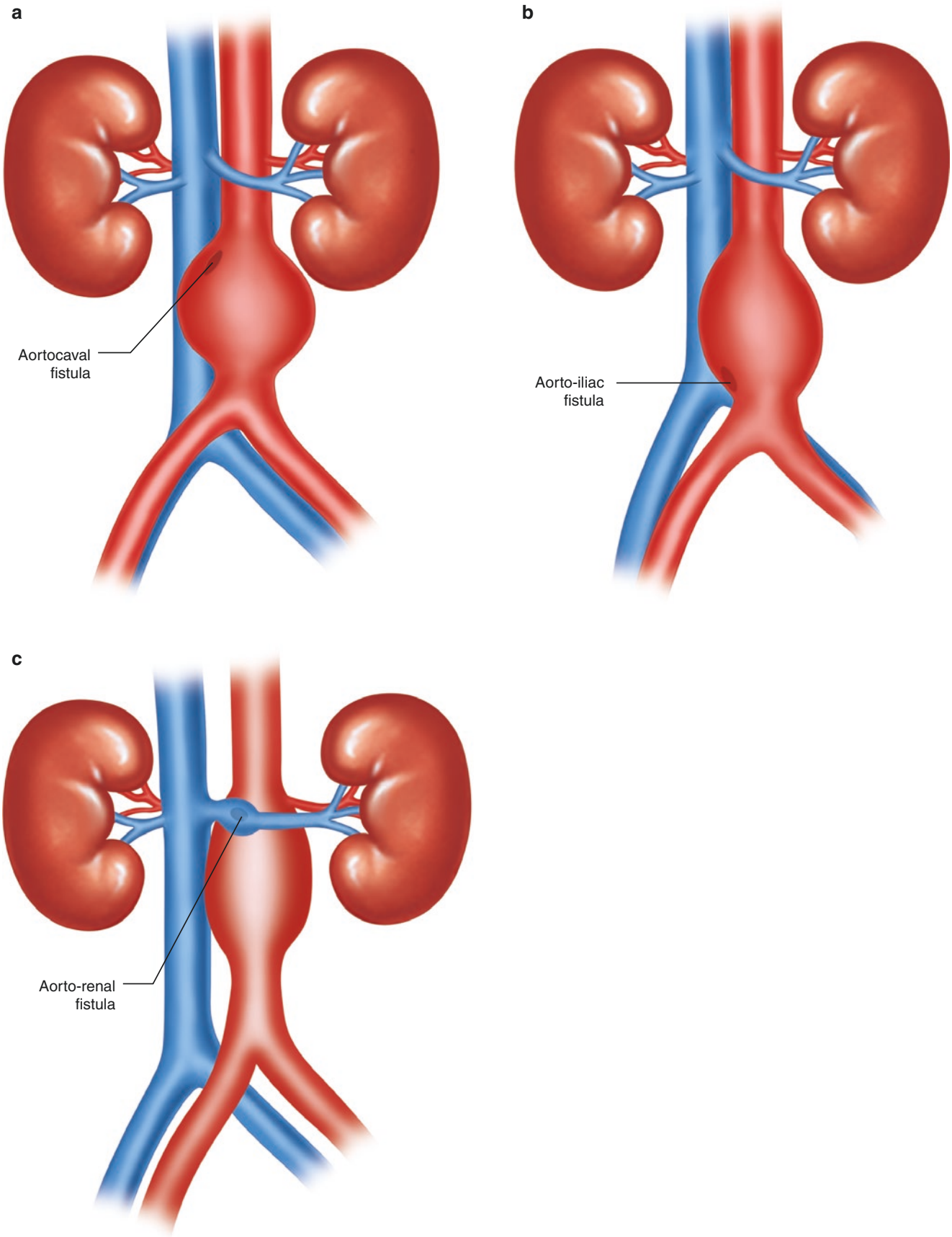

Fig. 22.1 (**a**) Aortocaval fistula, (**b**) aortoiliac fistula, (**c**) aortorenal fistula

weight gain and peripheral edema may be mistaken for diastolic heart failure. The net effect of increased cardiac output is accompanied by significant increases in total blood volume as the venous system pressurizes and venous dilation produce a large increase in capacitance. As the right heart develops high-output failure, pulmonary hypertension may also develop. In end-stage right heart failure from an AVF, rapid decrease in the fistula flow from occlusion may not be tolerated without hemodynamic collapse.

Diminished renal function has been described and thought to be related to both impaired plasma flow and renal venous hypertension [5, 6]. Finally, there is increased risk of pulmonary embolism, both from the deep venous system and atheromatous mural thrombus routinely residing within the aortic aneurysm.

Patient Presentation

Unfortunately, because of the elusiveness of the disease, there is frequently a significant delay in diagnosis. However, because of the mass introduction of computed tomography imaging for abdominal pain, surgeons can now make a preoperative diagnosis more commonly.

Patients may present in acute fashion or with a chronically evolving picture over time. An acute rupture of an abdominal aortic aneurysm typically causes unrelenting abdominal or back pain. Hemorrhagic shock may or may not be present. If the patient ruptures into the vena cava causing an aortocaval fistula, the classic symptoms and physical exam have been described: pulsatile abdominal mass, abdominal machine-like bruit, femoral thrill, lower body or leg edema, and heart failure. Only a minority of patients will present with a full spectrum of symptoms; however, most will demonstrate at least one. Variable presentation can occur in the chronic patient with high-output cardiac failure accompanied by increased jugular pressure, dyspnea, pulmonary edema, and a widened pulse pressure. Long-standing venous hypertension can cause varicose veins, hematuria, and even rectal bleeding.

Workup

Timely diagnosis and surgery before the onset of shock markedly increases survival. Traditionally, abdominal ultrasound is useful to diagnosis of both abdominal aortic aneurysm and can readily demonstrate an aortocaval fistula. Computed tomographic angiography (CTA) is now the primary imaging modality because of the availability and ease, and three-dimensional imaging may allow the practitioner to diagnose the location and diameter size of the AVF (Fig. 22.2). Timing of contrast can limit the diagnosis of smaller fistulas on CTA as reflux of contrast proximally and distally into the vein limits its exact visualization. Magnetic resonance imaging (MRI) provides detailed views and may give a sense of the amount of local inflammation, which can be helpful when planning an open repair, especially if infection is thought to be present. Invasive angiography, albeit a historical gold standard, is rarely needed to demonstrate the presence an aortocaval fistula given CT and MRI omnipresence.

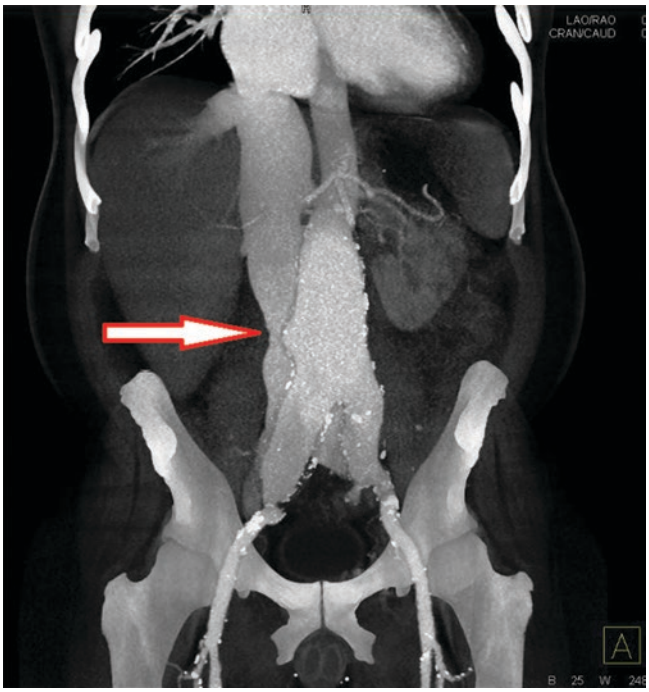

Fig. 22.2 Aortocaval fistula on CTA. (From Orion et al. [7]. Reprinted with permission from Elsevier)

Preoperative Care

Because of the risk of high-output cardiac failure, aortocaval fistulas should be repaired. Fastidious preoperative evaluation of cardiac function by echocardiography is vital. Unless there is prohibitive coronary artery disease, patients should be evaluated by a surgeon for operative repair. In many instances, correction of the AVF may normalize the preload and afterload imbalance of high-output failure; thus, there is little role for coronary intervention. Angiotensin-converting enzyme inhibitors and diuretics should be used to manage volume overload and improve cardiac contractility.

Surgical and Endovascular Care

The largest contemporary review of aortocaval fistulas evaluated both open and endovascular repairs, their outcomes, and complications [7].

Open Repair

In 1955, Dr. Cooley performed the first reported successful open repair of an aortocaval fistula. Forty years later, Dr. Wholey described the technique of aortic exclusion when he unexpectedly diagnosed an aortocaval fistula intraoperatively.

Patients are under general anesthesia and require invasive arterial blood pressure monitoring as well as adequate central venous access. Most recommend an intraoperative transesophageal echocardiogram and a pulmonary catheter intraoperatively (Fig. 22.3). These greatly assist the anesthesia team to monitor cardiac output as well as physiologic changes that occur upon closure of the fistula. The availability of an autotransfusion device, or cell-saver, is also critical for these cases.

The transperitoneal approach works best as this allows access to the vena cava; however, a thoracoabdominal incision is the safest approach if a supraceliac aortocaval fistula is suspected or extensive juxtarenal/pararenal AAA. More commonly, a generous midline incision is made in the traditional fashion for infrarenal abdominal aortic aneurysm repair. The aorta is exposed by placing the transverse colon cephalad and all small intestines to the patient's right upper quadrant. The ligament of Treitz is divided and left renal vein mobilized as needed. Proximal and distal control of the aorta and iliacs is compulsory; however, circumferential control and clamping of the cava should not be attempted as there is significant risk for injury of the very hypertrophied lumbar and renal veins. There is a palpable thrill in the cava which facilitates external assessment of the fistula location and can be manually compressed at the time of opening the aneurysm for control. After systemic heparinization, the aorta is clamped and the aneurysm opened. Evacuation of mural thrombus should be undertaken carefully as embolism, including both debris and air, can occur. If the aortocaval fistula was not preoperatively diagnosed, massive dark venous blood will be issued forth, and the location of the aortocaval fistula is promptly apparent. Manual compression with sponge sticks or finger is performed to stop the venous bleeding. The fistula is then repaired primarily from within the aneurysm sac with pledgeted mattresses of polypropylene suture (Fig. 22.4). Given the degeneration of the aortic wall and the IVC wall, no attempt should be made to surgically separate the two structures from the fistula site as the tissues will be too fragile to work with independently. It is infrequent that the vena cava needs a patch angioplasty even in large fistulas. In such cases, balloon control proximally or distally into the fistula can isolate the area needed for patch angioplasty. The abdominal aortic aneurysm is then replaced with a tube or bifurcated Dacron graft.

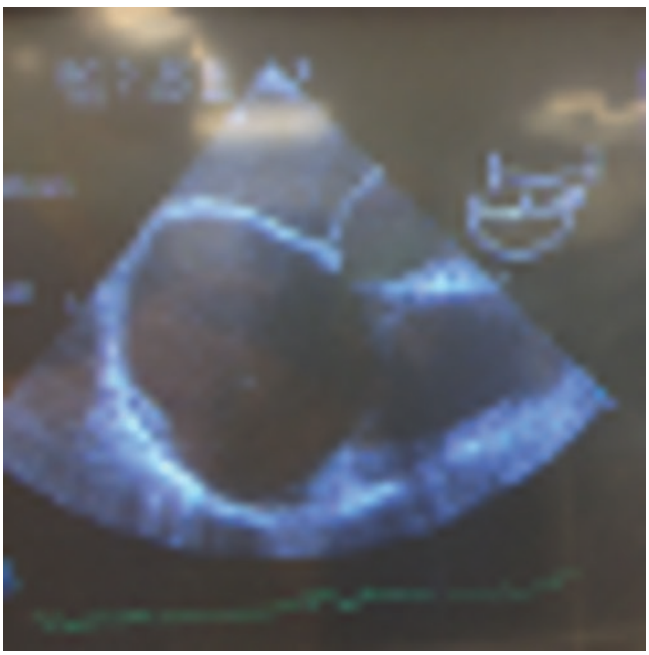

Fig. 22.3 Intraoperative transesophageal echo showing markedly dilated right atrium. (From Orion et al. [7]. Reprinted with permission from Elsevier)

Aortoiliac, iliac-iliac, or iliocaval fistulas are challenging because of close adherence among the vessels at the aortic bifurcation. Again, circumferential control may come at a fatal bleeding risk. These may do well with endovascular venous control (see section "Hybrid Approach"). In difficult cases, ligation of the aorta with extra-anatomical bypass is an option of last resort.

Open Repair: Outcomes

Although long-term patency rates for patients surviving surgery are excellent, postoperative complications are many. Renal failure, respiratory failure, bowel obstruction, acalculous cholecystitis, pseudomembranous colitis, wound infection, paralysis, and lower extremity ischemia are typical and are seen in frail patients whose preoperative heart failure is significant.

Historically, high rates of mortality were reported for open repair. There were many reasons for this, including massive and unexpected exsanguination upon opening the aortic aneurysm if preoperative diagnosis was not achieved. If there is a delay in diagnosis, the 30-day mortality markedly increases. Second, the concern for how to handle the overloaded right ventricle and pulmonary hypertension was far less manageable postoperatively. Today, critical care has vastly improved, and the issues of heart failure and resuscitation are commonly confronted issues in a surgical intensive care unit.

Thankfully, the pathophysiologic changes are quickly reversed upon closure of the arteriovenous fistula. In most patients, central venous pressure, pulmonary artery pressure, stroke volume, and cardiac output all decrease immediately. Given the low SVR of the periphery to facilitate perfusion distal to the AVF, many patients may require pressors in the

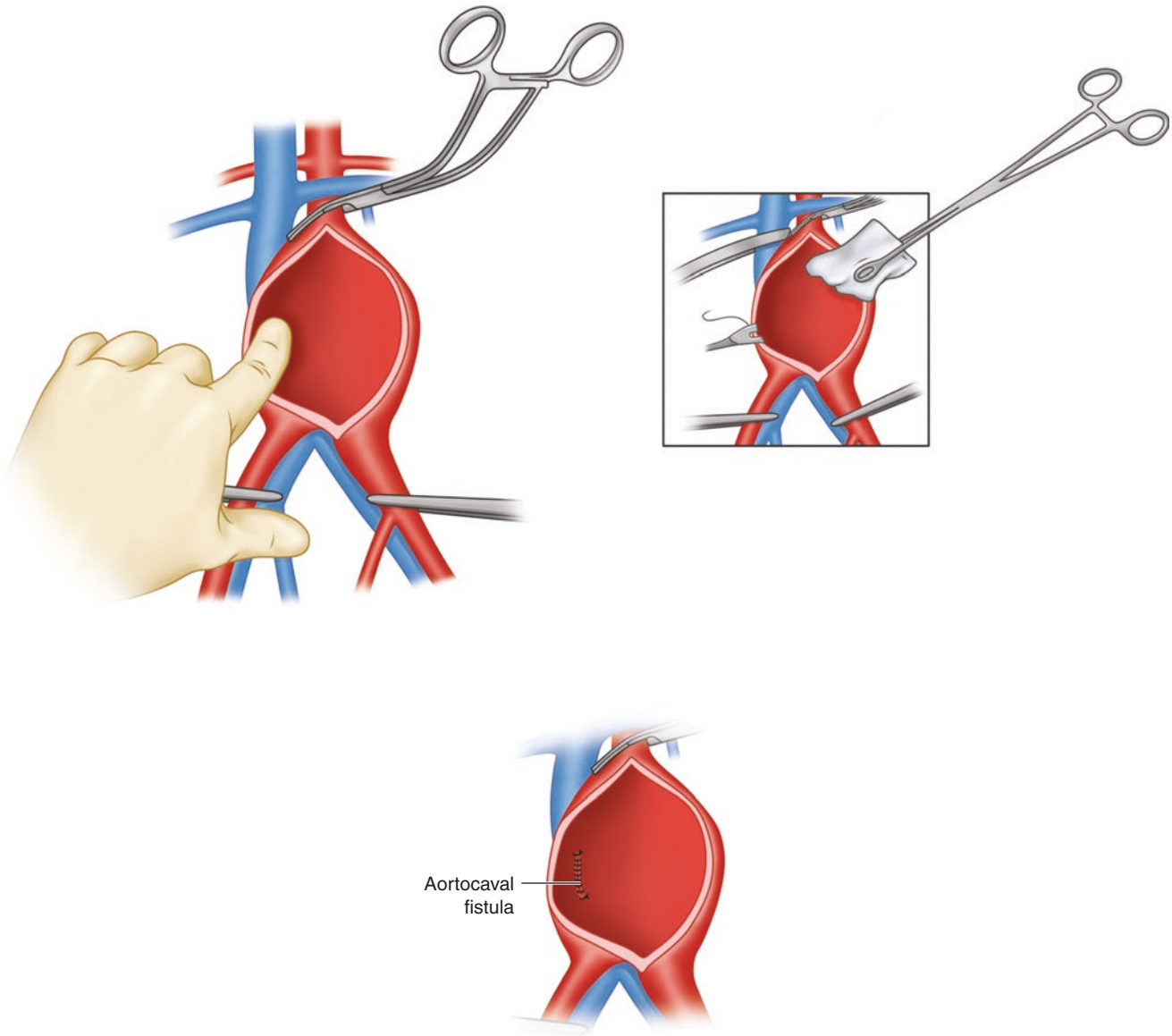

Fig. 22.4 Repair of aortocaval fistula from within the aneurysm sac

early postoperative period. Within 1–4 days, systemic vascular resistance increases and often may result in excessive hypertension. Therefore, it is paramount that there is continuous and clear communication between the surgical and anesthesia teams intraoperatively, as well as critical care specialists in the ICU.

Endovascular Repair

Since the advent of the endovascular era, many surgeons now look to this option first when faced with an aortocaval fistula. Endovascular repair negates the need for laparotomy, less blood loss, and perhaps less postoperative complications. Essentially, an appropriately sized aortic endograft is deployed within the aorta in the usual fashion for an abdominal aortic aneurysm. There may be an increased difficulty in opacification of the renal arteries if in close proximity to the aortocaval fistula. Stent graft and wire manipulation should be minimized if possible to avoid potential dislodgement of mural thrombus and pulmonary embolism. It is anticipated that after endovascular repair, cessation of the highly pressurized aortic inflow to the fistula will allow the concomitant aneurysm to seal.

Endovascular Repair: Outcomes

Discounting delay in diagnosis, 30-day mortality for the endovascular repair of aortocaval fistulas is <5%. The main challenge with this approach, however, remains endoleak. While early studies showed only a small or

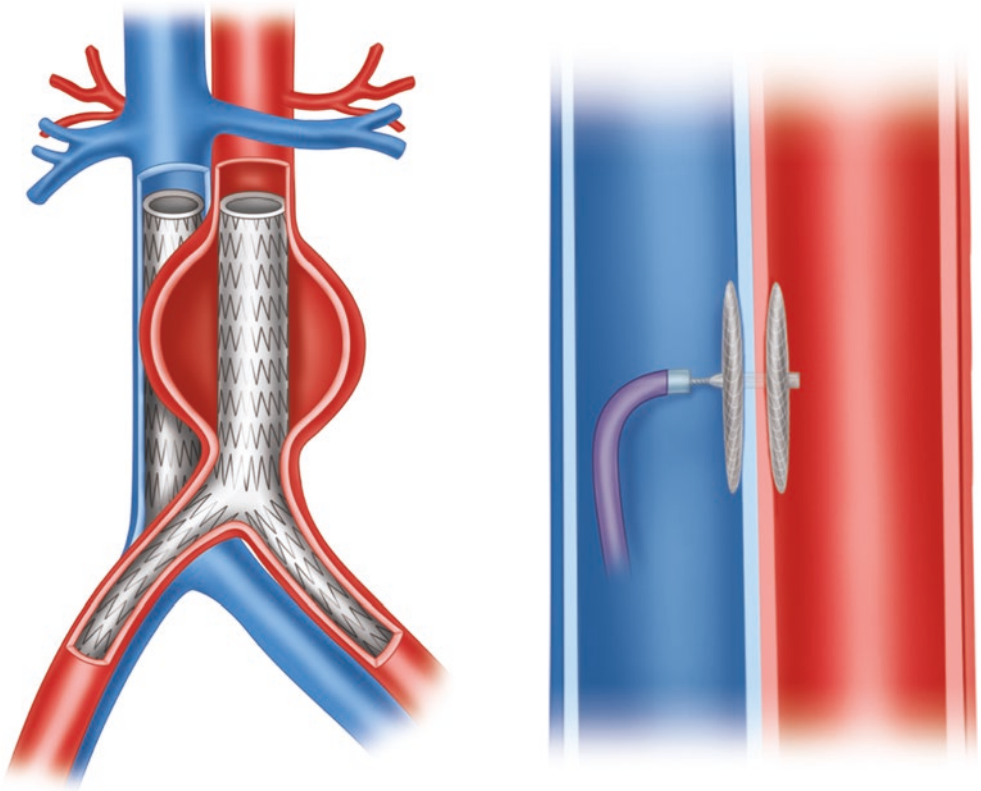

Fig. 22.5 Endograft stents within the aorta and Amplatzer™ plug within aortocaval fistula

moderate risk of endoleak [8, 9], a more contemporary analysis [7] showed a rate of 50%. Unlike the more benign type II endoleak, these continued endoleaks frequently lead to sac enlargement or the need for secondary intervention such as deployment of an Amplatzer™ occluder from the transfemoral venous approach (Fig. 22.5). To address the high incidence of endoleak, some surgeons have modified their endovascular approach in these patients. Placement of an intravenous stent graft in addition to the aortic stent graft has been described, but the risk of venous thromboembolism from the IVC stent graft is a significant worry. With sparse data that guide us on anticoagulation for such rare conditions, the question of anticoagulation is unsolved both in the acute postoperative period and in the long term.

Despite increased endoleaks, there seems to be certain clinical situations where endovascular repair is beneficial to open repair. Certainly, many surgeons believe that patients with a ruptured abdominal aortic aneurysm may do better with an endovascular approach despite the IMPROVE trial which did not show a significant reduction in 30-day mortality [10]. Furthermore, ruptured inflammatory aneurysms have a higher occurrence of aortocaval fistulas. Surgical dissection of an inflammatory aneurysm or retroperitoneal fibrosis is technically demanding with increased bleeding risk or injury to ureters. These particular patients may be best served with an endovascular repair with close attention to endoleaks.

Hybrid Approach

Today's surgeons have become more and more creative, now employing both their endovascular skills to assist them with definitive open repair. An occlusion balloon can be inserted from the femoral veins and inflated across the fistula at the time of opening the aneurysm sac to decrease blood loss. Alternatively, a covered stent graft can be deployed within the inferior vena cava prior to open repair. This approach was described in 2009 by Siepe et al. in a patient who presented with malperfusion and rapid deterioration. The aneurysm's juxtarenal anatomy excluded it from an additional aortic stent graft [11].

Conclusion

Aortocaval fistula is an uncommon aortic pathology. The ubiquitous nature of CT scans for diagnosis or evaluation have secured the diagnosis prior to surgery in most cases. It is incumbent for surgeons to communicate closely with anesthesia and critical care physicians to manage the conse-

quences of preoperative high-output cardiac failure and to monitor hemodynamics in the postoperative period. Endovascular and open surgery remain viable treatment strategies, but the effect of endoleak after endovascular repair may require secondary procedures to address aneurysm growth.

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Aortourinary Fistula: Ureter/Renal

23

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Introduction

Fistulous tracks occur rather frequently and primarily involve hollow organs. The active abdominal, genitourinary, and gynecologic surgeon will encounter an occasional enteric, urinary, or cutaneous fistula when performing difficult and extensive surgical resections or corrective surgery. The urinary fistula more commonly occurs after various surgical or therapeutic procedures. Usually, the fistula drains to the surface of the abdomen or pelvis, and it is annoying but not life-threatening. The abnormal drainage routes may involve the skin, the peritoneum, the retroperitoneum, the vagina, the intestine, and the vascular system. Various types of ureteral fistulas may occur with respect to the ureter.

Various Types of Ureteral Fistulas

I. Ureterocutaneous
II. Ureteral peritoneal/retroperitoneal
III. Ureteral vaginal
IV. Ureteral intestinal
V. Ureteral vascular

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Other urovascular fistula may include the renal pelvis and renal vein. Each of these fistulas require careful consideration and, in many instances, corrective surgery or diversion techniques. The risk to the patient varies according to the type and location of the fistula. Of particular interest is vascular to urinary tract (AUTF) fistulization, especially the aortoureteral (AUF) or aortorenal fistula (ARF), because of the difficulty in diagnosis and treatment with the potential life-threatening associated risks. In speaking with urologists from large urologic groups, they had not seen AUTF—demonstrating the rarity of the disease.

Signs and Symptoms

Even though aortourinary (AU) fistula ranges from uncommon to rare, the risk and complexity are appreciated by surgeons when consulting on the involved patient. Initially, the patient's symptoms may include a small amount of hematuria—even at first microscopic analysis. This may be associated with a fever and systemic symptoms. However, the initial bleeding symptom may also be massive and frightening at the first appearance of blood. When massive, the patient may present in a shocklike state and be critically ill [1]. The blood pressure may be normal, or the patient may be hypotensive on presentation. More commonly, the patient will have lower abdominal tenderness and discomfort. This is most frequent in the female—especially after gynecologic surgery. The initial bleeding episode may occur shortly after or as long as 25 years after the previous surgical intervention. There also may be a history of urine passing through the vagina. Morbidity may be minimal, with the mortality varying between 0% and 20% in this group of individuals.

Etiology

A fistula may develop de novo in the patient as a result of multiple primary disease entities. More commonly, these shunts will occur in the elderly individual who has developed vascu-

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lar diseases involving the aorta or the iliac arteries. Aneurysm formation of these vessels, the aorta and iliacs, may lead to pressure necrosis and primary fistulization into the ureter or kidney. Secondary causes of A-U (aortourinary) fistula formation after previous surgical intervention are multiple.

Etiology of Aortourinary Fistula

I. Primary fistula development
   A. Aortic aneurysm erosion/pressure
   B. Iliac artery aneurysm erosion/pressure
II. Secondary fistula development
   A. Prior surgery, especially vascular
      Example: aortofemoral or aortoiliac grafting
   B. Previous radical pelvic or oncologic surgery
      Example: Pelvic exenteration
   C. Prior pelvic radiation therapy
III. Trauma
   Comment: Some have thought that retroperitoneal fibrosis after insertion of vascular grafts may cause or predispose to fistulization. This has not been our experience as long as the graft is posterior to the ureter.

The most frequent secondary causes of AUF are the previous aortic or iliac aneurysm surgeries or the Leriche bypass and the insertion of a synthetic (e.g., Dacron) bypass graft, such as the aortofemoral Dacron graft [2–4]. In these situations, the surgeon must be certain to place the graft behind or deep to the ureters so that the ureters are not constrained or compressed by the aortic graft. Double checking that the femoral extensions of an aortic graft are retroperitoneal and under no tension will aid in the prevention of or avoidance of fistula formation. Other secondary fistula causes include various oncologic surgical procedures, the radiation therapy programs and the resultant fibrosis, and trauma [5–8]. Some individuals have speculated that the Dacron vascular grafts create an excess of retroperitoneal fibrosis which then is a stimulant or initiator of the aortoureteral fistula formation. From our experience, when the graft is placed retroperitoneally and deep to the ureter, the amount of fibrosis has been minimal and therefore has not been a concern or initiator of the arterial–ureteral fistula formation.

Urinary tract fistula may also involve the kidney. Almost universally, these fistulas involve the left kidney and include the aorta to the left renal cyst fistula [10]. Such a case may involve the aortic aneurysm eroding into a renal cyst with the production of abdominal pain, hematuria, and shock [9]. On a review of the literature, we have found a paucity of information regarding aortic fistulization into the urinary bladder or urethra.

Diagnostic Studies

These individuals will usually consult their primary physician when the systemic symptomatology develops. Blood in the urine associated with fever and malaise are common complaints for which a patient may seek medical treatment [1]. Most of these individuals, even those with prior surgical intervention, have urinary symptoms unrelated to their previous surgery or radiation. Thus, when seen by the physician, they usually will have a physical examination, urinalysis, and a urine culture and be placed on an antibiotic most appropriate for urinary infections. Depending on the symptoms, additional blood workup, including a complete blood count (CBC) and a multichannel diagnostic serum analysis (CMP)—blood urea nitrogen and creatinine—will be obtained. Depending on the symptom complex and the presentation, other interventional procedures may also be obtained, including pelvic examination and colonic examination. These may also have been done by the initial examining physician prior to seeking consultation.

When the presenting symptoms are more major, or more concerning, the patient will be directed to diagnostic imaging for radiologic evaluation.

Diagnostic Studies for Urinary–Vascular Fistula Definition

I. Hematology studies
   A. Multichannel blood (CMP) study
   B. CBC
II. Culture studies – urine ± blood
   A. Anaerobes
   B. Aerobes
   C. Mycobacteria
III. Ultrasound studies
IV. Radiographic studies
   A. Flat plate of the abdomen
   B. Abdominal/pelvic
      1. CT with/without contrast
      2. CT angiogram (CTA)
   C. Pyelogram
      1. Intravenous/descending (IVP)
      2. Ascending/retrograde
   D. Angiography
      1. Catheter from the upper extremity vessel

Initially, ultrasound studies or computerized tomography (CT) without contrast will be performed. With acceptable BUN and creatinine studies (renal function), CT angiography with contrast and magnetic resonance imaging (MRI) may be obtained. Depending on the findings, or the lack of findings,

the patient may then be scheduled for descending pyelography (IVP) or ascending pyelography (retrograde) to further assist in determining the cause of the hematuria or symptom complex. When there has been previous surgery, especially vascular, arteriography to define both the native and the surgical vascular anatomy may also be required. In order to avoid the femoral vessel region, especially if there is a prior graft present, catheter angiography from the upper extremity vessels may be utilized to determine if a possible aneurysm or fistula exists and to reduce the chance for iatrogenic graft infection, graft complications, or false aneurysm formation-some European physicians have even tattooed over the graft—"do not puncture."

Treatment

As mentioned earlier, initially, the treatment protocol may include urinary organism-specific antibiotics, awaiting both the therapeutic results and the urinary culture results.

When this has not relieved the situation or if the patient deteriorates, additional urgent diagnostic and therapeutic intervention is mandated. Presented below are many of the therapeutic and surgical procedures that have been utilized to treat aortourinary fistula.

Aortourinary Fistula Treatment Modalities: Past and Present

I. Nonoperative
   A. Urine-specific antibiotics/short or long term
   B. Blood transfusion
II. Previous surgical approach/direct intervention
   A. Simple arterial ligation
   B. Resect infected tissue and Dacron patch graft
   C. Primary closure of the vessel/seldom able
   D. Extra anatomic bypass
III. Urinary system surgery
   A. Ureteroplasty or end-to-end repair
   B. Ureteral stents or balloon
   C. Nephrostomy
   D. Nephrectomy
   E. No prolonged ureteral catheter—Prophylactic
IV. Aorta or iliac artery
   A. Resect aneurysm with primary repair
   B. Resect aneurysm with extra anatomic vascular graft
   C. Omental wrap
V. Endovascular therapy
   A. Temporizing stent or coil
   B. Embolization/rebleed
   C. Endograft/less invasive and avoids the scar tissue

Currently, depending on the findings of the diagnostic studies, a urologist, a general surgeon, a vascular surgeon, and an oncologic surgeon may all be consulted or physically present at the time of surgery. The therapeutic goals for the treatment of these patients include those delineated by Oliveira et al. [3]. As presented, the management of aortourinary and arterioureteral fistula should include the following: (a) control of bleeding, (b) restoration of vascular continuity, (c) urinary tract continuity, and (d) a limitation or elimination of the potentially infected prosthetic or tissue material [3].

Multiple approaches have been utilized with these goals in mind. The treatment programs have shown a therapeutic evolution from direct interventional therapy to the lesser invasive endovascular treatment and grafting.

Initially, interventional therapy included such procedures as ligation of the iliac artery, along with resection of the aortic aneurysm and grafting. Extra anatomic bypass procedures were frequently utilized to reinstate vascular flow. Unfortunately, this required a large amount of surgery and, frequently, several units of blood to be transfused. Other procedures included ligation or patch grafting of the aorta after control of the bleeding and resection of the infected areas. These open techniques have more recently been discontinued where possible, surpassed by the endograft or transaortic suture closure and ex vivo repair. In the case of a unilateral kidney and renal artery disease, our policy has been to either resect or repair the branch vessel fistula or aneurysm and to preserve the kidney.

With the advent of endovascular surgical techniques, stent grafting by the percutaneous transfemoral (or transiliac) route has been utilized to a greater extent for the treatment of aortourinary/ureteral fistula [9]. Several advantages favor the endovascular approach over the open surgical methods. These include (a) more prompt control of bleeding, (b) a less invasive approach, (c) avoidance in many instances of scarred surgical fields, (d) utilization in patients with unfavorable anatomy, (e) usually the requirement of less operative time, and thus (f) less trauma to the patient.

Advantages of Endovascular Stent Graft

I. More prompt control of bleeding
II. Less invasive
III. Avoid scar/other structures
IV. Use when anatomy difficult
V. Less OR time
VI. Less trauma/blood

Other endovascular approaches including embolization of the aneurysm or bleeding site have been utilized in addition to the endoluminal covered stent. The question has arisen

whether the endovascular approach is a temporizing approach or whether the patient will require later interventional open surgery [11, 12]. Various authors have considered this topic, and Malgor et al. found that, in most patients, open procedures are not always required [11]. Temporizing coils and embolization have also been utilized but with the concern of rebleeding ever present [11–13].

Depending on the situation, primary suture of the vessel or resection of the diseased vessel has been utilized in many of these patients. If no evidence of infection is present, endograft or suture closure of the fistula may, on occasion, be the only treatment required. Pelvic abscess formation and associated enteric fistulas may alter one's therapeutic approach to the AUF problems [14]. In these challenging situations, unilateral nephrectomy or nephrostomy tube insertion may be considered when the contralateral kidney and drainage system are intact with normal function.

Debate continues as to the most appropriate therapy for the aortorenal cyst fistula. Open surgical intervention with the repair of the aortic aneurysm and resection of the fistula has been the preferred treatment for years. Again, more recently, endovascular graft treatment has been initiated in a number of these patients as discussed by Chui et al. [10, 11]. The circulatory arrest and thoracoabdominal incision techniques have virtually been eliminated by the endograft technique for these lesions.

Certainly, when one considers the risk to the patient from urinary or ureteral fistula, prevention is the most important consideration. Therefore, avoidance of injury to the urinary system from direct dissection or from applying pressure or scar potential to the ureter becomes apparent.

Therapeutic Cautions to Prevent AUTF

I. Prevention, the best approach
   Avoidance of ureter injury
II. Maintain ureter anterior to vascular grafts
   Avoid graft tension
III. No long-term indwelling ureteral catheter
   Repair ureter per primum over a stent when injured
IV. Surgery contraindication
   Pelvic abscess or enteric fistulas
V. Omental wrap

When a patient is having radical pelvic surgery, including exenteration, safety of the urinary drainage system becomes most important. Others have found that the avoidance of long-term indwelling ureteral catheters reduces the chance of fistulization subsequent to a pelvic exenteration [5]. When the ureter is injured while performing complex retroperitoneal or repeat vascular surgery (e.g., aortoenteric fistula), we repair the ureter and place a temporary (up to 6 weeks) intraureteral catheter or stent. In addition, we have found that wrapping of omentum between the ureter, the aorta, and the iliac vessels has reduced the risk of infection, aortic fistula, and aortoureteral fistula formation. Also, in vascular surgery, synthetic grafts should be placed posterior to the ureter to avoid ureteric tension.

Other Urinary System Fistula

We have already mentioned that aortourinary fistulas are very uncommon to rare. The most common of these is the aortoureteral fistula. In reviewing the literature for urinary fistulas and especially for fistulas into the kidney or the bladder, we found only a few such incidents. The most common of these abnormalities located on literature review was an aorta to the left renal vein fistula. These fistulas usually occur when an abdominal aortic aneurysm ruptures into the left renal vein [15–17]. Such an occurrence is more common when the left renal vein is located posterior to the aorta and overlying the vertebral body. In this location, the aneurysm presses on the vein, compressing it between the aneurysm and the vertebral body. This is contrary to the aortocaval fistula, which usually occurs on the right side of the aorta.

The aorta to the left renal vein fistula may occur between a normal left renal vein or between the aorta and an aberrant renal vein [16]. The symptomatology may also be confusing in these patients [18].

Aortorenal Vein Fistula

I. Site
   A. Left retroaortic renal vein
   B. Aberrant renal vein
II. Symptoms
   A. Confusing
   B. Fatigue
   C. Dyspnea
   D. Leg edema
   E. Abdominal pain
   F. Hematuria
III. Physical exam
   A. Left-sided abdominal bruit
   B. Pulsatile abdominal mass
IV. Differential diagnosis
   A. Cardiac failure
   B. Pelvic congestion syndrome
V. Testing
   A. Decreased renal function
   B. Nonvisualized left kidney

Fatigue and severe dyspnea may develop along with lower limb edema to suggest a diagnosis of congestive heart failure [3]. In other situations, a pelvic congestion syndrome complex may develop when there is reflux retrograde from the renal vein into the left ovarian vein [19]. Other findings may include abdominal pain (81%), hematuria (100%), decreased renal function (85%), a left-sided abdominal bruit (73%), and a pulsatile abdominal mass (63%) along with nonvisualization of the left kidney (100%) [19–21]. In addition to the retroaortic left renal vein, other sources for aortorenal vein fistula formation include trauma, especially stab wounds, and post EVAR (endovascular) repair [20–23]. Therapy continues to favor the endovascular approach as reported in 1999 [24].

A literature review was also performed without success to locate aortic fistula formation into the uterus, fallopian tubes, or vagina (also, no reported cases of aortic fistula to the central nervous system or peripheral nervous system). There is a large volume of literature presenting experience in repair of the rectovaginal, ureterovaginal, and urinary bladder to vaginal fistula formation [25]. Knowing the ravages of aortic disease, it is surmised that gynecologic aortic fistulas have occurred and that we have merely been unsuccessful in the location of references to those fistulas. Yin et al. suggested that an aortic urinary bladder fistula developed in their patient after an endovascular repair (EVAR) of an abdominal aortic aneurysm. The patient had a fever, abdominal pain, hematuria, and bloody stools. Cystoscopy demonstrated the distal end of the left external iliac artery stent; thus, technically, this was not an aortic fistula but a branch vesical fistula. They do mention the occurrence of an aortic vesical fistula after open aneurysm repair in their discussion [26].

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Congenital Aortic Fistula and More

24

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Introduction

Lesions of the aorta may occur anywhere along the aorta from its origin at the aortic valve to its bifurcation into the right and left common iliac arteries. Aortic lesions may be diffuse or localized and of a varied nature. Congenital vascular abnormalities may involve virtually every structure and every organ in the body. The aorta is not immune from these newborn abnormalities, which also may be hereditary. Congenital lesions may vary from the multiple types of aortic arch and branch abnormalities to developmental aortic openings, fistula, or shunts. Depending on your definition, the presence of a fistula will depend on the type of shunting lesion that may be described as a congenital aortic fistula. If one's definition is rather straightforward and includes an opening from a high-pressure system into a low-pressure system, then a number of congenital aortic lesions may be included in this discussion. If one's definition is stricter and defines a fistula (shunt) to be a structure developing between a high-pressure and a low-pressure tubular vascular structure, then one may exclude many of the congenital aortic deformities.

Depending on the physician's practice, an individual pediatrician may see a large number of newborns and small children for examination. Only a few of these newborn individuals may present with a single or multisystem congenital vascular complex and have a loud precordial murmur. The etiology of the murmur or bruit may be rather simple and straightforward or the patient may require extensive noninvasive and invasive evaluation in order to establish a diagnosis. Most of the congenital anomalous aortic shunts (fistulas) in these small individuals will be diagnosed and subsequently treated. However, some A-V (arteriovenous) fistulas will not become apparent until the individual reaches his/her teens or adulthood. Some examples of aortic fistula – both congenital and acquired that may be diagnosed:

Examples of thoracic aortic fistulas – congenital and acquired

I. Ascending aortic fistula
   A. Aorta to right atrium rare – especially after infection and endocarditis
   B. Aorta to superior vena cava
   C. Aorta to azygos or hemiazygos vein
II. Aortic arch fistula
   A. Congenital – very rare
      1. Left SVC (superior vena cava)
   B. Acquired
      1. Trauma, surgery, or infectious processes
      2. Post aorta to brachiocephalic surgery
      3. SVC or bronchial
      4. Aorta to bronchial branches
      5. Coronary artery bypass graft to cardiac vein
III. Descending thoracic aortic fistula
   A. Aorta to IVC (inferior vena cava)
      1. Congenital
      2. Acquired
         (a) Trauma

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(b) Post-back surgery
(c) Infection
(d) Ruptured aneurysm
(e) Marfan's disease
(f) Usually posterolateral
B. Aorta to pulmonary artery
1. Congenital
(a) PDA (Patent ductus)
2. Acquired
(a) Marfan's disease
(b) Trauma
(c) Giant cell arteritis
(d) Endocarditis
(e) Syphilis
IV. Surgical – therapeutic/palliative
A. Not further discussed

Definition

Most connections between the aorta and other vascular structures represent a condition in which blood normally flows from a high-pressure system into a low-pressure or lower pressure branch vascular system. For our purposes and for delineation of this chapter, we will define the abnormal vascular connection between the aorta and other cardiovascular structures as fistulas or fistulous tracts – shunts. Thus, when discussing arteriovenous or aortovenous communications, the definition of a fistula as mentioned will herein imply that the usual situation represents the transfer or passage of blood from a high-pressure arterial system into a lower pressure but high capacitance – usually venous system. On occasion, however, the flow of blood may be from an arterial high-pressure system into another but lower pressure arterial or ventricular system simultaneous with the bruit production. Thus, there usually will be a large flow or volume of blood into the recipient or lower pressure system. Whether this flow is intracardiac or extra-cardiac will further define the patient and the diagnosis. Similarly, symptoms may develop as a result of this high-pressure to low-pressure transfer of blood volume such as shortness of breath, failure to grow, and congestive failure.

Various definitions of the types of congenital or acquired aortic or pulmonary vascular fistula may be applied when defining the pathology. A simple definition might include the location within the thoracic aorta from where the fistula takes origin.

Some examples of fistula classification

I. Definition – Transfer of blood from high-pressure to lower-pressure high-capacitance system
II. Cardiac direction
A. Extra-cardiac – vessel to vessel
B. Intracardiac – vessel to chamber
III. Site of aortic fistula origin
A. Ascending
B. Arch
C. Descending
IV. Direction of fistula
A. Aortovenous
1. Example: systemic-pulmonary
2. Left to right
B. Aortosystemic
1. Systemic-systemic
2. Left to right
V. Number of fistulas
A. Single – most
B. Multiple
VI. Etiology
A. Genetic/familial
B. Infectious
C. Traumatic
D. Developmental arrest
VII. Symptoms
A. None
B. Present/type
C. Temporary/permanent
VIII. Size
A. Large
B. Small
IX. Association
A. Other lesions
B. Syndromes
X. Age at diagnosis
A. Intrauterine
B. Birth
C. First month of life
D. 1–12 months
E. 1 year to adult
XI. Blood oxygenation

This definition includes the ascending aortic lesions, the arch lesions, and the descending thoracic aortic lesions. Each location will present a somewhat different presentation and different physical and diagnostic findings depending on the location of the fistula and the type of study performed. The murmur or bruit may or may not be diagnostic but certainly may be suggestive or directive. In most situations, determination of the fistula etiology is not possible as to an incident or causal relationship during pregnancy to cause these congenital lesions. Whether the fistula is single or multiple and whether the shunt developed as a result of intrauterine infection, trauma, and heredity or normal developmental arrest

are all speculative. When, or if, a fistula or abnormal connection will become significant or symptomatic is difficult to speculate or predict.

As mentioned, various classifications of the aortic shunt lesions may include the source and the endpoint of the fistula such as systemic-systemic and systemic-pulmonary. The blood shunted may be classified as oxygenated or non-oxygenated and include left to right or left to left from the aorta. Classification may also include vessel to cardiac chamber or vessel to vessel. Even the fistula etiology may be used for classification such as traumatic, congenital, acquired, or surgical complication. In addition, actual purposeful aortic fistula have been created for temporization or palliation of congenital heart disease. Such fistulas are not included in this discussion, but mentioned for completeness. Other classifications include (1) whether the fistula is symptomatic or not, (2) whether it's a large fistula or a small fistula, (3) whether it is temporary or permanent, or (4) whether it's associated with other lesions. One might also classify these lesions according to timing or cause of their findings: (1) intrauterine, (2) at birth, (3) first month of life, (4) at 1–12 months of life, and (5) age of life thereafter.

Another classification defines whether the fistula is aorto-venous or aortosystemic (e.g., aortoventricular).

Congenital aortic fistula

I. Left to right shunt
   A. Aorta – systemic vein fistula – aorta to brachiocephalic vein
   B. PDA
   C. Aorta to pulmonary artery
   D. Aorta to right atrium
II. Left to left shunt
   A. Aorta to left ventricle
   B. Aorta to left atrium

Many patients with vascular fistulas are seen as adults with previously unknown arteriovenous fistulas. Also, multiple fistulas that occur in the chest are not always of aortic origin.

Some Non-aortic Thoracic Fistulas

I. Left coronary artery arising from the pulmonary artery
II. Systemic artery of the lung
III. Venous abnormalities
   A. Anomalous pulmonary artery/venous return
   B. Hypogenetic lung
   C. Congenital absence pulmonary artery with extrapulmonary supply
IV. Pulmonary AVM/Osler-Weber-Rendu syndrome
V. Scimitar sign: pulmonary vein to IVC
VI. Pulmonary artery to coronary
VII. Persistent left superior vena cava to the left atrium
VIII. Right superior vena cava to the left atrium

An example of the above includes the unsuspected symptomatic pulmonary arteriovenous fistulas (AVMs). It seems appropriate to mention a family we treated with four generations of these lesions and variants of the Osler-Weber-Rendu syndrome.

Our first contact with this family was a daughter with recurrent inflammatory changes in the left lung. Following pulmonary angiography, four AVMs were resected from the left lung. The two right lung AVMs were followed periodically with x-ray. Two of her three brothers were then diagnosed and treated with embolization of the fistula. Her father had recurrent hemorrhagic lesions in his gastrointestinal tract and an "apple sized" (7–8 cm) symptomatic pulmonary AVM which required resection. According to the family, three prior generations with similar difficulties expired due to similar lesions. Despite other lesions, no aortic fistula was defined in this family. These lesions are usually not as conspicuous as the normotensive aortic fistula despite the fact that they might be multiple in nature. However, other lesions of the aorta may accentuate an aortic fistula and its associated bruit in some patients. A severe coarctation of the aorta may certainly create profound increased flow abnormalities from an aortic venous fistula proximal to the coarctation – such as with a PDA (patent ductus arteriosus) [2, 3].

Fistula Types

A number of fistulas originate in the aortic root or the ascending aorta. These include the aortopulmonary shunt or window, which may be classified, in various manners, according to their size and location in the aortopulmonary septum [4]. The window may be large and free-flowing. Or it may be a small connection between the two structures.

Depending on the size and location of the bruit, the auscultatory sounds may be diagnostic as to the vascular etiology. However in other cases, it may be difficult to discern the bruit caused by an AP (aortopulmonary) window defect from that of a patent ductus arteriosus (PDA). These A-P window lesions may thus be classified as septal defects or as the more classical window defect.

The aortopulmonary window lesion, representing an aortopulmonary septal defect, may be associated with other

cardiac or arterial abnormalities. Removal of the neural crest tissue, unlike in truncus arteriosus, does not result in this abnormality but does result in multiple other congenital defects including the truncus arteriosus and transposition of the great vessels [4]. This defect is usually positioned between the semilunar valves and the pulmonary bifurcation and has a "border" or rim about the lesion. These defects are unusual and have been classified by Mori into type I (a small defect), type II (more distal defect formed by the pulmonary artery bifurcation), and type III (a large defect involving the entire aortopulmonary septum) [5]. Due to the severity of the symptoms and prognosis, surgery is usually recommended to the patient (family) for correction utilizing a mid-sternotomy, transaortic repair, and cardiopulmonary bypass (CPB).

The aortic left ventricular defect (or tunnel) represents an aortic to left ventricle shunt. Cardiac catheterization and angiography will define the abnormality. Aortic arch variants include the double arch, the right arch, and the various branch origin abnormalities such as the anomalous origin of the right subclavian artery from the left-sided aorta [6]. Usually arising on the left side, they may also arise on the right side to form a vascular ring in association with the ligamentum arteriosum. MRI and barium esophograms may readily demonstrate the esophageal constriction effect of this abnormality as seen in our patient with a Kommerell diverticulum off the right descending thoracic aorta and obstruction of the esophagus [7]. If the ligamentous structure remains open, then an aortic (Kommerell diverticula) fistula may occur.

Anomalous origins of various vessels may occur including the pulmonary artery arising from the ascending aorta – a left to right shunt [1]. All of these lesions may associate with other congenital cardiac lesions. Such lesions may be classified as either fast flow lesions (arterial) or slow flow lesions (venous). These arteriovenous malformations related to the arch may involve vascular hypogenesis during angiogenesis. These AVMs may present with a continuous murmur during childhood, congestive symptoms, and, on physical exam, a bounding pulse with a roaring bruit. Cardiac catheterization and echocardiography may further define the differential diagnosis.

Rarely, a patient may have an aortic defect with flow from the aorta into the left atrium or left ventricle and thus form a left to left shunt. This shunt represents a systemic to systemic fistula – a very unusual situation. An aorta to the superior vena cava or other venous fistulas are more common due to trauma rather than of a congenital origin.

When one discusses the proximal aorta and fistula formation, the congenital coronary artery shunts must also be mentioned even though technically they do not arise from the aorta. These shunts take origin from the coronary branches of the aorta and seem to be more common than some of the other congenital aortic fistula, as do the abnormal origins of the right or left coronary artery. Less commonly seen is the absence of a coronary orifice or coronary orifice stenosis. A fistula may also develop between the aorta and the right atrium. Ghandour and Rajiah have described these abnormalities and the imaging techniques for delineation of these unusual fistulas [8]. Aortic arch fistulas are very rare, especially congenital, and usually are not described in most discussions regarding aortic fistula and their formation.

A number of congenital fistulas may be seen arriving from the descending thoracic aorta. The most common of these is the patent ductus arteriosus (PDA) which takes origin from the aorta just distal to the left subclavian artery and more commonly is seen in the premature infant (preemie) or the newborn. Most of these children have the typical bruit readily recognized on initial examination. These PDA fistulas, between the aorta and the pulmonary artery, usually close spontaneously in a matter of hours or a few days after birth (Figs. 24.1 and 24.2), thus eliminating the shunting of blood from the aorta into the pulmonary artery system. Embryologically the PDA is a remnant of the distal portion of the left sixth aortic arch in the fetus. The shunt connects the descending aorta to the main pulmonary trunk and is 5–10 mm below the left subclavian artery. The PDA allows blood flow shunting from the pulmonary system into the aortic system during gestation. The ductus may be located on the left or the right side or, on occasion, bilaterally. Differences in the aortic and pulmonary artery pressure and blood flow occur depending on the systemic and pulmonary vascular resistance. The ductus may close prematurely intrauterо or delay closure. In the premature infants, the PDA usually will have a left to right shunt and all its secondary effects.

Fig. 24.1 Cadaver specimens demonstrate the aorta with the ligamentum arteriosum residual of the ductus arteriosus (PDA) in the infant (with forceps) thus eliminating the flow from the aorta into the pulmonary artery. Also seen is the recurrent laryngeal nerve which must be safeguarded in surgical closure of the PDA. (Photograph courtesy of Michael F. Dauzvardis, PhD – Assistant Professor and Director – Structure of the Human Body, Stritch Medical School, Loyola University, Maywood, IL)

Fig. 24.2 Ligamentum without forceps. (Photograph courtesy of Michael F. Dauzvardis, PhD – Assistant Professor and Director – Structure of the Human Body, Stritch Medical School, Loyola University, Maywood, IL)

Kosecik et al. described an apparent arteriovenous fistula between the descending thoracic aorta and the left inferior pulmonary vein [9]. On evaluation of this 20-month-old female, echocardiography demonstrated a systemic artery (not the aorta) to pulmonary venous fistula. Computerized tomographic angiography demonstrated normal bronchial and pulmonary vascular structures. The fistula drained into the left atrium to create a left to left shunt. Percutaneous AMPLATZER™ vascular plugs resolved the condition. As mentioned earlier, even though we are discussing aortic fistula, other fistula may occur in the chest and be confusing as to the diagnosis and location. These include the pulmonary sequestration, the arteriovenous intercostal fistula, and a systemic artery originating from the aorta to the pulmonary venous system.

Many of these lesions that we have mentioned take origin from the aorta or its branches and are usually diagnosed in the pediatric population. But, on occasion, they may not be diagnosed until later in life when an adult develops a bruit and symptoms limiting their daily activities. These patients require careful diagnostic consideration to be certain that the developing or suggested congenital diagnosis is truly the cause of the symptomatology.

As suggested, aortic shunts or fistulas maybe classified in various manners, including the anatomic connection or the blood flow direction. Martinez-Jimenez classified the noncardiac shunts utilizing both the flow and the anatomic considerations [1]. Thus, a patient may have systemic to systemic shunting with an aorta to systemic vein and a left to right fistula. One may have a systemic to pulmonary shunt with a left to right shunting of the blood via the PDA, aorta to pulmonary fistula, or a unilateral absence of the pulmonary artery (as seen in our patient) with collateral systemic vessels to the lung or an aortic branch fistula to the lung or pulmonary artery [10]. The patient may have a left to left shunt with the bronchial AVM, or an intralobar pulmonary sequestration. One may also have a pulmonary to systemic shunt with a left to right flow in the hypogenetic lung syndrome. Further one may have a pulmonary to pulmonary shunt with the right to left flow as may be seen in the pulmonary AVM patients. The coronary artery fistulas are examples of an aortic branch fistula and may demonstrate flow between coronary AVMs or a cardiac chamber [11].

Coronary artery-related fistula

I. Non-iatrogenic
   - A. Aortic root: cardiac chamber
     right ventricle, right atrium, left atrium, and especially left ventricle
   - B. Coronary cameral: travels to the cardiac chamber
   - C. Coronary artery to systemic circulation
   - D. Coronary artery to pulmonary artery circulation
   - E. Coronary artery to coronary sinus
   - F. Coronary artery to SVC

II. Postdiagnostic or therapeutic intervention
   - A. Post-pacemaker insertion
   - B. Post aortocoronary therapy
   - C. Following cardiac angiography
   - D. After septal myomectomy
   - E. Post aorto-coronary bypass grafting
   - F. Post pulmonary artery procedure
   - G. Especially involving noncoronary transcatheter septal closure

Coronary branch fistula patients may have symptoms such as dyspnea, fatigue, chest pain, and orthopnea. Such fistulas may drain into a cardiac chamber (cameral fistula), pulmonary artery, or coronary sinus. Other coronary anomalies include the anomalous coronary origin, and the acquired cardiac bypass fistulas that lead to aortic shunts to the right atrium or the aorta to the inferior vena cava fistula. These fistulas may be congenital, postsurgical, or traumatic in origin. In addition, infected endocarditis or prosthetic valves may lead to similar fistula formations.

Other branch vessels may drain the intercostal artery to a cardiac chamber via an intercostal vein. These acquired systemic arterial fistulas of the lung may occur as a result of chronic pulmonary inflammatory processes such as tuberculosis and bronchiectasis. Usually there is a shunt between the systemic arterial supply and a pulmonary artery in these patients. The aortosystemic vein fistula which may result in

a left to right shunt, including the aorta to the brachiocephalic veins, consequent to infection, trauma, or postsurgery may create the SVC (superior vena cava) syndrome, a loud murmur, or heart failure. The aortopulmonary artery fistula shunts blood from the left to the right system in a systemic to pulmonary direction. Etiology for these conditions include trauma, surgery, aortic dissection, and the more common persistent PDA with its typical continuous murmur or bruit. The chronic non-closed PDA may increase the pulmonary artery pressure and create a "steal" syndrome, which may lead to congestive heart failure and angina pectoris.

Diagnosis

Diagnostic evaluation of these patients begins with fetal screening and newborn examination to note respirations, cardiac rhythm, and the presence of any murmurs. School physicals and sport screening are all important in discerning a potential abnormality – including the EKG and echocardiograms. Symptomatology during exercise will require repeated interviews and deeper interrogation regarding possible symptoms and congenital or acquired defects. When abnormalities are suspected, noninvasive and invasive evaluation may then be considered including electrocardiography, echocardiography radiographic studies, and pediatric cardiology consultation.

Heart rate and rhythm, blood pressure, pulmonary function, and respiration will all be evaluated in these individuals. Computerized tomography (CT) and magnetic resonance imaging (MRI) will be utilized as necessary. Contrast studies, including both cardiac and vascular angiography, are performed as necessary to delineate cardiac, aortic, and pulmonary lesions [1]. Comprehensive aortic anatomic and functional evaluation utilizing CMR (cardiovascular magnetic imaging) aids greatly in the definition of the congenital abnormality. MRI studies for evaluation of vascular rings and vascular anatomy is of great assistance for discerning complex situations including the patent ductus [7]. Contrast CT studies usually require sedation or general anesthetic in the infant or young person – depending on the child's age and the arterial abnormalities. In the adult or older child, sedation is usually adequate [12].

Treatment of Aortic Fistulas

When the PDA patient is symptomatic or not responding appropriately, then further evaluation and treatment may be necessary. Chest x-rays may show an enlarged heart, and an EKG (electrocardiogram) may show left ventricular hypertrophy. Following appropriate diagnostic studies, which may include echocardiography, cardiac catheterization, angiography, and MRI, treatment decisions will then be determined. In the premature infant dietary and hemoglobin levels above 40–50% are maintained.

Occasionally, in the premature and the newborn, therapeutic intervention will be required when medical therapy is not effective. The procedural occlusive approaches utilized for these children and their PDA are many. In the past, coil occlusion implants were utilized to close the patent ductus (PDA). Since then multiple newer techniques have been developed. Mini balloons, as well as other transcatheter closure techniques – including the Rashkind – were formulated. The Rashkind technique utilizes both an umbrella passed through the venous system and a right heart catheter. Once the catheter is positioned through the ductus, the device is deployed. Other techniques including the Mullins transvenous/trans-septal approach have also been utilized. Therapy is advised in most patients. Depending on the situation and the patient's age/size, one may also utilize cardiopulmonary bypass, lateral thoracotomy, a median sternotomy, or a transaortic catheter approach.

In the premature infant, intravenous lyophilized indomethacin is particularly effective when utilized before 10 days of age for PDA closure. Ibuprofen has also been evaluated for this treatment in preemies. Coil or device closures have been used in the infant, child, or adult, as necessary, to perform PDA closure with 98% success and few medical complications [13]. For the patent ductus of small diameter, the coil procedure has been used successfully and may still be utilized.

Similarly, coils or plugs, such as the M Platz or vascular plug, may be utilized for treatment of arterial fistulas or pulmonary arteriovenous fistulas [14, 15]. IIto is presently the device utilized by most surgeons or pediatric cardiologists and may be performed either retrograde or antegrade. Other devices or approaches have been utilized for the larger defects such as the AGA septal closure, the VSD device, or the cardioseal. The posterior intercostal surgical approach, where the proximal and distal ductus is clamped, ligated, or divided and then sutured proximally and distally, continues to be an effective treatment. In the unusual individual, when the PDA is very large, surgical closure may be required utilizing a lateral thoracotomy or the thoracoscopic approach for closure. However, there has been some suggestion of a greater incidence of recurrent nerve injury with the thoracoscopic technique. Endovascular treatment programs continue to advance for the betterment of the patient and reduction in the complication rate.

The various congenital, or acquired, aortic fistulas require careful evaluation and consideration as to the type of lesion, symptomatology, and therapeutic risks. Many lesions may be observed until child development and growth optimize the therapeutic approach. Severe lesions are treated early and with therapeutic resolve or palliation until the appropriate

size and symptoms warrant invasive approaches. Whether the lesion may be treated endovascularly or with open surgical intervention depends on the patient's progress, symptoms, and risk. With the progress in development of endovascular techniques and equipment, more and more lesions may be treated with various plugs, patches, and grafts, while also protecting or reducing cerebral injury and avoiding complications.

Complications of congenital or acquired lesions will require careful clinical and, when necessary, diagnosis and therapy. Some lesions such as aortocameral fistula may be either congenital or acquired due to sepsis or infective endocarditis [16]. Other lesions, including a pseudoaneurysm and aorto-bronchial fistula, may develop after balloon dilation of a recoarctation lesion. Thus congenital non-fistula and acquired lesions may lead to formation of aortic fistula [17]. Although rare, one must be aware of these complications of congenital lesions and their therapy.

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Aortotracheobronchial and Aortocutaneous Fistula

25

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Introduction

Aortic diseases are very common. Most frequently these are associated with aortic aneurysm formation – especially when the aneurysm is below the renal arteries. Similarly, aortic obstructive disease, usually due to atherosclerosis in the lower aorta, is fairly common – producing the Leriche syndrome. Less frequent in occurrence are multiple other lesions involving both the intrathoracic and the extrathoracic aorta which may eventually create aortic fistulas. These lesions may especially occur in association with other hollow organs or those organs having a tendency to form a lumen.

Some Examples of Aortic Fistulas

I. Aortovascular
   A. Congenital – persistent patent ductus arteriosus (PDA)
   B. Aortovenous
      1. Venacaval
      2. Renal vein
II. Aortotracheobronchial
III. Aortogastrointestinal
   A. Esophageal
   B. Gastric
   C. Small bowel
      1. Duodenum – most common
      2. Jejunal
      3. Ilial
   D. Colonic
   E. Aortoappendiceal
IV. Aortourinary
   A. Ureter
   B. Renal
V. Aortocutaneous
VI. Aortobiliary

The most common of these structures in the adult include vascular fistulization into the trachea or bronchus, the esophagus, the venous system, the stomach, the small bowel, the colon, and the urinary system.

All of these fistulas may produce both general and specific signs and symptoms. Treatment of aortic fistula may be accomplished using the less invasive transvascular procedures (endovascular, TEVAR), or with greater difficulty utilizing an open thoracotomy and many units of uncross matched blood in the extreme circumstances. Either way, these lesions are difficult patient diagnoses and carry high morbidity/mortality risks.

We have seen a number of patients with aortic fistulas. Most such patients present with acute potentially life-threatening processes along with the concomitant vascular lesion adding to the original underlying primary cause of the patient's difficulties. Interventional processes may be directed at either the "secondary" process – the fistula or both the fistula and the underlying cause or etiology of the fistula depending on the patient's symptoms and the clinical status.

Dealing with the original process which created the acute emergency may be very risky, while simultaneously control-

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ling the secondary fistula. Hopefully, both the initiating process and, if possible, the fistula may be controlled – usually by endografting techniques. Whether the endograft is definitive or temporizing depends on the circumstances and the underlying diagnostic etiology. When the patient develops a fistula between the aorta and the tracheobronchial system, a difficult life-threatening urgent or emergency situation ensues.

Aortotracheobronchial Fistula (AT-BF)

Patients who develop hemoptysis more commonly have a pulmonary etiology producing the bleeding. Chest x-ray and computerized tomographic scanning (C-T) usually will demonstrate the lesion or lesions suspected of the bleeding. Tracheobronchoscopy will confirm the lesion in most situations. On occasion, however, the actual cause of the hemoptysis may be vascular – especially when the bleeding is abundant or massive in amount. In the past, the patient with an AT-BF may have a history of previous aortic disease, such as syphilitic aortitis, or currently present with a picture of a progressive thoracic aortic aneurysm enlargement and subsequent surgical treatment (Fig. 25.1). Trauma, historically, may also be a possible cause of the patient's pain, symptom complex, and culmination in hemoptysis. The lesions which may produce these symptoms are not necessarily uncommon, but the resultant AT-BFs are extremely rare but highly lethal when they do occur [1–4].

The most common causes of aortic fistulization into the tracheobronchial tree revolve around the descending thoracic aortic aneurysms, the patient with severe thoracic and mediastinal trauma, and those with malignancies of the thoracic structures.

Causes of Aortotracheobronchial Fistulas

I. Thoracic trauma
   A. Gunshot
   B. Stab wound
II. Postmediastinal surgery
   A. Tracheal – especially stenting
   B. Post-unilateral lung transplant
   C. After coarctation repair
   D. After tumor resection
III. Aortic
   A. Aneurysm – especially enlarging
   B. Pseudoaneurysms – postsurgical or post-traumatic
   C. Postvascular resection
   D. Post-TEVAR
IV. Infectious
   A. BCG installation
   B. Mycotic
   C. Aspergillus – lung
   D. Historic
      1. Pulmonary tuberculosis
      2. Syphilitic
V. Malignancy
   A. Germ cell
   B. Malignant thymus

When the patient has had thoracic aortic surgery, a fistula may develop as soon as 3–4 weeks after the surgery or as late as 25 years after the aortic surgery [2]. Wheatley et al. reported on their experience in treating seven patients with aortobronchial fistula (ABF) between 2000 and 2005 and a meta-analy-

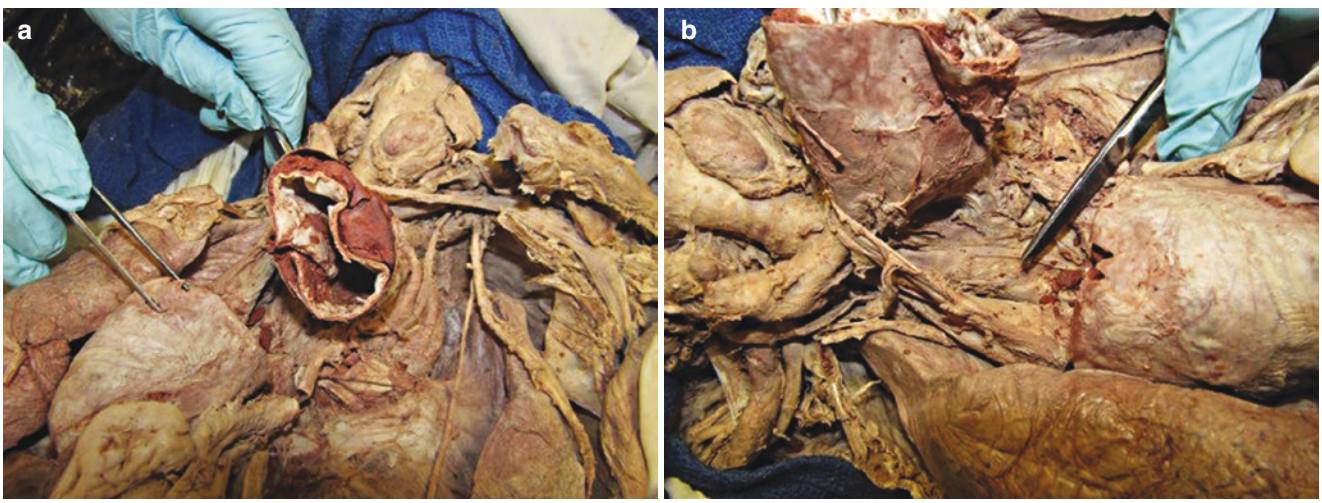

Fig. 25.1 (**a**) Cadaveric demonstration of an enlarging ascending aorta dissection. (**b**) Cadaveric demonstration of reflected aortic dissection with trachea and esophagus posterior – demonstrates how fistulas may occur. (Photographs courtesy Robert Frysztak, PhD, Assistant Director Department of Human Body Structure, Stritch Medical School, Loyola University, Maywood, IL)

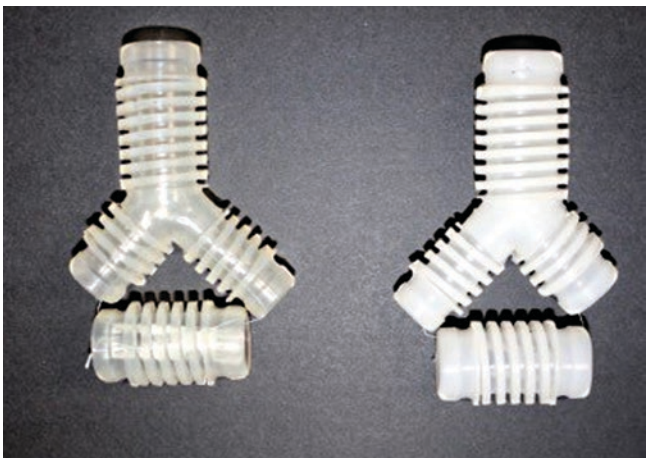

Fig. 25.2 Two examples of early synthetic tracheal grafts which could erode the nearby vascular structures when infection occurred and thus are no longer utilized. The long limb could be used for the left bronchus and the straight grafts could be used for the trachea

sis of previous published cases [5]. All patients had hemoptysis, and six of seven patients had a descending thoracic aortic aneurysm (DTA) or pseudoaneurysm subsequent to treatment of the DTA. These patients also had 28 comorbidities listed including hypertension, COPD, prior aortic aneurysm or valve replacement, renal insufficiency, and hepatitis B. Foreign bodies in the mediastinal area may potentially cause an A-T-B fistula. We have had patients with silver dollars erode the esophagus into the mediastinum (and then seal) and remain undetected for long periods of time without further erosion into the aorta [6]. But these mediastinal foreign bodies may eventually erode the aorta or T-B tree and cause massive hemoptysis [7]. However, tracheal resection with prosthetic stent graft replacement has also led to innominate or aortic erosion and massive bleeding as has carinal stent replacement (Fig. 25.2). But, our patients with primary tracheal tumors or tracheal tumor emboli (endobronchial or peripheral arterial), tracheal foreign bodies, and a patient with a carinal tumor during pregnancy did not fistulize into the aorta [8].

Medication-induced aortic aneurysms and aortic fistulas are very rare. Hui et al. described a patient who had received BCG (Bacillus Calmette-Guerin) treatment of a bladder carcinoma [1]. Their 2016 review discussed the 28 previously published cases of intravesical BCG-associated mycotic aneurysms primarily involving the infrarenal abdominal aorta. They reported vascular complications of the BCG treatment including aortoenteric fistula in addition to carotid, femoral, popliteal, and aortic arch infectious involvement. Their case of aortobronchial fistulization occurred in an 85-year-old patient, with a profound anemia (7.3 g/dL hemoglobin), who was also being treated for a *Mycobacterium bovis* infection utilizing multiple chemical agents including isoniazid (INH) and rifampin. Computerized tomography (CT) demonstrated a recent-onset thoracic aortic aneurysm. The left vocal cord was found to be paralyzed at the time of the tracheal intubation for bronchoscopy. At bronchoscopy, a pulsatile bulging pressure mass of the left mainstem bronchus was noted as was thrombus seen in the left main bronchial lumen. The endotracheal tube was advanced into the right main stem bronchus while blood was transfused intravenously. Due to the patient's condition, the family elected to withdraw further medical care. The authors present the argument for continued BCG and antibiotic usage along with endografting of these individuals [1]. Aortobronchial or aortotracheal fistulas are rare and usually fatal – as was the case with the above patient.

In our early experience, tracheal resection and stent placement for treatment of a malignant tracheal lesion could lead to pressure on the surrounding tissues and subsequent erosion into the adjacent tissue by a firm or rigid stent. Depending on the amount of tissue invasion or necrosis, a fistula may develop and erode into the surrounding tissues, including the esophagus and the aorta. Similarly, foreign bodies of the trachea or bronchi may, on rare occasion, erode the airway and create unusual or rare complications including abscess formation or fistulization into the nearby structures. Unfortunately, foreign bodies of the trachea may remain undetected for long periods of time prior to being recognized and produce significant complications. An example is a young man eating ice cream when struck by an automobile. After 4 months of hospital and rehabilitation care, we saw him for the inability to eat. Esophagoscopy demonstrated no lesion, but bronchoscopy demonstrated an intact previously undiagnosed plastic spoon filling his trachea [6]. The subsequent fistulization may occur in a matter of weeks or years after the original process or surgery.

Diagnosis

The usual patient presents with a history of chest pain or discomfort followed by hemoptysis – even massive – which may be recurrent or sudden and exsanguinating.

Symptoms of Aortotracheobronchial Fistula

I. Hemoptysis
   A. Sudden
   B. Recurrent
   C. Possible massive
   D. Frightening
II. Sepsis
   A. Fever
   B. Weak
III. Shock – morbid
IV. Pain
V. Shortness of breath
VI. Systemic weight loss

These lesions are frightening to the patient and the physician. Prior symptoms, including sepsis, may be present for a short time or be chronic in nature. If the hemoptysis is massive, the patient's chances for survival are slim.

The diagnosis revolves about the preceding history and the appropriate diagnostic studies. No one specific diagnostic test is available. Usually, noninterventional laboratory tests including complete blood count (CBC) and culture studies will be followed by radiologic exams, such as computerized tomographic (CT) studies, chest x-ray, and magnetic resonance (MR) studies to define the possible cause of the hemoptysis, pain, and shortness of breath.

Diagnostic Studies to Define Aortotracheobronchial Fistula

I. Laboratory
   A. CBC
   B. Metabolic panel
   C. Type and cross match
II. Radiologic
   A. Chest x-ray
   B. CT scan – with contrast
   C. MRI
III. Interventional
   A. Contrast aortography
   B. Endoscopy – with care

When intervention, such as diagnostic intravenous contrast CT or catheter angiography, and endoscopy are considered, and a possible aneurysm or fistula formation may be present, one should be aware of the possibility of significant bleeding, including massive bleeding during the procedure, and thus be prepared for such – including the possibility of emergency surgery. Such planning might include the cooperative intervention of other specialties and staff along with cardiopulmonary bypass standby contemplation while performing the tracheobronchoscopy or angiography (CT or catheter) in these patients. More likely a fistula will not be seen on angiography, but abnormal mediastinal infiltrates, an aneurysm or pseudoaneurysm, and displaced calcium in or about the aorta may be strong diagnostic clues. If the patient is able to tolerate endoscopy, then tracheobronchial examination may be performed judiciously without doing a biopsy.

Treatment

Treatment of these aortic airway lesions is complicated and high risk by their nature, but if not treated, the mortality is near 100%. In the past, open thoracotomy surgical intervention has been the most commonly utilized approach. Cardiopulmonary bypass standby or utilization for unusual lesions such as these has been the main support mechanism for the surgeon in these and other such difficult situations since the 1960s [4]. Surgical therapy and primary closure of the tracheobronchial defect is difficult in these sick and infected/septic patients – an example was a middle-age post-polio patient who previously required a pneumonectomy for carcinoma of the lung. A few years later, he developed a bronchoesophageal pleurocutaneous fistula with bloody drainage. The endoscope passed readily through the bronchial and esophageal openings into the pleural cavity. After additional consultation with experienced tracheal surgeons who recommended open surgical repair but to expect failure and demise, we elected intravenous fluids, antibiotics, and 24-hour ICU patient self-suctioning for 1 month without surgery. The eventual result was total healing of the fistula in this nonmobile patient and no further bleeding. However, we never finally proved involvement of the aorta or vena cava despite the considerations. Li et al. have applied expanding Y-type covered metallic stents for treatment of gastrotracheal or gastrobronchial fistulas but did not discuss their use for aortotracheobronchial fistula [9]. Surgical repairs of the associated vascular lesions are high-risk high mortality (up to 40%) situations.

As time has passed and with more experience, it is felt the endovascular approach will provide control of bleeding and, when necessary, allow time to prepare for repair of the airway as well as the vascular lesion to further reduce the untoward surgical and post-therapy complications. The endovascular grafting may be both temporizing and therapeutic – depending on the circumstances [2, 3]. The transfemoral endovascular catheter technique may then initiate a treatment plan to stabilize the patient and control bleeding.

In their 2006 review of therapeutic options, Wheatley et al. discussed their use of endovascular stent grafts [5]. They had seven patients who received ten stent grafts placed (7–20 cm × 28–40 mm) through the common femoral artery (five patients) or a retroperitoneal conduit (two patients). Prior to discharge, each patient received a CT angiogram of the chest, abdomen, and pelvis which demonstrated evidence of the fistula being sealed in each patient. Cefazolin was administered preoperatively, and five patients were discharged on antibiotics after 3 to 6 days of hospitalization. The following year, Kokotsakis et al. reported on their experience stenting primary aortobronchial fistula with massive hemoptysis in two patients [10]. After extensive urgent evaluation, patients had insertion of aortic endostents to cover the defects – one from a penetrating descending aortic ulcer and in the other a chronic type B aortic dissection.

Again antibiotics and stenting resolved the aortobronchial (AB) (left) fistula [7]. Of note, the usual site of AB fistulization is through the left membranous bronchus due to pressure from the aorta.

This technique first presented by Chuter is usually simpler and faster and incurs less bleeding [11]. Bailey et al. in 2011 discussed the safety of the procedure, while Riesenman et al. reviewed 32 reports involving 67 patients with a 1.5% 30-day mortality [12, 13].

Of further note, the Wheatley group routinely covers most of the left subclavian origins with only an occasional need to bypass or embolize a few of these patients. Antibiotic therapy of these unusual clinical situations is recommended for most patients. Acutely, preoperatively, and postoperatively, most patients will be placed on the antibiotic proven most effective in their experience and on laboratory sensitivity tests. When placing a permanent foreign body in these situations, long-term – either several months or lifetime – bacterial suppression seems appropriate in many of the patients [14]. When conditions mandate the open chest operation, one should be prepared for a long and possibly bloody procedure. Treatment may require resection of pulmonary, bronchial, or tracheal tissue with primary suture closure or tubular patch repair of the tracheobronchial (T-B) defect. A pericardial patch was utilized by co-author #2 successfully to close the tracheal defect when an aortic aneurysm eroded the trachea. The aorta must also be repaired or even an old synthetic graft replaced. As with all graft replacements, antibiotic therapy should be maintained during and after repair due to the possible tracheobronchial (T-B) contamination. Mosquera et al. stress the importance of resolution of the underlying primary A-B fistula and infection in order to achieve a long-term survival [15].

AT-BF and tracheoesophageal fistulae (T-EF) may occur as a result of multiple etiologies including tracheal intubation [14, 15]. Tracheoesophageal fistulas (T-EF) are more common than aortotracheobronchial fistulas (AT-BF) and may occur as a result of multiple causes. However, in a 10-year review of their benign tracheoesophageal fistulas due to tracheal intubation, no AT-BF was reported either preoperatively or in their list of complications in repairing such [16]. But aortobronchial fistula may occur following previous therapy for aortic lesions, such as aortic coarctation. Bozzani et al. reported their experience with such a patient who 17 years previously had a subclavian-aortic bypass for aortic coarctation. On the current admission, the patient was found to have a distal anastomotic aneurysm of the subclavian graft. They utilized an endograft placed through the femoral artery and a 10 mm AMPLATZER™ 2 Vascular plug II to occlude the aneurysm and bypass the A-B fistula [17].

Aortocutaneous Fistula

The aorta lies directly behind the sternum. Many open mediastinal surgical procedures require dissection or surgery around, with, or upon the aorta. These include the aortocoronary bypass, cardiac valve replacement or repair, ascending aortic replacement, mediastinal tumor surgery, and multiple other procedures. Periodically, sepsis and mediastinitis may develop during or after these procedures. Depending on the therapeutic response, the aorta may develop a leak and require further treatment or surgery. If the aortic leak becomes infected in association with the aortic pressure, a fistula may develop and tunnel or erode substernally and then subcutaneously to rupture through the skin.

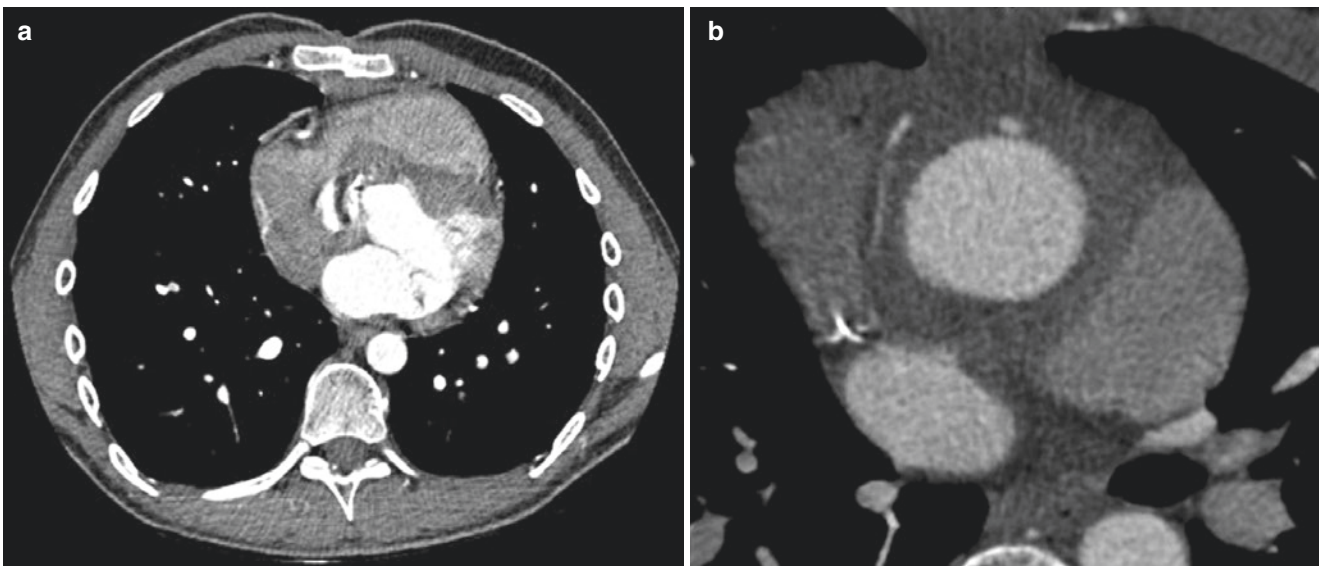

Fig. 25.3 (**a**) CT scan of the aorta demonstrating the contrast material deep to the sternum and superficial to the prosthetic aorta graft in a patient with an infected ascending aortic graft**.** (**b**) CT scan demonstrates contrast deep to the sternum

Such an aortocutaneous fistula developed in a patient with severe aortic insufficiency and a large aneurysm of the aortic root and ascending aorta. He had resection of the aortic root and the ascending aorta with replacement by a Hemashield graft, coronary replantation, and a pericardial valve inserted. Subsequently, he developed a sternal infection which was debrided along with removal of the sternal wires. Later, a bloody drainage was noted arising from the sternal incision. Emergency contrast CT scans were followed by repeat sternotomy and removal of the infected conduit with insertion of a #29 Homograft and replantation of the coronary ostia. He has progressed well from his aortocutaneous fistula and correction of the infected graft (Fig. 25.3). Almost always such a condition will require surgery to debride, and, if a prosthesis is present, replacement grafting, along with appropriate postoperative antibiotic sensitivity study control. This patient with the aortocutaneous fistula represents a very rarely reported situation [18].

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Aortoesophageal Fistula

26

Raymond A. Dieter Jr., Raymond A. Dieter III, and George B. Kuzycz

Introduction

The usual complaints of a patient who has an aortoesophageal fistula are those of pain, hematemesis, and fever. These individuals may have had no previous symptoms and may present with an acute onset of discomfort or they may relate to a more prolonged history of not feeling well followed by vomiting of blood. In addition, many of these patients will have a long history of digestive difficulties and secondary intervention. Some relate to no history of gastrointestinal illness or discomfort until their current onset of difficulty. A patient may present with a history of slowly progressive abdominal or gastrointestinal discomfort for which x-ray evaluations are obtained that demonstrate aortic and esophageal abnormalities. Depending on the findings, an aortoesophageal fistula may then be considered.

Symptomatology

The usual symptoms, for which the patient who has an aortoesophageal (A-E) fistula complains, include a history of left chest and back pain. These symptoms may be due to a thoracic aneurysm eroding into the esophagus, the left chest, the back, or the vertebral bodies. However, the pain, such as burning retrosternal pain or discomfort after eating, may also suggest chronic esophageal symptomatology. Many of these patients will also have a long history of back pain suggestive of spinal difficulties. Others will have a more acute pain syndrome – all depending on the etiology and progression.

Hemorrhage, either acute or recurrent, may be the initiating or first symptom the patient experiences. If the hemorrhage is small in volume, it may recur, and the patient will seek semi-elective medical evaluation. But if the hematemesis is massive and acute, the patient will progress to a shock-like state or exsanguinate. Massive – even pulsatile – vomiting of bright red blood, as the first symptom, is frightening and may cause vital sign changes including a drop in blood pressure, tachycardia, and syncope. If stabilization does not occur, the bleeding may lead to progressive deterioration and demise.

Chiari, in 1914, described the aortoesophageal syndrome to consist of (a) mid-thoracic pain, (b) dysphagia, (c) a sentinel episode of hematemesis, and (d) fatal exsan-

Signs and Symptoms of Aortoesophageal Fistula

I. Massive bright red hematemesis – pulsatile from the mouth
II. Pain
  A. Back pain, especially mid-thoracic
  B. Anterior chest discomfort radiating to the neck
III. Systemic symptoms
  A. Tachycardia
  B. Fever
  C. Malaise
IV. Dysphagia – food hang up
V. Critical Condition
  A. Hypotension
  B. Shock
  C. Death
VI. Chiari syndrome
  A. Pain – mid-thoracic
  B. Dysphagia
  C. Hematemesis
  D. Fatal bleed
VII. Differential diagnosis – extensive

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guination. This syndrome has been repeatedly described by authors discussing the aortoesophageal fistula since his original description [1]. Other symptoms may develop in these individuals including fever, tachycardia, and suggestions of sepsis.

These findings, present in approximately one-third of the patients, are similar to those seen with many other disease entities, thus, the need for further clarification of the patient's history – including any past gastrointestinal or thoracic symptoms. Hypovolemic shock as a result of sepsis or as a result of blood loss will require treatment while discerning the etiologic cause of the patient's condition. A past history of esophageal surgery or of food "hanging up" (dysphagia) may also suggest the etiology.

A few of these patients on initial presentation will relate to a history of multiple other diagnoses; due to their close anatomic relationship, confusion may occur (Fig. 26.1). When under treatment for cardiac or vascular disease, the patient may be on various anticoagulants including aspirin and Coumadin. If the patient presents with vague substernal chest discomfort which radiates to the arm, one may be led to consider cardiac or even acute myocardial infarction etiologies. Such symptomatology may lead the evaluation and testing in a different direction then that of consideration of an aortic or esophageal etiologic complaint. The past history of upper gastrointestinal complaints or symptoms may confuse the physician as may a history of foreign body ingestion.

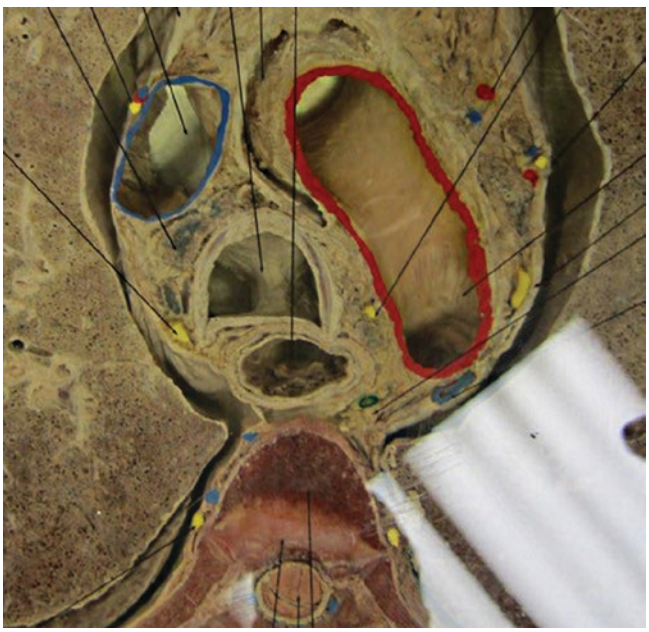

Fig. 26.1 Cadaveric trans-sectional specimen demonstrating the aorta (red), the vena cava (blue), the bifurcating trachea into the right and left bronchi, and the retrotracheal esophagus anterior to the spine. This photo demonstrates the potential for aortotracheal, and aortoesophageal fistula due to their closeness. (Photograph courtesy of Michael F. Dauzvardis, PhD, Assistant Professor and Director – Structure of the Human Body, Loyola University, Maywood, IL)

Diagnostic Evaluation

When these patients are initially seen by the family and by the physician, the symptomatology may be readily suggestive of an upper gastrointestinal problem or of an esophageal etiology. If the patient has had previous known disease entities requiring treatment, the diagnostic evaluation may not lead to an immediate and correct evaluation. If the patient has had a known aneurysm or peptic ulcer disease, the patient will be evaluated and treated accordingly.

However, if this is a new onset symptom complex the patient may require extensive evaluation to localize the area of concern. Some of the diagnostic studies that one would consider in evaluating these patients:

Diagnostic Studies for Evaluation of the Aortoesophageal Fistula Patient

I. CBC
II. Chest x-ray (AP and lateral)
III. Computerized tomography (CT) (possible contrast [CTA])
IV. Magnetic resonance imaging (MRI)
V. Esophagoscopy/with caution – unsure diagnosis
VI. Thoracic angiography
VII. Cardiac catheterization

On initial evaluation, a complete history and physical examination will be directive when time and the patient's condition allow. However, when the patient is in a shock-like condition, the individual will be prepared for blood transfusions, emergency surgical consideration, and testing as his/her condition permits. Acutely, blood count (CBC) and blood chemistry studies (SMR) will be obtained at the same time as the blood type and cross-match are drawn. Chest x-ray and computerized tomography (CT scan) of the chest and abdomen may be obtained in the emergency facility depending on the "direction" of the history. Radiographic definition of a thoracic aortic aneurysm or of an ingested foreign body may define the direction of the evaluation and treatment. When reviewing either the chest x-ray or the CT scan one should particularly note any vessel calcification, the location of this calcification with relation to the vessel, whether the vessel(s) appears to be widened or displaced, and any extravascular evidence of leakage.

When the condition permits and the symptoms warrant, upper gastrointestinal endoscopy may be obtained [2]. Depending on the patient's history, examination for varices,

bleeding ulcers, or suture line stability will all be considerations. However, if the bleeding is massive or the patient's condition does not permit this study, then attempts at diagnosis through other routes will be required. This is particularly significant when previous esophageal surgery or possible foreign body ingestion has occurred (such as a patient of ours who ingested nine double-edged razor blades) to obtain a warm place to stay when the outdoor temperature was minus 10° Fahrenheit. When utilizing esophagogastroduodenoscopy, one should particularly observe the 20 to 30 centimeter (cm) esophageal area for any "cherry red" spots of blood or tissue softness and be ready to remove the scope at a moment's notice to avoid the initiation of bleeding from the passage of the scope from the esophagus into the aorta.

CT angiography or aortic angiography to evaluate abnormal findings on a CT scan may be necessary to determine the presence of an eroding aneurysm or suture line. The chest radiographs performed in both the AP and the lateral positions along with the CT scans may be suggestive of, or diagnostic of, an aortic aneurysm with the possibility of a fistula. A magnetic resonance image (MRI) study may also be obtained in these individuals when pursuing the differential diagnosis. If a fistula is suspected or defined, further evaluation may be deferred in favor of emergent surgical evaluation and treatment.

Etiology

Aortoesophageal Fistula Causes

I. Vascular
   A. Thoracic aneurysm
   B. Aberrant right subclavian origin off the left descending aorta
II. Status post cardiovascular surgery
   A. Thoracic aneurysm graft/repair
   B. Post cardiac surgery
III. Foreign body aspiration – especially sharp
   A. Bones – chicken, fish, steak
   B. Razor blades/sharp objects
IV. Esophageal
   A. Post colonic esophageal bypass surgery
   B. Esophageal carcinoma
   C. Erosion of esophageal stents or clips into the aorta
   D. Esophagitis – corrosive
V. Infectious
   A. Mediastinal tuberculosis
   B. History of syphilis
VI. Caustic ingestion – lye
VII. Trauma

Listed above are several of the causes for aortoesophageal fistula [2, 3]. Approximately 40–50% of the fistulas occur as a result of thoracic aortic aneurysms and their surgical treatment thereof. Esophageal cancer and foreign bodies each accounts for approximately 25% of the cases. The remainder occurs as a result of surgical complications and other lesser etiologies [3]. With respect to the aortic aneurysms, both the direct erosion of the calcified and torturous aorta into the esophagus and the post-aneurysmectomy suture line may be associated with the graft eroding into the esophagus – creating a fistula. The latter situation more often will occur when the suture line is not covered by aortic tissue nor widely separated from the esophagus. The fistulization incidence seems to be similar whether a Dacron or Gore-Tex prostheses has been used for the aortic repair. Even the Kommerell diverticulum pressure effect may be a cause for the development of an A-E fistula due to their close relationship [4] (Fig. 26.2). The aberrant right subclavian artery arising from the left descending thoracic aorta may also create an esophageal concern due to its pressure effect [5].

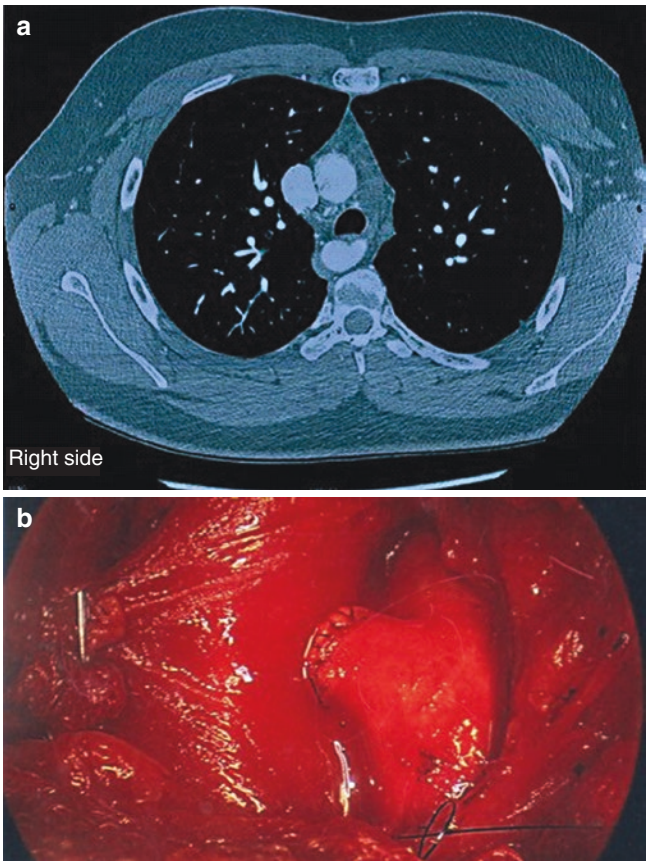

Fig. 26.2 (**a**) Close relationship of aortic Kommerell diverticulum arising from a right descending thoracic aorta and compressing the trachea and esophagus on C-T angiogram. (**b**) Operative photograph of divided Kommerell diverticular band crossing the esophagus demonstrating the potential for fistula formation

The earliest case of documented aortoesophageal fistula was reported in 1818 after an individual swallowed a sharp bone [6]. Both fish bones and steak bones are known to cause A-E fistula formation as did a patient treated by Author #2 successfully. A-E fistula may also occur during endoscopic removal of an esophageal foreign body (FB) which has penetrated the aorta or perforates the aorta during the FB removal. Such may lead to the emergent conversion of the endoscopic procedure from a diagnostic and therapeutic removal of a foreign body to an emergency requiring large volume blood transfusions and possible emergent thoracotomy. Thus one should be cautious with the amount of pressure and traction applied when removing esophageal foreign bodies – especially sharp, rigid, or pointed ones.

Other less common causes of aortoesophageal fistula formation have included the infectious processes such as mediastinal tuberculosis and the syphilitic aortic lesions of years ago (Fig. 26.3). Caustic agents, including the lye ingestions of the youth or depressed elderly, are known to cause aortoesophageal fistula which have been very difficult to correct.

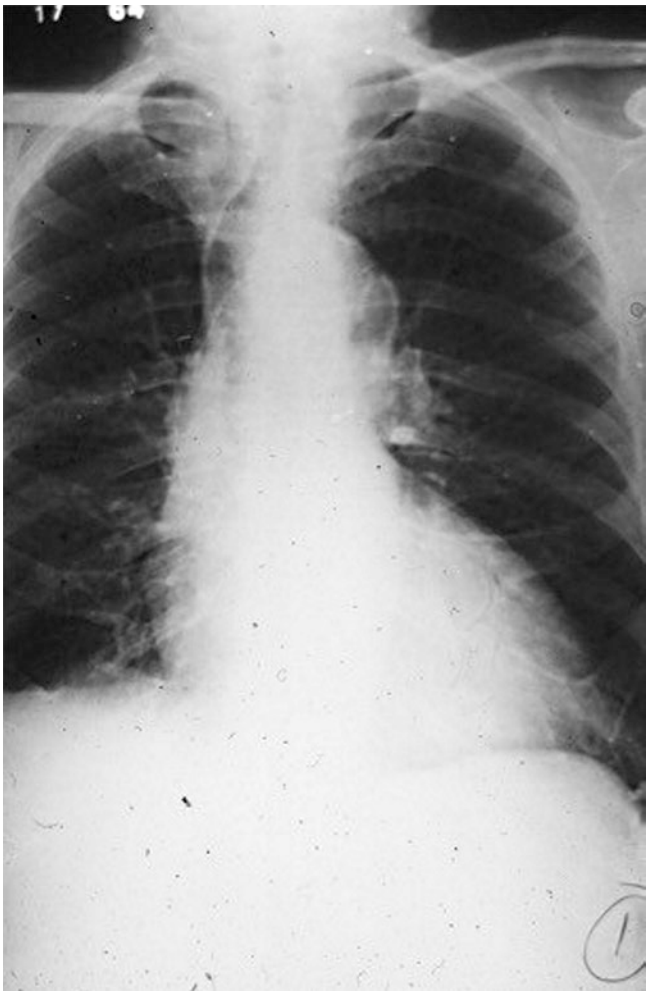

Fig. 26.3 Chest X-ray of a patient with syphilitic aortitis treated by us in the 1960s. These patients on occasion developed aortoesophageal fistula. Notice the tracheal air column deviated to the right as a result of the abnormal aortic enlargement

Vascular suture lines following aortic coarctation repair or grafting have also been a cause of aortoesophageal fistula. Certainly, thoracic trauma may create the opportunity for fistulization. Even therapeutic esophageal clips may erode through the esophageal wall into the aorta and create a fistula. Iatrogenic injury and chronic esophagitis are also rare initiators of an A-E fistula. Fistula formation may occur especially after aortic or esophageal surgery when a soft tissue pad or intercostal muscle flap has not been placed between the two structures at the completion of the procedure.

Therapy

Diagnosis of the underlying cause for the patient's bleeding is critical to the survival of the individual. Without an appropriate diagnosis and without urgent laboratory and x-ray evaluation, the patient's prognosis deteriorates rapidly and progressively. It is critically important in the treatment of these individuals that the diagnostic and therapeutic intervention program progresses rapidly and efficiently. From the time of their initial presentation, approximately 60% of the patients will be deceased within 6 hours after their presentation to the emergency room or physician [3]. These patients will require urgent attention as well as long-term follow-up care. Treatment options that have been utilized after the establishment of a diagnosis or a tentative diagnosis:

Treatment Options for Aortoesophageal Fistula

I. Blood – two large bore IV lines
II. Antibiotics
III. Surgery/options
  A. Endograft/FAVOR – transfemoral
  B. Resect/repair aneurysm – Dacron, Gore-Tex, cryopreserved graft
  C. Esophageal
    1. Ligation or resection
    2. Sengstaken/compression balloon
    3. Esophageal repair
  D. Muscle flap or omental wrap
  E. Intercostal ligation
  F. Thoracotomy/laparotomy
IV. Cardiopulmonary bypass consideration
V. Post-surgery
  A. Angiogram
  B. Intensive Care
  C. Rehab program

On presentation, large-bore intravenous access (one or more) and blood infusion (preferably cross-matched) will be initiated in most patients. Antibiotic therapy utilizing broad-spectrum drugs will be administered and the operating room or angiographic (aortic) suite requested. The Sengstaken-Blakemore compression balloons have been utilized in some individuals as a temporary stopgap measure for massive esophageal bleeding – but few such tubes are available and few individuals have experience inserting such.

Surgical intervention, first accomplished in 1962, was followed by the first successful operative repair in 1969. Multiple surgical procedures have been utilized since in an effort to control and contain the bleeding and to prevent further such episodes [7, 8]. Therefore, close postoperative observation is necessary. Currently, if possible and with a correct diagnosis, urgent transfemoral endograft insertion is the preferred method of treatment – especially in the acute situation [9]. In general, the aortic endograft approach, by obtaining better and more rapid control of the bleeding, has a better outcome than an initial open surgical procedure. However, subsequent to this "stemming of the tide," most surgeons and patients will require further open surgical intervention to (a) correct the fistula, (b) repair the esophagus, and (c) hopefully place viable tissue (such as muscle or omentum) between the vascular and esophageal structures. There have, however, been some individuals who have utilized only the endovascular treatment for their patients [10].

Recognizing the causes for a large proportion of these fistulas has been important in their prevention. For many years, all aortic lesions of the chest and abdomen were treated with open surgical control of the bleeding and aortic patch or tubular grafting along with esophageal repair [11, 12]. In open laparotomy or thoracotomy repair of the aortic aneurysm, one would insert a synthetic (Dacron) graft after control of the aorta. If this aneurysmal repair became infected or the suture line or graft became exposed, the chance for pressure necrosis or graft erosion into the adjoining tissues then became possible – especially when a false aneurysm developed.

More recently, the use of endovascular grafts for the repair of primary thoracic aortic aneurysms or of para-anastomotic aneurysms has reduced this possibility and thus decreased the incidence of serious complications [13]. Hopefully, concomitantly with the endograft approach we will see increased survival rates and a decrease in other complications such as paraplegia [14]. Locating the proper sealing zone along with insertion of the newer TEVAR grafts should assist in control of these A-E fistula with lessened risks of untoward complications.

Procedures that were utilized in the past and continue to be utilized in specific surgical circumstances include the use of esophagectomy, feeding jejunostomy, cryopreserved grafts and operative angiograms [15]. Some have felt that primary esophageal repair was the best approach while others have felt resection of the esophagus was the best way to prevent recurrence. Intercostal muscle and pleural flaps along with the placement of omentum between and over the suture lines have been utilized to protect the esophagus from anastomotic erosion. Others have utilized stent grafts, such as the Y-shaped stents, to treat the airway (tracheobronchial) to the GI tract connection, such as gastrotracheal or gastrobronchial fistulas post esophageal surgery, in the hopes of reducing further fistula formation, with some success [16]. More recently, cardiopulmonary bypass (CPB) and temporary aortic cross-clamping have also been considerations in these critically ill patients along with intercostal vessel ligation.

Prognosis

As already mentioned, the morbidity and mortality rate in these individuals is high. Complications of the underlying disease process (tumor or aneurysm) and complications of surgery to correct the fistula in these critically ill patients are frequent and significant. Not only is the mortality rate a concern during the preoperative, operative, and postoperative periods, but also there is a high rate of significant therapeutic complications. The chance for graft infection remains after treatment whether the procedure was performed with an endograft or open thoracotomy. Mycotic (bacterial) graft infection, recurrent fistula formation, and sepsis are a constant postoperative concern, along with extremity and gut viability.

Postoperative Aortoesophageal Fistula Concerns

I. Correct diagnosis
II. Hemodynamic stability
III. Repeat fistula formation
IV. Infectious concerns
    A. Bacterial
    B. Fungi
V. Repeat surgery
VI. Long term
    A. Nutrition
    B. Respiration
    C. Self-care
VII. Paraplegia

Avoidance of the infection or of its etiology is primary [17]. Prevention is the key to managing the risk. Research to prevent aneurysm formation in mice has been successful – a possible future aid [18]. Long-term respiratory and feeding (nutrition) options become very important in these patients to obtain positive rehabilitation results.

Summary

Aortoesophageal fistulas are uncommon to rare, but, when they occur, they present a high-risk, high-mortality situation for the patient, the family, and the health-care providers. Both the underlying cause of the fistula and the fistulous complications require consideration and treatment. Whether the patient's long-term survival after the acute situation has abated depends on the etiology or cause of the fistula – malignancy, aneurysm, and foreign body. Emergency evaluation and treatment have been aided by endografting techniques. Hopefully, with continued improvement in diagnosis and treatment of the underlying etiologies, there will be a decrease in the incidence of aortoesophageal fistulas. Continued placement, when possible during open thoracotomy surgery, of soft tissue between or over the aorta, aortic suture lines and grafts, and esophageal suture lines as taught by W. E. Neville – an early esophageal surgeon – will reduce the incidence of aortoesophageal fistula.

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Aortoenteric Fistula (Gastric, Small Intestine, Colonic, Biliary)

27

Raymond A. Dieter Jr., George B. Kuzycz, and Raymond A. Dieter III

Introduction

By definition, the aortoenteric fistula is a connection between the abdominal aorta and the gastrointestinal (GI) tract below the diaphragm. The fistula (shunt) may occur anywhere from the esophagogastric junction to the rectum but most commonly involves the infrarenal aorta and the duodenum—usually involving the third portion of the duodenum [1, 2]. The disease process may occur per primum between the aorta and the gastrointestinal tract with no prior symptomatology or the fistula may occur following extensive abdominal surgical intervention and disease [3, 4]. These lesions, therefore, cause a concern for both blood loss and sepsis.

This aortoenteric fistula section includes the aortogastric, the aortoduodenal, the aorto-small bowel (jejunum and ilium), the aortobiliary, and the aortocolonic fistula [5, 6]. Each of these fistulas has a typical as well as an atypical presentation. The manifestations and symptom complex may vary from patient to patient but almost always presents with significant blood loss. At times, the blood loss may be massive and fatal with the first bleeding episode. At other times, the bleeding may be slow, recurrent, and confusing in nature. Usually there is only a single fistulous communication between the aorta and the GI tract. Fistulas and patients may be classified in a number of manners. These classifications include (a) the etiology; (b) the location of the aortogastrointestinal fistula; and (c) whether primary or secondary; (d) acute, subacute, or chronic; or (e) symptomatic, infected, and hemorrhagic. The following are various classifications that one might utilize.

Aortoenteric Fistula Classifications

I. Primary or secondary: pressure induced
II. Anatomic enteric sites
  A. Upper GI: gastric or duodenal
  B. Small bowel: jejunum/ileum
  C. Colon: usually left
  D. Biliary tract
III. Etiology
IV. Traumatic
  A. Penetrating
  B. Postsurgical/secondary
V. Aortic Location
  A. Suprarenal
  B. Infrarenal
VI. Septic or not— – presence

Etiology

The usual causes for a gastrointestinal fistula include trauma—especially penetrating, post-vascular surgery, and pressure effects. Less commonly, malignancy—including metastatic germ cell or lymphoma—may be fistula producing [7]. Aortic fistula locations in the enteral system include (a) the upper gastrointestinal system such as the stomach and duodenum; (b) the small bowel; or (c) the lower GI tract including the right, transverse, and descending colon. Primary fistulas are those that develop with no known past surgery or trauma. Secondary aortoenteric fistulas usually occur after a prior interventional procedure such as resection and grafting of an aortic aneurysm or repair of a Leriche syndrome. Shunt location in the aorta may be defined as above the renal arteries (supra-renal) or below the renal arteries (infrarenal).

Both the isolated aortogastric fistula and the isolated suprarenal aortic enteric fistula are very rare. Thus a fistula might be classified as a secondary infrarenal aortoduodenal fistula following the repair of an abdominal aortic

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aneurysm. Another classification might define the fistula as an acute aortoinfrarenal duodenal or enteric fistula. These fistulas may further be defined with regard to the presence or absence of septicemia [8]. Septicemia may occur in either the primary or the secondary aortoenteric fistula as the initiating cause or as the result of the fistula formation. Terminology for the various fistulas includes the aortogastric, the aortoduodenal, the aortojejunal, aortoileal, aortobiliary, and the aortocolonic (particularly the sigmoid colon).

Aortoenteric fistula may also develop from a kidney graft site, following intravesical Bacillus Calmette-Guerin (BCG) treatment, or from other less common causes [9–11].

Symptomatology

Depending on the type and cause of the aneurysm, the patient may have no prior history to suggest a medical problem. The patient may develop a fever or other systemic complaints and a few days later develop abdominal symptoms. The history of another infection or potential infection-inducing procedure may be a precursor to the development of a septic aneurysm and an aortoenteric fistula. Dental work or other seemingly innocuous occurrences may lead to septic aortic infection and disaster. An example was an individual who had dental work and, the next day, back pain and a fever. CT scan was normal. One week later a 6.5-cm septic aneurysm present on an MRI required emergency surgery during the night [8]. These patients may develop acute rectal bleeding with subsequent demise unless treated emergently, as did the first patient reported with aortoenteric fistula in 1829 by Sir Astley Cooper [1]. A patient may have progressive abdominal discomfort and severe pain located in the epigastrium, in the flank, in the lumbar spine area, or in the lower abdomen. They may vomit blood or pass blood intermittently through the rectum. The blood may be dark in color or bright red in color depending on the fistula location. Patients may present in a shock-like state or merely complaining of bleeding. The patient may relate a history of a progressive pulsation in his abdomen and lack of appetite [12].

Depending on the location of the fistula, the individual may vomit large amounts of bright blood and be in a shock-like state. They may have had previous abdominal surgery and relate their symptoms to this therapy. Also, sepsis may lead the medical staff astray as to the potential diagnosis.

Physical Findings

Depending on the location of the fistula, the symptoms may define the potential location and cause of the problem. Patients usually will have a tachycardia and a low blood pressure. They may be too weak to stand. Examination may demonstrate a feeble pulse. Abdominal exam may reveal a palpable pulsatile mass. The mass may or may not be tender. A bruit may be present on auscultation. Certainly, the abdomen may demonstrate previous surgical scars as may the femoral or groin areas. In the case of secondary fistulas, the patient may relate valuable historic information regarding their previous abdominal surgical procedures. Rectal examination may present black tarry "stool" on the examining glove.

Associated Causes or Risks

The most common association in our practice has been the patient with a history of a ruptured abdominal aortic aneurysm treated with surgery on an emergency basis. These patients may come to the emergency room in profound shock, receiving cardiopulmonary resuscitation, with no EKG rhythm, and require emergency laparotomy or thoracotomy for control of bleeding. Consequently, many of these procedures have been performed in an expeditious and less than optimum surgical setting. The patient may have been operated, with a thoracotomy or laparotomy, in the emergency room or in the operating room with little or no sterile preparation as a result of their critical status. Control of hemorrhage, establishment of cardiac rhythm, and development of blood pressure are paramount. Endotracheal control of respirations is obtained. Cessation of cardiopulmonary massage followed by insertion of synthetic graft material to prevent further blood loss are performed under less than optimal conditions for complication-free resuscitation and survival. These patients thus become candidates for other multiple acute short-term and long-term considerations—including graft infection, aortoenteric fistula formation, and intensive care/rehab concerns.

However, these emergency-ruptured aorta cases are not the only precursors of vascular to the GI system fistula formation. Elective insertion of vascular grafts in the abdomen for repair of aortic aneurysms as well as for correction of the Leriche syndrome (aortoiliac occlusive disease) may lead to the scarring and pressure effects necessary to form a fistula. Thus, the aortofemoral graft as well as the aortoiliac graft may be etiologic culprits, especially when the surgery is performed transabdominal, utilizing a synthetic prosthesis such as Dacron.

Other related causes of fistulization include infectious diseases such as the primary aortic infection (mycotic infection) of either bacterial or fungal processes and, in the past, syphilis and tuberculosis. Previous gastrointestinal surgeries, including both gastric resection and pancreatic surgeries, have all been implicated.

Etiology of Aortoenteric Fistula

I. Abdominal aortic aneurysm
   A. Erosion
   B. Pressure effect
II. Past aortic surgery
   A. Aneurysm
   B. Leriche or aortoiliac (femoral) graft
III. Infections: bacterial or fungal
   A. Systemic
      1. Staphylococcus
      2. Postdental surgery
   B. Historic
      1. Syphilis
      2. Tuberculosis
IV. Past abdominal surgery
   A. Gastric resection
   B. Pancreatic procedures
V. Malignancy
   A. Rare
   B. Germ cell

A large number of these patients have other complicating factors, such as diabetes or severe cardiac abnormalities. Anticoagulants, anti-platelet medication, such as aspirin, and other medications may be related in the history and create therapy concerns for the physician and the patient.

Multiple organisms have been associated with aortoenteric fistula. In some patients, on antibiotics, Gram stain studies will show organisms but no growth on culture studies due to the antibiotic therapy. In other patients, cultures may yield a positive single-organism culture while, in others, multi-organism growth may be reported by the laboratory. *Salmonella*, *Klebsiella*, staphylococci (including methicillin resistant), streptococci, *Escherichia coli*, and others can be grown on the patient's culture studies [5].

Infectious Organisms Associated with Aortoenteric Fistula

I. *Staphylococcus*
   A. Epidermidis
   B. Methicillin resistant
II. *Salmonella*
III. *Klebsiella*
IV. *Streptococcus*
V. *Escherichia coli*
VI. *Enterococcus faecalis*
VII. *Clostridium perfringens*
VIII. *Lactobacillus*
IX. Fungus
X. Rare, in the past
   A. Tuberculosis
   B. Syphilis

Also, the immune system in these patients may be depleted due to chronic illness including diabetes, cardiac and HIV disease. In some patients abscess formation or infectious boney destruction of the spine may occur [13]. Polymicrobial gram-negative bacteria are becoming a greater concern [7]. Numerous research attempts to prevent synthetic graft infections have included sustained release vancomycin [14]. Fortunately, none of our patients have developed vertebral osteomyelitis or large abscesses.

Diagnosis

The diagnosis of an aortoenteric fistula may be readily apparent in some patients who present with a fistulous bruit while it may be very difficult in other patients. Multiple evaluations of the patient at multiple institutions may not demonstrate the shunt etiology despite extensive testing in most cases. The history and physical examination of the patient, especially of the abdomen, may suggest the diagnosis, the necessary evaluation, and then the treatment course. A large pulsatile aneurysm, an abdominal bruit, and a previous midline incision for vascular surgery all suggest the possibility of a fistula causing the bleeding and the symptoms. Despite this information, repeated upper and lower abdominal x-rays, contrast x-ray studies, CT studies, and angiograms may not be diagnostic. Also, repeated upper and lower gastrointestinal endoscopy may not define proper diagnosis. In many cases, the vascular diagnosis is not established until the time of exploratory surgery. Thus, on occasion, surgeons not equipped or experienced with major complicated vascular surgery may be the physician who establishes the diagnosis.

Many patients, on diagnostic evaluation, may be found to have abnormal gastrointestinal findings. The question then arises as to whether these positive findings are the true causes of gastrointestinal bleeding and other symptoms, hence the necessity to be aware of the possibility that more than one lesion or diagnosis may be present. If the patient has a history of a major bleeding or undiagnosed recurrent bleeding and a history of abdominal pain, a palpable pulsating lesion, and tenderness, one should consider the possibility of a vascular fistula or of an aneurysm with secondary fistulous bleeding. Massive bright blood hematemesis and a palpable abdominal mass could suggest a gastric lesion. If the bleeding is recurrent, black, and per rectum, one becomes concerned for a lesion of the small bowel or colon. Thus, many of the chronic patients, when able, will have both upper and lower endoscopy studies. If there is a gastric fistula, it may not be visualized when there is acute massive bleeding obliterating the telescopic mirrors. When the bleeding is below the ligament of Treitz, it most likely will not be visualized endoscopically and the aortoduodenal or aorto-small bowel fistula will not be recognized. Many of the patients will have colonoscopy, which, in our experience, may not be diagnostic. Again, the

interpretation as to the location and cause of the bleeding may be erroneous due to the many factors involved. Both the upper and lower endoscopy may be deferred by the gastroenterologist when the patient is unstable—at which time other diagnostic evaluations may be performed [12].

When these patients present to the ER, they have blood counts (CBC), laboratory tests, and blood type and cross-match studies performed. Computerized tomographic (CT) angiography may be considered in these patients, if or when they are stable enough to proceed to the radiographic suite [4]. Many emergency rooms (ER) are now equipped with the CT modality so that a minimum of time is lost from when the patient arrives in the emergency room or from when communication from the ambulance service is available to the ER staff. Initially, some studies are obtained while the patient stabilizes and before the endoscopic exams may be performed. On occasion, we have had the experience of observing the CT angiographic (radiographic) contrast material as it flows through the aorta, through the fistula, and then into the gastrointestinal tract. Obviously, the demonstration of this finding directs the treating physicians to the diagnosis and treatment options. However, most patients having angiography do not demonstrate this finding [4]. But delayed x-ray film studies with the CT scanner may demonstrate contrast material in the small or large bowel, despite not having visualized radiologically the actual fistula. It is important not to perform barium or Gastrografin oral or rectal gastrointestinal contrast studies prior to the CT scan or CT angiogram as these contrast materials may prevent visualization of the fistula, especially when barium is utilized.

When the patient is not acutely hypotensive, additional diagnostic evaluation may be delayed until the renal function, liver profile, and other hematologic studies have been obtained. If the patient has an acceptable blood urea nitrate (BUN) and creatinine level, intravenous contrast CT studies may be utilized. When the radiologist prefers not to use contrast due to an elevated BUN and creatinine, plain abdominal x-ray and non-contrast CT scans may demonstrate other findings in the abdomen regarding a previous graft, hematoma formation, and air bubbles about a graft or free intraabdominal air. Findings in and about the aorta or the bowel may be difficult to interpret. Mutual careful consideration of the CT scan by the radiologist, the attending physician, and the surgeon may assist in diagnosing a possible fistulous tract with demonstration of a tethered bowel loop, periaortic free fluid, ectopic gas, and effacement of periaortic fat [4].

Angiography in the more stable intermittent bleeding patient is frequently utilized to define or attempt to delineate the diagnosis [6]. Nuclear medicine studies including gallium scanning and positron emission tomography (PET) scanning have been utilized in the more stable, confusing, and complex patient [15]. A positive nuclear or white cell scan does not necessarily prove the presence of a fistula but may be suggestive of an infection. Most of these studies will be performed in elderly individuals and thus multiple diagnoses may be established. It then becomes necessary for the treating physicians to evaluate and determine which disease process is more likely the cause of the symptoms. This was particularly apparent in a patient we treated after he was admitted 11 times to a nearby university for treatment of acute massive GI bleeding with evaluation and testing during these emergencies being unable to define the aortoduodenal fistula [12].

The differential diagnosis of gastrointestinal bleeding is long and many times very perplexing, including arteriovenous malformation, inflammatory bowel disease, peptic ulcer, or Meckel's diverticulum. When the process is acute and the patient is in a critical situation, evaluation is directed at the most apparent etiology for their process. Consequently, mistaken diagnoses may occur and lack of appropriate personnel availability may create difficulty for treatment of these critically and acutely ill patients. Recognizing whether they have a malignant process that is the overwhelming etiology or whether they have a vascular lesion that may be treated and potentially corrected may place a great burden on the treating staff in just a few moments, especially in the cardiac arrest situation. Defining the most likely cause for the process and then initiating acute resuscitative treatment may be a challenge. Locating a carcinoma in the colon does not necessarily define the etiology for the acute anemia or the patient's condition. In 1 year, while doing emergency or urgent aortic aneurysm surgery, the senior author also found four carcinomas of the cecum. Similarly, in the patient with a primary aortic fistula and no prior abdominal surgeries, one must be aware of the potential for infection due to previous dental work or other such causes.

Also, the differential diagnosis of upper GI bleeding, including ulcers and varices, must be remembered simultaneously with physical examination, including the abdominal and rectal exam, appropriate laboratory, bleeding, and coagulation profiles, renal function tests, the liver profile, and other pertinent lab studies. Blood transfusion, large IV access sites, NPO status, fresh frozen plasma, and other treatments will be initiated along with other diagnostic studies to rule out other possible lesions, such as esophageal varices and bleeding ulcers.

Treatment

Patients afflicted with aortic disease frequently require an aggressive emergency response program. The treatment program requires communication between the ambulance or paramedic personnel, the hospital emergency room, the possible surgeon or interventionalist trained to handle these emergencies, the well-equipped operating room, anesthesiology, and

the nursing staff in order to provide adequate response to these emergencies. Depending on the situation, the patients on arrival to the hospital may be transported to (a) the emergency room for further evaluation and treatment; (b) the CT scan diagnostic room; or (c) directly to the operating suite—endovascular or surgical. The very acute patient will require totally different staffing and testing than the semi-elective relatively stable individual.

When the situation declares itself, the emergency room, the endo suite, the operating room staff, and the individuals responsible for the smooth but rapid treatment program will respond to the patient's needs [16]. The ability of the anesthesia department, the laboratory, and all of the support staff will be challenged to care for these acutely critical patients. When the situation is less dire, more elective and more effective diagnostic and treatment programs will be initiated.

Concomitantly, while treating these patients, we also treated a large number of ruptured abdominal aortas—as many as four patients in 24 hours with one patient in each of four hospitals. More frequently, we would see three ruptured aneurysms in 1 day. Such patients require experienced and willing physicians and staff to provide their care. Having seen this large volume of aortic aneurysms, we also had the unpleasant experience of seeing a number of individuals with aortoenteric fistula formation—whether primary or secondary.

Sample Case Reports

Patient #1

A middle-aged male was brought to the emergency room in profound shock with bradycardia and a huge abdominal aneurysm. The operating room staff was notified and mobilized to return to the hospital. In the emergency room, open laparotomy was performed in unsterile conditions to clamp the aorta. Uncross-matched blood was transfused and the patient taken to the surgical suite for definitive treatment. Postoperatively, he was treated with blood transfusion and high-dose antibiotics. After 2 months in the hospital, he was discharged home and followed as an outpatient. He returned to work and led a normal life for 3.5 years. At that time, he was readmitted to our hospital acutely with an aortoduodenal fistula. Following resection of the old graft, closure of the aorta, and subclavian femoral bypass, he slowly deteriorated after repeated difficulties with the extra anatomic grafts.

Patient #2

A 60-year-old Caucasian male was admitted to the hospital in shock and passing large amounts of blood per rectum. His history was complicated and detailed. He had a previous abdominal aortic procedure 20 years before with an aortofemoral Dacron bypass graft. He also had carotid endarterectomy followed by recurrent carotid symptoms and patch grafting of the carotid vessels. He then developed bilateral femoral false aneurysms (not infected) which were repaired. Cystectomy for bladder carcinoma and bilateral surgical ureterocutaneous fistula formation followed. He then required ureteral stomal dilation every 6 weeks with simultaneous prophylactic antibiotic treatment for possible sepsis. Recurrent gastrointestinal bleeding developed with large black "tarry" stools. After this, he was admitted to a nearby university on 11 occasions for treatment and evaluation of acute hypotension producing bleeding and had evaluation, including endoscopy, repeatedly without defining the source of bleeding.

With his 12th bleeding episode, he was brought to our hospital emergency room in a shock-like state with a systemic pressure of 60. He was immediately taken to x-ray for CT angiography, which visibly demonstrated the aortojejunal fistula. After discussion, he and his family decided to go home under hospice care. The next morning, after further discussion, he elected to have transfemoral endoluminal stent placement through bilateral recurrent large femoral false aneurysms in the radiology department. Postoperatively, he was placed on intravenous (IV) antibiotics and discharged home with no further bleeding. Three months later he was readmitted to the hospital with a fever. After initiation of IV antibiotics, he was taken to surgery and had removal of the previous aortofemoral Dacron graft, removal of the previous aortic bypass endograft, extensive lysis of abdominal adhesions, Betadine wound irrigation of the aortic bed followed by Bacitracin irrigation, insertion of a new aortic bifurcation graft in the bed of the previous Dacron graft, repeat extensive antibiotic and Betadine irrigation of the bed, and omental wrap of the new graft. Postoperatively he was maintained on antibiotics for 3 weeks and then discharged to home care following recovery. He did well for 7.5 years until he developed a laryngeal carcinoma and represented the second such endograft treatment reported in the literature [12].

Patient #3

A 65-year-old male was referred to us for maintenance care with a long history of coronary and vascular disease from another local university, having been hospitalized at two universities and two private hospitals for 11 months with an aortoduodenal fistula. Three weeks later he developed massive bleeding per rectum and was admitted to our hospital in shock and immediately taken to surgery. Previously, he had undergone coronary bypass surgery, open aortic aneurysm surgery with Dacron grafting, and

femoral artery bypass surgery. His aortic aneurysm had cultured salmonella and the femoropopliteal prosthetic bypass graft was infected. At surgery, repair of the aortoduodenal fistula included closing the duodenum in two layers and resecting the prior aortic graft. After extensive Betadine and Bacitracin antibiotic irrigation of the aortoduodenal bed (15 minutes), a new Dacron graft was inserted and wrapped with omentum. Inadvertently, the left ureter was transected during the procedure and repaired after insertion of a ureteral stent (maintained for 6 weeks). The patient subsequently had amputation of his left leg and lived for another 7 years without additional concerns regarding the aorta nor the small bowel, dying of acute coronary artery occlusion.

Case Study Summary

The above three patient examples illustrate our operative approach to the treatment of septic arteritis, infected grafts, and aortoenteric fistula. Our treatment has progressed from the early 1970s resection and extra anatomic bypass procedures to the (a) resection of the infected aorta, aneurysm, or graft; (b) primary closure of the enteric fistula; (c) extensive use of Betadine and antibiotic (usually Bacitracin) irrigation solutions; (d) insertion of a new Dacron graft in the old bed; and (e) placement of an omental wrap which we consider critical to obtain successful results.

Treatment of Aortoenteric Fistula

I. Appropriate diagnosis
II. Stabilization if possible
III. Endograft
    A. Most cases
    B. Faster/less blood loss
    C. May convert to open later
IV. Surgery
    A. Resection of infected graft/aorta
    B. Primary closure of enteric fistula
    C. Extensive wound irrigation
        1. Betadine
        2. Antibiotic (e.g., neomycin/polymyxin)
    D. New Dacron graft
    E. Omental wrap— - cover graft
    F. No retroperitoneal closure
V. Postoperative
    A. Stabilization
    B. Antibiotics
        1. Acute 3 weeks
        2. Selected patient for life
    C. Intensive care

Over the years, we have seen a number of patients who have had extra anatomic bypass procedures (such as subclavian femoral) who required extensive surgery and yet only had fair long-term bypass function. Other surgeons however continue to use this technique [17]. Having treated a number of patients with localized non-aortic graft infections, without resection of the graft, with open wound debridement, with graft exteriorization, with local Betadine solution, and antibiotics, we then developed this technique for aortoenteric fistula therapy.

Surgically, we always used two experienced vascular surgeons for the treatment of these patients. Each of these patients has been approached through the previous, usually midline, abdominal incision. The surrounding retroperitoneal scar is dense and dissection about the renal arteries difficult. With careful tedious dissection, proximal and distal aortic control may be obtained—at times above the renal arteries. After heparinization, the aorta and iliac vessels are clamped. The infected grafts are removed along with debridement of the necrotic infected tissue from the vascular bed, but not the dense fibrous tissue. After closure of the enteric fistula (duodenal, small bowel, colon) or ureter, the wound is soaked with Betadine for 15 minutes and then with Bacitracin solution (neomycin only if normal renal function and Bacitracin concern). Prolene sutures are utilized to suture the graft to the aorta and Vicryl or chromic sutures to attach and hold the omentum in place around and over the aortic anastomosis and the Dacron graft and to exclude the duodenum and bowel from touching the graft. Postoperative intravenous antibiotic treatment, depending on culture and sensitivity studies, is maintained for a few weeks to life as determined by the situation and the organisms cultured. The Prolene suture knots are placed to the left and sutured down with absorbable sutures if possible. Silk is not utilized for anastomosis as it deteriorates with age and may be a nidus for infection. A similar approach has also been discussed by Walker et al. [18].

If the patient is stable hemodynamically, the above approach is utilized on a semi-elective basis. When the patient is hemodynamically unstable and felt to be at prohibitive operative risk, and the femoral vessels are accessible, stent grafting has been utilized to stabilize the patient prior to open surgical therapy, as illustrated in patient two above. With the endostent in place, the patient may receive blood transfusions and simultaneously have antibiotic therapy initiated.

Cultures may be obtained and the patient electively returned to the operating suite for definitive closure of the enteric fistula and resection of the infected graft. Some surgeons have utilized transfemoral balloon insertion above the fistula to temporize until surgery is possible. We have not utilized this approach. After placement of the endostent, in

the more chronic fistula patient, oral nutrition may be resumed in these patients as they have been eating and tolerating the passage of food prior to their admission. However, we do not feed the patient with the first acute episode until they are stable and treatment initiated. Since using the above approach, the treatment of aortoenteric fistula patients has shown a remarkable improvement in patient recovery and long-term survival results. Using this approach, each of our patients has survived the procedure to lead a quality life unless they had other simultaneous non-fistulous health processes. These patients demonstrate the challenge of polymicrobial infections in vascular surgery. Both gram-positive and gram-negative bacterial organisms and fungi may be present at the time of the fistula culture. We favor the in situ or endograft approach except in the very unusual patient where an extra anatomic graft may be utilized as some advocate [19].

If one could predict which patients would develop a fistula, different surgical techniques might be utilized. When repairing aortic aneurysms or performing aortoiliac grafts, one needs to avoid the possibility of entering the bowel during dissection. We have closed the abdomen and awakened the patient upon inadvertently entering the bowel in elective patients—to return another day to perform the vascular surgery—in hopes of avoiding graft infections. Further, vascular grafts under tension should be avoided to prevent erosion of the contiguous tissue—such as the ureter or bowel [20]. Also when closing, the abdomen, the synthetic graft should be protected from direct contact with the surface of the bowel, to prevent or reduce the possible formation of pressure necrosis and a fistula. Placing the synthetic aortic bifurcation graft limbs beneath the ureters and covering the graft with aneurysmal wall, peritoneum and omentum should reduce the chance of fistula formation. When urgency dictates, we have utilized a transthoracic or a subdiaphragmatic approach for proximal control of the aorta as temporizing blood-sparing approaches in the critical patient. Each of these methods however may add other potential complications and thus are avoided when possible. We abandoned suture closure of the distal aortic stump as we developed the current technique and have had no aortic or iliac vessel disruptions since utilizing this approach.

When closing the intestinal defect, we have utilized a two-layer absorbable suture closure when possible with all potentially ischemic, irregular, or possibly infected material resected or inverted into the lumen of the small bowel or colon. If appropriate, edges of the intestinal defect may be debrided along with any necrotic material. It has been interesting to find that in some patients the fistula is more mature and the surrounding tissue is not necrotic but more fibrotic in nature. Also depending on the fistula type and the location of the fistula in reference to the graft, there may be areas of the aortic graft with no evidence of contamination or necrosis. The area around the fistulous tract may be densely adherent and fibrotic with no liquefied pus. On occasion, in these situations, when further dissection was felt to be highly risky, a short ring (1/2–3/4 inch) of previously placed prosthetic graft has been left in place along with prior sutures. We then suture the new prosthesis to the previous ring of the residual Dacron prosthesis.

In the instance of a primary infected aorta, we have resected the necrotic infected aorta and placed a prosthetic graft wrapped with omentum. These septic patients are critically ill and, consequently, carry a high morbidity and mortality risk. Certainly, repeat infection of the graft in these patients is a consideration but, fortunately, we have not encountered this concern.

Clamping of the aorta and the iliac vessels for the duration (up to 5.5 hours) of the operation has uncommonly led to limb ischemia and amputation unless previous ischemia, occlusion, or clot were present. Blood and fistula cultures along with cultures from about the graft have all been acquired to direct antibiotic treatment postoperatively. Secondary infections have not been a concern in our experience. Placement of omentum between the repaired duodenum and aorta to avoid direct contact and decrease the possibility of repeat aortoenteric fistula formation is a necessity.

We began using the endovascular stent (endograft) stabilization of the hemorrhaging fistula patient in 2002 [12]. In the selected patient, we have felt this was not only appropriate but life-saving. Some surgeons have reported long-time use of this approach without subsequent resection of the initiating or infected graft. We have taken the approach that the fistula needs to be closed (bleeding controlled), and in the future the previous infected graft resected, the endograft removed and a new replacement graft inserted. Other options, utilizing the endovascular repair for control of the bleeding, have included insertion of an intra-aortic balloon catheter and attempts at embolization. We have not used these techniques nor have we placed postoperative sump drains about the graft. Necrotic material and pus have been found on these grafts at surgery, but no large abscess has been encountered by us. Our approach has been to use the endovascular or EVAR graft in the select patient as a short- or possible longer-term treatment. This may be for a few days or a few months, but not necessarily for the duration of one's life unless the patient's other medical conditions contradict further intervention.

The patient with primary aortoenteric fistula presents a different concern because of the friability of the aorta and the cause of their original sepsis. Thus, the risk for additional complications seems to be much greater in these individuals, including mortality. Postoperative intensive care monitoring, stabilization, and treatment will include blood

counts, temperature checks, blood cultures, vital signs, and frequent physical exams in these individuals.

Prognosis

The lesions herein described present the patient and the treating team a difficult and high-risk situation. Left untreated, the mortality is almost 100%. When treated, the complication rate is great, but the possibility of survival and success are present [17]. In our experience, by using the newer techniques of endografting, proper vascular grafting and placement techniques, appropriate antibiotics, omental wraps and patient-centered nursing care, these patients have a reasonable chance for survival [21]. But reports of post-EVAR aneurysm therapy have shown that a 0.8% of the patients (32 of 3932) developed an aortoenteric fistula within 18.5 months of aneurysm treatment, especially when EVAR was utilized for pseudo-aneurysm or emergency therapy [22]. Whether the spiral saphenous vein reconstruction of the infected aorta by Heyligers and Vriens will prove superior to the endograft will require further evaluation [23]. Similarly, other research, such as lithoplasty, will require time for analysis [24]. All of the studies will be observed for the restrictive value in blood transfusion and, in morbidity, mortality, and cost [25].

Unfortunately, many of these patients have multiple simultaneous disease processes which require concomitant treatment. Amputation of an extremity, renal failure, prolonged intubation, bowel concerns, and long-term respirator care are all considerations. With the current aggressive multidisciplinary therapy programs, the mortality rate has been reduced, and long-term survival may be available to a large percentage of these patients [26, 27]. Infections, a challenge of vascular surgery, and other potential complications continue to be monitored [26].

Along with medical therapy, the expense of treatment of these patients continues to rise, unfortunately placing an additional burden on the patient, the family, and the treating medical team. These fistulae are an uncommon but life-threatening process requiring diagnosis and treatment on an urgent basis—many within minutes or hours. The associated age and medical condition of these patients have a great impact on their potential outcome. Another possible fistula might be an aortoappendiceal communication. We have never seen one of these, but literature review has demonstrated a few articles regarding aortoappendiceal fistula formation (A-A-F). Rectal bleeding seems to be a major sign of the A-A-F. As a result, colonoscopic examination has been used in the diagnosis of such a fistula [28]. These fistulas may also arise from the chronic, infected, and contained rupture of an abdominal aortic aneurysm [29].

Bronchobiliary and gastrobiliary fistula are uncommon but may occur in the young or the adult patient [30]. We have not seen a patient with an aortobiliary fistula, but arteriobiliary fistulas do occur on the rare occasion [26]. Kawakami et al. have reported their experience, utilizing a fully covered self-expandable metallic stent placed endoscopically to treat an arteriobiliary fistula [30]. Fedakar et al. published in 2011 an aortobiliary fistula in their report of 93 patients with an abdominal aortic aneurysm [27]. We have not encountered another possible fistula, an aortoappendiceal communication, but we have found references in the literature. Prosthetic aortic graft intervention may also lead to multiple aortic fistulas in the same patient and includes the aortoenteric (e.g., duodenal) and aorto-caval fistula. With the new and unusual approaches, including the transvenous approach to the aorta and cardiac lesions (e.g., valvular lesions), it is assumed more such fistulas will develop.

Anesthetic Consideration

It goes without saying that a competent anesthesiologist and OR team are very important to the provision of successful major vascular surgery, especially when that surgery involves the aorta and aortic complications. This capability requirement involves both the open aortic procedures and the closed or endovascular procedures. Various techniques have been espoused for the multiple requirements to accomplish stabilization and treatment of patients with aortic lesions. The elective correction of aortic lesions may be approached much differently than the emergency patient in shock or receiving cardiopulmonary resuscitation.

Thus, in our experience, the patient in critical condition must have respiratory and cardiac control as the primary goal during the resuscitative efforts. Endotracheal intubation along with venous access (usually two or more) to maintain oxygenation, to improve or obtain a blood pressure, blood infusion, cardiac monitoring and attempts to stabilize the patients are primary. Additional assist considerations such as an A-line, central venous access, antibiotics, and TEE may all be considered when the situation is better controlled.

In the elective prior planned surgery in a patient with an aortic lesion, preoperative planned programs progress at a different speed and utilization. In these patients, when possible, an anesthetic consultation before procedure should clarify some of the desired steps to be utilized. In these patients, preoperative antibiotics, blood typing and screening, and the possible requirement for a central venous access are all determined. In the OR or special procedure room, the requirement for or not of an arterial line or TEE (transesophageal echo) may be assessed along with the possibility of an epidural (including possible bleeding considerations).

Postoperatively, the patient is usually taken to the recovery unit and then the intensive care unit as necessary. Nasogastric intubation may or may not be necessary.

Of note, more recently, an increase in deaths due to abdominal malignancy have been reported following aortic endograft procedures for abdominal aortic aneurysm therapy. These malignancy deaths are presumably due to the increased radiation dosage received during endograft implantation and the post procedure serial studies of the endovascular implanted aortic aneurysm grafts.

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Malignant and Benign Aortic Tumors

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Raymond A. Dieter Jr., George B. Kuzycz, Raymond A. Dieter III, Jessica Gulliver, and Robert S. Dieter

Malignancy represents one of the more common afflictions of the human body, but benign or malignant tumors of the aorta are very rare. Several causes or etiologies of tumors have been defined and related to various human habits or acquired infection. Smoking and herpes infections represent two of the etiologic agents related to tumor inducement in the adult human. Neither of these, however, has been associated with primary vascular tumor development nor has any other defined risk factor.

Malignancy of the vascular tree is very uncommon to rare. Rarely, if ever, are primary or secondary malignancies of the major arterial or venous systems encountered by the average vascular or thoracic surgeon. Certainly, as tumors develop, nutrition for the growth and multiplication of the malignant cells must be provided by the surrounding arterial system. But the vascular network providing such necessities is usually of the smaller arteriole and venous system.

Only on occasion does the neoplastic process involve the larger vessels. When this occurs, the patient may develop either acute or chronic symptoms related to the vessel(s) involved. When tumor involvement occurs in the lung, hemoptysis may develop. When tumor involvement of the major vessels to the extremities occurs, either acute or chronic extremity ischemia may create major consequences for the patient [1]. In the latter group, major peripheral vessels, the heart, or the aorta may be the source for the ischemic process by either embolic, obstructive, or constrictive mechanisms.

Aortic tumors, either primary or secondary in origin, are very uncommon, and thus, many physicians, including cardiovascular surgeons, have never had the opportunity to treat patients with these concerns. The original presentation may be confusing and thus suggest other non-neoplastic disease entities as the cause for the patient's complaints. Even initial diagnostic testing may be misinterpreted or suggestive of a non-neoplastic etiology for the patient's complaints, as discussed in the Critical Extremity Ischemia book [1]. However, both primary and secondary aortic tumor involvement does occur and, in most instances, creates major diagnostic and therapeutic challenges.

Primary Aortic Tumors

Lesions involving the aorta are common, and their symptomatic results are familiar to both the healthcare profession and the lay public. To mention that an individual has an aortic process affecting their health immediately brings forth an image of possible risks and the possible result. The aorta is well recognized as a major structure by the medical and nonmedical community to be necessary for the development and maintenance of one's body and its function. The usual aortic aneurysm rupture or occlusive concepts are generally understood. However, discussion with a pathologist of the incidence of primary or secondary aortic neoplasm involvement is usually met with a pause and then, "I don't believe I have ever seen such a tumor." They then will discuss the occasional hemangiopericytoma, and similar small vessel tumors, or the benign/malignant endocardial tumors which may embolize. Both of these examples are much more frequent than the aortic neoplasm and still are not common.

Aortic tumors may be classified in a variety of manners depending on the type of classification to be utilized. Lesions may be categorized as malignant or benign. They may be categorized according to their location in the aorta, or they

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may be grouped according to symptomatology. The major pathologic tumor types that one may encounter directly involving the aorta are as follows.

Types of Benign and Malignant Aortic Tumor Classifications

I. Primary
  A. Malignant (sarcoma—most common pathologic diagnosis)
    1. Angiosarcoma (25%)—epitheloid
    2. Pleomorphic sarcoma
    3. Intimal sarcoma (27%)—actually define location
    4. Malignant fibrous histiocytoma (15%)
    5. Leiomyosarcoma (14%)
    6. Undifferentiated/high-grade sarcoma (9%)
    7. Fibromyxosarcoma
    8. Myofibrosarcoma
    9. Hemangiopericytoma
    10. Chondrosarcoma
  B. Benign
    1. Myxoma
    2. Lipoma
II. Secondary/metastatic involvement
  A. Lung
    1. Non-small cell
      (a) Squamous cell
      (b) Adenocarcinoma
      (c) Large cell
    2. Small cell
  B. Esophageal
  C. Retroperitoneal lymphoma
  D. Mediastinal
    1. Malignant thymoma
    2. Malignant germ cell
III. Associated tumor
  A. Fibrous histiocytoma
  B. Cardiac embolic
IV. Benign lesions—only a small percentage of the total aortic tumors
  A. Localized polypoid lesions
  B. Thrombotic mass-like lesions

The most frequently reported tumor involving the aorta is the sarcomatous group. Primary epithelioid angiosarcoma is the most frequently reported primary malignancy of the aorta, and non-small cell lung carcinomas (squamous cell and adenocarcinoma) are the most frequent metastatic lesions involving the aorta. Less frequent malignancies and other very uncommon lesions are also diagnosed. The primary aortic tumor may metastasize to other locations.

Primary Aortic Tumor Metastatic Sites

I. Intraluminal—embolic
  A. Legs
  B. Mesentery
  C. Kidneys
II. Periaortic—direct
  A. Thoracic
  B. Retroperitoneal
III. Hematogenous
  A. Bones
  B. Skin
  C. Organs
IV. Liver
V. Spleen
VI. Lung

Most reports of primary aortic tumors are of single or a small number of malignancies involving the aorta [2–19]. The paucity of series reports further demonstrates the rarity of this disease. The sarcoma groupings (epithelioid; pleomorphic; angio-, fibro-, myofibro-, leiomyo-, and undifferentiated sarcoma groupings) are varied in frequency, occurrence, and appearance. Less commonly reported are the fibrous histiocytomas [18]. But, all these sarcomas are highly malignant with a guarded prognosis. Lipomas are the most common benign aortic tumor [6, 9].

Similarly, the secondary or metastatic malignancies of the aorta also carry a guarded or unfavorable prognosis. These lesions usually occur in the 50- to 70-year age group and may result primarily from the pulmonary or bronchopulmonary group of carcinomas (CA of the lung) or esophageal carcinomas. All cell types of the lung have been involved. These include both the small cell and non-small cell malignancies, including the large cell, the adenocarcinoma, and the squamous cell tumors [20–31]. Malignant thymomas and germ cell involvement have also been known to involve the aorta.

The primary aortic tumors also metastasize in a fashion similar to many of the other malignant tumors which an individual may develop. The primary tumor, especially the sarcomas, initially may present with both local and distant spread. One of the more common aortic tumor presentations is the distant embolic phenomenon of the tumor cast or secondary clot with occlusion of the iliofemoral or enteric systems, especially creating sudden secondary ischemic

symptoms of the abdomen or legs [3]. Also, periaortic direct local extension of the malignant thoracic or retroperitoneal aortic lesions is a natural consequence of these malignancies. Similar to many other malignancies, hematogenous spread to the bones, liver, and spleen is reported [3, 7, 17, 19]. Some patients have also developed multiple palpable skin or subcutaneous metastatic nodules [7, 10].

Aortic Tumor Symptomatology

As with so many diseases, development of one or more symptoms may direct an individual to finding the primary disease entity almost immediately after development of the symptom. But as with many disease entities, the presentation, the symptom complex, and the patient's history may be both confusing and misleading. The literature demonstrates that both the diagnosis and the potential suggested treatment routes by the physician have frequently been led astray due to the lack of specificity of symptoms and diagnostic studies. Such a dilemma occurs with both primary and secondary tumor involvement of the aorta.

The symptomatology most commonly revolves around four main areas: (1) embolic, (2) occlusive, (3) pain, and (4) generalized or systemic.

Potential Aortic Tumor Symptomatology

I. Embolic symptoms
   A. Acute
   B. Chronic
   C. Loss of function
II. Occlusive—progressive
   A. Abdominal aorta
   B. Coarctation/dissection type
III. Pain—sudden or progressive
   A. Abdominal
   B. Extremities
   C. Thoracic
IV. Generalized/systemic
   A. Weight loss/fatigue
   B. Fever
   C. Night sweats
   D. Nausea
   E. Anorexia
V. Renal—infarction
VI. Clubbing—hand
VII. Neural
   A. Horner's syndrome
   B. Hemiplegia
VIII. Extremis

Embolic symptoms may develop in both the upper and lower extremities and in the abdomen. Most commonly, the embolic tumor or clot may produce acute symptoms with sudden and total occlusion of the recipient distal artery.

Symptoms Due to Embolic Aortic Tumor

I. Extremity
   A. Ischemia
   B. Claudication
   C. Acute or chronic pain
   D. Loss of function
II. Skin
   A. Pallor
   B. Hematogenous lump or rash
III. Stroke
   A. Unable to speak
   B. Major paralysis
IV. Coronary occlusion
V. Buttock pain
VI. Gastrointestinal—ischemic bowel

Depending on the artery involved, the patient may develop stroke, severe acute leg pain, renal concerns, or skin lesions [2, 3, 8, 11, 18, 32, 33]. In the legs, the acute embolic pain may be sudden and excruciating with pallor and loss of function. Or, with smaller emboli, the pain may be slow and insidious in onset depending on the vessel occluded and size of the clot or tumor embolus. Abdominal symptoms also may be sudden and catastrophic with embolization to the enteric (e.g., superior mesenteric artery) or renal vessels. The patient who develops a sarcoma in the abdominal aorta may have progressive and confusing discomfort similar to that of an aortic aneurysm.

Pain due to a thoracic aortic tumor may resemble that of an expanding aortic aneurysm. The tumor may also embolize distally—downstream—or more proximally to cause a stroke [11, 32]. The distinction of a primary tumor-induced cerebral infarction from a stroke due to aortic dissection may be difficult even after diagnostic studies. Retrograde occlusive coronary artery involvement has also been demonstrated acutely in a patient [16]. The thoracic aortic tumor symptoms may also present with pain similar to an acute dissection [7]. Horner's syndrome along with hemiplegia was also reported in the patient with acute coronary [16]. Less common symptoms may result from fistulization into the bronchus, vena cava, and esophagus along with gastrointestinal bleeding.

Other systemic symptoms include weight loss and fatigue in many of the patients. Nausea, unilateral clubbing, night

sweats, and fever may suggest other maladies in these patients.

Associated Symptoms and Risks of Aortic Tumor

I. Concommitant—atherosclerosis
II. Age—40s, 50s, 60+
III. Sex—more common in males
IV. Hypertension—resistant to diagnosis/treatment
V. Aneurysm formation
   A. Leakage—descending thoracic
   B. Multiple
VI. Smoker/cough
VII. Death—acute
   A. 1 year—most
   B. 3+ years—more than 90% deceased

The patients tend to be older, over 60 years of age. A few are in the 40- to 50-year age range, and the age range of occurrence is from 3 months to 82 years [5, 32]. It also seems that the male gender predominates, with only a few females reported with these tumors [16, 19]. Single or multiple aneurysm formations with suspected leakage present diagnostic concerns. Elevated blood pressure has been found in a number of these patients as has the smoking habit.

Morbidity is great in these patients, and the aortic tumor diagnosis suggests a highly morbid outcome. As a group, these sarcomatous lesions are highly fatal. The individual may present acutely in a moribund state, and surgery in this acute state is very risky. By the end of 1 year, a large portion of the patients have passed away despite therapy. A few patients survive up to 3 years. However, there is 90% mortality by the end of 3 years [7]. The survivors are primarily patients with low-grade malignant or benign tumors.

Aortic Tumor Diagnosis

As already mentioned the patient's symptomatology and findings may be difficult to sort out and confusing. The patient's history may be classical for other more common lesions and lead the physician down the wrong diagnostic pathway. Thus diagnostic testing options and consultants may be led astray by the patient, the history, the physical findings, and the diagnostic studies. The sorting out of pertinent historical and testing interpretations may prove difficult.

But, symptomatology and physical findings may lead the diagnostic and treatment approach in the correct direction. Even then, the diagnosis may not be established until after therapeutic intervention has occurred. Such is the case, for example, when a thrombus has been removed from the lower extremity and the pathologist, a few days later, forwards the microscopic findings and pathologic diagnosis [1].

The usual initial approach to the patient's problem is to obtain a history from the patient or of an accompanying individual regarding the patient's complaints. This is followed by a complete physical examination—head to toe. Having assessed the situation, this initial assessment will guide the number and type of studies to be obtained. Initially, a CBC (complete blood count) and x-ray may be ordered to help differentiate the problem. With the modern-day emergency room programs, most of these studies will be obtained in the emergency room (ER) along with other blood tests and radiologic scans.

The physical exam may demonstrate a relatively stable and less emergent situation or may dictate urgent or emergency diagnostic testing, blood typing, consultation with potential diagnosticians, and intravenous access which may all be required during the initial evaluation.

Laboratory testing may show a marked anemia, an elevated sed rate, an increased C-reactive protein (CRP), or an increase in the number of white blood cells (WBCs). All of these are nonspecific and may be misleading. The physical diagnosis may reveal a stable nondistressed individual or a patient in severe pain. He/she may be pale, febrile, and tachycardic and have a heart murmur. The legs may be pale and pulseless or immobile. The patient may have severe abdominal or chest pain and be in extremis.

The skin may contain multiple nodules and petechiae. The patient may be aphasic or hemiplegic. The abdomen may be tense and distended. A Horner's syndrome or ocular disturbance may be present. Urine may be abnormal and the BUN and creatinine elevated. The blood pressure may be elevated and vary between the right and the left arm [33]. Evidence of weight loss and clubbing may be obvious to all.

Testing will proceed along the most likely and appropriate route to establish the diagnosis and course of treatment. Different findings and results may lead to the best and most expeditious course of treatment. Less complicated studies such as an arterial Doppler, electrocardiogram (EKG), and emergency room (ER) echocardiogram may all be obtained with varying results.

Diagnostic Studies to Delineate Aortic Tumors

I. Radiologic imaging
  A. CT (computerized tomography)
    1. May be misleading
    2. CT angiogram
  B. MRI (magnetic resonance imaging)
    1. Gadolinium
    2. MRA (magnetic resonance angiogram)
  C. Angiography
    1. Arterial—diagnostic
    2. OR (operative room)
    3. Venography
  D. PET scan (positive emission)
II. Biopsy/tissue
  A. Microscopic
    1. Mass
    2. Skin
  B. Immunohistochemical (best)
  C. Vascular system
  D. Surgical specimen
III. Lab—CBC—nonspecific
  A. Increased sed rate
  B. CRP (C-reactive protein) increase
  C. WBC (leukocyte count) increase
  D. Video microscopy
IV. Echo
  A. TEE (transesophageal echocardiography)
  B. Cardiac Doppler
  C. Arterial ultrasound
V. Autopsy

Many of the studies performed in these patients are presented above. A fairly frequent approach may include an emergency CT (computerized tomographic) scan. These may be misleading or misinterpreted as an aneurysm or thrombus due to the rarity of a primary aortic tumor [2, 12]. A CT angiogram, with intravenous contrast, may follow due to the lack of an established diagnosis [2]. Others have performed magnetic resonance imaging (MRI) in an effort to delineate the patient's diagnosis and extent of disease. MR angiography and the use of gadolinium have been advocated in the diagnostic "tree" due to the inability to differentiate lumen from the arterial wall [3, 8, 16, 32]. None of these scans have proven sufficient in all situations, and thus, angiography including operating room (OR) angiography has also been required [8]. Distal aortic angiography has been utilized to rule out a Leriche syndrome [15]. Using these techniques and transvascular angiography, one must guard against distal embolization [16].

Due to the difficulty in diagnosis of these patient's problems, other studies have included a TEE (transesophageal echo) and temporal artery biopsy [3, 16, 31]. PET (positive emission tomography) has further been utilized to delineate the extent of the patient's disease—especially in suspected metastatic disease. Skin or nodule biopsy may prove confusing and diagnostic. Obviously tissue biopsy and associated immunohistochemical studies are the most accurate diagnostic studies available. But this requires obtaining tissue and the recognition that tissue is necessary [17]. Even video microscopy has been utilized.

Preoperative biopsy of aortic tumors or transarterial tumor biopsy has been discussed in the literature. In the past, 17 gauge 7 1/2 inch translumbar aortography was a routine and rapid testing procedure for aortic, renal, or iliofemoral disease with little morbidity in our experience of its usage in hundreds of patients. This technique has been largely supplanted by catheter angiography for diagnosis and treatment. Transvascular biopsy techniques have been developed for multiple disease entities such as liver and renal disease, or cardiac rejection [34–36]. This transvenous approach for the biopsy of neoplasia has been utilized for cardiac tumors, retroperitoneal tumors, cavoatrial tumors, and pancreatic tumors [37–39]. Despite the availability of transarterial and transvenous needle and catheter techniques, the use of these approaches is uncommon for aortic tumors. The final tissue diagnosis usually does not occur until the surgical exploration and removal of the tissue specimen. The final, but unfortunate, diagnostic approach may be an autopsy in the difficult situation. Utilization of transarterial or transaortic biopsy techniques has not gained favor for the diagnosis of primary aortic tumors due to the embolization concerns [16]. Also, arterial endoscopic techniques have not been utilized for diagnostic purposes in these patients.

Differential Diagnosis

As already presented, diagnosing and differentiating the true nature of an aortic neoplasm may be very difficult and the correct pathway to the tumor definition tortuous. The patient's symptoms may be confusing, misleading, and strongly suggestive of other disease entities.

Concurrent preexistent disease and treatments may confuse the issue and mask the underlying sarcoma. Depending also on whether the aortic tumor is primary or metastatic from a non-arterial primary tumor may cloud the diagnosis and even be difficult to diagnose under the microscope. Also, a benign primary aortic tumor may present differently than a malignant aortic tumor.

Consulting radiologists or cardiovascular surgeons may misinterpret the history, physical, laboratory studies, or radiographic evidence as to the true etiology. Cardiac murmurs or aortic bruits may suggest underlying vascular disease, such as mitral regurgitation with valvular prolapse or a chronic Leriche syndrome. A lateralizing stroke can suggest aortic dissection or cardiac emboli. Abdominal pain with distention and bruit may imply atherosclerotic disease—especially if previous history is compatible. Some of the disease entities that may be misapplied to the patient's symptoms are the following.

Differential Diagnosis of Aortic Tumors

I. Valvular heart disease—mitral regurgitation with prolapse
II. Aortic occlusion—abdominal/Leriche
III. Primary intra-aortic thrombus
IV. Horton's disease
V. Infections
  A. Mycotic aneurysm
  B. Positive cultures
VI. Lung cancer—in association
VII. Anatomy: congenital
  A. Right aortic arch
  B. Confusing
VIII. Multiple malignancies

The presence of chronic symptomatology due to other nontumor lesions may suggest superimposed acute progression of a vascular process, such as arterial or aortic atherosclerosis of the aortoiliac vessels, rather than an embolic tumor thrombus. A suspected mycotic aneurysm may be pursued with blood cultures, angiography, and antibiotic therapy [3, 7]. When other lesions exist, such as bronchopulmonary malignancy, the aortic association or involvement may be difficult to differentiate. Bronchoscopy may yield the tumor diagnosis, but not define the aortic concern. Similarly, congenital aortic arch and branch formation such as the right arch and descending aorta with aneurysm formation may further cloud the diagnosis [25, 27].

Multiple malignancies may also confuse the physician [32]. Development of primary angiosarcoma in a previous aortic graft will be confusing [40]. Other surgical procedures, such as cholecystectomy, have been performed while attempting to improve the patient's condition—without benefit [41]. Presence of exophytic-calcified atheroma may, but not correctly, suggest the presence of a benign papillary fibroelastoma [42]. Further, floating thrombus or polypoid thrombus may also be found distal to the aortic valve and produce confusing distal systemic symptoms.

Similarly, one must carefully review the CT scan, MRI, or other studies to eliminate the possibility of another non-aortic origin site of tumor such as the left ventricle or other cardiac locations—even in infants [43]. The diagnosis may be further confusing when infectious complications develop during the course of the disease.

Aortic Tumor Location/Classification

The aortic tumors (mostly of mesenchymal origin) may occur in any location from the aortic valve to the aortic bifurcation. The type of tumor, benign or malignant, defines to some degree the primary location of the tumor. If the broadest tumor definition includes a mass of any type, then the floating thrombus or polypoid aortic thrombus seen in the ascending aorta, especially just above the aortic valve, probably represents the most common aortic tumor [44]. The subsequent distal embolic symptoms may also be confusing as to their origin.

Echocardiography has proven helpful in this determination as to site of origin. These lesions demonstrate one of the growth patterns of aortic tumors, namely, the intraluminal form. Three forms of aortic tumor growth have been defined morphologically: (1) intraluminal, (2) intimal, and (3) mural (to include adventitial) [41].

Location of the tumor has also been delineated anatomically as to the level of the aorta involvement. Forty-six percent of the tumors are located in the chest, 25% as thoracoabdominal, and 27% in the abdominal aorta [7]. Further localization to the aorta is shown below. The transverse aorta and arch seem to be particularly prone to the primary aortic tumor and also may be confusing when they create a dissection. The descending aortic lesions may be subclassified into proximal, mid, and distal thoracic lesions and include both primary and metastatic malignancies.

Aortic Tumor Location and Differential Diagnosis

I. Ascending aorta
  A. Lipoma—adventitial
  B. Polypoid thrombus—endoluminal
II. Arch—especially transverse aorta
  A. Atheroma
  B. Dissection
III. Descending thoracic aorta
  A. Proximal—primary aneurysm
  B. Mid-thoracic
  C. Distal thoracic
IV. Abdominal
  A. Suprarenal
  B. Aneurysm
  C. Paravascular—renal occlusive
  D. Infrarenal
    1. Leriche
    2. Intra-aneurysm
V. Metastatic sites—bone, liver, adrenal, and lung

Intra-abdominal aortic tumors may also be subclassified according to the aortic lesion location. These tumors may be suprarenal, paravascular, or infrarenal, and symptoms may vary according to location—for example, they may cause renal artery occlusion. The general anatomic locations for the tumor-originating site can thus have some effect on the type of symptoms a patient may develop. For example, the ascending and arch locations may produce pain and stroke type of symptoms while the descending or abdominal primary sites may produce renal, gastrointestinal, systemic, or lower extremity complaints.

Non-aortic location of aortic tumor metastases may develop in multiple organs throughout the body. These sites include the bones, liver, kidneys, adrenal glands, and lung. Non-aortic primary tumors involving the aorta further confuse the issue as to the symptoms and diagnosis. The most common of these invasive tumors causing aortic involvement include the bronchopulmonary carcinomas and esophageal and the retroperitoneal tumors, which have a direct or contiguous contact with the aorta. This further confuses the diagnostic and treatment attempts. To date, however, we have not seen direct tumor invasion requiring aortic resection due to mesothelioma nor malignant thymoma.

Aortic Wall Involvement

These tumors may involve any layer of the aorta. Microscopically, they may be difficult to diagnose and to differentiate as to the cell type and point of origin. We have already mentioned the primary locations from which these tumors originate. Additional classifications exist as to the type and site of initial growth.

Location of Tumor in Aortic Wall

I. Intraluminal thrombus—polypoid
   A. Obstructive
   B. Embolize
II. Endothelial
III. Intimal
   A. Tunica intima
   B. Usually descending thoracic or abdominal
   C. Prone to embolize
IV. Intramural
   A. Extravascular dissection
   B. Media—extravascular growth may cause S and S
   C. Adventitia
V. Aortic branches—subclavian aneurysm

The most common point of origin seems to be the intimal or tunica internal layer [3, 5, 19, 33]. Because of their origination site, many of these tumors may grow into the aortic lumen and produce polypoid-type lesions that may further be classified as obstructive or nonobstructive. It seems that these lesions are more commonly located in the descending thoracic and the abdominal aorta. This tendency may lend itself more to the formation or creation of emboli in association with narrowing of the aorta. Primarily polypoid lesions may also be felt to originate in the endothelium [17, 19].

The intramural-originating aortic tumors (18%) may lead to dissection or a differential diagnostic concern resulting from dissection like findings as a result of their media origin. Extravascular growth from tumors originating in the media or adventitia usually creates greater mass-like tumors [16]. Ten percent of the malignant aortic tumors involve all three layers of the aorta. The intraluminal benign mass lesions are usually of thrombus or plaque in origin. Whereas the benign lipomatous lesions usually arise in the adventitia or in the outer layer of the aorta, major luminal encroachment may and does occur with most of the malignant aortic tumors. Such encroachment may lead to vascular occlusion as a result of growth, thrombus, or embolus. When the tumor involves the vessel media in and about the major cerebral circulation, cerebral ischemia or infarction may then create preoperative uncertainty as to the diagnosis.

Secondary complications due to the tumor depend in many instances on the wall location of the primary tumor origin. Stroke, renal infarction, and other embolic sites may result from the intraluminal lesion embolus, intramural growth and dissection, as well as additional adventitial mass formation. Such mass formations may thus be primary or secondary in origin. Nonprimary malignant growths involving the aorta primarily originate from contiguous invasive malignancies such as the pulmonary or retroperitoneal lesions. Periaortic contiguous tumor masses may be malignant—such as lymphoma or carcinoma of the lung—and difficult to diagnose and treat. Such lesions may be benign, partially calcified, and delineation from an actual aortic aneurysm, small vessel aneurysm, or benign tumor lesion vexing (Fig. 28.1).

Treatment of Aortic Tumors

Successful treatment of the patient and his/her disease usually depends on having a correct initial diagnosis. With knowledge of the type of process afflicting the patient, appropriate therapy may then be initiated. Medical, oncologic, and surgical treatments are all utilized when the diagnosis indicates. Unfortunately, with the malignant tumors of the aorta, diagnosis is often not established early in the process and, in a large number of the patients, only established

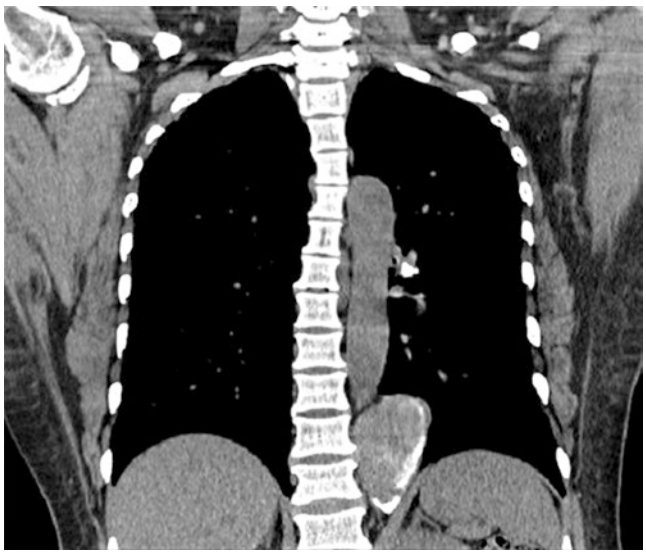

Fig. 28.1 Photograph of partially calcified lesion abutting the thoracic aorta seen on CT scan

after surgical intervention. Thus, initial treatment may be delayed, misguided, or directed to a lesser potential patient success.

Benign and malignant aortic lesions usually require surgical intervention. Many of the treatments and procedures that have been utilized in assisting these patients are as follows.

Aortic Tumor Treatment Options

I. Resective operations (OR)
   A. Graft—tube
      1. Dacron
      2. Descending thoracic
   B. Circulation
      1. CPB (cardiopulmonary bypass)
      2. Left atrium to left femoral bypass
   C. Patch graft—more common when the lung is the site of the primary malignancy
II. Embolectomy
   A. Leg
   B. Aortoiliac
   C. Mesenteric
III. Fasciotomy
IV. Chemotherapy
   A. Lung primary
   B. Pre- or postsurgery
V. Radiation
   A. Percutaneous radiofrequency ablation
   B. Pulmonary carcinoma
VI. Endovascular—grafting
VII. Palliative—metastases (82% of patients)
VIII. Primary lung resection
   A. Pneumonectomy
      1. No aortic resection
      2. Aortic stent placement
   B. Lobectomy
   C. Cardiopulmonary bypass (CPB)
   D. T4 N 0–1 (IIIA) Rec OR +/− induction therapy
   E. T4 N 2–3 (IIIB) Many Rec no OR—others, yes
IX. Anticoagulation
X. Antibiotics
   A. Surgical
   B. Sepsis

The benign endoluminal lesions originating near the aortic valve or in the ascending aorta may be treated with anticoagulation or surgical resection utilizing cardiopulmonary bypass—depending on the circumstances and the type of lesion. Adventitial benign tumors such as lipomas may be resected primarily.

Depending on the location of the tumor and the symptoms involved, surgical resection (the preferred method) with primary aortic repair may be accomplished for smaller or more localized lesions. Ascending aortic and arch lesions will require cardiopulmonary bypass (CPB), vascular grafting after resection, and usually hypothermia [5, 7, 8, 45–47]. Endovascular techniques have also been utilized with the possibility of subsequent resection [7, 20]. Left atrial to left femoral bypass assistance for surgical resection and patch angioplasty has also been utilized in some patients [8, 29]. Unfortunately, the surgical complication rate and mortality rate (15–20%) are high with the worst surgical survival for intimal, ascending, and arch tumors [44]. Preoperative multidimensional "modeling" of the aorta and the tumor has been utilized more recently to plan surgical resection of these tumors [48].

When symptomatic life- or limb-threatening emboli occur, intervention must be considered, as well as other potential salvage procedures. Embolic mesenteric emboli will require removal [49]. Thus, thrombectomy, embolectomy, and fasciotomy may all be performed for both primary and metastatic aortic malignancies [50–52]. Endovascular aortic procedures without tissue resection have also been utilized [7]. Peripheral lesions may be palpable and resected for both diagnosis and treatment.

Metastatic or direct aortic involvement by adjoining bronchogenic carcinoma was first resected by us in the late 1960s utilizing cardiopulmonary bypass [46]. Others have reported lobectomy or pneumonectomy for these lesions with or without aortic resection [20, 29, 30]. Surgical resection of T4 N2–3 (IIIB) pulmonary lesions is not recommended by most [22, 53]. But, others have taken a more aggressive approach to the patient with T4 non-small cell lung cancer using cardiopulmonary bypass. Utilizing cardiopulmonary bypass, Langer et al. from France reported on 20 such patients with a 1-year survival rate of 73% and a 10-year survival of 26%. They used a posterolateral thoracotomy in most patients and replaced the aortic defect with Dacron [54]. Others in Japan, for resection of T4 lesions after chemoradiation, have utilized a median sternotomy for these major resections [55]. All of these aggressive therapies may assist the patient—but only after appropriate diagnosis and evaluation of aortic invasion [56].

Depending on the cell type and patient condition, additional therapies which may be considered include chemotherapy, cobalt, and percutaneous radiofrequency ablation as appropriate [26, 28]. Most such therapy is palliative and patient supportive programs are required. These patients will require other modalities including antibiotics and anticoagulants [32]. As mentioned earlier, the prognosis for the patients with malignant aortic primary tumors or metastases from other primary locations is guarded. Few patients, particularly those with aortic sarcoma or bronchogenic carcinoma, will survive beyond 3 years, and the average primary aortic tumor patient survival time is 14–15 months. In addition, the diagnosis may only be determined after death utilizing autopsy material in some instances due to the confusing presentations. Surgery may only increase survival to approximately 5–10% at 3 years. Whereas partial resection of symptomatic primary cardiac tumors in infants and children may be followed by regression, this does not seem to be the case with adult aortic primary tumors [57]. We are not aware of tumor regression following therapy leading to or being the cause of aortic rupture.

With the current use of endografts, as well as open surgical procedures for various disease entities, a patient may eventually have more than one graft in a single body cavity. Thus, when resecting retroperitoneal periaortic tumors, a venous graft as well as an arterial graft may be inserted during the tumor and vascular resection. Each of these grafts may potentially become infected or erode adjoining tissues to form one or two fistulas or abscesses. As with other vascular procedures, an arterial graft may be placed, as well as a transfemoral endograft. Each of these grafts may create or erode adjoining tissue—especially when no soft tissue buttress is placed about each of the grafts or when the graft is too rigid. Both endovascular IVC (inferior vena cava) and open prosthetic IVC grafts may be utilized during aortic and caval tumor treatment [56]. The potential of these grafts to occlude or erode through the surrounding tissues and create a fistula is always present, especially when the two grafts are near each other. Thus, we may expect more such combinations in the future.

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Trauma of the Aorta

29

Jeffrey Cornell Perumean and Joseph P. Minei

Introduction

Traumatic aortic injury is the second leading cause of prehospital mortality in patients with blunt injury [1]. Despite blunt aortic injury being such a major cause of death, a relatively small number of patients make it to the hospital early enough to undergo intervention to reduce the risk of mortality. Since the detailed description of non-penetrating aortic injury by Parmley in 1958, the prehospital resuscitation and transportation have increased the number of patients with this injury that are fortunate enough to undergo management [2]. Additionally, the treatment algorithm has undergone significant change. Specifically, the improvement in the pre-definitive medical management of these injuries and the timing and invasiveness of the definitive operation has seen a whirlwind of change in the last few decades [3, 4]. This chapter will discuss the background of traumatic aortic injury, common clinical presentations, and pathophysiology of the injury. Moreover, advancements in diagnostic modalities and preoperative, non-operative, and operative approaches will be explored.

Epidemiology

Classically, traumatic aortic injury is defined by location, between thoracic and abdominal cavities, which can be further subdivided by blunt or penetrating mechanism. The most widely studied traumatic aortic injury is blunt thoracic aortic injury (BTAI). BTAI by far outweighs the number of reported penetrating traumatic aortic injuries. The vast majority of BTAI is caused by automobile collisions and motorcycle crashes, which make up a staggering 80% of all blunt aortic injures. An overwhelming majority of these patients never make it to the hospital. In a recent autopsy study completed at the Los Angeles County Coroner's office, a reported 34% of patients who died in a motor vehicle accident had a BTAI. Among those patients that had BTAI, 80% died at the scene. This is higher than the previously reported, 45–57% of patients who died with BTAI. Despite the implementation of new safety mechanisms, the incidence of aortic injury in fatal vehicle collisions has remained essentially the same. This shift in mortality is likely attributable to the advances in the management of BTAI once patients make it to the hospital and was exemplified in a comparison of two large, multicenter American Association of the Surgery of Trauma studies that reported a decrease in mortality from 22% to 13% in patients who arrived to the hospital alive [3, 5–7]. In 2013, the CDC reported >32,000 motor vehicle deaths [8]. If these data are extrapolated to the US population, it would suggest that nearly 11,000 patients who die each year have BTAI. It remains clear that advances in automobile design to specifically address these issues could significantly reduce the number of deaths each year from BTAI. Other causes of BTAI that make up the remaining injuries are auto versus pedestrian collisions, falls, crush injuries, and other blunt mechanisms [9].

Despite the lethality of BTAI in the field, about 20% of patients arrive to the hospital alive [10]. Nonetheless, the risk of dying with BTAI carries a reported in-hospital overall mortality between 13.5% and 46%, typically, as a result of associated injuries [1, 2, 4, 9, 11]. This is a vast improvement from previous reports.

The timing of death after injury is an interesting topic, which was first described in 1958 by Parmley and colleagues. This paper is often referred to as a landmark description for the pathological classification of BTAI. His group reviewed 1174 autopsies at Walter Reed Hospital of patients who died from non-penetrating thoracic injuries (mostly secondary to automobile collisions) and found that 275 patients perished due to aortic rupture (only 171 had

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isolated aortic rupture—the remaining had combined cardiac and aortic injury). Of the 38 who survived their initial injuries, 32% died within 1 day and nearly 60% died within 1 week. This underscored the importance of early diagnosis and shined a spotlight onto blunt aortic injury, as only 12% of the patients who survived were diagnosed prior to aortic rupture [12]. At the time, the best screening modality for patients was a mere chest x-ray. More recent studies demonstrate that the timing of diagnosis remains paramount but that improvements have been made. Fabian et al. estimate that the majority of the patients who survive the initial 12 hours would be diagnosed and treated with current screening capabilities, which would significantly reduce the mortality prior to diagnosis. Failure to diagnose and treat these lethal injuries, either medically or surgically, will in many cases lead to rupture and subsequent death.

Blunt abdominal aortic injury (BAAI) is a rare entity making up only 0.03% of all blunt trauma cases. Even the busiest of trauma centers in the USA experience between 0 and 3 cases annually. Additionally, BAAI is also rarely studied compared to thoracic aortic injury, and most of the information about this injury pattern is derived from case reports, case series, and retrospective cohort studies, the most comprehensive being the Western Trauma Association Multicenter Trials Group published in 2014.

BAAI is classically defined as an injury to the abdominal aorta between the diaphragmatic hiatus and the aortic bifurcation. Shalhub and colleagues classified blunt injuries to the abdominal aorta based on zones of possible endovascular surgical approaches [13]. Zone I represents the aorta from the diaphragmatic hiatus to the base of the superior mesenteric artery (SMA). Zone II is defined as the portion of the aorta from the base of the SMA to just distal to the renal arteries, and Zone III represents the segment just below the renal arteries to the aortic bifurcation (Fig. 29.1).

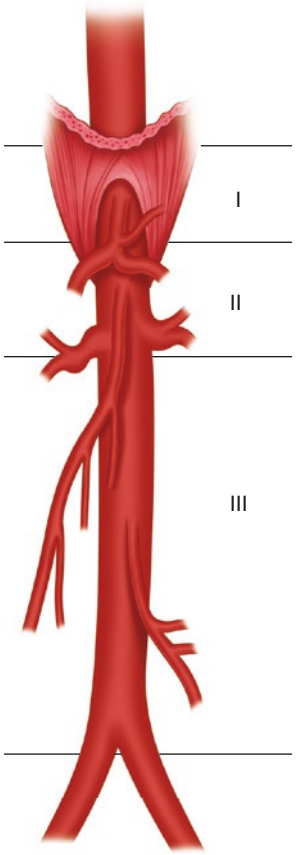


Fig. 29.1 Classification of abdominal aorta zones of injury based on possible endovascular surgical approaches. Zone I injuries occur from the diaphragmatic hiatus above the SMA. Zone II injuries include the SMA to the renal arteries. Zone III injuries are from below the renal arteries to the aortic bifurcation. Zone I and III injuries are more easily amenable to endovascular repair. Zone II injuries are feasible with an endovascular approach but require advanced surgical techniques and fenestrated grafts. (From Shalhub et al. [13]. Reprinted with permission from Wolters Kluwer Health, Inc)

Similar to thoracic aortic injury, BAAI is most commonly caused by motor vehicle collision (MVC). Two large studies have evaluated the most common mechanism of injury for BAAI. A large review of the National Trauma Database reported in 2012 that 80% of BAAI were caused by MVC. The previously mentioned Western Trauma Association Multicenter Trials Group reported that 60% of BAAI were MVC related [13, 14]. The second most common cause of this injury is pedestrians struck by autos at 11.5%. BAAI is a dangerous injury; 20% of patients die prior to arrival or while in the emergency department. In-hospital mortality remains significant at about 39%, with the vast majority (60%) of those patients who arrive alive to the hospital dying within 24 hours, usually from hemorrhagic shock. This is in contrast to BTAI, where most patients die from associated injuries. Interestingly, the majority of patients with abdominal aortic injuries who died had injuries located at Zone II. The zone of injury is an important distinction as it guides recommended therapy [13].

Pathophysiology of Injury

The first distinct description of the pathophysiology of blunt thoracic trauma to the aorta was published by the previously mentioned Parmley and colleagues. In his sentinel paper, he elucidated specific force vectors that the thoracic aorta undergoes that led to the injuries he observed. This initial description paved the way for further investigation. More recent studies derived from the *CIREN* investigations have utilized a more inductive approach to decipher what causes the injury patterns we observe in victims of blunt thoracic trauma. In

contrast, blunt abdominal injuries are hypothesized to be caused by different mechanisms that are thought to stem from compressive forces. There is no unified consensus on the pathophysiology of blunt aortic injury, but there are some notable hypotheses.

Parmley et al. described that the forces that lead to the observed injury patterns in blunt thoracic aortic injury are a combination of direct and indirect, deceleration, compression, and blast forces. They suggested that direct forces are caused by a shearing action as a result from a dislocated or fractured vertebrae compressing the mediastinal organs against the anterior bony complex (clavicle, manubrium, or first rib); this is sometimes referred to as an "osseous pinch" [15, 16]. This can be visualized as the anterior chest wall is compressed against the bony spine causing direct injury to the aorta. Conversely, indirect forces are described as being produced from an intraluminal pressure wave that leads to aortic rupture or injury. In 1958, studies of aortic tissue suggested an intravascular aortic pressure of 2500 mmHg was necessary to cause rupture. The authors suggested that the deceleration forces experienced during trauma lead to differential forces between organs and cavities. Parmley postulated that these differential forces produce the greatest strain at locations of differential decelerating tissues. He further described that these junctions were located at the sites where he observed the most common injuries, that is, the aortic isthmus where the fixed aortic arch meets the mobile descending aorta and where the relatively fixed ascending aorta meets the mobile heart. This is supported by tensile strength tests of aortic samples indicating that the isthmus is an inherently weaker area of the thoracic aorta [17]. Furthermore, of the 275 identified aortic injuries in his cadavers, he found that the majority were spontaneous, full-thickness injuries with no particular site in the circumference of the aortic wall predisposed to rupture. He did note that partial injuries were more often posterior. Furthermore, he was the first to classify aortic injury based on the involved layer(s) of the vessel wall and identified six variations of injury: (1) intimal hemorrhage, (2) intimal hemorrhage with laceration, (3) medial laceration, (4) complete laceration of the aorta, (5) false aneurysmal formation, and (6) periaortic hemorrhage. Additionally, he reported no direct association between injury pattern observed and atherosclerosis or other aortic pathology. It is important to note that Parmley's seminal classification of aortic injury is based solely on pathological findings and carries little value to the clinician diagnosing these injuries on patients who survive their initial injuries. This has led to the development of other classification systems that carry more weight clinically and assist in guiding therapy.

More detailed descriptions of the mechanism of injury have been postulated since Dr. Parmley's definition of the various types of injury and most common location: the aortic isthmus. These various mechanisms can be more simply classified as tension, torsion, and bending. The location of injury is most commonly peri-isthmus, which can be further defined as proximal or distal to the aortic isthmus. The isthmus is the location of the aorta just distal to the left subclavian artery where the aorta has a slight constriction at the ligamentous arteriosus. This proximal descending location is the most common site of injury, accounting for 93–96% of BTAI admissions and 80% of autopsy studies. This is likely due to the weak portion of the isthmus compared to the remaining aorta, measuring at only 63% tensile strength compared to the remaining wall of the more proximal aorta [3, 18–20].

Using the isthmus as a reference point, Sevitt hypothesized that injuries to the ascending aorta and proximal to the aortic isthmus are a result of severe direct blows to the chest resulting in a stretching tension within the aorta combined with displacement of the heart downward and to the left (torsion) away from the relatively fixed ascending aorta that is compressed between the anterior chest wall and the spine. Consistent with this hypothesis, animal studies have demonstrated that the heart is mobile up to 5 cm during traumatic injury [21]. Furthermore, this combined torsion and tension injury leads to transverse tears of the supravalvular ascending aorta ultimately leading to rupture and death. Sevitt's hypothesis has been demonstrated in animal and cadaver studies [22]. More distal thoracic aorta injuries, those to the proximal descending aorta (proximal to the isthmus), are thought to be caused by a "shoveling mechanism" which is described as significant compression of the lower chest causing a posteriorly and cranially directed force. This deforms the chest wall in such a way as to cause the mid chest wall to bow anteriorly and the lower chest to compress against the spine. This cranially directed force theoretically causes upward displacement of the mediastinal organs, especially the proximal descending aorta, against a fixed ligamentous arteriosum leading to aortic wall tension that results in a transverse tear and/or subsequent rupture. Injury in this fashion can be imagined when a high-speed auto strikes an immovable object throwing the driver into the steering wheel which deforms the lower chest wall into a "shovel" as it displaces the mediastinal organs cranially transmitting significant force in the process and tearing the aorta proximal to the ligamentous arteriosum at the descending portion [22, 23].

Another mechanism has been proposed: an acute rise in intravascular pressure or the "water-hammer" effect. The thought is that aortic tears are caused by a rapid pressure increase of a non-compressible fluid (blood) within the aorta leading to a pressure wave. This pressure wave is then transmitted to the aortic wall leading to transverse tears and possibly rupture. This can be visualized when the lower chest wall/abdomen of an automobile driver strikes the steering wheel causing a functional occlusion of the aorta at or near

the level of the diaphragm. The impact creates a fluid wave opposite the normal direction of flow in the aorta that transmits significant energy into the aortic wall. The proposed and most logical site of this "water-hammer" effect is transmitted to the aortic arch and thus places the greatest tension at the level of the isthmus leading to aortic wall tears and/or rupture. Conversely, in animal and cadaver models, the pressure required to cause rupture of the aorta is in excess of several thousand mmHg. Furthermore, these studies suggest that pressurization alone should cause linear tears of aortic tissue [24]. Autopsy studies have demonstrated that blunt traumatic aortic injuries are overwhelmingly transverse and often peristhmic and likely occur at pressures well below those seen in ex vivo models [23].

Another described version of the super-pressurization of the aorta is proposed by Zhao et al. in 2008. These authors describe the aorta being placed in a "high tensile, vulnerable state" by the occupant's anticipation and subsequent bracing for impact and that the deformation (bending or torsion) of the aorta during impact ultimately leads to injury [25], i.e., injury is a result of a deformed pressurized aorta. In their model, they were able to show that rupture occurred at significantly lower pressures than previously demonstrated by applying a combination of intraluminal hypertension and aortic deformation. Interestingly, they also reported that bending forces were more commonly associated with primary adventitial injuries, while tension and torsion were more likely to produce primary intimal injury, both of which ultimately lead to rupture. This would indicate that aortic injury is a result of a combination of mechanisms that ultimately lead to channeled injury to the isthmus. This common pathway injury to the isthmus remains to be elucidated. A combination of injury mechanisms appears to be the most widely accepted modality by which the aorta is injured [17, 22, 23, 25].

Most of what has been proposed thus far is in relation to frontal collision of blunt thoracic aortic trauma. This was heavily studied up until recently, following the institution of mandatory airbags and improved vehicle restraint systems in modern autos. The recent focus of the study of blunt thoracic aortic injury has shifted to lateral-impact automobile collisions. In a large retrospective review of motor vehicle crash databases, side-impact collisions were more likely to lead to traumatic rupture of the aorta than frontal collisions, 2.4% vs 1.1%, respectively [26]. However, the association between directional impact (frontal vs lateral) and pathophysiology remains to be defined in the literature.

As described earlier, blunt abdominal aortic injury (BAAI) is classically defined by zones. The most common zone of injury is Zone III at 66% of BAAI, followed by equal rates of Zones I and II [13]. Abdominal aortic injuries make up less than 5% of all aortic injuries [6, 14]. The paucity of BAAI is likely related to the fixed retroperitoneal location of the abdominal aorta and its relative protection from the adjacent spine. The rarity of this injury has resulted in a disproportionate incidence compared to the thoracic aorta and subsequently a paucity of theorems on the mechanism of its injury. We are limited to a varying array of case reports and only one large retrospective, multi-institutional review. That said, most authors agree that the inciting aortic injury is a result of the combination of direct and indirect forces. Direct forces are a result of the aortic wall undergoing stress transmitted from the adjacent spinal column or fractured bone fragment. There are two commonly described indirect forces. One is that transferred from adjacent organs or tissues compressing the aortic wall against a fixed column of blood leading to an acute rise in intravascular pressure. However, the pressures needed to cause rupture of the abdominal aorta are in excess of 1000 mmHg, higher than those reportedly produced during in vivo traumatic injury. Patients who undergo this type of transmitted force likely do not survive their injuries. The second type of indirect force is related to deceleration that causes a shearing force which usually results in tearing of the aortic wall at its vascular tributaries but can extend to the aortic wall [27]. The theories of direct and indirect forces have not been thoroughly studied or repeated in human models to the extent of thoracic models of aortic injury. One may easily conceptualize these forces as the passenger or driver meets significant resistance during deceleration against a seat belt, steering wheel, or dashboard. This concept of injury has been previously named "seat-belt aorta" [28]. Supporting evidence for direct force mechanism is the association of spinal fracture, especially lumbar spine fractures, with aortic injury [13]. The subsequent aortic wall injury can be contusion, intimal disruption, or dissection with or without rupture. These injuries can easily progress to luminal stenosis, or thrombosis, leading to a cascade of deteriorating clinical manifestations (neurological impairment, acute limb ischemia, etc.) [29]. Conceptually, BAAI can be thought of along a spectrum with minimal intimal injury on one end and complete transection on the other [13, 29].

Clinical Presentation

Symptoms of traumatic aortic injury are usually nonspecific and often masked by other significant injuries such as traumatic brain injury. Patients who survive the traumatic encounter will typically fall into two groups: those who are lucid and relatively stable and those who are in extremis and have little time before dying. This is an important distinction as it requires that the trauma team maintain a high index of suspicion for those patients who seem otherwise stable but harbor a significant aortic injury. For the patient in extremis, it means that the trauma team has little time to diagnose and attempt treatment of the aortic injury before exsangui-

nation. A lucid patient may complain about chest or back pain, dyspnea, or cough. Hoarseness is also an indication of aortic injury if the recurrent laryngeal nerve is affected by a developing hematoma [30]. Other times, patients will be in extremis or too obtunded to disclose any symptoms. These patients may demonstrate subtle signs of aortic injury such as acute coarctation syndrome (upper extremity hypertension with diminished or absent distant lower extremity pulses or Doppler signal) secondary to aortic hematoma (extraluminal, intraluminal, or intramural) or isolated extremity hypertension. Reflex hypertension presents in 17% of thoracic aortic injuries due to stretching and stimulation of the cardiac plexus located near the isthmus [31].

The most important consideration is to maintain a high index of suspicion in patients who have undergone high-energy decelerating trauma or who present with an injury pattern or trauma burden associated with aortic injury. This should prompt the trauma team to investigate for occult injury of the aorta. The typical trauma team will be immediately focused on respiratory distress, hemodynamic instability, obvious pelvic fractures, head injury, extremity deformities, and chest injuries as these are commonly associated injuries. Early recognition and treatment of aortic injuries provides the best opportunity to reduce the risk of rupture and exsanguination.

Associated Injuries

Because most patients who present with blunt aortic injury are obtunded or distracted by associated injury, it remains paramount that the clinician remains astute for aortic injury in any patient who presents with a significant deceleration injury. The injury pattern is the most telling sign for patients with blunt aortic injury, and it can vary among patients with thoracic versus abdominal aortic injury.

In a major prospective, multicenter American Association for the Surgery of Trauma (AAST)-sponsored study that included nearly 275 patients, the most common associated injury for the thoracic aorta was head injury, 51%. Chest injury, which included rib fractures (46%), pulmonary contusions (38%), and myocardial injury (4%), accounted for 61% of aortic injuries. Thirty-four percent had pelvic (31%) and/or long bone fractures, and 22% had intra-abdominal injuries (see Table 29.1) [4]. The key point to understand with this patient population is that there is no single injury that represents an obvious thoracic aortic injury; more importantly it is the pattern of injury and the significance of the suspected deceleration that caused the trauma that must alert the trauma surgeon to an underlying aortic injury and thus prompt appropriate investigation.

The message is similar for abdominal aortic injury but with a slight variation in the pattern and circumstances of the trauma mechanism. With blunt abdominal injury, the mechanism is still usually an automobile collision as previously described (>80%). Abdominal aortic trauma also commonly presents with pneumothorax/hemothorax (42%), with or without rib fractures (34.5%), and head trauma (31%). However, the majority of these patients present with lumbar spine fracture (29%) and/or pelvic fractures (25%). They also tend to have intra-abdominal and/or retroperitoneal organ injury with the small bowel (34.5%), spleen (22%), liver (20%), kidney (17%), and colon and rectum (10%) being the most commonly associated organ injuries. Associated vascular structures are less frequently affected, but their presence should raise suspicion of abdominal aortic injury. Vessels most likely associated with abdominal aortic injury include the thoracic aorta (8%), iliac artery (6%), and renal arteries (5%) [13, 14, 32].

Therefore, patients presenting with severe injury with multiple injuries from a significant deceleration injury should alert the trauma team to a high index of suspicion of aortic injury. Investigation and early diagnosis lead to the timely, appropriate therapy and reduced mortality from this injury.

Table 29.1 Associated injuries occurring in 274 patients with blunt aortic injury

Closed head	140 (51)[a]	Spinal cord	10 (4)
Multiple rib fractures	123 (46)	Pelvis	84 (31)
Flail chest	34 (12)	Femur	67 (24)
Pulmonary contusion	103 (38)	Tibia	60 (22)
Myocardial contusion	10 (4)	Upper extremity	54 (20)
Diaphragm rupture	20 (7)	Maxillofacial	36 (13)
Spleen	39 (14)	C-spine	12 (4)
Liver	61 (22)	T-spine	11 (4)
Small bowel	19 (7)	L-spine	10 (4)
Other abdominal	38 (14)	None	

From Fabian et al. [4]. Reprinted with permission from Wolters Kluwer Health, Inc

Numbers in parentheses are percentage of patients with that injury

[a]Thirty-four (24%) had intracranial hemorrhage

Diagnosis

Primary Survey

The primary survey provides the initial opportunity to trigger the index of suspicion of traumatic aortic injury. It is the report of the injury modality that should prompt the thought of aortic injury, most commonly a significant deceleration from a head-on or broadside vehicle collision. This can be reflected in the initial overall visual evaluation of the patient. A subtle strip of ecchymosis across the neck, upper chest, or abdomen from the automobiles safety restraint system indicates rapid deceleration. The trauma team will begin

treating immediately life-threatening injuries such as a traumatic brain injury, respiratory distress, pneumo-/hemothorax, or severe pelvic fracture. This injury pattern should be the second subtle sign that this patient may be harboring an underlying aortic injury. There are few overt physical exam findings that clearly demarcate aortic injury, and thus a high index of clinical suspicion is prudent.

Secondary Survey

Proceeding to the adjunct diagnostic modalities provides a third opportunity to prompt suspicion for traumatic aortic injury. The first and most widely used adjunct is the chest x-ray. It has become an essential part of the secondary survey, and no trauma evaluation is complete without one. The benefits of a CXR are obvious; it is simple, quick, and efficient. However, the utilization of CXR to identify aortic injury is limited. The most widely identified sign is a widened mediastinum (85%); nonetheless, there are a slew of signs that we mostly remember to quiz the rising house staff and medical students. These include indistinct aortic knob, left pleural effusion, apical cap, first/second rib fracture, tracheal deviation, depressed left bronchus, and NG tube deviation [4]. Identification of any of these radiographic signs should prompt further evaluation for thoracic aortic injury or be incorporated into the trauma centers' algorithm for blunt aortic injury (see Table 29.2). It is also possible to identify large abdominal aortic injury during the Focused Assessment with Sonography for Trauma (FAST) exam; however, the trauma team has to specifically look for this injury and assessing the aorta is not currently part of the routine exam. A subtle sign during the FAST that may prompt a trauma team to assess for aortic injury is hemoperitoneum, which is present in about 40% of abdominal aortic injuries [13]. The astute trauma team recognizes that the best chance of identifying aortic injury is by maintaining a high level of suspicion in patients to present with the appropriate injury pattern consistent with the appropriate mechanism of trauma, which will subsequently lead to the appropriate diagnostic modality.

Table 29.2 Initial chest x-ray findings in 259 patients with blunt aortic injury

Wide mediastinum	221 (85)
Indistinct aortic knob	63 (24)
Left pleural effusion	49 (19)
Apical cap	49 (19)
First and/or second rib fracture	33 (13)
Tracheal deviation	32 (12)
Depressed left bronchus	12 (5)
NG tube deviation	29 (11)
Negative x-ray	19 (7)

From Fabian et al. [4]. Reprinted with permission from Wolters Kluwer Health, Inc

Numbers in parentheses are percentage of x-ray films with the particular finding

Imaging Modalities

Chest Radiograph

In 1958, the chief obstacle to attempts at treatment of aortic injury was the early diagnosis of the injury [2]. The most available modality for diagnosis in that era was the CXR. Today, the chest radiograph is routine and mandated in nearly every trauma evaluation. However, the utility of CXR to accurately identify thoracic aortic injury is limited. In 2008, four experienced trauma surgeons were shown chest radiographs from BTAI patients and control patients with no BTAI. They were able to accurately identify radiographic signs suspicious of BTAI in 89% of patients and appropriately proceeded to further diagnostic testing. The most commonly identified sign in this study was the widened mediastinum, which was seen in 76% of BTAI cases [33, 34]. However, in 11% of cases, they failed to identify signs of BTAI, or the CXR failed to reveal evidence of BTAI. Others have reported rates of missed aortic injury with the use of CXR ranging from 8% to 23% [4, 35]. CXR offers a reasonable screening test; however, it lacks the sensitivity to capture all blunt thoracic aortic injuries. There are too many instances when the subtle signs of thoracic injury are overlooked or unrevealing, which can lead to a missed injury with subsequent untreated BTAI, the results of which could be catastrophic for the patient. Therefore, in patients who fit the profile of high-speed deceleration and appropriate injury pattern, the use of further diagnostic modalities is mandated.

Computed Tomography

Following the CXR in a stable trauma patient, the next step in evaluation is typically computed tomography (CT). Some trauma surgeons recommend the routine use of CT in patients involved in "high-speed" deceleration injuries [35]. Rapid deceleration is generally defined by a speed greater than 56 km/h (35 mph), fall from greater than 4 m (13 feet), or pedestrian being displaced greater than 3 m or struck by a vehicle traveling greater than 35 km/h (21 mph) [35, 36]. Although the modality and significance of deceleration of injury is relevant in any trauma patient, the use of routine CT scans as screening tool for BTAI in all patients with rapid deceleration injuries has not yet gained widespread acceptance. The exponential advancement of computed tomography has provided an excellent diagnostic tool for the identification of aortic injury. This has been reflected in the substantial increased use as a screening tool for BTAI in

patients who present with the appropriate profile. It has nearly replaced all other initial diagnostic modalities according to a large, prospective, multicenter, observational study sponsored by the AAST in 2007 [3]. In this study, CT scan was used as the definitive diagnostic tool for BTAI increasing from 35% in 1997 to 93% in 2007. High-resolution multi-row-detection computed tomography has proven to have excellent sensitivity, outperforming the previous "gold standard" of aortography reaching sensitivity, specificity, accuracy, and negative predictive values of nearly 100% [37, 38]. The improved slice profiles, acquisition speed, reduced motion artifact, and enhanced image processing software have solidified CT as the optimal diagnostic technique for aortic injury. These advancements in conjunction with the availability of modern computed tomography have essentially replaced all other diagnostic modalities for aortic injury [1, 3, 38, 39]. In fact, the advancements of CT have created the scenario of identifying clinically insignificant injuries and angiographically occult injuries that are presenting new management challenges for trauma and vascular surgeons [40].

There are a number of findings on CT scan that are indicative of aortic injury. Intimal flaps, intramural hematomas, dissections, pseudo-aneurysm, pseudo-coarctation, and loss of aortic wall contour are some of the most common CT findings in aortic injury. The most commonly reported thoracic aortic injury identified on CT is pseudo-aneurysm, and it is usually located at the isthmus [40–43]. Occasionally, the precise location of injury can be seen as in an intimal flap. Other findings may strongly suggest injury but without a definitive, precise location as in mediastinal hematoma or saccular outpouching of the aortic wall. The mediastinal hematoma can be misleading. If it is localized to the retrosternal space, near a sternal fracture without extension to the aortic wall, this likely represents a sternal fracture with the surrounding hematoma. Whereas a mediastinal hematoma that appears to surround the aorta and extends to the retrosternal space likely represents an aortic injury, mediastinal hematomas are identifiable without contrast and can be indicative of aortic injury when the pattern of injury is appropriate. However, to confidently identify aortic injury, contrast material is mandatory [44–48]. In abdominal aortic injuries, the most commonly reported CT abnormality is intramural hematoma and the location most commonly seen is the infrarenal aorta (Zone III) at or near the inferior mesenteric artery [27, 49].

One of the most significant clinical relevancies of CT is the development of an image-related aortic injury classification system. Patients with aortic injuries who survive long enough to undergo imaging are now classified in a systematic way that guides therapy. This system was first introduced by Starnes et al. in 2012 and is now used by many societies to classify aortic injuries [50]. This classification scheme separates aortic injury by the presence of an external aortic contour abnormality. If absent, the patient is further classified by the significance of the intimal flap. Minimal aortic injury (MIA) is classified as an intimal tear <10 mm. If the intimal tear is greater than 10 mm, then the injury is deemed a long intimal flap (LIF). When the injury causes an external aortic contour abnormality, it is classified as a pseudoaneurysm when contained and as a free rupture if uncontained. This classification scheme is summarized in Fig. 29.2.

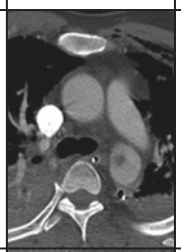
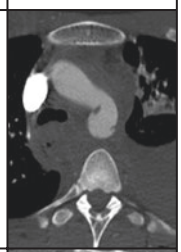
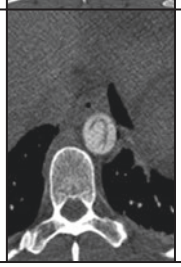
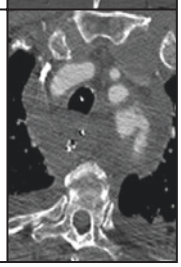
Absent external contour abnormality			Present external contour abnormality		
Type of aortic injury	***Definition***	***Example***	***Type of aortic injury***	***Definition***	***Example***
Intimal tear	No aortic external contour abnormality: tear and/or associated thrombus is <10mm		**Pseudoaneurysm**	Aortic external contour abnormality: contained	
Large intimal flap	No aortic external contour abnormality: tear and/or associated thrombus is >10mm		**Rupture**	Aortic external contour abnormality: not contained, free rupture	

Fig. 29.2 Blunt aortic injury classification scheme based on the presence or absence of aortic external contour abnormality on axial computed tomography imaging. Representative images are shown. (From Starnes et al. [50]. Reprinted with permission from Elsevier)

Aortography

Prior to the advent and advancement of computed tomography, aortography was the definitive gold standard to diagnose aortic injury. Generally, two separate views with iodinated contrast injection are necessary to diagnose aortic lesions. The sensitivity, specificity, and negative predictive value of aortography when compared to computed tomography is very similar, and no significant difference has been identified in major systematic reviews of the literature [1, 35, 38, 51–54]. Aortography findings are similar to those seen on CT and include demonstration of an irregular contour of the aortic wall, luminal out-pouchings, or luminal irregularities. Any combination of these findings could indicate the presence of an intimal flap, dissection, pseudo-aneurysm, or intramural hematoma. Aortography is invasive and time-consuming, can delay other diagnostic and therapeutic interventions, removes the patient from the optimal resuscitation and observation area, and carries the risk of vascular injury during the procedure [45, 46]. As a screening and diagnostic modality, aortography has fallen from favor. Nonetheless, it does carry utility as a confirmatory test for equivocal CT findings and during intraoperative planning and placement of endoluminal stent grafts.

Other Imaging Modalities

Previous diagnostic techniques that have been replaced by the more reliable, efficient CT scanner may still have utility in the evaluation of the trauma patient. Transesophageal echocardiography (TEE) is a modality that gained popularity prior to the development of high-fidelity computed tomography. In 1997, TEE was used as the primary diagnostic modality in nearly 12% of cases [4]. However, this figure dropped precipitously to 1% in 2007 [3]. There still exist a few instances where TEE remains useful, for instance, an unstable patient who cannot be transferred from the safe confines of the intensive care unit or as an adjunct in the operating suite to assist with identifying a thoracic aortic injury [55]. TEE has been well studied and directly compared to aortography. The results vary with each study, but most authors report that when performed by a trained operator, TEE has sensitivity approaching 100% for identifying thoracic aortic injury [56–58]. Common findings on TEE that indicate this injury include intraluminal stripes, intimal lesions, and hemomediastinum [59]. Despite the portability advantages and lack of ionizing radiation, TEE has its limitations. Most notably, TEE is operator dependent, and this can significantly affect accuracy [60]. Another drawback with TEE is that it lacks the ability to evaluate aortic branch vessel injury, which is more readily seen with CT [61]. Unless the patient is unstable for transfer to a CT scanner or is undergoing another procedure and diagnosis is of imminent concern, TEE is not for the primary diagnosis of thoracic aortic trauma.

Magnetic resonance imaging (MRI) is another option to identify and diagnose aortic injuries. MRI offers similar findings as those found in computed tomography, with similar sensitivity, specificity, and accuracy [45, 62]. The identification of these injuries without the use of iodinated contrast removes the potential nephrotoxic side effects of the contrast material required when using CT. It also allows evaluation of the entire aorta. However, there are a number of limitations with the use of MRI, the most obvious being the time required to obtain an MRI. Trauma evaluations require judicious utilization of resources, the most important being time. Aortic injuries carry such a high risk of rupture and mortality that the trauma team often cannot afford waiting for the results of an MRI. Additionally, MRI precludes the presence of any magnetic metallic medical equipment including implantable devices. Much of the time, the medical history of the patient is not known by the trauma team prior to initial workup, and frequently, the team is utilizing medical equipment made up of magnetic metallic material. Lastly, patient movement during an MRI can produce artifact that mimics aortic injury [63]. These current limitations with the use of MRI restrict its use to a secondary or tertiary diagnostic modality reserved for specialized instances such as a confirmatory or surveillance test and only in hemodynamically stable patients [44].

Management

Many authors describe a bimodal distribution of traumatic aortic injury. One group has life-threatening hemorrhage with a hovering threat of imminent death upon arrival to the trauma bay. The other group of individuals develops aortic injury-related hemorrhagic shock several hours to days after admission to the hospital secondary to a progression of the aortic injury. Today, the management algorithm varies for each of these groups. Previously, the focus of management for all identified aortic injuries was immediate surgery. This remains the case for hemodynamically unstable patients with hemorrhagic shock. In the second group, the management algorithm has undergone some revision and refinement over the last couple of decades. Nonetheless, traumatic aortic injury needs to be identified early in all cases, and it is imperative to initiate management strategies promptly to reduce the risk of rupture and exsanguination.

Timing of Repair

There is no question that the rare patient who arrives to the trauma bay in extremis or with free aortic rupture mandates immediate operative intervention. However, the vast majority of patients who survive their initial insult and associated injuries do not need immediate operative intervention for their aortic injury. The risk of rupture remains highest for

these patients within the first 24 hours of injury and their aortic injury cannot be ignored. However, the treatment for these patients has proven to be immediate and strict blood pressure and heart rate control with delayed surgery. Parameters for antihypertensive therapy are a systolic blood pressure of <120 mmHg, primarily with the use of beta-blockers and vasodilator (e.g., nitroprusside) utilization as an adjunct [1, 11, 38]. Reducing wall stress at the location of the injury subsequently reduces the risk of rupture [38, 64]. Wall stress can be visualized mathematically with the equation $\Delta p/\Delta t$; wall tension is directly proportional to the change in pressure and indirectly proportional to the heart rate (change in time) [12]. This treatment approach was initially introduced in patients with significant associated injuries who were stabilized and resuscitated before undergoing aortic repair but was eventually expanded to nearly all patients with blunt thoracic aortic injury, even when their trauma burden was low [20, 64]. Substantiation for delayed repair of BTAI came from another major AAST-sponsored study. The authors prospectively compared early versus delayed repair in patients with BTAI. The patients had similar trauma profiles and associated injuries. The two groups were separated by the timing of repair: early vs delayed. On average, the early repair group underwent repair 10 hours after injury versus 126 hours for the delayed repair group. Overall crude mortality was significantly lower in the delayed group (5.8% vs 16.5%). On further multivariate and subgroup analyses, the survival benefit was maintained. These results have been confirmed on subsequent studies and have since been widely adopted by the trauma community [9, 20, 64, 65].

The reasons for the success of delayed repair for patients with BTAI are not entirely clear. Maybe it is due to the reduction of aortic rupture or better resuscitation of critically injured patients or improved management of other life-threatening injuries, subsequently optimizing conditions for aortic repair [64]. Immediate repair is clearly not the answer for patients with a significant trauma burden. What remains to be answered is the optimal timing of repair. Blood pressure and heart rate control provides valuable time for the stabilization of the poly-traumatized patient. Deciding on when to surgically intervene, if at all, on a blunt thoracic aortic injury remains individualized and at the discretion of the multidisciplinary trauma team and vascular and/or cardiothoracic surgeons. However, it has been shown that delaying repair beyond the immediate resuscitation improves outcomes.

Often patients with blunt aortic injuries have concomitant head injuries, and maintaining a systolic blood pressure of <120 mmHg creates an insufficient cerebral perfusion pressure to prevent secondary traumatic brain injury. For this reason, intracranial pressure monitors are used to assist with antihypertensive management to ensure adequate cerebral perfusion pressure.

Treatment timing of blunt abdominal aortic injury is generally performed the same as thoracic injury. This is largely due to the lack of scientific evidence to appropriately guide therapy. The infrequency of blunt abdominal aortic trauma creates a challenge in its study of optimal timing. Existing published literature is limited to retrospective single-institution case series, retrospective cohort reviews, and large retrospective evaluations of the national trauma database. Nonetheless, there has been success in delaying repair with concurrent blood pressure and heart rate control until stabilization of the poly-trauma patient when more optimal operative conditions exist [13, 66].

Delayed repair for aortic injuries is the standard of treatment for all patients irrespective of risk factors. However, there is a subset of patients that mandate immediate repair. Those include patients with high risk of aortic rupture based on imaging characteristics, clinical suspicion, or patients found to have grade III (pseudoaneurysm) or IV (free rupture) injuries. This subset of patients should undergo immediate repair of their aortic injury when clinically feasible. Additionally, patients with clinical or radiologic evidence of pseudocoarctation may be considered for urgent surgical intervention [1, 13].

Surgical Management

As many as 30% of patients who present to the trauma bay will do so hemodynamically compromised. This group of patients will likely undergo immediate surgical intervention. Many patients in this group will undergo an emergency department thoracotomy or in cases of known abdominal aortic rupture, resuscitative endovascular balloon occlusion of the aorta (REBOA) in an attempt to stem exsanguination. Patients with aortic rupture are likely to fall into this population. The results of any of these lifesaving maneuvers are dismal. Aortic rupture carries a very high mortality rate even upon reaching the hospital with signs of life. However, not all aortic injuries require surgery. In fact, the majority of aortic injures are managed non-operatively [50].

Endovascular Technique

The first report of an endovascularly placed stent graft for the treatment of BTAI was in 1997 by Kato et al. Shortly thereafter, the use of radiographically placed stent grafts increased in the treatment of elderly or severely injured patients not thought to tolerate open operative repair. Given the early success of this treatment modality, the practice was expanded to young and even mildly injured patients with aortic tears. The indications for use in these patient populations were scantly supported by small case series and case reports. This prompted a large-scale scientific investigation. In order to delineate the outcomes of patients who underwent repair with these devices, an AAST-sponsored, large, prospective, multicenter study was performed. Specifically, the study evaluated the early outcomes of open surgical repair with that of endovascularly placed stent grafts. This study confirmed that the use of endovascular techniques had sky rocketed

from 0% in 1997 to 65% one decade later [3, 9]. This study also demonstrated overall lower mortality, reduced rates of paraplegia, and less blood transfused in patients who underwent endovascular stenting compared to those who had open surgical repair. When subgroup multivariate analyses were performed, the reduced mortality was again noted in patients with severe associated injuries as well as patients without major associated injuries indicating that endovascular stenting was safer for patients, at least in the short term. Other studies reported reduced spinal cord ischemia and end-stage renal disease in patients undergoing endovascular repair when compared to open surgery [11]. These findings were repeated in a subsequent large population-based analysis of the Canadian trauma registry [67]. In the most recent meta-analysis performed during the development of the practice management guidelines by the Eastern Association for the Surgery of Trauma (EAST), the authors confirmed reduced overall mortality and paraplegia rates but comparable rates of stroke [1]. Given the success of endovascular stent grafts and despite the lack of prospective, randomized controlled trials, the use of endovascular techniques when applicable have been strongly recommended over open techniques for blunt thoracic injuries.

There are some noted drawbacks to the endovascular technique. The incidence of device-related complications is reported as high as 20%, mostly secondary to endovascular leaks (14.4%) [9]. Conversely, a more recent study in 2014 regarding device-related complications with over 2-year follow-up demonstrated a rate of 2.4% [68]. The majority of these endovascular leaks require intervention either with additional stents or open surgery. Other complications are related to access site injuries and occlusion of the left subclavian and/or left common carotid artery. Most surgeons now routinely occlude the left subclavian artery when necessary to gain maximum apposition of the stent graft. This was previously thought to cause steal syndrome or strokes if the vertebral anatomy was unfavorable. However, this complication has not been demonstrated as significantly as purported in the literature. A meta-analysis of endovascular repair of thoracic aortic injuries that included over 139 studies reported coverage of the left subclavian artery in nearly 30% of cases [69]. The reported incidence of steal syndrome after left subclavian artery occlusion is inconsistent, ranging from 2% to 10% [70]. Others have reported no difference in left arm symptoms or the ability to return to normal activities between patients who had left subclavian artery coverage and those who did not on an average 3-year follow-up [71]. The most recent guidelines from the Society for Vascular Surgery recommend left subclavian occlusion, if necessary, to obtain appropriate apposition and coverage of the injury with selective revascularization of the left subclavian artery. Selective revascularization should be based on the patient's condition, surgical expertise, and the vertebral anatomy, which can be assessed with intraoperative angiography [11].

The reports of paraplegia related to the repair of thoracic aortic injuries have decreased, especially with the increased utilization of endovascular techniques. Paraplegia related to endovascular stents is between 0.5% and 1% compared to about 3% for open repairs. Due to trauma-related coagulopathy, multi-injured patients have an increased risk of epidural hematoma related to a spinal drain placement. Moreover, the segment of aorta coverage during stent graft placement is relatively short. For these reasons, the prophylactic placement of spinal drains is not recommended [1, 11]. Rather, utilization of spinal drains should be preserved for patients who develop new-onset post procedural symptoms of spinal cord ischemia.

Other technical limitations to endovascular repair are related to access site, stent sizing, stent conformability, and deployment mechanisms, all of which have already and will continue to improve with continued development of these techniques and devices [68]. Two major concerns following placement of these devices are conformability to the aortic arch and oversizing of the stent. The lack of conformability leads to inadequate apposition to the aortic wall. This can predispose the stent graft to endoleaks and/or endograft collapse, which require further intervention and placement of additional devices or conversion to an open operation for repair [9, 11, 72]. Currently, there is no generally accepted stent sizing consensus among authors and surgeons. Most agree that oversizing should be limited to 10%, but this is not sufficiently substantiated in the literature [11]. Excessive oversizing of the aortic endograft can lead to stent graft collapse or infolding, which can lead to occlusion of the aorta. These device-related limitations are currently being addressed with newer stent grafts that are more appropriately sized for the younger trauma patient with a relatively smaller aorta with improved conformability for the aortic arch. Access sheath and deployment methods have improved as well. However, these newer devices are still in early phases of development and utilization. In due time, these devices will continue to improve and complications related to these technical limitations will likely fade [73–75].

The optimal follow-up strategy is a point of contention and concern related to the endovascular treatment of aortic injuries. More recent protocols image patients with CT angiography at 1 month, 6 months, and then every 12 months following injury for at least 5 years after placement of the device [74, 76]. In a young trauma patient, this is a concerning amount of ionizing radiation. These practices are not evidence based, as the long-term data regarding the durability and behavior of these stent grafts is unknown. More specifically, the comportment of the stent graft to the distorting, dilating aorta as a young trauma patient ages is uncertain. A recent single-center, retrospective study that followed 17 patients who had undergone endograft placement for thoracic aortic injury for a minimum of 10 years demonstrated that the natural history of the aorta was to dilate but that there

were no long-term device-related issues in this patient population [75]. Nonetheless, on average, there is a 1 cm increase in aortic diameter at the aortic isthmus of normal patents between the teenage years and octogenarians [77]. Giving the lack of a large, centralized database tracking the progress of these patients, some authors believe that a national registry could assist in fulfilling this deficiency of knowledge and ultimately improve the development and safety of these devices [20].

Not all blunt thoracic aortic injuries can be treated with endovascular stents. The surgeon has to remain vigilant to the aortic anatomy, branch anatomy, and type of injury to determine which patients would benefit from endovascular stent graft placement. Aortas that are less than 15 mm are too small to be treated with current devices. Additionally, aortic tears that extend to the mid-arch would require coverage of the left common carotid artery. This injury pattern precludes the use of endovascular stent grafts for repair. Vertebral arteries that originate off the aorta without patent posterior inferior communicating arteries are also a contraindication to repair with endografts. Also, some injuries repaired with stent grafts may undergo complications such as stent collapse or occlusion that are not amenable to repeated endovascular techniques. It is for these reasons that practice management guidelines from EAST recommend that endovascular techniques be attempted in centers where the ability to convert to an open repair remains viable [1].

Despite the paucity of evidence for the management of blunt abdominal aortic injury, there are guidelines for the utilization of endovascular stent grafts. Specifically, stent grafts are best suited for Zone III injuries where complicated long intimal flaps (>10 mm) have been identified. A complicated LIF is one that is associated with thrombus formation, clinical signs of neurologic demise, or evidence of ischemia to organs or lower extremities. Endovascular stent grafts can also be utilized for Zone II injuries if fenestration is technically feasible and available [32]. Zone I injuries are usually a candidate for endovascular repair as well, but typically this repair is individualized based on favorable anatomy and technical capabilities of the institution and surgeon (Figs. 29.3 and 29.4).

Open Technique

Overall the need for and use of open aortic techniques have diminished over the last couple of decades, especially in the treatment of blunt thoracic aortic injuries. This has largely been due to the success and access of endovascular techniques. However, there are still several instances of aortic injury that mandate an open repair. Patients who present in extremis will often undergo an open operation, especially in the case when an emergency department thoracotomy has been performed. As discussed previously, there are times that the anatomy of the patient or characteristic of the injury is not amenable to endovascular repair. Blunt and penetrating injuries to the ascending aorta and aortic arch require an open surgical approach. An aortic arch repair could be attempted with a fenestrated endovascular approach if the patient was fit for this time-consuming novel approach. The available open surgical techniques are primary repair, patch angioplasty, and interposition graft. Whether one of these techniques is performed with a temporary shunt, clamp and sew technique, or while maintaining distal aortic perfusion with cardiopulmonary bypass has been relatively well studied.

The use of cardiopulmonary bypass carries with it specific criteria. First and foremost, the institution itself must be equipped with machines to carry out this repair. More importantly, the necessary technicians and support staff must be available and well trained to properly use the bypass equipment. Lastly, the patient must be fit to undergo the procedure. In cases of intraoperative aortic free rupture, there may not be time to mobilize the team necessary to utilize the cardiopulmonary bypass equipment, and the priorities of the operation focus on preventing death from exsanguinating hemorrhage. In this instance, most would agree that the best option seems to be the clamp and sew technique. But the stable patient manifests different priorities of concern, mainly that of paraplegia. The blood supply to the thoracic spinal cord is tenuous and unreliable, mainly deriving from the intercostal branches of the aorta and the artery of Adamkiewicz. Maintaining spinal cord perfusion to this area of the thoracic region has proved challenging and has prompted considerable study. The first major investigation was completed by Fabian et al. in 1997 [4]. This prospective, multicenter cohort study identified that the rates of paraplegia may differ based on the type of technique utilized during aortic repair. Most notably, the authors reported that aortic cross clamp time >30 minutes and the clamp and sew technique were independently associated with paraplegia development postoperatively [4, 12]. This confirmed the results of several retrospective studies that had similar findings [78–80]. Many inferred from these findings that if cross clamping of the thoracic aorta was reduced to less than 30 minutes, then the protective benefit of bypass on preventing spinal cord ischemia is lost. However, it is impossible to predict the length of a case or the unforeseen obstacles that surgeons may encounter once the aorta is cross clamped.

The most recent large-scale, prospective analysis of open surgical correction of blunt thoracic aortic injuries places the risk of paraplegia at 2.9% [9]. This surprisingly low risk of paraplegia included patients who underwent clamp and sew or bypass and was significantly lower than the previously reported 8.7% paraplegia rate in the same cohort of patients studied one decade earlier [4, 9]. Moreover, neither of the two patients who underwent clamp and sew developed paraplegia in that study. The data would suggest that patients undergoing open surgical correction for aortic injury would benefit from the bypass technique when feasible. However,

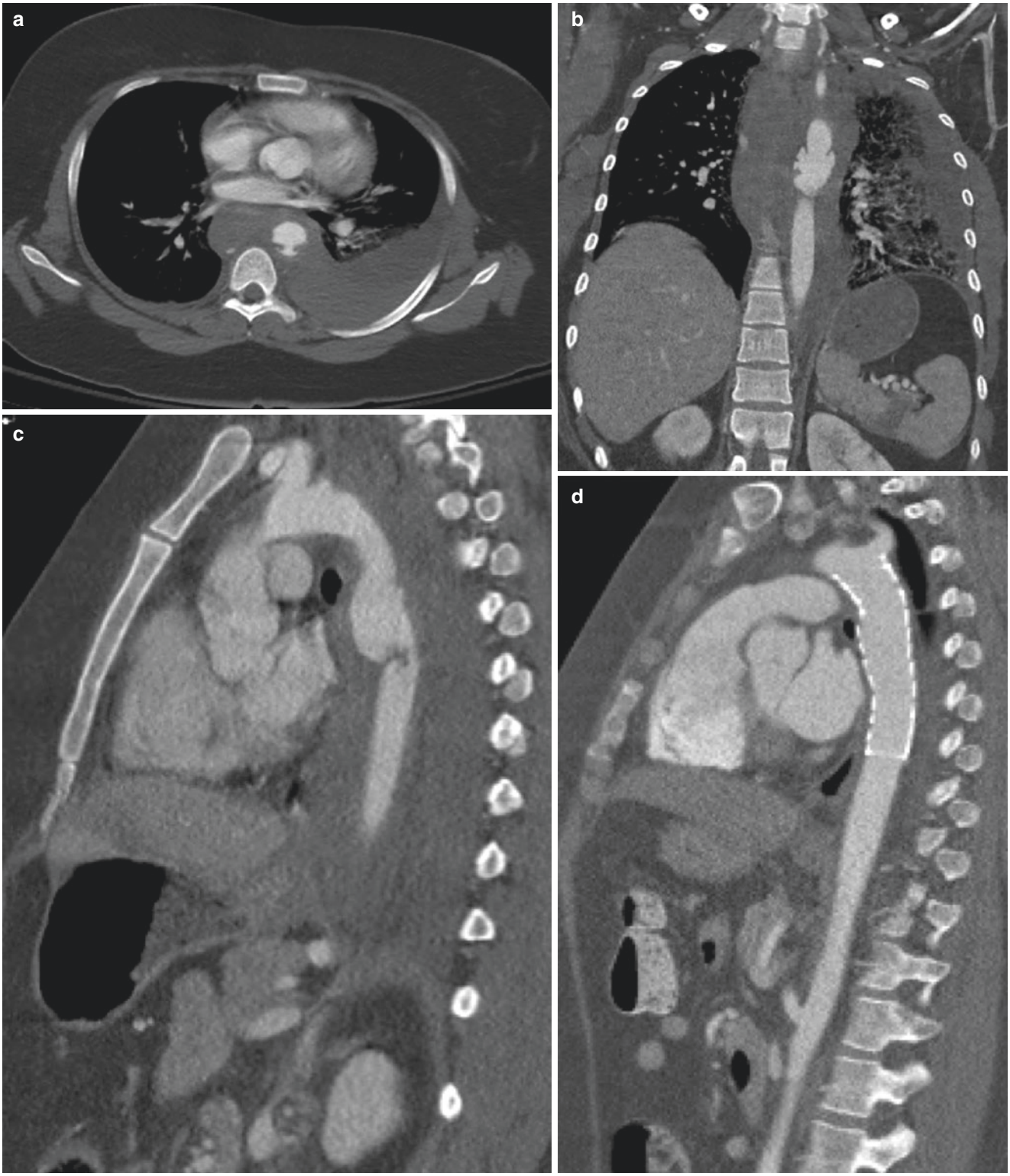


Fig. 29.3 This is a 25-year-old female involved in a high-speed, head-on motor vehicle collision with a tree. Upon arrival to the trauma bay, she was complaining of abdominal pain, back pain, and lower extremity pain. She was notably hemodynamically normal. (**a**) Axial image of the chest CT revealed a traumatic thoracic aortic injury with pseudoaneurysm. (**b**) Coronal image of the chest CT illustrates the significance of the injury with the surrounding hematoma. (**c**) Sagittal image of the chest CT. (**d**) Sagittal image of the chest CT after the patient underwent successful TEVAR

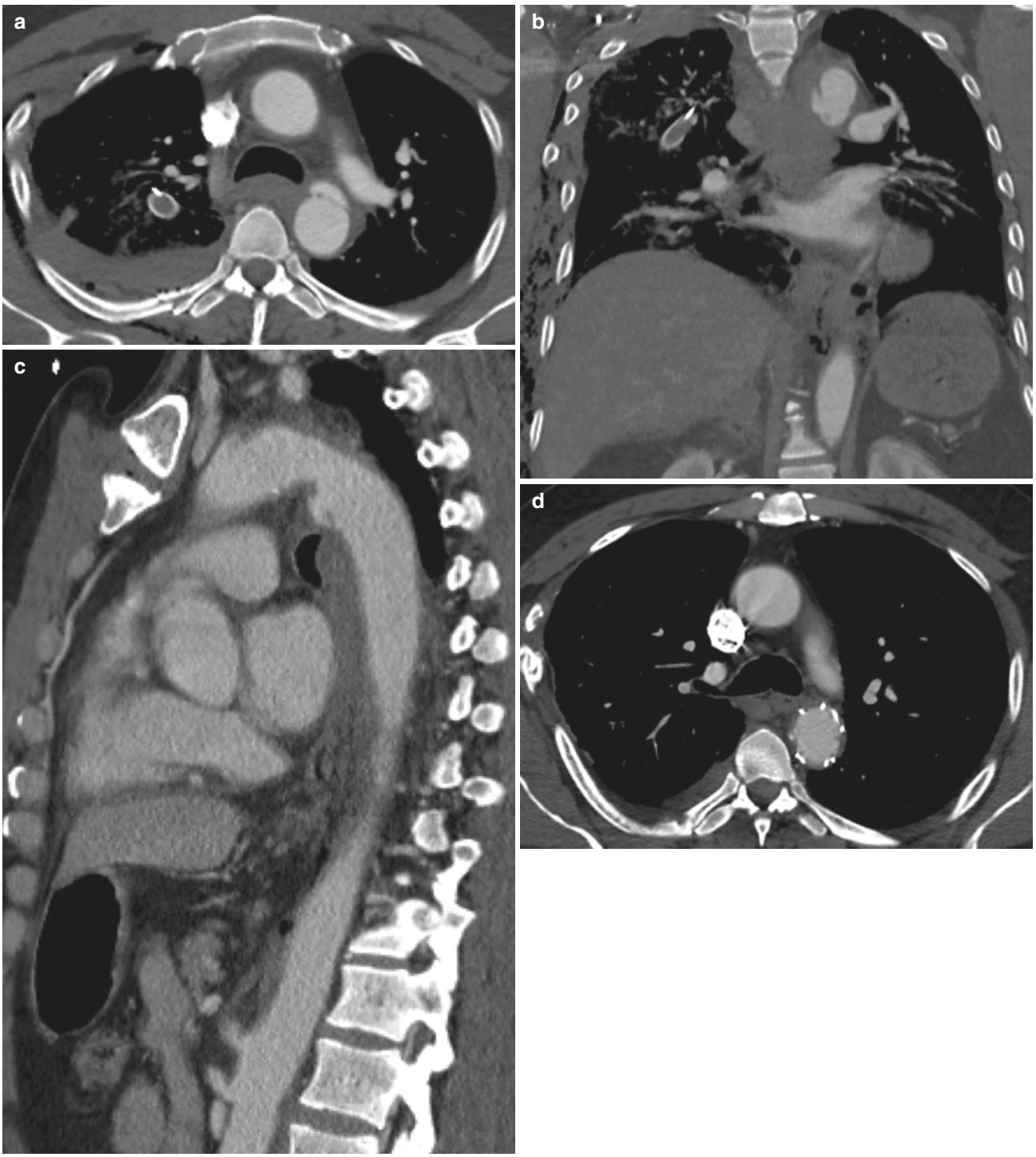


Fig. 29.4 This is a 55-year-old male involved in a head-on collision with an 18-wheeler at high speed. Significant intrusion into the passenger compartment with a prolonged extrication was noted by the emergency medical service personnel. (**a**) Axial image of the chest CT demonstrates a traumatic thoracic injury with a moderately sized pseudoaneurysm. (**b**) Coronal image of the chest CT reveals a hematoma surrounding the aortic injury but no active extravasation. (**c**) The sagittal image of the chest CT shows compression of the descending aorta from an extra-luminal hematoma. Note that pseudoaneurysm is at the location of the isthmus. (**d**) Axial image of the chest CT after successful TEVAR. (**e**) 3-D reconstruction of the chest CT following TEVAR

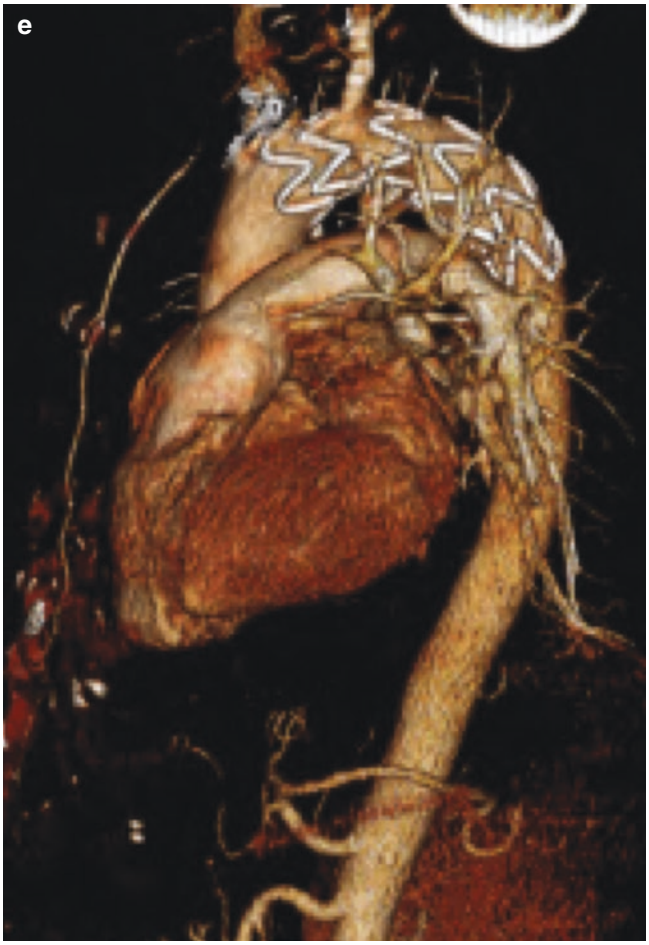


Fig. 29.4 (continued)

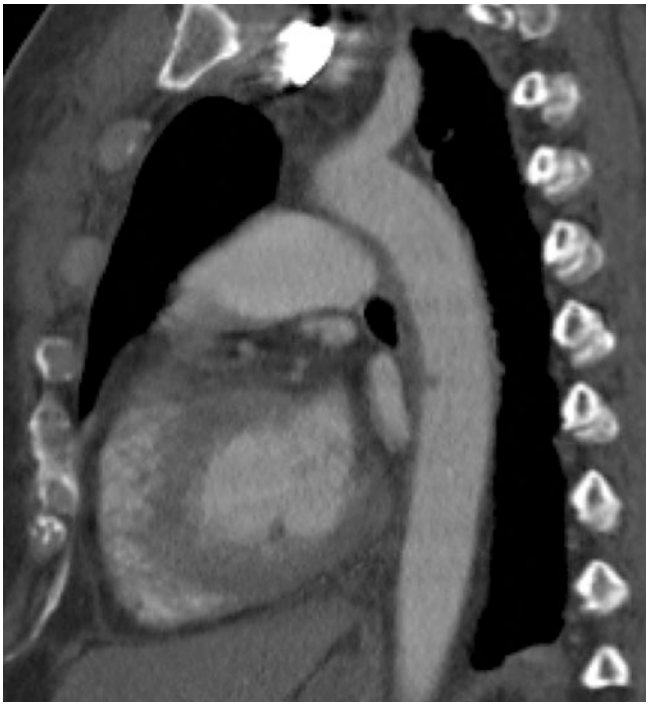


Fig. 29.5 This is a 42-year-old female who drove her motor vehicle head-on into the back of a flatbed truck at high speed. Emergency medical personnel noted a prolonged extrication. This sagittal image of the chest demonstrates a small intimal flap located in the mid-descending aorta

this likely needs to be a more individualized approach. In centers that are low volume and have bypass techniques available, the patients may benefit from its use. However, in high-volume centers with excellent results with the clamp and sew technique, there is an argument for doing what works.

Non-operative Management

Patients with aortic injuries are increasingly being managed non-operatively, at least initially [67]. Non-operative management is simply blood pressure and heart rate control with observation. Observation is defined as serial CT imaging until resolution or lack of progression of the aortic lesion [20]. There are two potential reasons for the increased utilization of non-operative management. More patients with low-grade aortic injuries (grade I or II) are being diagnosed with improved imaging modalities (e.g., CT angiography). Secondarily, the enhanced safety of automobiles has improved the overall survival of patients and reduced the incidence of more lethal aortic lesions, thereby increasing the number of minimal aortic injuries that are being managed non-operatively. Nonetheless, there is early evidence to support the appropriate use of non-operative management in a select population of patients with aortic injury. The definition of this population is crucial as not all patients fall into this less invasive modality of therapy. The Society for Vascular Surgeons recommends non-operative management of all BTAI minimal aortic injuries (MAI), further defined as grade I (intimal tear) injuries [11].

Others have reported success in managing minimal aortic injuries with non-operative modalities. Caffarelli et al. reported on 29 patients with BTAI whom they managed non-operatively with an in-hospital survival rate of 93% (no aortic injury-related deaths). Interestingly, only six of these patients had a MAI. The remainder had a significant aortic injury (SAI), defined by an associated mural hematoma or pseudoaneurysm. Of the 27 patients who survived, 21 had stable aortic injuries without progression, 5 had radiographic resolution of their injury, and 1 underwent open repair for increase in size of their pseudoaneurysm [81]. Another study also reported on the expansion of non-operative management of aortic injuries with reasonable success. Rabin et al. reported on 41 patients with BTAI who were managed non-operatively. This subset of patients was also made up of MAI and SAI. Upon short-term follow-up, no patient managed non-operatively died, and only one of

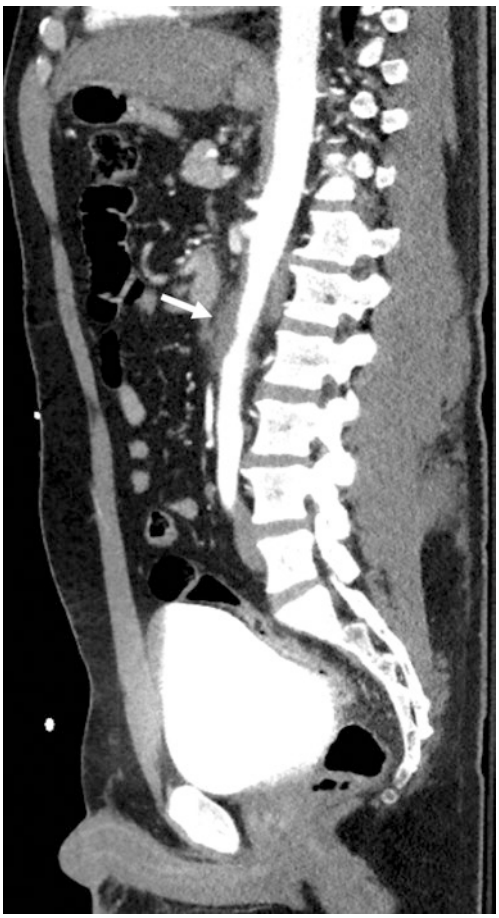


Fig. 29.6 This is a 33-year-old man who was a restrained, backseat passenger of a high-speed motor collision. He arrived in the trauma hall hemodynamically normal, complaining of right forearm pain and thoracic and lumbar pain. A CT of the abdomen was obtained due to the mechanism of injury and highway speed. This sagittal view of the abdominal CT shows a Zone III intramural hematoma of the aorta. He was also noted to have L1–L5 transverse process fractures of the lumbar spine. His abdominal aortic injury was managed non-operatively with antihypertensive medication and early interval imaging. His repeat CT of the aorta revealed complete resolution of the injury 4 days after injury

those patients underwent subsequent repair at the surgeon's discretion (not due to progression of the injury) [82]. These two studies underscore the successful management of MAI with non-operative, expectant management. Furthermore, they emphasize that this strategy may be safely expanded to non-threatening, significant aortic injury. However, there remains a lack of long-term follow-up with this patient population, and the possibility of scientific bias exists with these limited retrospective reviews. Prospective, multicenter studies are needed with long-term follow-up to elucidate this treatment modality and the appropriate patient population.

Although the limits for non-operative management are being tested and possibly expanded for thoracic aortic lesions, the surgical society guidelines for non-operative management for abdominal aortic injury are more clearly defined despite the lack of substantial literary evidence. There are several parallels between the management of blunt thoracic and abdominal aortic injury. Most authors agree that intimal tears and/or flaps (<10 mm) and uncomplicated long intimal flaps (>10 mm) can be managed conservatively with antihypertensive medication, antiplatelet therapy, and early interval imaging. If the lesion progresses on repeat imaging, then surgical intervention may be warranted. Additionally, complicated intimal flaps necessitate intervention; those include LIF with aneurysmal degeneration, thrombus formation, or pseudoaneurysm formation. The recommended intervention is individualized based on the involvement or proximity of major branch vessels and/or the level of contamination from associated injuries. Regardless of these practices and scantly supported guidelines, much research is needed in the area of abdominal aortic injury as it is a rare event (Figs. 29.5 and 29.6).

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Aortic Iatrogenic Injuries

30

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Iatrogenic Aortoiliac Injury

Aortic disease discussion, a fairly common occurrence, usually includes both aneurysm formation and occlusive disease processes. Other lesions of the aorta, which may involve any part of the aorta, include the aortic wall dissections, infectious processes, and the aortic fistula. Anatomically, the aorta extends from the aortic valve (AV) in the heart to the aortic bifurcation in the abdomen. Pathologic lesions or abnormalities, including iatrogenic injuries, may occur at any location along the course of the aorta from the AV to its abdominal division. Iatrogenic or physician-induced aortic lesions are uncommon but may be insidious in onset or acute and catastrophic.

As a physician, whatever we do in the care of a patient, the potential for complications is always present. These untoward results, in a few instances, are a direct result of our actions or iatrogenic in nature. Usually, these untoward occurrences are minor difficulties and of little or no major concern. But, when dealing with more complicated or more central aspects of the patient's health, these unexpected issues present greater challenges as to avoidance, prevention, therapy, and management of the complication. This certainly applies to the cardiovascular system and, in particular, to the aorta and the heart during diagnostic and therapeutic procedures.

Some causes of iatrogenic aortic injuries

I. Esophageal foreign body removal – thoracic aorta
II. Abdominal trocar placement
  A. Renal dialysis
  B. Laparoscopic surgery
III. Transhiatal esophagectomy – tumor
IV. Ruptured aneurysm – encircling aorta at diaphragm
V. Radical tumor resection
  A. Mediastinal
  B. Bronchogenic
  C. A-P (aortopulmonary) window dissection
VI. Translumbar angiograms
  A. "Eggshell" aorta
  B. Catheter or 17 gauge 7 1/2″ needle
  C. Renal artery
VII. Catheter studies
  A. Plaque dissection
  B. Thrombus formation
VIII. Orthopedic surgery- aortoiliac
  A. Posterior spinal surgery
  B. Hip surgery, especially redo
  C. Intra-abdominal bleed
  D. Thoracic erosions
IX. Balloon therapy
  A. Aortoiliac
  B. Coarctation
X. Sternal reoperation
XI. Positional/occlusive – stirrup position

Etiology

Aortic complications of cardiac diagnostic and therapeutic procedures are uncommon but do occur and tend to increase in frequency as more complicated transaortic cardiac procedures are developed.

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Some iatrogenic aortic lesions produced during cardiac procedures

I. Ascending aorta
  A. Aortic wall dissection during percutaneous procedures
    1. Associated with coronary artery procedures
    2. With intramural hematoma formation
    3. Association with cystic medial necrosis
  B. Dissection during aortic cross-clamp
    1. Heavily calcified aorta
    2. Cross-clamp site
II. Descending aorta
  A. Dissection
  B. Embolic
III. Abdominal aorta
  A. Thrombotic
  B. Dissection
  C. Intramural hematoma
IV. Embolic
  A. Central/CNS
  B. Coronary
  C. Distal
    1. Mesenteric
    2. Extremities

During cardiac catheterization, tiny, thin, and flexible catheters usually pass through the iliofemoral or radial artery systems into the aorta with relative ease. But Dandabe and El-Haress both report ascending aortic dissection in association with interventional coronary procedures [1, 2]. As a result of the complication, El-Haress et al. were required to perform coronary bypass and ascending aortic replacement for a Stanford type A-DeBakey type II dissection. Nuñez-Gil et al. retrospectively reviewed 74 type A aortic dissections over a 14-year period and found that 47 of the complications occurred while engaging the right and 30 during the left main coronary engagement for an incidence of 0.06% and mortality in 2 patients [3]. Thirty-five of their patients had angioplasty and stent placement, 36 were managed conservatively, and 3 required cardiac surgery.

During open coronary surgery in the presence of a severely calcified aorta, aortic cross-clamping may produce both aortic and coronary dissection [4]. These aortas may be prone to the development of dissection along the site of aortic cross-clamping, and thus, one attempts to avoid the sites with heavy calcification. When the left main coronary artery dissects, an oval area of calcium is resected from the coronary artery by some to create an elliptical opening for grafting [5]. Dissection of the descending or abdominal aorta may occur during various interventional procedures, including transcatheter aortic valve implantation (TAVI), in most cases may be treated with endografts when conservative treatment is unsuccessful [6, 7]. The following are some of the therapeutic approaches when aortic dissection has occurred:

Treatment options for aortic wall iatrogenic dissection

I. Close observation
II. Medication
  A. Anticoagulation
  B. Antihypertensives
III. Emergency
  A. Coronary bypass
  B. Open repair
  C. Aortic resection and grafting
IV. Endografting
  A. Transfemoral
  B. Transiliac

Other aortic lesions may develop after cardiac surgery as exemplified by a patient who developed an aorta to right ventricle fistula (AVF) after repair of a ventricular septal defect (VSD) and resection of a sub-aortic membrane [8]. Also, an aorta to right atrium iatrogenic fistula was treated percutaneously by Ruparelia [9]. The close anatomic relationship between the paper-thin central and pectinate muscles may lead to a perforation of the right atrium and aorta during atrial pacemaker lead implantation and even death [10]. Certainly, infection may occur following either transaortic cardiac or open cardiovascular procedures and rarely will the cause for such become apparent.

Lesions involving the aorta may occur at any level from the aortic bifurcation to the aortic valve. We have mentioned several cardiac procedure-related aortic lesions which may develop in the ascending or descending aorta. These lesions or injuries may be induced throughout the aorta and may occur during or shortly after the aortic intervention. Other injuries may not become apparent until months after the treatment. Such was the case of a child who had a persistent ductus closure at 3 months of age and development of an iatrogenic obstruction of the aorta with a fatal outcome several months later [11]. Endovascular thoracic aneurysm repair may lead to aortic dissection, while right ventricular or pulmonary artery transcatheter procedures may lead to aortopulmonary fistula formation [12, 13].

Iatrogenic aortic considerations also include the acute aortic trauma lesions, such as dissection, rupture, or perforation +/− hematoma (intramural or extramural), aneurysm formation, and infection (mycotic or fistulization). An example of the acute perforation includes the aortic perforation during laminectomy. Pseudoaneurysm formation with secondary

rupture and massive hematuria after pelvic surgery may occur [14]. Insertion of chest tubes for drainage of a fluid-filled thorax has resulted in inadvertent tube drainage of the aorta, the heart, and the pulmonary artery vessels [15]. The insidious or slow-onset injuries to the aorta are uncommon, but potentially may occur when the patient with periaortic malignant disease requires high-dose radiation therapy for control or cure of a malignancy. Symptomatology related to such changes are seldom recognized as a significant concern and rarely reported even after symptomatic treatment.

Diagnosis

Diagnostic studies are not required in a large number of these patients. When a sudden gush of blood occurs during a procedure, the problem is acute and the physician urgently turns to control of the situation. C-T (computerized tomography), C-T-A (C-T angiogram), MR (magnetic resonance) studies, or diagnostic angiography may be obtained in the less acute situation.

Hemoglobin/hematocrit levels will be obtained along with blood type and cross-match studies. Coagulation studies may be obtained – especially if the patient has a past history of bleeding/clotting problems or has been on anticoagulants as time permits. Acuteness of the situation will define the extensiveness and time factor related to any diagnostic testing.

Treatment

Acute injury associated with massive bleeding and shock-like situations are dramatic and require urgent or emergency therapeutic intervention.

Examples of iatrogenic acute arterial injuries for which we were consulted

Popliteal arteries – arthroscopic surgery
Iliac arteries – hip surgery
Brachial arteries – catheter studies
Subclavian arteries – access procedures
Aortic injuries – trocars/disruption

Many of these arterial injuries required immediate repair or correction, such as the popliteal artery during cartilage surgery or the iliac/aortic lesions during hip surgery, while under the same anesthetic. Other concerns could be evaluated and possibly followed closely – such as the brachial artery after catheterization studies.

Some therapeutic approaches to aortic injuries

I. Elective
   A. Ascertain seriousness
   B. Determine need
   C. Obtain history/physical
II. Diagnostic anticipation
   A. Hemoglobin/hematocrit
   B. Coagulation studies
III. Acute
   A. Control bleeding – open
      1. Thoracic approach
      2. Abdominal approach
      3. Suture repairs
      4. Grafting
      5. Transfuse
   B. Compression
   C. Balloon therapy – endografts
      1. Occlusive
      2. Dilation
IV. Medical
   A. Coagulation therapy
   B. Anticoagulants

We've outlined many of the treatment options available when aortic injury occurs. The aortic lesions may be acute life-threatening or chronic in nature and requiring little intervention. When sudden or massive bleeding occurs, the patient requires urgent control of the injury and, usually, large volume of blood transfusion. When the patient is in the operating room (O.R.), the opportunity for hemorrhage control has a better chance for success than when the patient is in a procedure room or a diagnostic room. Even in the O.R., the aortic bleeding may be difficult or impossible to control in some situations (i.e., transhiatal esophagectomy or giant mediastinal tumor resections).

Different situations present difficult and almost impossible challenges such as the inadvertent percutaneous insertion of a peritoneal dialysis or endoscopic trocar into the aorta or vena cava when in either the procedure or operating room (O.R.). When these events occur in the O.R. and the patient has been prepped for surgery, such as a laparoscopic operation, control may be accessible. A number of the iatrogenic aortic injuries, many of which occur during surgery, require rapid but often futile interventions (see *Some Causes of Iatrogenic Aortic Injuries* box above). Endoscopic removal of a sharp esophageal foreign body in the G-I lab would present a distinct acute challenge when the aorta is perforated, when compared to when an esophageal perforation. The nonconstricting "eggshell" aortic wall may bleed when perforated or needled, but one usually will have the opportunity for control of the aortic perforation and hematoma. The same

is also true for dissection of the aorta or a plaque and the removal of an aortic thrombosis. Urgency versus emergency control of the situation requires rapid assessment and appropriate action.

The patient having spinal surgery in the prone position presents a devastating challenge when the aorta is injured. The lumbar discectomy may result in an aortic laceration [16]. Unfortunately, many of these patients do not survive the injury. Such injuries not only involve the aorta but may also affect the pelvic vessels. Delayed thoracic aorta injury after anterior spinal instrumentation may also include thoracic screw penetration of the aorta [17]. Similar induced leaks, including spinal fluid from the old surgical wounds, have been seen by us, when misinterpreted to be draining cysts by the referring physician. Rupture of an aortic coarctation during repeat balloon angioplasty requires similar awareness and interventional therapy [18]. Fortunately, this is a rare situation, but we have been called to the O.R. for a number of more common orthopedic vascular considerations.

The most common orthopedic-induced vascular injury for which we have been called to surgery include the infected and redo hip surgery patient. Usually, the bleeding has been tamponaded with large sponges and hand pressure while awaiting our presence. Proximal and distal vascular control involving the aorta and iliac vessels are obtained. If the bowel is involved, primary closure/repair of the GI defect is then accomplished. This treatment is similar to the simultaneous gunshot wound of the aorta and injury to the bowel and aorta. Following this, we have either performed a primary vascular repair or insertion of a vascular graft. When available, an omental overlay is utilized to aid healing and clearing of infection. Suction drainage or open wound therapy then follows. The final prosthetic hip repair is usually then delayed for 2–3 months until clearing of the infection and complete wound healing have occurred. In other situations, when an aortic plaque is dissected or a thrombus induced by catheter intervention, the situation is evaluated and treated conservatively if possible, with anticoagulation or semi-elective intervention as necessary.

In many circumstances, the acute iatrogenic hemorrhagic aortic injury may require intervention. The most concerning of these are the acute massive bleeding episodes in which shock and loss of large volumes of blood occur. There usually is little time for discussion or option consideration. These patients usually require emergency control of the aorta – either via thoracotomy or laparotomy – especially when packing or compression is not feasible or successful. When possible, a direct approach to the area of injury will afford the best chance for control. But if not possible, then more proximal temporizing aortic control/clamping may be assistive, or we have utilized emergency cardiopulmonary bypass for several noncardiac conditions [19, 20]. These patients are usually critical or moribund when we have been consulted and the endovascular techniques were not felt appropriate but may be a consideration when time and expertise permit. When compression packing and pressure application are controlling, eventually judicious removal with vascular control and repair will follow.

When the aortic injury occurs in the O.R., for example, during insertion of a laparoscopic trocar, then immediate laparotomy and digital aortic compression or aortic clamping should provide an opportunity for control. When performing extensive tumor surgery, especially after radiation therapy, tissue planes may be difficult to delineate, thus increasing the risk of aortic injury. In redo mid-sternotomy procedures, especially for cardiovascular procedures, inadvertent and usually unavoidable cardiovascular injury may occur. This may be controllable by pressure application and/or urgent femoral access cardiopulmonary bypass. Fortunately, this unpleasant experience of inadvertent injury to the aorta or a cardiac structure during redo sternotomy is very uncommon. Primary suture repair, when possible, is the preferable approach but grafting may be considered on occasion.

When the aortic problem is of a less acute nature and not of a major bleeding concern, then appropriate diagnostic and etiologic evaluation may be undertaken with the hope for resolution in a more conservative approach. Thus, coagulation evaluation and endovascular approaches may be more readily utilized, as well as diagnostic imaging, especially when aortic wall dissection occurs. If aortic thrombosis develops, for example, during the stirrup position for surgery, balloon thrombus extraction after diagnostic C-T-A may usually be utilized. When dissection has occurred, the treatment required will depend on the extent and location. Thus, emergent open grafting in some patients will occur, while in others, close observation or endostents will be the treatment preference.

Aortic injury consequent to other and nearby interventional diagnostic and therapeutic procedures are very uncommon and may be minimized to some degree by careful patient and procedural selection. But due to the complexity of disease and anatomic relations, they may not be totally avoided. In the past, translumbar aortofemoral angiography was accomplished with a 17 gauge 7 1/2 inch needle passed paraspinally. One patient with an “eggshell” aorta required an open suture of the nonconstricting defect. Physicians have avoided the use of transaortic biopsy of tumors in most patients due to possible aortic complications. Iatrogenic disease or injury does not imply physician error, but rather inadvertent or nonpredictable results as illustrated by this latter patient.

Iatrogenic lesions of the aorta are known to occur with an increased incidence in some procedures as compared to others. Iatrogenic lesions may be intentional, accidental, or a result of inadvertent intent. Such lesions do not imply any lack of ability or caution on the part of the procedure

performing physician or surgeon. In addition, a certain percentage of patients having a defined procedure are expected to develop an iatrogenic lesion, such as an iatrogenic aortic intramural hematoma [21]. Further, unexpected complications are more frequent when the patient's situation is the most critical, for example, during cardiac arrest and resuscitative efforts, requiring immediate split-second approaches.

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Acute Aortic Thrombosis

31

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Aortic disease is a fairly common medical condition. Vascular clotting is also well known to the lay public, especially venous thrombosis after medical and surgical conditions. Arterial thrombosis is less commonly recognized except after arterial/vascular intervention. If the arterial thrombotic process is slow in onset and/or involves smaller vessels, the medical condition and the patient are usually successfully treated, either medically or surgically. But if the process involves a larger vessel such as the aorta, the condition may be difficult to treat or catastrophic in nature despite interventional and therapeutic approaches.

Etiology

When one discusses aortic occlusion, a number of vascular disease processes come to mind. The usual patient has the slowly progressive Leriche syndrome (progressive atherosclerotic occlusion of the aortic bifurcation) or a thrombosed aortic aneurysm. The Leriche syndrome may be evaluated and diagnosed in an elective fashion in most circumstances. The acutely ruptured or thrombosed aortic aneurysm – usually abdominal – is investigated and diagnosed urgently for possible emergent therapy. Early on, aneurysms were treated with wire coil thrombosis and cellophane wraps. Since then, progressive improvement in diagnostic and treatment techniques led to catheter angiography and computerized tomographic angiography (CTA) and open aortic and now transfemoral endografts.

However, there is another group of patients who develop acute aortic thrombosis and occlusion [1]. These patients are seen as sudden-onset, usually unexpected, acutely ill individuals. There are a number of potential etiologies which may produce such a problem. As listed, the number of etiologic diseases, which may create sudden and complete occlusion of the aorta, is large and varied:

Possible acute aortic occlusion etiologies

- I. Obstructive lesions
  - A. Embolic
    - 1. Cardiac source
    - 2. Proximal aortic thrombus
  - B. Acute dissection
  - C. Tumor obstruction
- II. Positional – physician or patient
  - A. Iatrogenic
    - 1. Surgery with legs in stirrups
      - (a) Colonic
      - (b) Gynecologic
    - 2. Clamping aorta – without heparinization
    - 3. Passage of percutaneous catheters/grafts
  - B. Accidental
  - C. Self-initiated
- III. Malignancy associated
  - A. Chemotherapy related
  - B. Obstructing tumor
- IV. Hematologic/coagulation disorders
  - A. Essential thrombocytosis
  - B. Protein C and S deficiency syndromes
  - C. Thrombotic thrombocytopenia

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D. Lupus anticoagulants
E. Elevated lipoprotein (a)
F. Antiphospholipid syndrome
V. Blood flow stasis – postendoluminal graft
VI. Vessel wall
A. Injury
B. Atherosclerotic disease
1. Leriche syndrome
2. Plaque dissection
C. Primary aortic mural thrombus
D. Aneurysm thrombosis
VII. Septic aortitis – associated
VIII. Idiopathic
A. Crohn's associated
B. Neonates
IX. Medication
A. White clot syndrome – heparin antibodies

In the younger, and particularly in the Marfan-type, patient, sudden severe pain and ischemic symptoms may develop as a result of aortic wall dissection. Such lesions may be of familial or hereditary origin. These lesions usually occur in the proximal or thoracic aorta with symptoms involving the chest, the abdomen, and the lower extremities. Similarly, spontaneous proximal thoracic aortic dissection and thrombus formation may lead to both thoracic aortic thrombosis and distal aortoiliac embolic situations.

A localized thoracic aortic thrombosis was noted in an asymptomatic patient with a history of a carcinoma of the lung resected 1.5 years previously [2]. Anticoagulation therapy with warfarin was followed by dissolution. These coauthors had previously reported a patient with malignant lymphoma, splenic infarction, and multiple aortic thromboses, all of which were treated successfully pharmacologically [3]. Symptomatic thrombus of the descending thoracic aorta is uncommon, but recurrent distal embolization may be catastrophic and difficult to treat [4]. Thrombus formation, including free floating, may occur in the aorta, left atrium, or the left ventricle with acute distal embolic occlusion potential [5, 6]. Primary descending thoracic aortic acute thrombosis fortunately is rare. More commonly, acute complete or near-complete acute occlusion of the aorta may occur as a result of an anatomic defect such as a Marfan's disease-type aortic dissection.

There are a large number of unusual causes of acute aortic obstructive or thrombotic lesions. These more commonly occur in the abdomen than in the thoracic aorta. Acute occlusive disease of the abdominal aorta usually is the result of a previous aortic lesion – such as a partial Leriche – progressing to acute complete occlusion. Acute dissection involving the abdominal aorta as well as a thrombosed aneurysm may also be the culprits. Kim et al. reported on four cases of acute aortic thrombus induced by chemotherapy [7]. Thrombosis of the abdominal aorta in congenital afibrinogenemia has been reported by Sartori et al. [8].

Aortic thrombosis may occur as a result of thrombotic thrombocytopenia (Werlhof's disease), disseminated sepsis such as aspergillosis, and coagulation defects such as lupus anticoagulant positivity [9]. Aortic thrombosis associated with an elevated lipoprotein (a) and the antiphospholipid syndrome are also reported [10, 11]. Multiple unusual causes for aortic thrombosis – especially in the abdomen – include such considerations as vessel wall injury, plaque dissection, and blood flow hemostasis due to an unusual pressure or patient position for a long period of time, especially in the elderly. The protein C and S deficiency syndromes along with essential thrombocytosis and malignancy must be considered in the differential diagnosis of acute aortic occlusion [12]. Of interest, one of our patients with protein C deficiency and gangrene of the small bowel required six surgical procedures to save only 12–24 inches of the small bowel. He subsequently married his ICU nurse and is on lifetime anticoagulation. In addition, vascular surgeons are aware of the risk of clamping (or not) the aorta during vascular surgery – especially when no heparin has been administered.

Positional considerations are always present when patients are placed in unusual positions for major prolonged surgical therapy. When patients require prolonged stirrup positioning and control of the lower extremities for major pelvic tumor surgery, such as exenteration, we have been asked postoperatively to consult on these patients with aortoiliac occlusive disease and loss of limb function or sensation. In the recent years, additional nongynecologic surgical procedures have required the lower extremities to be placed in stirrups for surgeon positioning and appropriateness of the operation. The physician attempts to position the patient and legs in as neutral a position (not too high or too wide) as possible and yet to be able to perform the necessary operation. Despite these prophylactic attempts, on an unusual occasion, the patient on awakening may be found to have "moribund" extremities. The physician may assume such finding was due to the positioning but, in fact, other factors may also be involved and should be investigated for – when possible and time permits.

Case Report

An elderly gentleman presented with multiple complaints, including colorectal symptoms due to a T3 adenocarcinoma of the rectum. PET scan (positive emission tomography) evaluation demonstrated an adenocarcinoma of the lung, which was treated with focused radiotherapy, in addition to the rectal carcinoma. The patient also had diabetes mellitus,

hypertension, COPD, a history of cholesterol elevation, claudication, and a history of two cerebral strokes. A whole-body C-T (computerized tomography) scan demonstrated two aortic aneurysmal dilations with maximum diameter of 3.2 cm (one thoracic and one abdominal) and an open aortoiliac system.

Following a standard T3 chemoradiation colorectal protocol, the patient had a hand-assisted low anterior resection of the colon with splenic flexure mobilization. A postcolectomy vascular dye study demonstrated adequate superior mesenteric artery flow. During surgery, the lower extremities were in low (30°) stirrups to accommodate the surgeon and the surgical instruments. In the recovery room, despite frequent relaxation of the legs during surgery, the nursing staff noticed discoloration of the lower extremities and no leg movement. Emergency C-T angiogram (CTA) demonstrated bilateral iliofemoral and distal aortic thrombosis. Immediate bilateral transfemoral balloon thrombectomy produced a large volume of thrombus from vessels with calcific plaques.

Diagnosis

Diagnosis of the patient's condition may be rather straight forward. But, initial assumptions may be incorrect, and diagnostic studies should not be limited to a few laboratory tests or radiologic studies in all situations. Certainly, one will attempt to delineate the basic cause and the anatomic lesion(s) as soon as practical. The past and current history and physical may elicit the etiologic cause for the occlusion. Then studies should consider blood counts, coagulation studies, and C-T angiograms when practical.

Some diagnostic tests for acute aortic occlusion

I. History and physical – medication history
II. Laboratory
  A. CBC
  B. Coagulation profile – coagulation factors
  C. Complete metabolic profile (CMP)
  D. Arterial blood gasses
  E. Cultures – blood/fluid
III. Radiologic
  A. Flat plate abdomen/chest x-ray
  B. Computerized tomography (CT) + dye (CTA)
  C. Magnetic resonance angiogram (MRA)
  D. Contrast interventional (catheter) angiogram
IV. Cardiac
  A. Electrocardiography (EKG)
  B. Echocardiogram (Echo)
  C. Cardiac enzymes

As soon as reasonable, after a decision regarding medical or vascular surgery intervention urgency is completed – which depends on the level of extremity discoloration and the patient's medical condition – further diagnostic or therapy evaluation is undertaken. CTA, diagnostic studies, and intervention will be guided by and after the therapeutic approach elected has been determined. MRA studies and more esoteric coagulation profile studies may not be necessary or practical initially but obtained when conditions are more appropriate. Invasive catheter angiography will not be required nor practical in a large number of these acutely and very ill patients but assistive when conditions permit.

Therapeutic Approach

Recognition of the problem is primary in deciding the therapeutic course to follow in these patients. When the patient is asymptomatic or has few complaints, the approach will be different from that for the patient who has morbid functionless and discolored extremities. Some of the options available to treat these unfortunate individuals – depending on their condition – are outlined below.

Therapeutic options for acute aortic thrombosis

I. Prophylaxis
  A. Avoidance of known causes
  B. Monitor disease/progress
II. Medical therapy
  A. Appropriate diagnosis
  B. Review history and medications
  C. Anticoagulation
    1. Consider urgent heparin
    2. Hematology consult
    3. Multiple/simultaneous anticoagulants
  D. Continue/discontinue medications – chemotherapy agents
  E. Antibiotic therapy after culture
  F. Thrombolysis/tissue plasminogen activator
III. Surgical
  A. Review CT/MRI/angiogram
  B. Balloon thromboembolectomy
  C. Exploration aorta
    1. Thrombectomy
    2. Aortic window
  D. Transfemoral endograft (watch for emboli)
  E. Blood cross-match
  F. Aortic wall fenestration
  G. Bypass procedures – extra-anatomic
IV. Post reperfusion
  A. Reperfusion syndrome/fluids
  B. Possible amputation

As demonstrated by Sugiura et al., when the intraaortic thrombus has been found coincidentally with diagnostic testing for other reasons, anticoagulation therapy with warfarin may be adequate [2]. They did discuss Virchow's triad for thrombogenesis (hypercoagulability, blood flow stasis, and vessel wall injury) but were uncertain as to how this applies to the arterial thrombus presumably of nonacute onset [2, 3]. Kim et al. also utilized selective systemic anticoagulation in their patients with chemotherapy-induced aortic thrombus [7]. If a known cause exists for the aortic thrombosis, removal or elimination of the thrombogenic etiology followed by noninvasive techniques is a reasonable approach when the patient is stable. Sartori et al. were also able to successfully treat their congenital afibrinogenemia patient with an abdominal aortic thrombosis below the renal arteries and a distal floating component utilizing fibrinogen concentrates, enoxaparin, fondaparinux, and low-dose aspirin [8].

Kaschwich et al. have outlined their approach and management of acute aortic thrombosis after reviewing the literature and report no improvement in mortality over the past 20 years [13]. When the endoaortic thrombus is causing recurrent or potentially catastrophic concerns, more aggressive therapy and intervention are indicated. Depending on the location of the thrombus and the patient's condition, aggressive therapy will be initiated. This was done by Ha et al. after cardiac catheterization-associated aortic occlusion [14]. Siani et al. utilized the endovascular stent graft for a high-risk patient with a thoracic aortic medial thrombosis [4]. Verma et al. reviewed 88 patients with acute arterial occlusion and found 19 patients (mean age 41.2 years and male/female ratio 1:2.1) with aortic mural thrombus. Ten of the patients had thoracic aorta thrombus and six had infrarenal aortic thrombin origin [15]. Thoracic aortic lesions were treated with stent grafts (4), bare-metal stents (3), and anticoagulation (2). Three suprarenal lesions were treated with a trapdoor aortic thrombectomy and six infrarenal patients with aortobifemoral embolectomy, aortic stenting (2), surgical thrombectomy (1), and anticoagulation alone (1). Four of the patients died due to these major thromboembolic insults (21%) [15].

The cause and the severity of the patient's symptoms will determine the type and majority of the treatment. A floating aortic thrombus developing in a 71-year-old obese female after a long-distance airline flight was successfully treated with a bare-metal stent [16]. The patient with sudden occlusive symptomatic disease of the aorta will require urgent evaluation and treatment whether the cause is an acute obstructing dissection or an acute thrombosis occurring during surgery.

Distal aortoiliac thrombosis occurring during emergency clamping for massive bleeding and profound shock will require thrombectomy and, hopefully, return of extremity circulation. Morbid discoloration and absence of pulsation or function after prolonged positioning of the legs (usually bilateral) in stirrups have universally required emergency diagnosis and intervention – either transfemoral or transabdominal. Such unexpected findings, however, have met with few therapeutic recovery successes. The positional thrombosis herein mentioned is the reason; when performing thoracic outlet-type surgery, the senior author placed the upper extremity in a neutral position every 10–15 minutes to avoid arterial thrombotic concerns of the arm. Patients with preexisting significant distal aortic stenosis may also develop an acute distal aortic thrombus with accompanying acute symptoms. Usually, these patents will also require urgent surgical intervention. When significant vascular considerations and potential vascular complications exist, the physician and the patient will modify their approach, when possible, to best fit the situation.

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Management of Aortic Atherothrombi

32

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Atherosclerotic Lesions: Types of Plaque

The formation of plaque starts with the development of atherosclerosis, a slow process that takes years to reach a critical point but can become catastrophic within minutes [1]. Some plaque will remain stable, but others will be prone to rupture and cause complications [2]. The plaques that tend to rupture more are characterized by having a large lipid core and a thin fibrous cap. Originally thought differently, atherosclerosis is now considered a dynamic process and plaques can progress or regress, and this is believed to be influenced by modification of risk factors.

Plaques that develop in the aortic arch are among the main causes of stroke and peripheral emboli. Pujadas Capmany et al. found that there is a high risk of embolic events when complex aortic arch plaques are present; this was defined as a plaque thicker than 4 mm or with mobile components. They found that the risk is elevated in ulcerated plaques or hypoechoic plaques which likely represent the presence of high lipid content [3].

The American Heart Association provided a definition of the advanced types of atherosclerotic lesions and a histological classification of atherosclerosis [4] (Table 32.1). The main growth mechanism of lesion types I–IV is due to lipid accumulation, type V due to accelerated smooth muscle and collagen increase, and type VI due to thrombosis and hematoma.

Table 32.1 Lesion histology and classification [4]

Histology and classification	Characteristics
Type I – Initial	Isolated macrophage foam cells
Type II – Fatty streak	Mainly intracellular lipid accumulation
Type III – Intermediate	Type II changes + small extracellular lipid pools
Type IV – Atheroma	Type II changes + core of extracellular lipid
Type V – Fibroatheroma	Lipid core and fibrotic layer, or multiple lipid cores and fibrotic layers, or mainly calcific, or mainly fibrotic
Type VI – Complicated	Surface defect, hematoma-hemorrhage, thrombus

Cardiovascular disease associated with atherosclerotic changes is still the leading cause of death in the world, with the exception of the sub-Saharan African region. Because of the advancement in understanding atherosclerotic disease, there has been a growth in disease prevalence, which places a financial burden to the health system. Describing specific costs goes beyond the scope of this chapter.

Despite the different manifestations of atherosclerotic disease and the systems affected, such as aortoiliac disease, aneurysms, symptomatic carotid disease, or coronary artery disease, the lesions associated with it have a lot in common. It starts with the accumulation of cholesterol in the arterial wall with different degrees and characteristics of plaque that ultimately lead to the ischemic manifestations of the disease.

Medical advances in diagnosis and imaging have helped us obtain a better understanding of the progression of the disease, which in turn has helped develop new treatment and management strategies. Regardless of the treatment, either open or endovascular, medical management is added to ensure long-term results. Newer imaging techniques can detect unstable plaques that are more likely to result in rupture, thrombosis, and distal embolization. New risk factors

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for late progression have been identified separate from the traditional risk factors. These are elevated blood levels of biomarkers like inflammatory cytokines, metalloproteinases, insulin, glucose, and other smooth muscle growth factors.

In a retrospective study by DeBakey et al. on the patterns of atherosclerosis in which they describe a review of 13,827 patients who were admitted one or more times at the Methodist Hospital in a medical center in Houston, Texas, between 1948 and 1983, they described five categories of distribution of disease: (I) coronary arteries, (II) major branches of the aortic arch, (III) visceral arterial branches of the aorta, (IV) terminal abdominal aorta and its major branches, and (V) a combination of two or more of these categories at the same time. In this review, they described the progression of the disease as well as re-occurrence and development of disease in new sites other than the ones for which the patient had been originally treated [5]. Criqui et al. published on the mortality over a period of 10 years in patients with peripheral arterial disease and found that there was a high risk of death from cardiovascular causes in patients with large-vessel peripheral arterial disease [6].

When planning for treatment, it is important to evaluate the type of lesion; a stable plaque that is causing some degree of ischemia distally is much safer than a plaque that has lots of atheroma debris under a thin cap. This is also affected by the vascular bed in which the lesion is located, as described by Herisson et al. where they compared carotid and femoral atherosclerotic plaques and found that those plaques in the carotid arteries had more frequent fibrous cap atheroma whereas the plaque in the femoral arteries was more fibrocalcific, and due to these characteristics, the results with treatment were different [7].

Endothelial dysfunction has been linked to the development of atherosclerotic lesions. Studies have found that flow-induced vasodilation is an endothelium-dependent process in humans, and it is mediated by nitric oxide. Interestingly, flow-induced vasodilation is markedly reduced in young patients with CAD [8]. These findings propose that not only the vessels with atherosclerotic disease have endothelial dysfunction, but that it is more of a diffuse process and could perhaps be used as an early marker for the progression of disease.

More recently, some studies have shown a connection between diseases that affect the endothelial function, advanced glycation end products, and protein kinases with alteration in vasodilation and contribution to the progression of atherosclerosis [9, 10].

The subendothelial space is where the atherogenic particles will deposit and where macrophages and smooth muscle cells take in the particles and start the atherogenic process [11]. It is in this space where the proteoglycans present interact with low-density lipoprotein and its associated apolipoproteins [12].

Aortic Thrombus

Arterial embolization is a problem that carries increased morbidity and mortality. Among the complications associated with distal embolization are acute ischemia with an approximate rate of 13–14% and mortality with a rate of 9–12% [13]. The main cause of embolic events has been associated with alteration in cardiac rhythm either as a consequence of myocardial infarction, atrial fibrillation, endocarditis, or after prosthetic valve replacement. When it comes to noncardiac pathology, the origin of these emboli is within the aorta, and it is due to aneurysmal degeneration, dissection, ulcers, or trauma. When they are found, most of them are in the abdominal aorta and the rest in the thoracic aorta [14].

On a paper published in the *Journal of Vascular Surgery*, it was found on autopsies that 0.45% of the patients who had a normal aorta had some degree of mural thrombus. From those patients, only 17% had evidence of distal embolization. Also, they found that 20% of those mural thrombi were present in the thoracic aorta [15]. Some studies have indicated that up to 15% of emboli may originate from a noncardiac, unidentified focus [16].

Emboli may originate from any segment of the aorta from the arch to the aortoiliac bifurcation. These emboli can cause cerebrovascular accidents, mesenteric ischemia, renal ischemia, and acute limb ischemia. Frequently, the thrombus is found because of the embolic event. These embolic events can occur spontaneously or as a complication from certain procedures such as endovascular interventions [17].

Diagnosis can be made with transesophageal echocardiogram if the thrombus is present within the thoracic aorta and the heart. Katz et al. [18] recommend a five-point grading system for aortic atheroma on transesophageal echocardiography reporting patients with a mobile atheroma had a 47% incidence of stroke (Table 32.2).

The increased use of CT angiography has helped in the diagnosis as well as planning of management when indicated. There are other imaging modalities that can be used such as contrast-enhanced ultrasound, intravascular ultrasound, magnetic resonance imaging, multiple-row detector CT, and positron emission tomography [19] (Figs. 32.1, 32.2, 32.3, 32.4 and 32.5).

Table 32.2 TEE grading of aortic atheroma [18]

Grade	Description	Incidence of stroke (%)
1	Normal aorta	0
2	Extensive intimal thickening <3 mm	0
3	Protrudes <5 mm into aortic lumen	5
4	Protrudes >5 mm into aortic lumen	10.5
5	Mobile atheroma	46.5

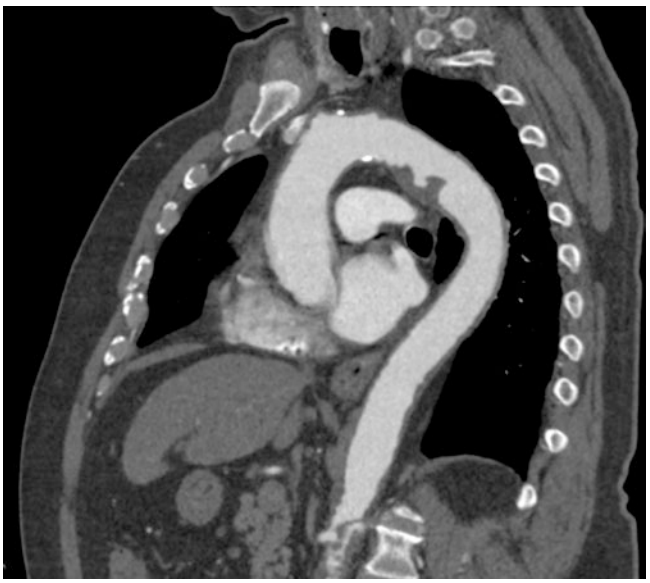

Fig. 32.1 This patient presented with blue toe syndrome (emboli to the feet) and was treated medically

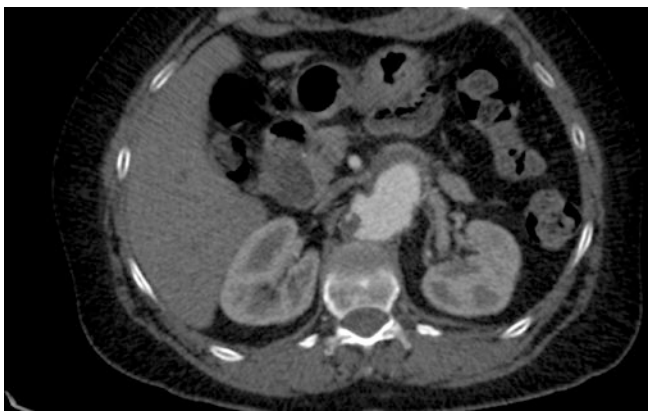

Fig. 32.2 This patient developed acute left lower extremity. She was found to have a 6 cm abdominal aneurysm (AAA) and diffuse atherosclerotic disease and was treated with open AAA repair and left leg embolectomy

Management of aortic thrombus is not well established due to the lack of available data. Usually, the initial management consists of systemic anticoagulation if no contraindications are present, aspirin, and then surgical intervention or long-term anticoagulation. In a study by Pagni et al., they found that half of the patients who developed aortic thrombi without any predisposing condition had some sort of underlying and sometimes unrecognized hypercoagulable state. They also found that small lesions of less than 1 cm tended to respond more favorably to anticoagulation than larger lesions did [17]. The treatment will be detailed below and should aim at prevention of embolization and possible stabilization and resolution of the clot.

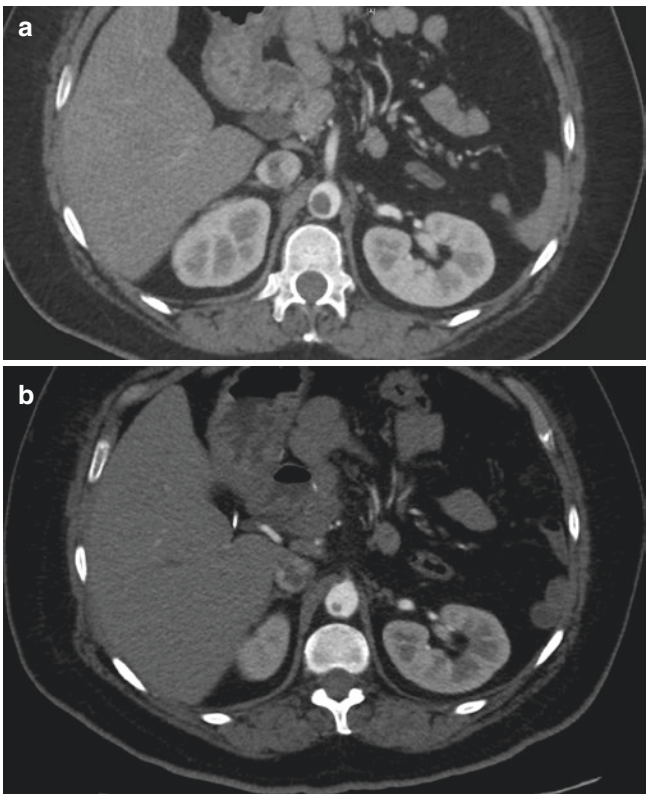

Fig. 32.3 This patient presented with abdominal pain and bilateral renal infarcts. CT scan shows heavy thrombus burden at the level of the superior mesenteric artery and renal arteries (**a**). She was treated with oral anticoagulation. (**b**) is her repeat scan after 4 weeks showing reduction in the thrombus burden. She had no further embolic episodes

If the lesions are larger or freely mobile, surgical intervention might be warranted. Traditionally, open thrombectomy has been used. With the progress made in endovascular procedures, these have become more common. The location of the lesion determines the type of endograft to be used.

Medical Treatment

Atherothrombosis is the unhealthy coupling of atherosclerosis and thrombosis. Atherosclerosis leads to many systemic diseases such as coronary artery disease, cerebrovascular diseases, aortic atherosclerosis, and peripheral arterial disease. Disease in one vascular bed increases the risk of disease in others which is known as "cross-link" [20]. One of the most detrimental consequences of atherosclerotic plaque is an embolic event especially in those suffering from significant aortic atherosclerosis. These embolic events may be spontaneous or induced by mechanical interventions such as guidewire or catheter manipulation during cardiac or peripheral vascular catheterization. The risk of embolism in aortic atherosclerosis is drastically increased for plaques that are mobile and/or protruding, especially if it is >4 mm in thickness [21]. These

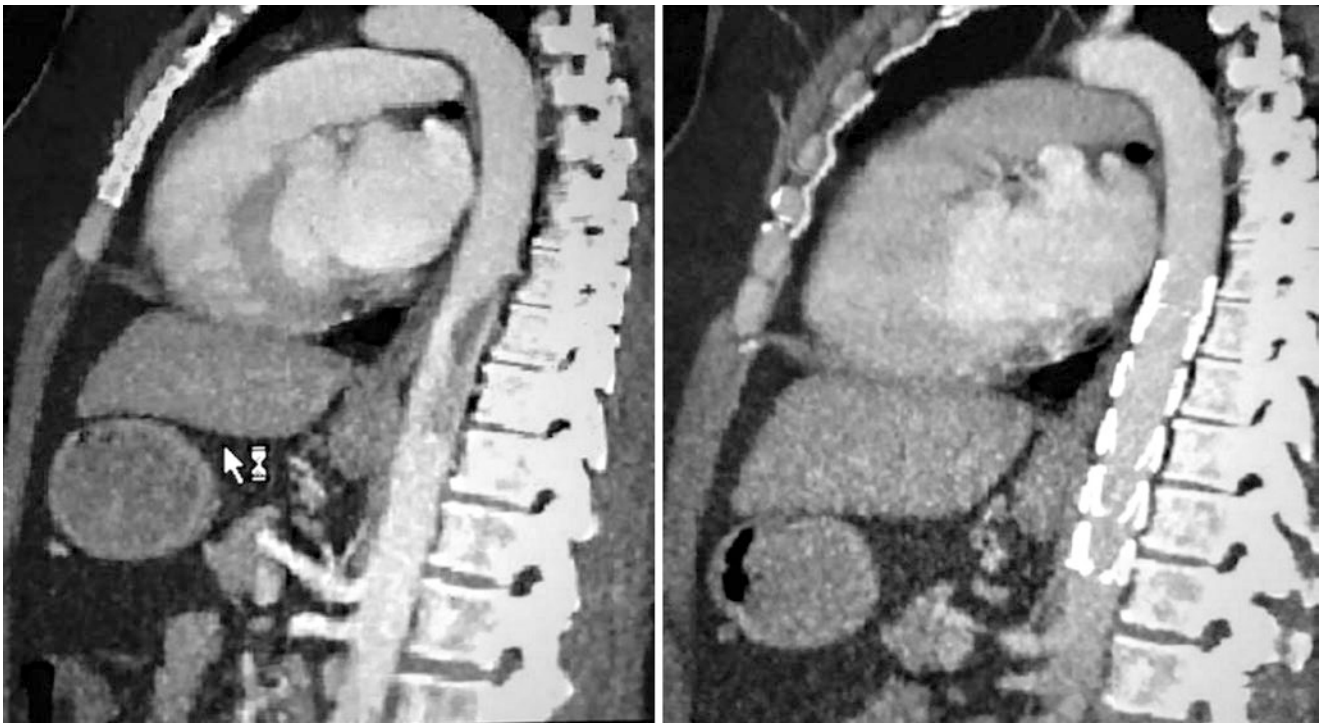

Fig. 32.4 A young female presented with recurrent blue toe syndrome despite optimal medical management. The thoracic thrombus was covered with a stent graft, and no further emboli occurred. She did well and was discharged home 3 days later

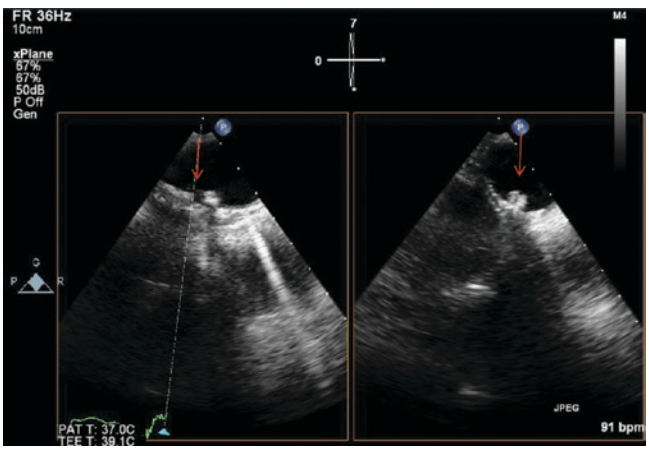

Fig. 32.5 Transesophageal echocardiogram of a complex atheroma in aortic arch

thromboemboli tend to lodge in small or medium arteries which often lead to stroke or TIA, limb ischemia, renal infarction, intestinal ischemia, or other organ ischemia [22]. Since atherothrombosis is a progressive process with an inflammatory component where platelet adhesion, activation, and aggregation are the final stage that ultimately is responsible for arterial occlusion and ischemia, many drugs have been designed to target the various stages to provide primary and secondary prevention in the treatment of atherothrombosis including antiplatelet therapy, antihypertensive, anticoagulation, and statin medications.

Dual antiplatelet therapy has been shown to be an effective treatment choice for secondary prevention. One of the most commonly used dual antiplatelet therapy medications is aspirin and clopidogrel. Aspirin binds to and irreversibly inhibits cyclooxygenase (COX), which is the first-step enzyme in the biosynthesis of prostaglandins in platelets. This effectively shuts down the formation of thromboxane A2 which is a potent platelet agonist and vasoconstricting substance. Clopidogrel is an adenosine diphosphate receptor antagonist on platelets that ultimately blocks platelet activation and aggregation. The Antithrombotic Trialists' Collaboration meta-analysis demonstrated aspirin alone yielded an absolute reduction of 3.1% in vascular event rates vs. control (12.9% vs. 16%) [23]. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, a randomized comparison of clopidogrel 75 mg and aspirin 325 mg, ADP receptor antagonists such as clopidogrel were associated with a significant absolute reduction of 0.51% in the rate of the primary composite endpoint of MI, ischemic stroke, or vascular death compared with aspirin (5.32% vs. 5.83%; $p = 0.043$) [24]. However, evidence from the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial demonstrated that the combination of clopidogrel and aspirin was more effective than aspirin alone in

reducing asymptomatic embolization [25]. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial evaluated the effects of dual antiplatelet therapy with clopidogrel and aspirin in a broad population of high-risk patients including established MI, stroke, or PAD. While this trial attempted to explore the primary prevention of dual antiplatelet therapy which remained unclear, it did further concur the secondary prevention benefits shown in previous trials [26].

Several studies have demonstrated possible efficacy of warfarin for secondary prevention in patient with aortic plaque. SPAF-III trial compared adjusted-dose warfarin with INR 2–3 to low-dose warfarin with INR 1.2–1.5 plus aspirin for the prevention of stroke in patients with atrial fibrillation with at least one thromboembolic risk factor. They found that those treated with adjusted-dose warfarin had 4% incidence of stroke vs. 16% incidence in those with low-dose warfarin plus aspirin, which demonstrated a 75% risk reduction [27]. In another study in patients who had undergone transesophageal echo found to have protruding plaque, there were no embolic events in 27 patients who were treated with warfarin compared to clinical embolic events in 5 of the 23 patients who were treated with antiplatelet therapy [28]. Thus, these studies demonstrated a possible efficacy for warfarin in plaque stabilization.

Another important target for treating atherothrombosis is lipid-lowering therapy, specifically statins. Statins are coenzyme A reductase inhibitors which reduce atherothrombotic events through a variety of mechanisms including reduction of cholesterol biosynthesis, modulation of lipid metabolism, and a notable way to prevent thrombosis by improving endothelial homeostasis by increasing the bioavailability of nitric oxide that subsequently orchestrates the paracrine antiatherosclerotic functions of the endothelium [29]. Tunick et al. demonstrated in their retrospective analysis of 519 patients that statin therapy was associated with an absolute reduction of 17% in thromboembolic events (12% vs. 29%) compared to those who were not treated with statins. This signified the clinical benefit of statin-induced plaque stabilization [30]. Other studies attempted to evaluate possible regression of aortic plaque with imaging such as MRI. One trial was able to demonstrate the maximal wall thickness of thoracic aorta was reduced by 13.8% in combination therapy of atorvastatin and etidronate vs. 12.3% in patients who took atorvastatin vs. only 2.2% in those who took etidronate for 12 months. In the abdominal aorta, combination therapy showed 11.9% reduction in vessel wall thickness vs. 0.9% in atorvastatin group and 5.5% in the etidronate group [31]. Thus, statin therapy is imperative in the prevention and treatment of atherothrombosis.

The renin-angiotensin system (RAS) has been shown as a key pathway modulating atherosclerotic plaque vulnerability. It is a series of enzymatic reactions that leads to the generation of angiotensin II which promotes vasoconstriction, aldosterone secretion, water and sodium reabsorption, thirst, activation of the sympathetic nervous system, and cardiac ionotropic and chronotropic actions [32]. There is emerging evidence indicating RAS might regulate all stages of atherogenesis, from initiation to disease progression including determining plaque vulnerability and rupture. Many studies have shown direct relationship between inflammation and the RAS where activation of NF-kB by angiotensin II in endothelial cells and vascular smooth muscle cells induces the upregulation of cell adhesion molecules, which favor adhesion, tissue recruitment, and accumulation of inflammatory cells. These inflammatory cells can lead to intraplaque proliferation of macrophages and further increase cytokine and chemokine expression which result in a positive feedback response. The persistent proinflammatory state plays an essential role in the conversion of a stable atherosclerotic plaque into a vulnerable phenotype [32]. Thus, angiotensin-converting enzyme (ACEi) inhibitors play an important protective role where it antagonizes atherogenesis and atheroprogression. While the exact mechanism behind atherosclerotic plaque stabilization with ACEi is not fully understood, ACEi are known to reduce formation of Ang II and increase bradykinin levels which result in increased NO release, thus attenuating the oxidation of LDL and inhibiting MMP-9 activity [33].

The current guideline for medical management of aortic atherosclerotic disease is consistent with the American College of Chest Physicians (ACCP) guidelines for antithrombotic and thrombolytic therapy for valvular disease, ischemic stroke, and peripheral artery disease.

- For patients with no contraindications (low risk of major bleeding) with stroke and complex aortic plaque, or patient without stroke but atheroma with a mobile component, medical therapy includes lipid-lowering therapy plus aspirin monotherapy, or clopidogrel 75 mg daily monotherapy is appropriate.
- For patients without stroke and simple plaque (<4 mm without a mobile component), the evidence behind medical therapy is limited; however, they still recommend lipid-lowering therapy plus aspirin or clopidogrel monotherapy.

While warfarin may play a more significant role in patient with atrial fibrillation or mechanical prosthetic valves in the setting of aortic atherosclerotic disease, it is generally not recommended in patients with stable aortic atheroma and thromboembolism. Based on nonrandomized retrospective studies, oral anticoagulation has shown benefit in patients with mobile thrombi in the aortic arch; thus, the 2012 ACCP currently recommends oral anticoagulation in the setting of cryptogenic stroke and mobile aortic arch thrombi pending

ongoing randomized controlled trials comparing oral anticoagulant with antiplatelet therapy [34].

There are many different targets in the attenuation of the progression of atherothrombosis. Atherosclerotic plaque stabilization remains to be one of the most important goals in the treatment of atherothrombosis whether it is through primary prevention or by secondary prevention using dual antiplatelet therapy, anticoagulation with warfarin, lipid-lowering drugs with statins, or ACEi. It is crucial to initiate the appropriate treatment to minimize the detrimental consequences of atherothrombosis.

Surgical Intervention

Surgical management is another approach in the treatment of aortic atherothrombosis. Surgical interventions for aortic atherosclerosis include aortic replacement with interposition graft, thrombectomy if focal, and endovascular stenting. Wareing et al. assessed a strategy for reduction of stroke incidence in patients undergoing cardiac surgery by screening for ascending aorta atherosclerosis and carotid disease. For the purpose of this chapter, we will focus on atherosclerosis of the aorta and not the carotid arteries. They found that none of the 27 patients with moderate or severe atherosclerosis of the ascending aorta who had ascending aortic replacement had stroke, while 6.3% of 111 patients with moderate or severe disease who had only minor interventions had stroke. This study suggested that screening and aggressive surgical treatment could reduce the frequency of stroke in cardiac surgical patients [35]. However, interposition graft requires significant consideration for myocardial, brain, spinal cord, and lower body protection and rigorous surgical technique. Thus, careful selection of surgical candidates needs to be done to limit mortality and morbidity. Another study compared interposition graft in severe atherosclerosis group versus arterial cannulation in mild or moderate atherosclerosis group and found that there was no significant difference in mortality and stroke rate but there was a statistically significant difference in operation time, ICU stay, and hospital stay that were all longer in the interposition graft group [36]. This raises the question if interposition graft would ultimately be the optimal surgical option for patients with aortic atherosclerosis.

Another option for treating severe ascending aorta atherosclerosis is endarterectomy. In one study, arch endarterectomy was performed in 268 patients undergoing heart surgery who were found to have >4 mm aortic plaque in an effort to reduce intraoperative stroke risk; however, these patients ended up having higher rates of stroke than those who did not have endarterectomy (35% vs. 12%) as well as higher mortality rate and longer hospital stay [37]. Thus, aortic arch endarterectomy should not be recommended in patients with aortic atherosclerosis.

We have no randomized studies to suggest surgical treatment for emboli from sources such as the descending thoracic aorta or the abdominal aorta, but the same principles apply. It is indicated for those who fail medical therapy and are at low risk of complications. In addition, endovascular therapy has replaced open surgical treatment for these anatomic areas when it is feasible. Endovascular treatment allows for intervention in patients who previously were considered as nonsurgical candidates as well as carries a lower morbidity rate. The early results have shown 100% technical success, no early recurrences, and no wire- or device-related complications. However, several conditions should be considered when approaching aortic atherosclerotic lesions [38]:

- Careful manipulation of wires to prevent iatrogenic emboli
- Use of angiography and/or intravascular ultrasonography to accurately identify and exclude the affected segment of the aorta
- Planning of at least 1–2 cm proximal and distal landing zones
- Postprocedural evaluation of mesenteric and lower extremity vessels

Conclusion

Aortic atherosclerotic plaques are important potential sources of systemic emboli which can lead to significant consequences such as stroke, transient ischemic attack, renal infarction, and embolization to other arterial beds that could lead to end-organ ischemia and, occasionally, require intervention such as renal thrombectomy for acute renal injury or popliteal thrombectomy for acute limb ischemia. The risk of thromboembolism in aortic atherosclerosis is increased when there is a complex plaque which is defined as thickness > 4 mm or ulceration. Secondary prevention with various medications that target the atherosclerotic process has been used to prevent thromboembolism. These medications include lipid-lowering therapy with statins, anticoagulation therapy such as warfarin, antiplatelet therapy including aspirin and clopidogrel, and antihypertensive medications such as ACE inhibitors. Surgical treatment, open and endovascular, should be reserved for those who fail medical treatment and at low risk for complications.

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Aortic Disease in Pregnancy

33

Caroline A. Ball and Sara Sirna

Introduction

Pregnancy represents a unique physiologic period, with significant implications on the cardiovascular system [1]. Although rare, aortic disease is a known potential complication of pregnancy. Aortic dissection and rupture can be of particular concern for pregnant women with underlying connective tissue disorders [2]. In the next chapter, we will explore aortic disease in pregnancy, including pathophysiology, epidemiology, and specific conditions. We will pay particular interest to aortic dissection and rupture, given the increased incidence in pregnancy, and the devastating potential consequences.

Vascular Changes in Pregnancy

Pregnancy causes a unique set of physiologic changes (Table 33.1), which place an increased burden on the cardiovascular system and the aorta [3]. Throughout a normal pregnancy, there is a decrease in systolic, diastolic, and mean blood pressures. Compared to baseline, there is a 20–25% increase in heart rate over the course of pregnancy. Cardiac output also increases throughout pregnancy. Peripheral vascular resistance decreases, and there is systemic vasodilation in addition to increased vascular distensibility [2, 4].

Pregnancy is associated with an increase in vasomotor sympathetic activity [5], in addition to hormonal changes. Estrogen and progesterone increase vasodilation [4], as does relaxin, a hormone produced by the placenta [6]. Relaxin affects the cardiovascular and renal systems, increasing cardiac output and renal blood flow. Pregnancy increases angiotensinogen, total blood volume, plasma volume, and red blood cell mass. It is also associated with an increased left ventricular thickness and wall mass [4].

Table 33.1 Physiologic changes of pregnancy

Parameter	Expected change
Systemic vascular resistance	Decreases throughout pregnancy
Blood pressure	Decrease in systolic and diastolic blood pressure over the course of pregnancy, with a nadir in the second trimester
Heart rate	Increases by 20–25% over the course of pregnancy
Cardiac output	Increases throughout pregnancy
Plasma volume	Increases throughout pregnancy
Aortic root diameter	Increases throughout pregnancy

The aorta undergoes structural changes during pregnancy, as well. The changes described above cause increased shear stress on the aortic wall, predisposing the aorta to aneurysmal dilation and dissection [7]. In late pregnancy, the gravid uterus can cause aorto-iliac compression, resulting in increased peripheral resistance [8]. Pregnancy also affects the structural integrity of the aorta. Circulating estrogen and progesterone cause reticulin fiber fragmentation and elastin fiber disorganization [8]. Pregnancy is also associated with fragmentation of the reticulum fibers of the aorta, loss of the normal corrugation of elastic fibers, and hypertrophy and hyperplasia of the smooth muscle cells [3, 9, 10]. The aortic root increases in diameter by at least 1 mm during a normal pregnancy. The peak diameter occurs in the third trimester [1]. In women with hypertension during pregnancy, the increase of the diameter is more pronounced [9].

Epidemiology

Aortic dissection is a rare occurrence in normal pregnancy. In the United States, the incidence of aortic dissection in pregnancy is 0.0004%, based on data from the Nationwide Inpatient Sample database from 1988 to 2008. The study identified 44 cases of aortic dissection out of 10 million

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pregnancies. Seven of the 44 patients who experienced a dissection had Marfan syndrome [11]. Aortic dissections that occur during pregnancy represent 0.1% of all cases of aortic dissection in the United States [11]. The risk of aortic dissection increases over the course of the pregnancy, with the greatest risk in the third trimester and postpartum [8]. Despite its rarity, the consequences to both mother and child can be devastating [12].

For women with underlying conditions that affect the aorta, the physiologic changes of pregnancy can further increase the risk of aortic dissection and rupture. For example, the risk of aortic dissection in women with Marfan syndrome increases eightfold during pregnancy, particularly in the postpartum period [13].

There is limited data available on the incidence of aortitis in pregnancy. Takayasu arteritis, a rare form of large-vessel vasculitis, which is known to affect women of childbearing age, is neither affected nor worsened by pregnancy [7, 14]. However, hypertension is not uncommon in patients with Takayasu arteritis, and close monitoring of blood pressure is recommended.

Management of Aortic Disease in Pregnancy

Management of aortic disease in pregnancy is based primarily on case series and expert opinion. Management decisions depend on the stage of the pregnancy, the condition of the mother and child, as well as the disease process involved. Treatment should involve a team approach, including maternal-fetal medicine specialist, cardiologists, and cardiovascular and vascular surgeons [7].

Aortic dissection in pregnancy presents a potentially life-threatening situation to both mother and child. For women with known genetic syndromes that cause thoracic aortic aneurysm or dissection, screening can be done both before and during pregnancy to mitigate risk. Screening and preconception strategies for particular genetic syndromes will be described later. American College of Cardiology/American Heart Association guidelines recommend that all pregnant women with known thoracic aortic dilatation or a familial or genetic predisposition for aortic dissection should undergo strict blood pressure control [15] (Table 33.2). Additionally, all pregnant women with known aortic root or ascending aortic dilatation should undergo monthly or bimonthly echocardiographic measurements of the ascending aortic dimensions until delivery. Pregnant women with aortic aneurysms should be delivered at a center where cardiothoracic surgery is available [15]. Women with an aortic diameter > = 45 mm at the time of delivery should undergo elective cesarean section [7].

For women presenting with type A aortic dissections, surgical treatment should be undertaken immediately, regardless of the trimester. For women presenting with type B aortic dissection, medical management is recommended, unless the dissection is complicated by malperfusion [7]. Surgical intervention for pregnant women with aortic dissection requires careful discussions between the surgical, obstetric, and anesthesia teams. European Society of Cardiology guidelines recommend surgical repair of an aortic dissection while the fetus is in utero for type A dissections that occur before the fetus is viable. After the fetus is considered viable, prompt cesarean delivery is recommended prior to surgical repair of the aortic dissection so as to prevent cesarean delivery while on aortopulmonary bypass [16].

For women with Takayasu arteritis in pregnancy, steroids are the recommended treatment, despite their potential role in increasing the risk of aortic dissection [14].

Table 33.2 Antihypertensive medication use in pregnancy

Medication	Mechanism of action	Priority of therapy	US FDA pregnancy category [19]
Methyldopa	Central alpha$_2$-adrenergic agonist	First line	B
Labetalol	Peripherally acting nonselective beta-blocker	Second line	C
Nifedipine	Calcium channel blocker	Second line	C
Hydralazine	Arteriolar smooth muscle relaxation	Second line	C
Clonidine	Selective central alpha$_2$-adrenergic agonist	Third line	C

Data from: [17, 18]

FDA Pregnancy Categories: A = Adequate, well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters. B = Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. C = Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risk. D = There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. X = Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in the use of the drug in pregnant women clearly outweigh potential benefits [19]

Pregnancy and Aortic Disease in Specific Conditions

As described above, women with underlying aortopathies have an increased risk of aortic dissection and rupture during their pregnancy. There are recommendations available for the management of aortic disease in several of these conditions.

Marfan Syndrome

Marfan syndrome is one of the most thoroughly studied congenital aortopathies in pregnancy. Still, there are discrepancies between major society guidelines for the management of Marfan syndrome in pregnancy with respect to preventing aortic dissection, and recommendations are based on observational studies and expert opinion. Women with Marfan syndrome may experience exaggerated growth of the aorta during pregnancy, up to 0.3 mm per month [1]. Experts and professional societies agree that women with Marfan syndrome should discuss their plans for pregnancy with their cardiologist and obstetrician-gynecologist prior to conception. This team of physicians should carefully consider medical or surgical therapy for any underlying aortopathy prior to conception and can develop a plan for monitoring during pregnancy. For some patients at particularly high risk of complication, pregnancy should be avoided altogether [13].

The European Society of Cardiology guidelines indicate that women with Marfan syndrome with an aortic diameter of <40 mm have a low risk of dissection and should therefore be able to proceed safely with pregnancy. Women with an aortic diameter of >45 mm should be encouraged to avoid pregnancy, although there is limited data on the safety of pregnancy in these women. For women with an aortic diameter between 40 and 45 mm, individual decisions regarding the management of pregnancy should be made based on the patient's body surface area, family history, and the rate of growth of the aorta [16]. ESC guidelines recommend considering prepregnancy surgery for women with an aortic diameter > 45 mm or an aortic diameter index >27 mm/m^2 who would like to consider pregnancy. ESC guidelines recommend the use of beta-blockers in pregnant women with Marfan syndrome to prevent dissection, although data to support their use is limited [16]. Alternatively, the ACC/AHA guidelines recommend prepregnancy surgical correction of an aortic root between 40 and 44 mm in diameter and consider an aortic root diameter > 45 mm to be a contraindication to pregnancy [20].

Loeys-Dietz Syndrome

Management of Loeys-Dietz syndrome, an autosomal dominant connective tissue disorder involving aortic aneurysms and tortuosity and craniofacial abnormalities, in pregnancy is similar to the management of other congenital aortopathies in pregnancy. However, women with Loeys-Dietz syndrome are thought to have a higher rate of aortic dissection than those with Marfan syndrome [13]. Patients should undergo preconception counseling and should consider surgical correction prior to pregnancy. Patients with Loeys-Dietz syndrome who are considering pregnancy should consider elective surgery when their aortic root is >42 mm if measured by TEE and if their aortic root is >44–46 mm if measured by CT/MRI [7]. The European Society of Cardiology guidelines recommend surgical repair prior to pregnancy for Loeys-Dietz syndrome patients with an aortic root diameter ≥45 mm [16]. Patients with Loeys-Dietz syndrome should follow the general ACC/AHA recommendations for monthly or bimonthly echocardiographic screening of the aortic root during pregnancy and strict blood pressure control.

Ehlers-Danlos Type IV

Ehlers-Danlos syndrome is a group of genetic connective tissue disorders, with at least six major disease types, each with their own phenotypic features and patterns of inheritance. Ehlers-Danlos type IV (also referred to as vascular type) is associated with uterine rupture, and pregnancy is therefore contraindicated in Ehlers-Danlos type IV patients. For patients who are diagnosed with the condition after conception, or for patients who become pregnant despite contraindications, management can be particularly challenging. Aortic dissection may occur in Ehlers-Danlos type IV without dilatation. European Society of Cardiology guidelines recommend beta blockade for pregnant patients with Ehlers-Danlos type IV to reduce the risk of aortic dissection. Pregnant women with Ehlers-Danlos type IV are also recommended to undergo early cesarean delivery [16].

Turner Syndrome

Turner syndrome is a chromosomal abnormality associated with short stature, webbed neck, bicuspid aortic valve, and coarctation of the aorta. Turner syndrome patients have lower fertility rates than the general population [21]. However, for both spontaneous and facilitated pregnancy in patients with Turner syndrome, particular attention should be dedicated to preventing aortic dissection. As seen with other congenital aortopathies, there are slight differences in recommendations for the management of patients with Turner syndrome due to limited available evidence. The American Society of Reproductive Medicine recommends that pregnancy is contraindicated if there are any cardiac defects seen on MRI prior to pregnancy, and if the preconception aortic size index is >2 cm/m^2 [22]. For women with Turner syndrome who become pregnant, the American Society of Reproductive Medicine recommends periodic echocardiogram or MRI during pregnancy and treatment of hypertension to prevent aortic dissection. The American Society of Reproductive Medicine also recommends vaginal delivery if the aortic size index (ASI, aortic diameter in

centimeters divided by body surface area in meters^2) at the time of delivery is <2 cm/m^2 but recommends elective cesarean section with epidural anesthesia for patients with an ASI >2 cm/m^2 before labor [22, 23]. The Turner Syndrome Consensus Group describes a relative contraindication to pregnancy in women with Turner syndrome who have had prior surgical repair of cardiovascular disease, bicuspid aortic valve, aortic dilatation, or hypertension. The Turner Syndrome Consensus Group also recommends prepregnancy management with ECG, echocardiography, and cardiac MRI and that vaginal delivery is reasonable for some patients [22, 24].

Coarctation of the Aorta

Although many patients with coarctation of the aorta undergo surgical repair prior to pregnancy, there are reported cases of pregnancy in women with unrepaired coarctation. Known potential complications of pregnancy in patients with coarctation include an increased risk of hypertensive disorders of pregnancy. Patients with coarctation of the aorta and a peak-to-peak coarctation gradient ≥20 mmHg or <20 mmHg with anatomic imaging evidence of significant coarctation and collateral flow should consider surgical repair prior to pregnancy. Both prior to and during pregnancy patients with coarctation of the aorta should have their blood pressure checked in all four extremities [20].

Conclusion

Aortic disease during pregnancy is exceptionally rare but associated with high morbidity and mortality for both mother and fetus. Diagnosis, management, and treatment require a team approach, including cardiologists, obstetrician-gynecologists, and vascular and cardiovascular surgeons. Although there are guidelines and recommendations available to guide management, each case needs to be addressed on an individual basis. Particular attention should be paid both before conception and during pregnancy to women with genetic syndromes known to be associated with aortopathy.

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Fetal Aortic Disorders

34

Raymond A. Dieter Jr. and Marshall Goldin

Introduction

Aortic disease is fairly common in the adult. Aortic processes include aneurysm, aortic occlusive disease, and dissections—especially of the thoracic aorta. Congenital aortic diseases, aortic arch atresia, vascular ring, right-sided aorta, coarctation, A-P (aortopulmonary) window, and PDA (patent ductus arteriosus) may all occur [1]. The prenatal ultrasound programs facilitate the diagnosis of structural abnormalities and the enhancement of prenatal and postnatal treatment. Consequently, the obstetrician, the high-risk neonatologist, and the pediatric cardiologist are all involved in the diagnosis and treatment of the newborn with pathologic cardiovascular anomalies which require treatment [2]. Noninvasive diagnostic advances have resulted in optimal planning regarding definitive treatment in this milieu.

Diagnostic evaluation modalities for fetal cardiovascular abnormalities

I. Routine obstetric periodic evaluation and family history
II. Screening ultrasound
III. Consultation
  A. Neonatologist
  B. Perinatologist
IV. Targeted ultrasound
V. Fetal referral center
VI. Echocardiogram
  A. Fetal
  B. Maternal
  C. Postnatal
VII. Amniotic fluid evaluation
VIII. Magnetic resonance imaging
IX. Genetic testing

Diagnosis

Prenatal ultrasound diagnosis of cardiovascular pathology facilitates optimal planning of therapeutic interventions. Directed history and treatment of the mother and family add to a potential suspicion regarding anomalies. Neonatal (N-echo) and fetal (F-echo) echo studies and MRI have further added to the physician's armamentarium for perinatal diagnosis of congenital lesions in many sites.

These diagnostic modalities have resulted in the development of tertiary neonatal centers with subspecialized physicians, nurses, technical staff, and equipment, which enhance treatment of at-risk pregnancies and the developing fetus [3]. Intrauterine management of these lesions may decrease gestational mortality, and postnatal therapy can further add to survival.

Of significance, F-echo diagnosis of a PDA is best followed by N-echo, which often confirms the findings. Diagnosis of an aortic coarctation is often difficult in a fetus with an early PDA diagnosis. Right aortic arch (RAA) is often associated with TOF (tetralogy of Fallot), and genetic testing in these cases has led to the diagnosis of additional cardiac and noncardiac genetic anomalies [4]. Such genetic testing in the fetus with RAA has led to the diagnosis of the

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autosomal dominant Loeys-Dietz syndrome in a fetus with intrauterine diagnosis of aneurysmal dilation of the aortic root [5, 6].

Physical examination and family history may be suggestive of potential cardiovascular pathology. Fetal heart tones (FHT), if irregular or diminished, may be indicative of a congenital anomaly. In the 1960s, in Alaska, when the FHTs were discovered to be 50 or so, our only recourse was close monitoring of the mother and the FHTs. Subsequent to delivery, the infant was sent to Seattle for further evaluation and, later, a pacemaker, with no other diagnostic abnormality detected. No familial congenital C-V (cardiovascular) history was known. Early in our residency, we were not allowed to discuss genetics and the possibility that future children could be born with congenital heart defects to adult individuals who had previously undergone repair of congenital cardiac defects. We now know that congenital cardiovascular disease may have a genetic origin, requiring comprehensive fetal monitoring utilizing F-echo and MRI [7, 8].

Color Doppler, EKG, and fetal growth records may raise suspicion of fetal abnormalities. Postnatal studies and neurodevelopmental assessment may suggest the need for additional investigation. Biometry consistent with age, normal amniotic fluid, and no known extra cardiac lesion are considered when evaluating for fetal C-V lesions. Echocardiographic evaluation will aid in decision-making for diagnosis and treatment of cardiovascular lesions. Genetic amniocentesis studies may be considered—especially when multiple lesions are present and fetal karyotype studies may define a deletion (ex. 22 q) defect.

Examples of fetal aortic abnormalities

I. Anomalous origin
   - A. Origin right pulmonary artery from the aorta
   - B. Aortopulmonary window

II. Stenotic/obstructive lesions
   - A. Coarctation of the aorta—association with left ventricular noncompaction
   - B. Neonatal aortic thrombosis—prenatal transfer of anticardiolipin antibodies
   - C. Aortic arch interruption
     1. Associated left ventricular aneurysm
     2. Associated with chromosomal abnormalities

III. Aortic aneurysm
   - A. Descending thoracic aortic aneurysm in hydropic fetus
   - B. Ascending due to benign nodular myofibroblastic lesion
   - C. Abdominal—associated with porencephaly

IV. Valve area
   - A. Transposition of great vessels
   - B. Giant sinus of Valsalva aneurysm
   - C. Aortic valve stenosis—hypoplastic left heart syndrome
   - D. Aortic root dilation

V. Aortic wall inflammation

VI. Right aortic arch
   - A. Vascular ring
   - B. Chromosomal abnormalities
   - C. Aberrant right subclavian artery

Findings

Most newborn congenital cardiac and vascular lesions are evident at or shortly after birth. These lesions were not detectable in utero until recently as both diagnostic and therapeutic measures were either not available or of limited diagnostic scope. With the advent of more regular obstetric visits, coupled with more advanced diagnostic approaches, an increasing number of fetal abnormalities are being detected. Currently, many congenital lesions are diagnosed and treated during pregnancy or shortly after delivery [9]. Remarkably, many of these fetuses may then continue normal gestation progress to the newborn stage with the potential for a full lifespan to follow.

Review of the literature demonstrates multiple fetal cardiovascular defects detected by F-echo. These defects, such as the fistulous anomalous origin of the right pulmonary artery from the aorta, may be relatively simple or more complex in nature as seen with the presence of an aortopulmonary window [10, 11]. Stenotic or obstructive lesions, including aortic coarctation in association with left ventricular noncompaction, may have many different characteristics [12].

Presented above are many of the congenital lesions, including aortic arch interruption associated with a left ventricular aneurysm and chromosomal abnormalities [13]. These aneurysms may or may not be associated with pentalogy of Cantrell. In a review of 8 fetal and 20 neonate IAA (interrupted aortic arch) cases from 1994 to 2010, 10 type A and 18 type B IAA patients were accurately diagnosed—with microdeletion of the 22q 11.2 chromosome in 6 patients [14].

Hematologic abnormalities include neonatal aortic thrombosis after prenatal transfer of anticardiolipin antibodies and aortic wall inflammation have been described [15, 16]. The latter finding has been considered a precursor to possible early findings predictive of future atherosclerosis in the adult. Aneurysm formation, a frequent finding in the adult, has been diagnosed in a number of fetal studies. An ascending aortic aneurysm was thought to arise histologically from a benign nodular myofibroblastic lesion of hamartomatous origin [17]. A hydropic 28-week gestation fetus was found to have a saccular descending thoracic aortic aneurysm. The marked fibrointimal hyperplasia with tunic media attenuation and thrombus were speculated to have caused after load

cardiac failure [18]. Pediatric abdominal aortic aneurysms are rare but may result from a number of causes [19]. Listed below are a number of these etiologies, including prenatal porencephaly (a condition characterized by an intracerebral cyst association) [19].

Pediatric thoracic and abdominal aortic aneurysm associations

I. Intrauterine infection
II. Connective tissue diseases/gene mutations
   A. Ehlers-Danlos syndrome
   B. Marfan syndrome
III. Iatrogenic trauma—umbilical artery catheterization
IV. Porencephaly—intrautero vascular obstruction

Lesions located proximally near the aortic valve may involve the root, the valve, or the sinus of Valsalva. Such lesions include transposition of the great vessels, aneurysm of the sinus of Valsalva, and aortic valve stenosis with hypoplastic left heart syndrome, along with aortic root dilation [6, 20–22]. Vascular ring and right aortic arch (RAA) often occur together (reported in one series of 97 fetuses) [20]. Multiple vascular anomalies involving the RAA include vascular ring and double arch (incidence of 15.3%) and chromosomal anomalies (with 22q 11.2 microdeletion in half the patients). As diagnostic ability has increased, the earlier recognition of fetal disease and aortic lesions has also increased.

Therapeutic Considerations

Since 1963, when intrauterine transfusion for hemolytic anemia was initiated, an ever-increasing number of fetal therapeutics has evolved—especially in the cardiovascular and thoracic fields. Diagnosis of intrauterine congenital lesions has led to a more intense prepartum follow-up and increased opportunities for the treatment of these fetal lesions. Depending on the diagnosis, treatment options include prenatal and postnatal patients. Planning and preparation must take into consideration immediate and long-term risks regarding viability and risk of intervention to the fetus, infant, and mother. But subspecialty care and tertiary fetal referral care facilities must be considered for the mother and fetus during the remaining period of pregnancy.

Consideration for intrauterine surgery must outweigh the risk of delaying intervention until the postpartum period. Ideally, intervention will be performed prior to irreversible physiological compromise. Risk and cost must be factored into the decision-making process. The various vascular and cardiac procedures are both complicated and risky when performed in these situations with neurodevelopmental delay a consideration in fetal aortic valvuloplasty [1]. Coarctation screening pre- and postnatally for optimum diagnosis and treatment timing will require close evaluation [3]. Many of the lesions involving the proximal aorta require complicated interventional manipulation and are not possible during fetal development. Thus, if the lesion is low risk during delivery and early development, intervention will be delayed until the optimum postpartum period [23].

Vascular ring patients may have an 83% freedom from intervention surgery at 2-year follow-up [24]. Early diagnosis of coarctation allows the family to be aware of the options, including prostaglandin, therapy, and to delay intervention to the ideal time [3]. Ferschl et al. have outlined therapeutic indications for congenital cardiac lesions using percutaneous fetal intervention [22]. But when the situation permits, or the lesion accessibility prevents, intervention is delayed until the postpartum period. The field of fetal diagnosis, fetal therapy, and awareness of genetic abnormalities have recently provided a basis for the evolution of treatment and improved long-term success in this milieu. Molecular, genetic, and electron therapy will progress with further enlightenment and avoidance or elimination of many of these fetal, and possibly fatal, cardiovascular diseases.

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Aortic Trauma in Children

35

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Introduction

Aortic trauma in patients under the age of 21 is an uncommon occurrence but does occur. A review of the literature demonstrates the rarity of such concerns [1–3]. Most reports contain less than 10 pediatric aortic trauma patients unless the report is a review of the literature [4]. We report herein our experience with patients who had a traumatic aortic injury. Diagnostic and therapeutic indications require one to be alert to the potential for and the severity of an aortic injury requiring treatment and the associated risks. Our patients represent varied etiologies, types of injury, and therapeutic options in children under the age of 21 years.

Patients

These patients presented to the emergency room with a varied complex of signs and symptoms and thus are best illustrated by brief descriptions of each of their situations (Table 35.1).

Patient #1

On responding to a code blue from the ER (emergency room), I found three patients in shock (one was due to a Cadillac fin entering the abdomen from a bicycle accident, and one was due to peritoneal sepsis). The third child, a 4-year-old, was endotracheally intubated and had a gunshot wound to the left anterior chest and a posterior left chest paravertebral exit wound. He was unresponsive and the left chest was opacified on x-ray. An ER left thoracotomy revealed an entrance and exit wound of both the heart and the aorta. We rapidly closed the cardiac lesions and clamped the aorta. Despite intense resuscitative efforts, there was no response and the resuscitation efforts were withdrawn.

Patient #2

A 3-year-old child racing to her father at his desk tripped and fell upon a sharp paper spindle on the floor, which penetrated the anterior chest, the heart, and the aorta and exited the back. The child's mother pulled the spindle out of the chest and rushed her to the hospital. Following physical and radiologic diagnosis, and 1 week of hospitalization, she was discharged home without surgery to close uneventful follow-up.

Patient #3

A 16-year-old female was playing league softball and received a blunt injury to the abdomen and left flank. Following emergency room resuscitation, an aortic angiography was obtained. At surgery, the aortic defect was repaired and a salvage left aortorenal bypass graft failed to preserve the kidney. Following left nephrectomy, the teenager did well.

Patient #4

An 18-year-old male received multiple injuries following a motorcycle accident including multiple long bone (all but one) fractures, descending thoracic aorta disruption, the left

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Table 35.1 Some examples of pediatric aortic trauma

Patient	Age	Gender	Type of injury	Injury location	Cause	Symptoms	PE
1	4	Male	Anterior and posterior chest penetration—thru and thru	Anterior and posterior perforation of the heart and aorta	Gunshot	Shock cardiac arrest	Entrance and exit wounds left chest—no response
2	3	Female	Thru and thru penetration anterior and posterior chest	Descending thoracic aorta and heart	Fall on metal paper spindle	Crying, pain	Perforation anterior posterior chest skin
3	16	Female	Blunt	Left renal artery torn off aorta	Blunt trauma due to softball game	Abdominal flank—pain	Tender bruise
4	18	Male	Blunt	Descending thoracic aorta transected. Left renal artery torn off aorta bladder torn off urethra	Motorcycle accident	Shock, pain, all long bones fractured, urethra transected	Multiple injuries, shock
5	19	Male	Blunt sudden	Descending thoracic aorta trans-section cervical fracture	Dive in pool—not full	Shock	Paralyzed
6	20	Male	Blunt	Descending thoracic aorta below left subclavian	Auto accident	Pain shock	Paralyzed multiple injuries

renal artery torn off the aorta, liver and spleen trauma, and the bladder torn off the urethra. The thoracic aortic disruption was repaired through a left thoracotomy with proximal and distal clamping. After splenectomy, a saphenous vein graft to the left renal artery from the aorta, repair of the abdominal aorta, and bladder to urethra repair/anastomosis, liver repair, the patient recovered with survival of the kidney, a functional aortorenal graft, and normal blood pressure. He did well after hospital discharge.

Patient #5

A teenager dove into an underfilled pool. He received a cervical fracture and aortic disruption below the left subclavian artery. Following the aortic repair with a good aortic pulsation and cervical stabilization, he remained paralyzed.

Patient #6

This 20-year-old had multiple injuries with blood from the trachea, mediastinal widening, and paraplegia following an automobile accident. Despite surgical repair and blood transfusion, he failed to respond and died 8 days later due to the head and spinal cord injury.

Comment

In our suburban area, we have a large human population and high vehicular speeds. Thus, a number of additional late teen or early adult patients under the age of 25 years have been treated in our county with thoracic aortic disruption below the origin of the left subclavian artery during the past 45 years. Those individuals are not included in this discussion, but we anticipate the continued occurrence of the accidents which cause the aortic injuries.

Treatment

Correction of a traumatic aortic injury, whether in an adult or a child, requires a correct diagnosis in a timely fashion along with the availability of an angiographic and diagnostic lab, of an operating room (OR) or an endovascular room (EnR), and of the medical and support staff. Currently, communications from the scene of an accident, the emergency transport crews, and the emergency room staff provide frequent comprehensive updates. With the relayed information, the diagnostic considerations may alert the emergency room (ER) staff, and radiologic scanning department. Thus, the surgery staff and the OR may be prepared for the rapid diagnosis, treatment, and possible correction of an aortic lesion within a few minutes of arrival at the hospital.

The ER gunshot wound did not provide an opportunity for cardiovascular diagnostic studies and surgical planning. The situation was grave and required immediate possible salvage intervention—which eventually proved fruitless. Despite the seriousness of the injuries, the remainder of the patients herein presented had adequate time for hospital transport, diagnostic study, and implementation of the recommended therapy and surgery.

Table 35.2 presents the x-ray findings in these young individuals. The condition of the patient at presentation determined the diagnostic and therapeutic decisions to best treat the patient and the injuries at the time of examination. In the emergency room, with no blood pressure, no pulse nor car-

Table 35.2 Some pediatric aortic trauma results

Patient	X-ray	Treatment	OR	Result	Hospital location
1	Left chest opacified	ER—open left chest. Plug holes with fingers	Left thoracotomy in ER suture heart and aorta	Pronounced dead in ER	Emergency room pediatric teaching hospital
2	Left pleural fluid	Observed serial x-ray	None, mother pulled out spindle	Good—home in 1 week	Small community hospital [1]
3	Left renal artery torn off aorta CT	Aorto-renal bypass repair aorta	Surgery laparotomy left nephrectomy	Good	Community hospital
4	Thoracic aortic transsection. Multiple long bone fractures. Left renal artery torn off aorta CT/several angiography	Repair with graft aorta. Aorta renal vein bypass. Bladder and bone repair	OR Thoracotomy Laparotomy Splenectomy 14 units of blood. Repair urethral separation from the bladder	Good 3-month rehab all function	Community hospital [1]
5	CT	Stabilize/repair	Open left thoracotomy	Paralyzed long-term survival	Large community hospital
6	CT/MRI Angio	Repair	Open left thoracotomy	Died due to head injuries	Community hospital

diac activity, and an opacified thorax, the determination for an immediate thoracotomy was readily decided. Unfortunately, four holes (two in the heart and two in the aorta) were the finding. After suture of the cardiac perforations and control of the aorta, we were unable to successfully resuscitate the child despite large volume blood and electrolyte fluid administration. The 3-year-old child, with penetration of the heart and aorta both anteriorly and posteriorly by the 2–3-mm metallic straight spindle, already had the spindle removed prior to arrival at the hospital. Diagnostic x-rays and contrast studies were consistent with penetration of both the heart and the aorta. A bloody pleural effusion was present, but the patient was stable hemodynamically, on serial chest x-rays and on laboratory studies. Thus, close observation was successfully elected by the parents as the treatment of choice.

Blunt trauma was the cause of the aortic injury in patients 3–6 causing either thoracic or abdominal aorta rupture. Diagnostic evaluation was followed by operative treatment in each of the deceleration thoracic injury patients with two long-term survivals—one remained paralyzed due to the spinal cord injury. The blunt abdominal low velocity injury occurred in a young female while playing softball. She developed marked abdominal and left flank pain, tenderness to touch, and bruising. CT (computerized tomography) scan and diagnostic aortic angiography revealed the left renal artery to be torn off the aorta, a renal contusion, and formation of a large hematoma. Surgical exploration with closure of the aortic defect and attempted renal salvage with an aortorenal saphenous vein graft was not successful and she later had a left nephrectomy. The child did well and was cautioned to avoid contact activities which might injure the remaining right renal artery or kidney. Our patients were between 3 and 21 years of age, and two were female. Two patients had penetrating injuries and four patients (three males) had blunt trauma—two low velocity.

Automobiles, diving into a pool with little water, or a motorcycle accident may all be causes of accidental thoracic aortic trauma. The blunt trauma patient with an aortic contusion, laceration, or transaction usually will have other traumatic injuries involving the long bones, spine and spinal cord, heart, and abdominal contents. Patient #4 had extensive vascular (two aortic lesions), thoracic, and abdominal injuries including the left renal artery torn off the aorta and the bladder torn off the urethra. In this patient, rapid ER diagnostic CT and x-ray studies were followed by emergency repair of the aorta, long bones, diaphragm, splenectomy, renal artery saphenous vein bypass, and urethral reanastomosis. Following 3 months of intensive care, he was discharged and recovered completely. Two of the patients (#5 and 6) had concomitant spinal cord injury with paralysis and no improvement of their paralysis after aortic repair.

Discussion

Vascular trauma, according to Feliciano, was first described by Celsus in 25 BC to 50 AD in his text *De Medicina*, in which he described applying pressure or ligature of bleeding vessels [5]. Vascular trauma reporting was then ignored for over 1000 years until control of bleeders and the use of a hemostat was described by Ambroise Paré in "Bec de Corbin" in the 1500s [5]. Wars then became instrumental in developing lifesaving and bleeding control techniques. In the 1900s, WWI, WWII, and the Korean and the Vietnam Wars all required surgical intervention in young traumatized soldiers for thoracic, abdominal, orthopedic, and vascular concerns.

Penetrating and blunt injuries created challenges that required urgent and corrective therapeutics. Thus, control of hemorrhage using compression, clamping, primary repair, and vascular grafting was attempted and the results were reported. A large number of these injuries occurred in the young—many under 21 years of age—male in the combat situation. Rapid field transport, control of bleeding, stabilization of the soldier, and then timely repair were required.

With the above experience, the returning war surgeons fostered the same care in the community. They transferred their knowledge and results from the penetrating and traumatic war scenes to the university and community hospitals. No longer were rifle shots, exploding bombs, and land mines the only cause of a critical injury. It was now community-oriented trauma related to the deceleration automobile or motorcycle accidents, work accident, and entertainment accidents that required treatment. Blunt traumatic accidents became more concerning to the physician and the family including the bluntly injured individual who also had peripheral vascular and aortic concerns.

These concerns were not limited to the adult—especially if one defines childhood to include individuals up to 18 or 21 years of age. Reports now describe the aortic or vascular traumatic injury in the age range of infant to 21 years. A review of the literature provides a large source of pediatric patients who have suffered from blunt or penetrating aortic injury. Some reports present their findings in the 3- to 11-year-old patients and the treatment program utilized to repair their lesion. In a review of the literature, one notes that the ages of those reported include the infant (18 months) to 14, 16, 17, 18, and 19 years of age. In our area, many pediatricians treat patients up to the age of 21, and thus we have defined our cases as 0–21 years of age. Using this definition, many of the armed or military forces members would fall into the children or pediatric age group.

Takach reported on three pediatric aortic disruption patients aged 4–16 years from the Medical College of Georgia injured from a motor vehicle accident [3]. Hormuth reported 11 patients with blunt trauma treated at Clarian Methodist Hospital in Indianapolis (three drivers, four passengers, three pedestrians, and one bull thrown) [6]. Of note, most aortic injuries in this age population are due to motor vehicles [7, 8]. Tiao also demonstrated the association of cardiac and other major vascular and nonvascular injuries at autopsy in these patients [8]. Tashiro et al. reviewed the Kids' Inpatient Database (1997–2009) to identify thoracic and abdominal aortic injury (*International Classification of Diseases—9th edition*) and found 468 patients under 20 years of age with motor vehicle (77%), penetrating (10%), and firearms (8%) injuries with an overall survival of 65% [9]. Our patients fell into all three groups-motor vehicle, penetrating, and firearm with equivalent survival.

Most traumatic aortic injuries occur in the chest—usually just below the left subclavian artery origin. But abdominal aortic injuries may also occur—especially at or below the renal arteries (note our two patients). Sadaghianloo et al. reviewed three injuries to the abdominal aorta in France and reviewed the literature listing various authors' experience, the associated injuries, and the causes [10]. Choit et al. reported on the chance of abdominal aortic injuries occurring in association with fractures in the pediatric patient [11]. In 2009, Heck reported on a 16-month-old child with blunt traumatic injury to the aorta [12].

Early in the treatment of aortic injuries, only a few diagnostic studies were available. These included the CBC (complete blood count), chest roentgenograms, and exploratory surgery. With the development of CT (computerized tomography) scans and the use of contrast vascular studies, more reliable diagnoses were established, and simultaneously, more advanced and aggressive treatment for the aortic lesion as well as other associated injuries became available. Open thoracotomy and clamp-clamp aortic repair were followed by cardiopulmonary bypass support during the repair—depending on the type, location, and number of injuries [6, 7]. In 2005, the Texas Heart Institute reported on the use of partial left heart bypass during aortic cross clamping in these patients [3].

With continued advances in technical and therapeutic interventions, including MRI (magnetic resonance imaging), the treatment of these patients has continued to evolve. Concomitant significant nonaortic injuries (especially cranial, spinal, and hepatic) are now more readily assessed, and their treatment may take preference. Determinations as to the advisability of surgery, or when to perform such, are discussed by the attending physicians (e.g., neurosurgeons, orthopedic, cardiovascular, etc.). Both operative and nonoperative programs utilizing medication and close observation have been followed [2, 13]. More recently, endovascular therapy utilization for the adult with aortic lesions has increased throughout the world. Thus, Saad reported on the endovascular repair of a traumatic aortic transsection in a 12-year-old [14]. Goldstein then reported on the use of six covered stents in four patients aged 11 to 14 years with one death due to intracranial trauma [15]. Two teenagers after correction of their concomitant traumatic lesions had stents placed for their thoracic aortic transections with ultimate recovery, while another female teenager had an iliac limb prosthesis placed as an interim bridge for future correction of an aortic lesion [15–17].

In our operated patients, treated transthoracically without a stent, the long-term results were primarily related to the underlying trauma and not the aortic therapeutic approach [18]. Kalkwarf et al. reviewed 1292 severely injured children to determine if predictive laboratory determinations exist to ascertain mortality odds and resuscitative

effort futility in severely injured children under the age of 16 years. A total of 1169 children survived, and 123 (9.5%) died. Those who died were usually younger, had head injuries, and severe Injury Severity Scores. When two laboratory values of pH less than or equal to 6.95, base excess less than 22, platelet counts less than or equal to 30,000, hemoglobin less than or equal to 5.0 g/dL, rapid thromboelastography less than or equal to 30 mm, and/or the presence of traumatic brain injury were present, the potential salvage of the child was extremely guarded. Specific injury location, exclusive of the brain, is not listed, but reference to lack of response to resuscitative efforts after 15 minutes (pupils, pulse, and EKG) suggested a potential fatal outcome as noted in our patient #1 [19].

A registry has been developed for evaluating the effect of resuscitative balloon aortic occlusion or open thoracotomy aortic control in profound hemorrhage situations. This registry attempts to define the value of descending thoracic aortic occlusion in individuals without penetrating thoracic injury but hemorrhagic shock. Five percent of the 285 patients survived to discharge with a slight favor to the balloon ER occlusive technique. The study involved patients older than 18 years of age and thus would not apply to our patients #1 and #2 due to age and thoracic penetration. Patients #4 through #6 could possibly be considered for this technique, but the aorta was successfully handled without utilizing this study protocol. One does wonder however if all trauma-oriented ERs should also have a complete ER OR located within the ER for care of these emergency patients [20].

Summary

Aortic trauma in the age group from 0 to 21 years is uncommon to rare except in the individual ages of 18–21 years. In this latter group, automobile and motorcycle injuries cause a number of cardiac, aortic, and other bodily injuries. Many of these patients may be treated conservatively until the most opportune treatment time. The individual may then be treated with either transfemoral endografting or open thoracic aortic surgery. Aortic trauma under the age of 10 is very uncommon but may be lethal. With future development of newer diagnostic techniques, such as 3D imaging and reconstruction, a better anatomic knowledge may be assistive in the therapeutic approach to the patient and his/her aortic injury.

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Aortic Valve Repair

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Introduction

Surgical management of aortic valve presents a difficult dilemma. On the one hand, early surgery protects the myocardium from volume and pressure overload and decreases the chance of fibrosis and remodeling. On the other hand, early valve replacement is suboptimal because of the lack of an ideal valve substitute that does not need anticoagulation or frequent replacement. Autologous pulmonary valve has emerged recently as an attractive aortic valve substitute that fulfills these criteria, but concerns persist over the long-term fate of the pulmonary valve in the aortic position.

The dichotomy created by the absence of the ideal valve substitute and the deleterious effects of long-standing ventricular volume and/or pressure overload associated with aortic valve disease has renewed interest in aortic valvuloplasty. Although several techniques, such as annular reduction, commissural resuspension, and cusp extension, were used in the past, aortic valvuloplasty remained an evolving approach rather than a definitive treatment, due in part to incomplete understanding of the functional anatomy and geometry of the aortic valve. Recently, success in atrioventricular valve repair, progress in myocardial protection, refinements in three-dimensional imaging of the aortic valve, and detailed analysis of valve anatomy and function have led to improved results of aortic valve reconstruction [1, 2].

Anatomy and Function of the Aortic Valve

The three leaflets of the aortic valve are attached to the aortoventricular junction. The collagenous condensation at the point of attachment of each leaflet has been termed the annulus fibrosis. There is, however, no true "ring" of the annular tissue supporting the leaflets in a straight circular plane. The hemodynamic stresses on the leaflets, therefore, are counteracted at several structural levels. The margin of coaptation of a competent valve is more than a finite point of contact. It extends along the whole margin of the leaflet in length and several millimeters in depth. Beneath the apices formed by leaflet attachment, the so-called commissures, there are subcommissural or interleaflet triangles. The wide base of these triangles follows the ventricular contraction pattern and allows optimal retraction of leaflets during systole. The sinotubular bar marks the junction with the ascending aorta. It is thicker than the adjacent sinuses. It is circular with areas of increased collagen. It acts as a suspension post that supports the peripheral attachments (the commissures) of the valve leaflets. The parabolic shape of the leaflets resembles a suspension bridge. Their attachments to the sinotubular bar are several millimeters above the level of coaptation. As these support poles stretch outward by as much as 16–44% during early systole, the leaflet edges (the cables) become straighter, aiding in the opening of the valve.

The aortic root is also a complex hemodynamic system. Its component parts change in size and shape during the cardiac cycle. Its distal portion is exposed to the aortic pressure. It expands to allow leaflet retraction. Its base is exposed to ventricular dynamics. It contracts during the peak of systole to decrease the distance the leaflets have to close and to reduce the stress forces applied to leaflets in early diastole.

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Moreover, the leaflet-sinus assembly behaves as an independent unit to store the diastolic pressure within. It allows the aortic valve to remain competent. The instantaneous changes in the aortic valve orifice have been shown to precede movement of the blood in the ventricle. The transformation of the aortic orifice from a closed position to a triangle and then to a circle without causing flexion deformity of the cusp tissue is related to aortic root distensibility and the mechanism of leaflet suspension.

Pathology and Function of the Abnormal Aortic Valve

Aortic Valve Stenosis

The Congenital Bicuspid Aortic Valve

In type I, there is no median raphe at the junction of two cusps. As a result, there are two rather symmetric aortic sinuses and leaflet base attachment. The valve orifice is central. The commissural triangle is rather well developed. The leaflets are suspended at the sinotubular bar and have adequate depth. In type II, which is more prevalent, a median raphe is present. The cusps are asymmetric, and the fused leaflet is longer and shallower and takes up more of the circumference of the valve. In contrast to the normal tricuspid valve, the leaflet edges are excessive and sagging. As a result, there is increased folding and crossing and a compensatory extension of the area of leaflet approximation from their edges (doming). The opening of the valve is eccentric due to discrepancy in leaflet sizes. The orifice also has an elliptical rather than a circular opening. The resultant distortion in blood flow pattern exaggerates turbulence and predisposes to degenerative changes. Frequently, there is commissural fusion that limits the leaflet movement and exaggerates the eccentricity of valve opening and the decrease in its effective orifice diameter. The narrowed opening, often combined with annular hypoplasia, impairs the ability of the leaflets to escape systolic or diastolic pressure load, further exaggerating the stress on the valve. The subcommissural triangle is severely attenuated. It limits leaflet movement in early systole and the change in orifice configuration necessary for appropriate leaflet coaptation at the end of systole. The leaflet edges are suspended below the sinotubular bar. This, combined with redundant leaflet edges, results in shallow sinuses, decreases coaptation area, and exaggerates leaflet-deforming dynamic forces [3].

The Rheumatic Aortic Valve

The continued inflammatory process causes progressive scarring and thickening of the leaflets and fusion of the commissures. The valve becomes progressively stenotic.

Aortic Valve Regurgitation

There are three types of regurgitant aortic valves. Type I is dilatation of the aortic annulus, the ventricular aortic junction, or sinotubular bar. Type II is leaflet prolapse. Type III is leaflet restriction and scarring. It is the most common pathology of the congenital regurgitant valve.

Regurgitation in Patients with Congenital Valvar Stenosis

The continued trauma to the leaflet edges produced by hemodynamic stress and abnormal flow patterns results in progressive scarring, thickening, deformity, and retraction of the leaflet edges and subsequent lack of coaptation (type III).

Aortic Regurgitation Secondary to Subaortic Fibromuscular Stenosis

The abnormal blood flow pattern produced by the subaortic stenosis results in progressive deformity of the leaflet. Tethering of the leaflets by the subvalvar fibrous tissue, causing obstruction, exaggerates the regurgitation (type III).

Regurgitation in Marfan Syndrome

The pathology is progressive dilation of the aortic root wall due to fragmentation of its elastic support. The dilated sinotubular bar and valve sinuses stretch apart the commissural suspension and leaflet edges. The increase in hemodynamic stress due to changes in the leaflet suspension mechanism combined with an enlarged aortoventricular junction leads to poor leaflet coaptation and central regurgitation (type I).

Postballoon Regurgitation

This condition is usually caused by leaflet(s) tear close to the fused commissure. The leaflet becomes flail and eccentric regurgitation results (types II and III).

Aortic Regurgitation Secondary to Rheumatic Disease

There is cusp retraction secondary to inflammation and scarring. The hemodynamic sequelae result in progressive annular dilation and worsening of the regurgitation (types II and III).

Timing of Surgical Intervention

To achieve optimal short- and long-term results, surgical intervention should be timed appropriately. The decision relies on achieving the goals of valve surgery, which include relief of symptoms, restoration of exercise capacity, improved quality of life, and, most importantly, protection of the myocardium from chronic pressure and/or volume overload. Most of the reported guidelines for the timing of valve surgery are based on studies that use mortality rates as a

follow-up endpoint but fail to analyze myocardial performance and reserve several years postoperatively. They utilize as their database several single-center observational studies and very few prospective, randomized trials.

The introduction of and refinement in valvuloplasty techniques has prompted critical evaluation of these older guidelines for timing of surgical intervention on the diseased aortic valve. The availability of a surgical alternative that avoids valve replacement or anticoagulation has liberalized the older rigid criteria [4]. Although large-scale, long-term data on repaired valves are not available, there is unquestionable evidence that valvuloplasty extends the functional longevity of the native aortic valve and may safely delay the need for replacement, thus justifying earlier surgical intervention. Waiting for symptoms to appear or for ejection fraction to decrease prolongs the duration of ventricular pressure and volume overload and may lead to irreversible ventricular dysfunction [5].

Techniques of Surgical Valvuloplasty

Several principles have evolved that helped in improving short- and long-term outcomes of valve repair. These include the following:

1. Detailed pre- and intraoperative analysis of pathology. This is best achieved by two- and three-dimensional echocardiography. Pliability of each cusp is estimated by the apparent change in its area from systole to diastole. Adequacy of cusp tissue for coaptation is estimated by measuring the curvilinear height of the leaflet. In addition, 3D echocardiography helps in measuring leaflet free edge, the depth of the sinus, and areas of tissue deficiency or prolapse.
2. More than one technique needs to be performed to achieve both competence and relief of obstruction. The different steps in the procedure should be tailored to address the specific pathology types.
3. Reconstructive steps should be preceded by relief of obstruction as completely as possible. All areas of leaflet fusion or stenotic lesions should be relieved first even if that reduces leaflet support. Subsequent reconstructive steps of such leaflets should aim at restoring the normal morphology, function, and support.
4. Isolated repair of only one leaflet or cusp without addressing the pathology of the whole aortic root is inadequate and leads to early failure.
5. Fresh autologous tissues such as pericardium or fascia lata cannot withstand dynamic stress when used for repair and tend to retract and scar with time; therefore, glutaraldehyde fixation is necessary.
6. "Overcorrection" in cases of aortic valve incompetence might be needed, but excessive correction may lead to crowding and distortion of the repaired valve if the root is normal or smaller than normal in diameter.
7. Centralizing blood flow through the valve decreases turbulence and extends the longevity of the repair; therefore, tricuspidization of the valve is advantageous when possible.
8. It is essential to incorporate in the procedure the necessary steps that address the interaction between aortic root dynamics and valve mechanics, namely, maintaining annular and commissural flexibility and movement in order to avoid accelerated stress-induced valve degeneration. Mobilization of the subcommissural triangle and avoiding subtotal excision of the leaflets close to the aorto-ventricular zone are important to avoid the disruption of the delicate and complex relationship between the root and leaflet.
9. Continued root dilatation whether at the aorto-ventricular or sinotubular bar junction induces recurrent aortic insufficiency and renders the repair ineffective. The integrity of these junctions should be restored whenever they are dilated.
10. The abnormal ascending aorta should be replaced at the time of valvuloplasty especially in patients who demonstrate associated morphologic, histologic, or molecular abnormalities of the aortic wall.
11. Realization that there is a dynamic interplay between the valve and the aortic root that is essential for valve function has refocused attention on the importance of repairing all the root components, namely, the annulus, the sinus, the cusps, and the sinotubular junction.

All valvuloplasties are performed through an oblique aortotomy above the sinotubular bar. Antegrade and retrograde blood cardioplegia is used. Placement of commissural sutures aids exposure. Axial traction (perpendicular to the annulus plane) applied to the commissural sutures allows assessment of the valve leaflets and annulus. In addition, a centrally placed suture helps in evaluating the structure, the deficiency, and the redundancy of the different cusps by traction on the suture and pushing the leaflets gently toward the ventricle.

Approach to the Aorto-Ventricular Junction

In regurgitant valves, there is a variable degree of annular dilatation that is accelerated in patients with bicuspid valves or distorted septo-aortic angle. Significant dilatation ($Z \geq +2$) impacts negatively on long-term outcome if not addressed at the time of valvuloplasty.

Various internal or external annuloplasty techniques have been described. In the internal approach, a double row of sutures are placed in the subannular area or at midcommissural level to avoid injury to the conduction system (Fig. 36.1). The sutures are tied around a dilator, the diameter of which is determined by the use of a nomogram or approximated to 12–14 mm/m^2. It is beneficial to have the annuloplasty sutures slightly on the tight side, as some of these sutures might cut through the tissue or erode into the membranous septum in a small percentage of cases. Braided suture material has the advantage of allowing tissue ingrowth but could cause more trauma and uneven reduction of the annulus when compared with monofilament material. External annuloplasty requires extensive mobilization of the aortic root and involves placement of a circumferential suture or complete/incomplete ring. It has better long-term outcome than internal fixation [6–9] (Fig. 36.2).

Surgical Approach to the Aortic Sinuses

Management of the dilated sinus consists of sinus wall plication at mid-distance between the involved two commissures. In occasional cases, when the valve opening is not at the center, asymmetric plication may centralize blood flow through the valve. Severe dilatation of the sinuses may necessitate reduction of the sinus wall by resection of a triangular piece [10] (Fig. 36.3). Restrictive sinus wall, on the other hand, limits cusp movement, attenuates the Eddie currents, and leads to dysplasia of the leaflet. Management consists of sinus enlargement with a triangular patch (Fig. 36.1). The degree of enlargement or reduction of a sinus diameter is determined by the use of published nomograms that outline the appropriate sinus diameter for age and weight (Fig. 36.4).

Surgical Approach to the Valve Cusps (Leaflets)

Prolapse is managed by central plication of the leaflet (Fig. 36.5). Triangular resection of the involved area is needed in cases with severe redundancy or calcification. An alternative approach is enforcement of the prolapsing margin with a running suture (Fig. 36.6) [11, 12]. Additional sinus wall plication is helpful if there is an associated significant dilatation of the sinotubular bar.

Reconstruction of the defective leaflet is the cornerstone of any valvuloplasty. It involves thorough debridement and extensive but safe thinning of the effected leaflet of all nodularities or calcification. An appropriately shaped patch that matches the irregular edge is then sutured to the leaflet defective-free margin. More patch length than leaflet length is sutured at the center of the cusp to give it the normal bulging "cusp" configuration (Fig. 36.7). The reconstructed leaflet is suspended to the aortic wall at the level of the sinotubular junction (Fig. 36.8). Patch dimensions are crucial for optimal immediate and long-term results. Excessive height and width results in stenosis due to crowding or may cause coronary ostial obstruction. On the other hand, a short and narrow patch results in residual regurgitation. The actual length and depth of the patch is inferred from the intercommissural distance based on correlation equation or, less reliability,

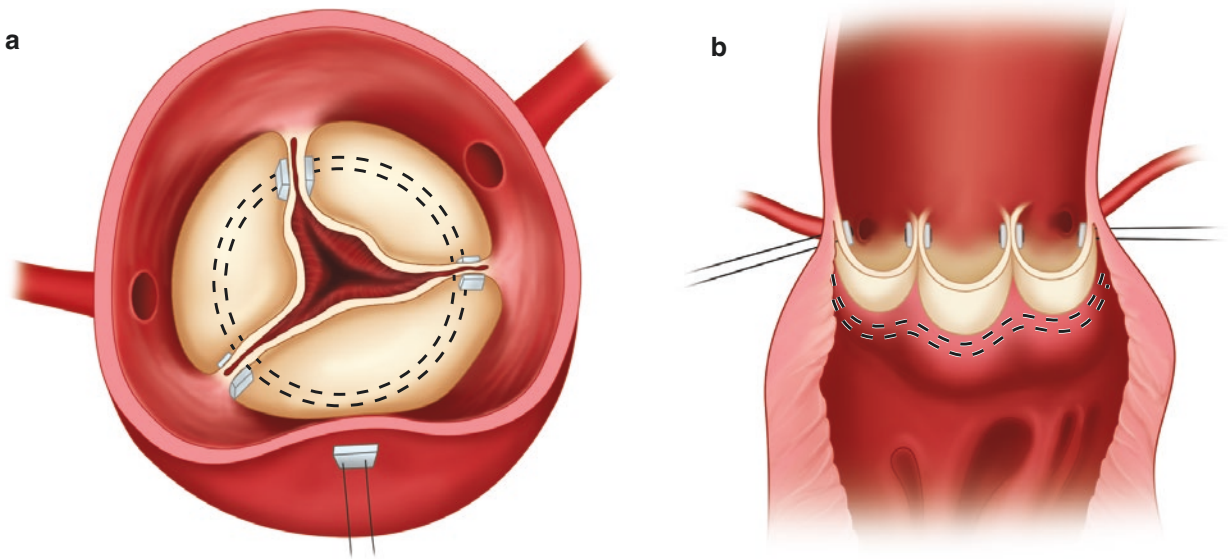

Fig. 36.1 Internal subvalvar annuloplasty with two rows of suture. (**a**) Transaortic view. (**b**) Longitudinal view showing the annuloplasty sutured in the subvalvar area

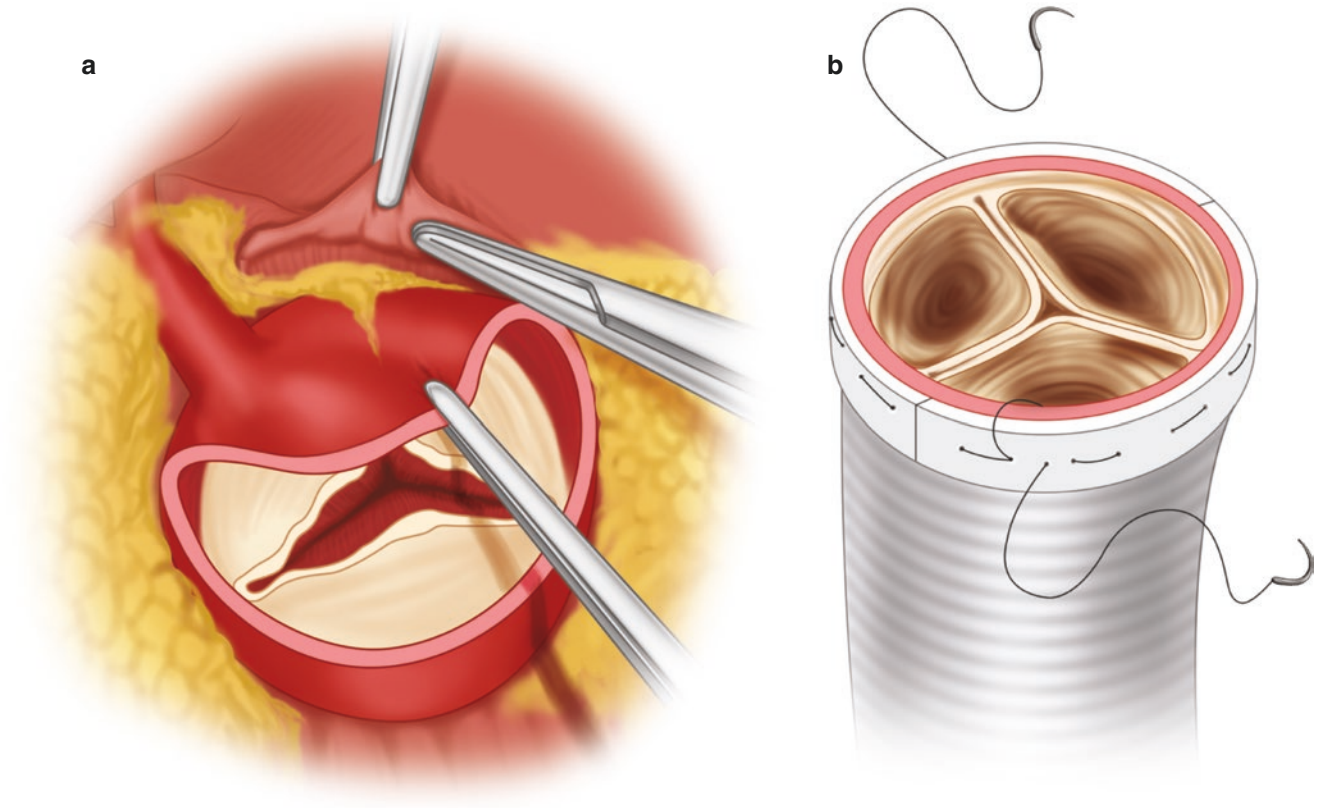

Fig. 36.2 Techniques of annuloplasty. Following complete mobilization, an external suture or ring is placed at the base of the root. (**a**) External placement of annuloplasty sutures. (**b**) Completed annuloplasty ring at the base of the aortic root

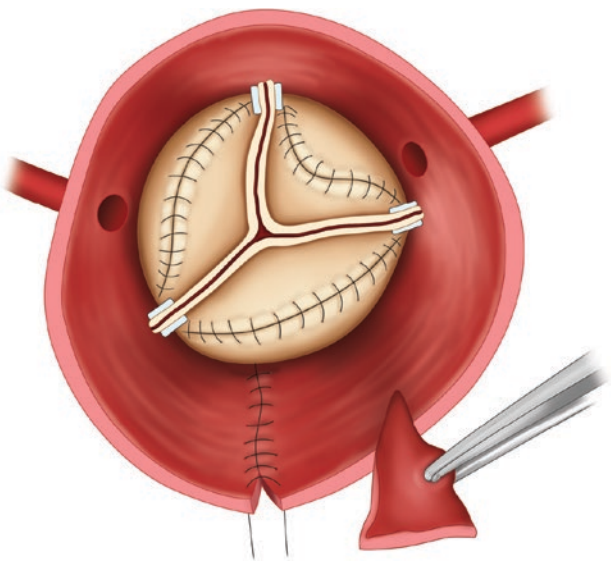

Fig. 36.3 Reduction technique for dilated sinus of Valsalva. (From ElZein et al. [21]. Reprinted with permission from Elsevier)

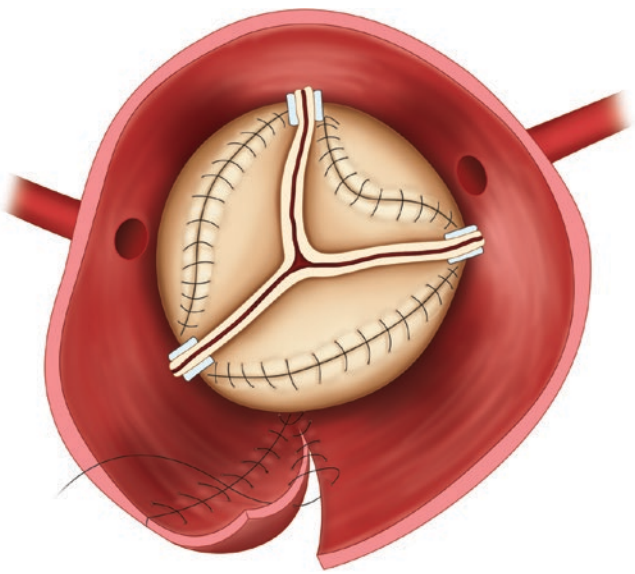

Fig. 36.4 Augmentation technique for restrictive sinus of Valsalva. (From ElZein et al. [21]. Reprinted with permission from Elsevier)

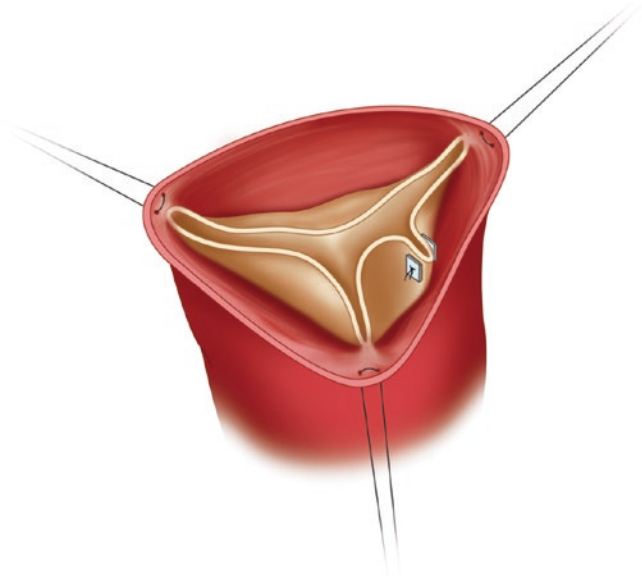

Fig. 36.5 Leaflet plication using pledgeted sutures. (From ElZein et al. [21]. Reprinted with permission from Elsevier)

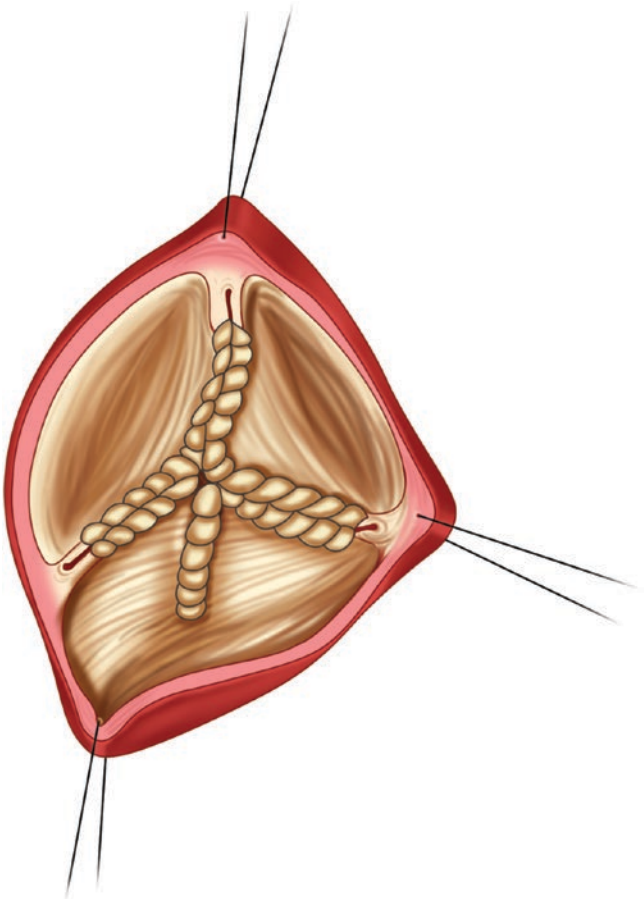

Fig. 36.6 Suture plication of redundant leaflets. The sutures are exteriorized at the commissures and tied. (From ElZein et al. [21]. Reprinted with permission from Elsevier)

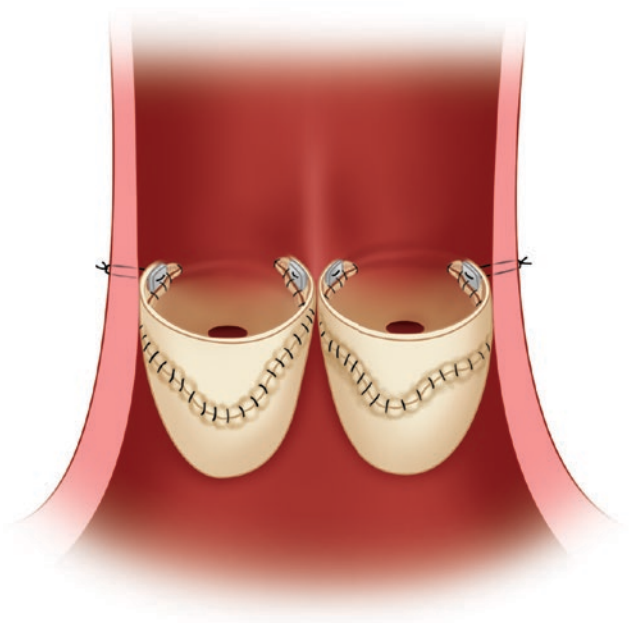

Fig. 36.7 Patch augmentation of the defective leaflets. The patch width normalizes the leaflet depth. Note the irregular edge of the patch. (From ElZein et al. [21]. Reprinted with permission from Elsevier)

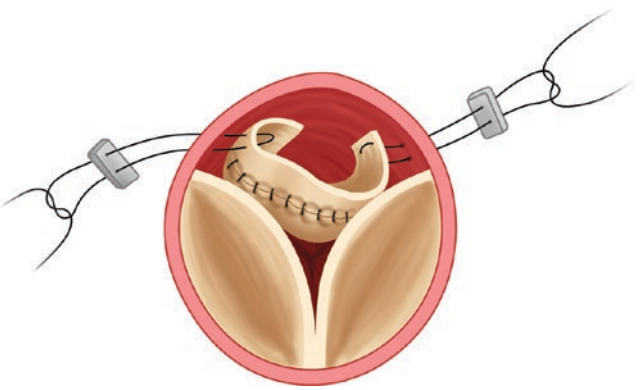

Fig. 36.8 The reconstructed leaflet is suspended at the ST junction. (From ElZein et al. [21]. Reprinted with permission from Elsevier)

from nomograms, or an approximate estimate of cusp height of 10 mm/m^2 [13, 14]. The width of the patch is determined by subtracting the normal leaflet depth from the actual depth of the defective leaflet. Leaflet augmentation should achieve central coaptation of 3–5 mm in height [15, 16].

There is no ideal patch material. Several commercially available patches have been used. Most of these, however, develop fibrosis and calcification, limiting the functional life of the valvuloplasty. Autologous pericardial patient debrided thoroughly from all fat and adventitial tissue, treated with glutaraldehyde 0.625% for 2 minutes and rinsed thoroughly has proven to be the best option.

Surgical Approach to the Sinotubular Junction

Management of dilated sinotubular junction is plication at the intercommissural point. It is tightened until the junction-to-annulus diameter ratio is 1.3:1 or the normal diameter predicted from nomograms is achieved. Another approach is to reduce the diameter of the ascending aorta at the dilated junction by resecting a triangular piece of the aortic wall. Anastomosis to reestablish aortic continuity is reinforced with a circular pericardial strip (Fig. 36.9) [17].

Tricuspidization

Tricuspidization of the bicuspid aortic valve is indicated in cases where the valve opening is eccentric. It centralizes blood flow, thus minimizing turbulence and hemodynamic trauma to the reconstructed valve, and consequently prolongs the functional life of the repaired valve [18]. However, it may increase the complexity of the repair and weakens the reconstruction because of increased length of suture line and use of an excessive patch material. Technical aspects consist of incising the rudimentary commissure and patch augmentation of the resultant three defective leaflets (Fig. 36.10). An alternative approach to tricuspidization is changing the commissural orientation by plicating the dilated sinus and annulus at midpoint of the larger leaflet. This maneuver centralizes the valve opening to a certain extent but is not as effective as tricuspidization in restoring the valve structure to normal.

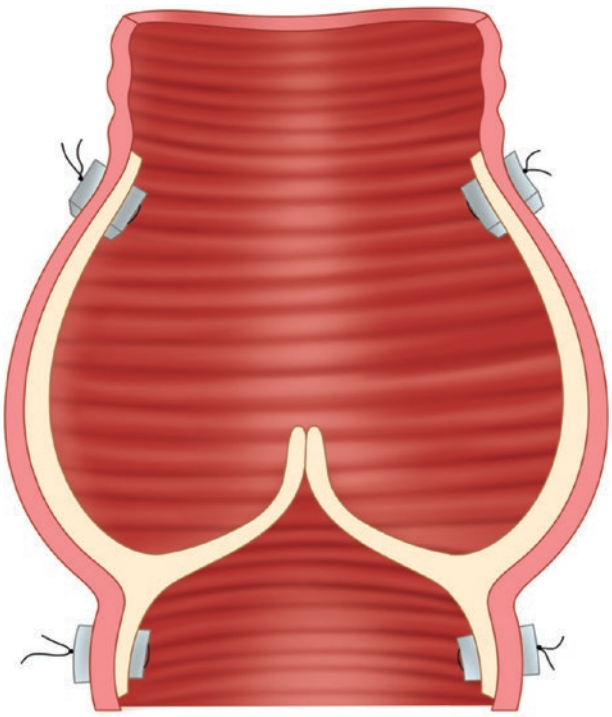

Fig. 36.9 The reduction technique of the ST junction. Note the ratio of the ST junction diameter to annulus diameter. (From ElZein et al. [21]. Reprinted with permission from Elsevier)

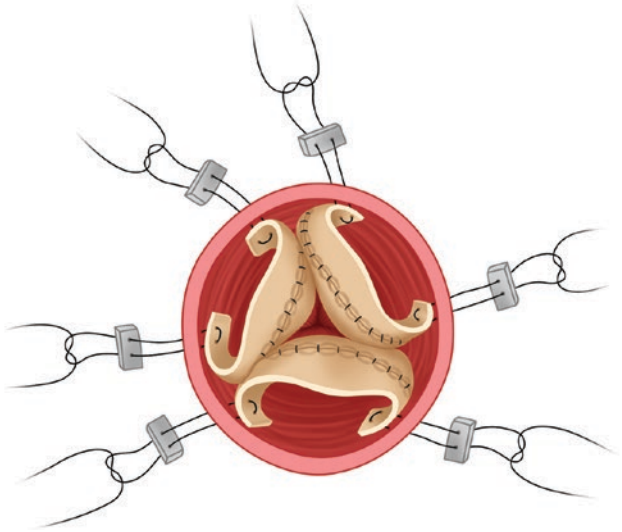

Fig. 36.10 Tricuspidization technique. (From ElZein et al. [21]. Reprinted with permission from Elsevier)

Ozaki Technique

Described by Ozaki et al. in 2006, this technique involves independent replacement of the three cusps by three separate autologous pericardial patches. The size of the cusp is determined from a template that incorporates the intercommissural distance as the reference point. Long-term fate of subtotal replacement of the leaflet with patch material has not been determined especially in pediatric patients [19].

Results

The techniques of aortic valvuloplasty are in evolution. Several series have reported results using one or more of the techniques mentioned here. None of these results, however, reflects the present knowledge of the surgical anatomy or the outcome of valve repair when these technical steps are used in combination.

A review of our total experience with these different approaches revealed a significant drop in pressure gradient across the valve, a decrease in aortic regurgitation as judged by grade and by ratio of the regurgitant jet to aortic annulus diameter, and a decrease in indexed left ventricular end-diastolic volumes [20].

Long-term postoperative follow-up revealed a progressive increase in pressure gradient in 42% of patients, associated

with stiffening or calcification of the patch used for leaflet augmentation. When restenosis was analyzed, it was apparent that patients who had valvar stenosis and annular hypoplasia had the highest incidence of restenosis. This increased incidence might have been due to the crowding of the hypoplastic aortic root when aggressive overcorrection is used. Recurrence of regurgitation was not a problem in follow-up, and most patients maintain competent valves. Therefore, a selective approach to aortic valve disease should be adopted. Patients with primary valvar stenosis and associated annular hypoplasia should undergo Ross with Konno Procedure or valve replacement. On the other hand, patients with primary regurgitation or annular dilatation are best managed early by using the described valvuloplasty techniques.

Conclusions

Aortic valvuloplasty as currently used has very low operative mortality. It provides an excellent alternative to valve replacement. It maintains the patient's own valve and does not preclude other alternatives when deemed necessary. It is probably superior to the Ross procedure in patients who are very young or have significant annular dilation due to regurgitation or other causes. Its use in patients with aortic annular hypoplasia should be limited to avoid recurrent stenosis. The use of patch material not fixed with glutaraldehyde might provide a decrease in the incidence of restenosis.

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Aortic Pseudoaneurysms

37

Leonie K. Stabenow

Introduction

Aortic pseudoaneurysms are blood-filled cavities formed between the two outer layers of the vessel, the muscularis propria and adventitia. The dilated segment of the aorta of the pseudoaneurysm is lined only by the adventitia which distinguishes pseudoaneurysms from true aneurysms in which all three layers of the vessel wall are involved. Pseudoaneurysms can occur after injury to the vessel, and most cases arise due to prior aortic or cardiac surgery. Other causes leading to impairment in the integrity of the vessel wall can be blunt trauma, percutaneous surgical procedures, autoimmune diseases, inflammation, and mycotic pseudoaneurysms secondary to tuberculosis [1]. Complications of pseudoaneurysms are unpredictable, and they have the potential to create life-threatening conditions. Therefore, early diagnosis and treatment is essential to maximize survival. Even though endovascular techniques to repair aortic pseudoaneurysms are emerging, open surgery plays an important role and still counts as the standard treatment [2, 3]. Endovascular repair methods are limited to high-risk surgical patients, but these methods including stent grafts, coil embolization [4], thrombin injections [5], septal occluder devices [6], and vascular plugs become more and more popular.

Epidemiology

The occurrence of aortic pseudoaneurysms is rare, but they are often serious complications mostly caused iatrogenically. Throughout the literature, the incidence rates of pseudoaneurysms are highly variable. Concerning ascending aortic pseudoaneurysms, the occurrence has been reported to be as low as 0.5% [1]. Nevertheless, in a surveillance imaging series after cardiac or aortic surgery, the incidence rates reported were up to 13% [1, 7]. For thoracic aortic pseudoaneurysms, the incidence rates are also less than 0.5% [8]. Other rare complications are anastomotic and para-anastomotic pseudoaneurysms after abdominal aortic reconstruction. Here, the incidence rate has been reported to be 5% 8 years after cardiac surgery and 27% after 15 years [4]. Regarding anastomotic pseudoaneurysms after ascending or aortic arch replacement, rates range from 2% to 38% [9].

Pathophysiology

The most common cause of aortic pseudoaneurysms is injury to the vessel wall due to prior aortic or cardiac surgery. For instance, ascending aortic pseudoaneurysms are nearly always associated with a history of aortic surgery and cannulation of the ascending aorta [1]. Other causes leading to impairment in the integrity of the vessel wall can be blunt trauma, percutaneous surgical procedures, autoimmune diseases, inflammation, and mycotic pseudoaneurysms secondary to tuberculosis (Table 37.1) [1]. Mycotic pseudoaneurysms arise from bacterial infection of the vessel wall. This term was first used in 1885 by William Osler who used the description mycotic aneurysm to describe the mushroom shape [10]. Furthermore, also spontaneous formations of aortic pseudoaneurysms have been reported, where none of these factors were found to be the cause. Aortic pseudoaneurysms communicate with the aorta through a hole in the vessel wall. Depending on the size of the dilatation, spontaneous clot formation and complete thrombosis can occur, leading to spontaneous resolution, but this has rarely been reported. However, most frequently, the enlargement exceeds a critical size, and progressive expansion can then cause rupture or compression of surrounding structures which can lead to severe complications.

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Table 37.1 Classification of aortic pseudoaneurysms

Location categories	Ascending aorta	Aortic arch	Thoracic aorta	Abdominal aorta
Etiology	Prior aortic or cardiac surgery Blunt trauma Percutaneous surgical procedures Infection Autoimmune diseases [1]	Prior aortic or cardiac surgery Blunt trauma Percutaneous surgical procedures Infection Autoimmune diseases [1]	Prior aortic or cardiac surgery Blunt trauma Percutaneous surgical procedures Infection Autoimmune diseases [1]	Prior aortic or cardiac surgery Blunt trauma Percutaneous surgical procedures Infection Autoimmune diseases [1]
Treatment methods	Open surgery Stent crafts Coil embolization Thrombin injection Septal occluder devices and more	Open surgery Stent crafts—mostly used in the distal arch [1] Coil embolization Thrombin injection Septal occluder devices and more	Open surgery Stent crafts Coil embolization Thrombin injection Septal occluder devices and more	Open surgery Stent crafts Coil embolization Thrombin injection Septal occluder devices and more
Indications for treatment	Large/symptomatic pseudoaneurysm (>2.0 cm) [13] Shock Cardiovascular instability Evidence of vascular compromise [13] Rapid expansion of the pseudoaneurysm [13, 18]		Hemorrhage Infection [13] Skin necrosis [13]	
Factors which may contribute to the formation of pseudoaneurysms [13]	Obesity [13] Age > 65 years [13] Hypertension [13] Complex interventions [13]		Anticoagulation [13] Antiplatelet agents [13]	
Organisms causing infected (mycotic) pseudoaneurysms	*Staphylococcus aureus* (most common) [19, 20] *Escherichia coli* [21] *Streptococcus* species *Mycobacterium tuberculosis*	*Staphylococcus aureus* (most common) [19, 20] *Escherichia coli* [21] *Streptococcus* species *Mycobacterium tuberculosis*	*Staphylococcus aureus* (most common) [19, 20] *Salmonella* species [19] *Escherichia coli* [21] *Streptococcus* species *Mycobacterium tuberculosis*	*Staphylococcus aureus* (most common) [19, 20] *Salmonella* species [19] *Escherichia coli* [21] *Streptococcus* species *Mycobacterium tuberculosis*
Etiology of infected pseudoaneurysms	Arterial trauma Local infection Endocarditis Bacteremia	Gastrointestinal tract Retroperitoneal abscess		

Locations

Pseudoaneurysms can generally develop in any artery in the body. Due to a progressive increase in cardiac catheterizations, pseudoaneurysms most often occur in the femoral artery. In the aorta, pseudoaneurysms can develop at various locations: in the ascending aorta, aortic arch, thoracic aorta, and abdominal aorta (Table 37.1). True aneurysms are more likely also to be found on the bifurcation of vessels, whereas pseudoaneurysms are rather found along a vessel wall [11].

Treatment Methods

Aortic pseudoaneurysms are a severe and rare complication. The progressive expansion can create life-threatening conditions by increasing the risk of rupture, bleeding, and compression of surrounding structures. Additionally, they can serve as a source of infection or even lead to the development of embolic thrombi [1, 12]. It is essential to detect this condition before complications occur in order to maximize the chances of a successful management. Many noninvasive diagnostic methods exist to diagnose pseudoaneurysms. However, conventional angiography, even though it is an invasive procedure, also remains as one of the standards for diagnosis (Fig. 37.1). The most frequently used techniques are ultrasonography (Fig. 37.2), computed tomographic scan/angiography (Fig. 37.3), and magnetic resonance angiography. Using a Doppler ultrasound, the visualization of the typical "to and fro" waveform is possible, which shows that blood flows into the pseudoaneurysm and then back into the lumen of the vessel [13]. All these techniques are essential to determine the location of the aortic pseudoaneurysm, rupture risk, morphologic features, comorbidities of the patient, and surrounding vascular anatomy. If possible, all these factors should be considered in the workup which is the key to a successful management. The optimal treatment should then be based on all these considerations. Many treatment methods have been reported for aortic pseudoaneurysms, and especially minimally invasive techniques are evolving, giving an alternative to surgery with fewer complications. Endovascular repair methods including stent grafts, coil embolization [4],

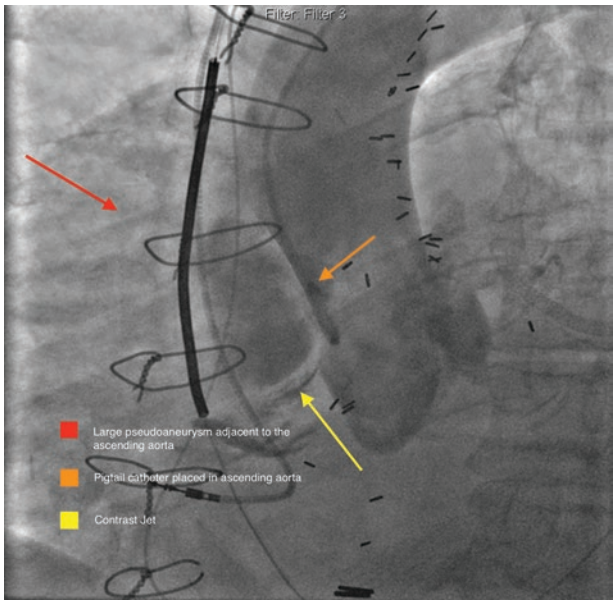

Fig. 37.1 Arch aortogram showing a large pseudoaneurysm adjacent to the ascending thoracic aorta (red arrow). The orange arrow points toward the pigtail catheter, placed in the ascending aorta. The yellow arrow points toward the contrast jet. (From Stabenow, et al. [6]. Copyright 2018 by the HMP Global. Reprinted with permission)

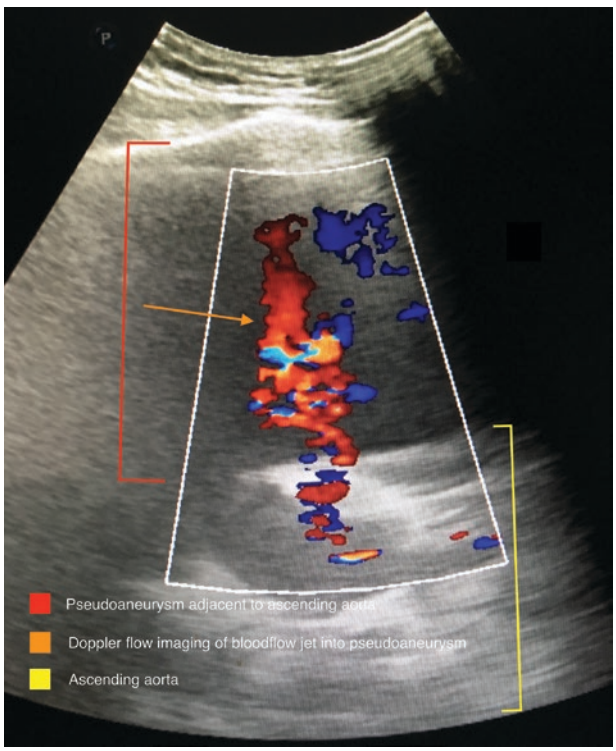

Fig. 37.2 Preoperative transthoracic Doppler ultrasound image of the pseudoaneurysm in the ascending thoracic aorta. Area marked in red shows the pseudoaneurysm adjacent to the ascending aorta. The yellow marking borders the ascending aorta. The orange arrow points toward the blood flow jet into the pseudoaneurysm. (From Stabenow, et al. [6]. Copyright 2018 by the HMP Global. Reprinted with permission)

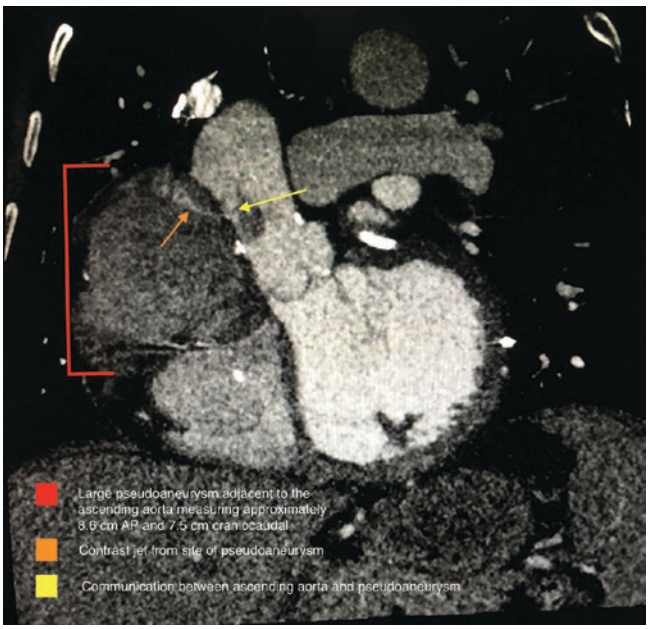

Fig. 37.3 Preoperative CT image of a large pseudoaneurysm adjacent to the ascending thoracic aorta. The area marked in red shows the large pseudoaneurysm adjacent to the ascending thoracic aorta. The orange arrow points toward the contrast jet from the site of the pseudoaneurysm. The yellow arrow indicates the communication between the ascending aorta and pseudoaneurysm. (From Stabenow, et al. [6]. Copyright 2018 by the HMP Global. Reprinted with permission)

thrombin injections [5], septal occluder devices [6], and vascular plugs are listed in Table 37.2. Nevertheless, open heart surgery is still considered as the standard treatment. Due to its longer period of experience, there are significant data on survival benefit [14].

Open Surgery

Open surgery can be performed to remove the pseudoaneurysm by tube replacement, or a vein or synthetic graft can be anastomosed proximally and distally from the pseudoaneurysm. By using a vein or synthetic graft, the blood flow can be redirected around the pseudoaneurysm which prevents it from expanding. The use of patch repair and the use of woven or knitted grafts have also been reported [8, 15]. Open surgery has been a successful treatment for many years, but disadvantages among others are more postoperative pain and the risk for wound infection (Table 37.2). Nevertheless, the treatment of aortic pseudoaneurysms remains a challenge. Mortality rates have been presented by numerous authors ranging from 29% to 46%, and in most cases, the death cause is a fatal hemorrhage due to rupture of the pseudoaneurysm during the procedure [2, 16]. Endovascular repair is preferred and more beneficial in elderly patients and patients with many comorbidities, which are at risk for surgery.

Table 37.2 Advantages and disadvantages of treatment methods for aortic pseudoaneurysms

Treatment methods	Advantages	Disadvantages
Open surgery	Significant data on survival benefit [14] Dealing with intraoperative bleeding is easier	More postoperative pain Risk for wound infection Not suitable for high-risk patients General anesthesia is required It may be necessary to block the circulation
Stent crafts	Minimally invasive High success rate Effective also for high-risk patients	Paucity of information about long-term prognosis Endoleaks/incomplete exclusion Risk for infection of the stent [5] Stent migration [22] Fracturing of the stent [22]
Coil embolization	Minimally invasive Superior to stent grafts regarding endoleaks [4] Detachable coils can be retrieved and repositioned High rate of successful occlusion Short procedure and easy technique Effective in excluding small-necked aneurysms [9, 17]	Paucity of information about long-term prognosis Embolization brings limitations, and suitability depends on size, location, and shape—good for small-necked aneurysms [9, 17] Risk of embolization Large number of coils needed for complete occlusion
Thrombin injection	Minimally invasive Minimal discomfort to the patient Easy and short procedure High rate of successful occlusion Superior to stent grafts concerning mycotic pseudoaneurysm—no risk of stent infection [5]	Paucity of information about long-term prognosis Risk of failure to seal the hole Local and distal thrombosis/clot formation Risk of allergic reactions and anaphylaxis [23] Limitation depending on the size of the neck of pseudoaneurysm—wide neck: risk of distal emboli
Septal occluder devices	Minimally invasive Effective also for high-risk patients High success rate Available in many sizes and configurations Can also be used for wide-necked pseudoaneurysms	Paucity of information about long-term prognosis Risk of perioccluder leakage [13] Risk of recurrence of pseudoaneurysm

Stent Grafts

Aortic pseudoaneurysms are in communication with the aorta through a hole in the vessel wall. In order to abrogate this communication, a stent may be placed endovascularly across the communication site. The hole is then covered preventing further incoming blood flow and further expansion and without this continuous blood flow the pseudoaneurysm thromboses. An important factor that needs to be considered before placing a stent graft is the possibility to exclude coronary or aortic branches for which fenestrations would be required. Stent grafts are mostly used in the distal arch and in the descending and abdominal aorta [1]. For safety measures, there should be a 2-cm safety margin of the healthy aorta to deploy the stent, and in addition, the diameter of the stent should be larger than the diameter of the aorta [1]. By implanting a stent graft, the goal is that the blood only flows through the prosthetic and that no more blood flows into the pseudoaneurysm, eliminating the risk of rupturing. Incomplete exclusion or endoleaks are a common complication leading to a still persistent blood flow into the pseudoaneurysm. Furthermore, with the implantation of stent grafts, there is a risk for infection of the stent or the arterial insertion site. Additional complications can be stent migration due to hemodynamic forces and fracturing of the stent. Advantages of this technique are that there is no need for an open surgery and stent grafts also have a high success rate.

Coil Embolization

For coil embolization, a microcatheter is used to introduce coils into the aneurysmal cavity, and the coil is deployed by pushing the device when the occlusion is adequate. The coil can still be retrieved if it is unstable or too large. This technique can be performed in saccular aneurysms, and the diameter of the sack must be larger than the neck to ensure intra-aneurysmal coil packing [9]. Therefore, it has been reported to be especially effective in excluding small-necked aneurysms [9, 17]. The closure of aortic pseudoaneurysms by coil embolization has been used to avoid possible complications of stent grafts, like endoleaks [4]. Coil embolization is also used as an additional therapy in combination with stent grafts, occluder devices, or vascular plugs [1, 12].

Thrombin Injections

Another minimally invasive technique used today to treat aortic pseudoaneurysms is ultrasound-guided thrombin injection. To induce thrombus formation, thrombin can be injected intra-arterial via a transcatheter directly into the pseudoaneurysm. Thrombin then converts fibrinogen into fibrin, and the polymerization of fibrin leads to the thrombus formation [1]. Thrombin injection can be used as a possible treatment for high-risk patients when an aortic pseudoaneurysm occurs because of an infection. In this case, an implantation of a stent graft would be a contraindication due to the potential risk of graft infection (Table 37.2) [5]. A clear advantage of this procedure is that it is minimally invasive

but distal thromboembolism can occur; therefore, it should be monitored closely by ultrasonography.

Septal Occluder Devices

Several occluder devices have been used in high-risk patients to treat aortic pseudoaneurysms. The decision on which type should be used is based on the size of the neck but also based on the location of the pseudoaneurysm. Quevedo et al. summarized 36 reported cases using Amplatzer Septal Occluder devices or vascular plugs to repair ascending aortic pseudoaneurysms, and successful deployment with only minimal residual shunt was reported in 75% of the cases. The Amplatzer Septal Occluder devices were used in 52.7% of the cases and Vascular plugs in 27.7% [1]. The use of septal occluder devices is not limited to small-necked aneurysms because they are available in different sizes and configurations. Nevertheless, the size of the pseudoaneurysms neck should be precisely measured before selecting the device [17]. The Amplatzer Septal Occluder is an occlusion device usually used for atrial septal defects. It self-expands and has a narrow connecting waist that links two discs together made out of a nitinol mesh [14]. To prevent any flow through the mesh, the parallel discs and waist are filled with polyester fabric [14].

Outcomes/Follow-Up

Several factors define the chances of a successful outcome, including size and location of the pseudoaneurysm as well as comorbidities of the patient. For high-risk patients, endovascular repair has evolved to be a good optional treatment. Many different techniques have emerged, but they all also bring along certain limitations, in combination with the already severe and risky condition of an aortic pseudoaneurysm. The mortality rate for thoracic aortic pseudoaneurysms was reported to range from 14.3% to 17.2%, and due to the rarity of this condition, there is almost no information reported on long-term outcomes [8]. Mulder et al. analyzed 158 surgical procedures for the repair of pseudoaneurysms that occurred after aortic reconstruction with prosthesis. The highest mortality rate accounted for patients receiving nonsurgical treatment (61%) mostly due to rupture. Operation was performed as an emergency in 25 cases, and the emergency mortality rate was 24% being higher than for elective procedures with 4.5% [12]. Concerning ascending aortic pseudoaneurysms, a study reported in-hospital mortality of surgical repair to range between 6.7% and 41%. The survival rates reached 94%, 79%, and 68% at 1, 5, and 10 years postprocedure [1]. There is still a paucity of long-term survival data regarding percutaneous therapies compared to significant data on survival benefit concerning surgical repair. However, as more cases of successful percutaneous techniques emerge to repair aortic pseudoaneurysms and more long-term data is provided, further prospective studies of percutaneous closure and surgical repair can be compared [1, 6].

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Ocular Diseases with Aortic Involvement

38

Robert J. Barnes

Introduction

Although rare, some serious aortic diseases, including aneurysms, dissection, and arteritis, can be initially discovered by a good ophthalmologic exam. This will be a brief summary of some of these examples.

Marfan Syndrome

Marfan syndrome is an inherited connective tissue disorder, which most commonly affects the eyes, heart, aorta, and skeletal tissue. Patients are disproportionately tall and thin, with long arms and legs, fingers, and toes. The eye exam may be the first sign of the disease to be discovered with patients presenting with high myopia and astigmatism. Half of the patients develop ectopia lentis, where the lens becomes dislocated at an early age. Patients have an increased risk of retinal tear or detachment, glaucoma, and cataracts in childhood. Cardiovascular complications of Marfan syndrome include aortic dissection and aneurysms near the aortic root.

Syphilis

The incidence of syphilis has been on the decline, but over the last 10 years, it is showing resurgence despite the era of good antibiotic treatment. The risk of new cases appears to be most commonly in homosexual males who are also HIV positive. The ocular findings include ectopia lentis in congenital syphilis, corneal interstitial keratitis, and chronic uveitis and retinitis. It is always included in the differential diagnosis of chronic iritis and retinal inflammation. Syphilis involving the aorta can be seen usually in the tertiary stage, which can be clinically undetectable. Tertiary syphilis usually causes an inflammatory arteritis of the aorta arch and leads to a narrowing of the vasa vasorum. Dissection of the aorta is rare, but because of the inflammatory involvement with narrowing of the lumen, standard angiography and angioplasty may be impossible. The ascending aorta is the segment most commonly involved, followed then by the arch, and lastly the descending aorta [1].

Rheumatic Diseases

Rheumatic diseases involving the aorta with ocular signs can include rheumatoid arthritis, lupus, Behcet's disease, ankylosing spondylitis, giant cell/temporal arteritis, Takayasu arteritis, Kawasaki disease, and Cogan syndrome.

Rheumatoid Arthritis

Rheumatoid arthritis frequently presents with ocular signs of anterior segment iritis and overall inflammation in the absence of a history of trauma, although rare patients can develop aortitis and aortic regurgitation [2].

Systemic Lupus

Systemic lupus erythematosus also presents with ocular manifestations first with again an anterior segment inflammation and photophobia. Younger patients with lupus who have been treated with long-term corticosteroids are at a higher risk for developing an aortic aneurysm, especially in the ascending aorta [3–5].

Behcet's Disease

Behcet's disease is a systemic vasculitis of unknown etiology that typically affects young patients, especially from countries in the Middle East and Far East including Turkey,

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Iran, Japan, and China. It is seen in both young men and women but usually more severe in young men. They present with recurrent oral ulcers, hand and skin lesions, genital sores, and ocular signs of inflammation. Patients with Behcet's disease present with a severe uveitis most commonly in both eyes and frequently develop a hypopyon. Vascular involvement in Behcet's disease is seen especially in young males reported to be 20–50% of patients. Arterial involvement is less common than venous involvement with a vascular thrombosis. Clinically significant aneurysms of the aorta have rarely been reported, but patients can be seen to develop a false aneurysm on x-ray [6, 7].

Ankylosing Spondylitis

Ankylosing spondylitis is an arthritis affecting the lower spine and the sacroiliac joints, with an associated HLA-B27-positive antigen more commonly in young males than females. Often the diagnosis is made by the ophthalmologist after a young male in his 20s presents with iritis, photophobia, and a vague history of a sore or stiff back. After blood testing for HLA-B27 and an SI joint x-ray, the diagnosis can be made. Patients with ankylosing spondylitis have been reported to develop a number of cardiovascular diseases including aortitis, aortic valve disease, and ischemic ocular disturbances. The primary aortic involvement in patients with ankylosing spondylitis is aortic insufficiency [8, 9].

Giant Cell/Temporal Arteritis

Giant cell arteritis is an inflammation of the small- and medium-sized arteries in older patients presenting with complaints of headache, jaw claudication, scalp tenderness, and sometimes vision loss. Ophthalmologists evaluating these patients rely on the history and physical exam but with an elevated sedimentation rate and C-reactive protein, and temporal artery biopsies, confirm the diagnosis, and 50% of patients with giant cell arteritis are associated with polymyalgia rheumatica. Inflammation of the aorta with aneurysm rupture, aortic valve regurgitation, and aortic arch syndrome has been reported. Patients should be followed up with serial chest x-ray [10, 11].

Takayasu Arteritis

Takayasu arteritis is a rare form of inflammatory arteritis with associated ocular findings. Unlike giant cell arteritis, which affects small- and medium-sized arteries, Takayasu arteritis involves large arteries. The typical patient with Takayasu arteritis is a young under 40-year-old female, often from Asia. Ocular signs can be seen from two different locations, with occlusive arteritis affecting either of the aortic arch branches, leading to an ischemic retina versus an arteritis affecting the renal artery and thus presenting with a severe and uncontrolled hypertension and signs of retinal venous distention and microaneurysms. Takayasu arteritis is commonly called the pulseless disease because of the difficulty in detecting peripheral pulses secondary to vascular narrowing. Takayasu arteritis is pathologically indistinguishable to giant cell arteritis. Fortunately, Takayasu arteritis is a very rare disease entity [12, 13].

Kawasaki Disease

Kawasaki disease, also called mucocutaneous lymph node syndrome, is another rare arteritis affecting blood vessels throughout the body, most commonly seen in children under the age of 5 years affecting boys more than girls and more commonly seen in Japan than in other countries. Patients present with high fever lasting beyond 5 days and red inflamed eyes with iritis and have large lymph nodes and classic strawberry tongue. It is the main cause of acquired heart disease in the United States and Japan, replacing rheumatic fever. Coronary artery disease aneurysms can occur in untreated cases as the most frequent complication, but both aortic aneurysms involving the abdominal aorta have also been seen [14].

Cogan Syndrome

Cogan syndrome is a nonsyphilitic inflammatory disease typically occurring in younger adults who present with eye and ear involvement. The clinical picture is more of a vasculitis, while the etiology is unknown. Ocular findings include a nonsyphilitic interstitial keratitis of the cornea and iritis, and the patients also have an associated Meniere's vestibular syndrome with progressive hearing loss to complete deafness in 2 years. Cardiovascular abnormalities are seen with aortic valve insufficiency, arterial stenosis or thrombosis, aortic arch syndrome, and renal artery stenosis [15, 16].

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Applications of 3D Printing for Aortic Disease

39

David J. Laczynski, Robert S. Dieter II, and Michael J. Javorski

Introduction

Advances in 3D printing have expanded our ability to diagnose and treat patients with aortic disease. 3D printing is a multidisciplinary approach that involves taking an image, most commonly from a CT or MRI scan, and recreating a virtual 3D model. This virtual model is then printed into a physical prototype that mimics the anatomic and tissue characteristics specific to that patient. The applications for 3D printing in cardiovascular medicine have been geared toward using anatomic models for pre-procedural planning and simulation, the development of patient-specific endografts, and resident and physician education.

Printing Process

SLS printers (Selective Laser Sintering) are the most common type of 3D printers used for medical purposes. To start, the build plate for the printer is loaded with a thin layer of powder (oftentimes powdered glass, ceramic, or plastic). A concentrated laser beam is shot at the powder at slightly under the powder's melting point, causing the powder to harden and fuse to other nearby powder particles. Once that layer is completed, the build plate moves down a fraction of a millimeter and reveals another thin layer of the powder. Again, the laser is shot at the powder to solidify it and fuse it to other nearby hardened particles. This process repeats until the print is completed.

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An alternative to SLS printing is SLA printing (Stereolithography). These printers utilize a liquid resin, which is UV sensitive. A build plate starts upside down, with its surface just barely touching the liquid resin in the chamber below. An ultraviolet laser beneath the resin hardens the resin onto the build plate, which then moves up to repeat the process. Although this type of 3D printing is less expensive, the prints require additional support material to go under large overhangs. Thus, the prints are not as precise and do not come off of the printer ready to be used immediately.

Preoperative Planning

Anatomic models are one of the most common uses of 3D printing in the surgical field. Preoperative planning with 3D printed models involves using patient-specific anatomic models to understand complex anatomy, simulate a given procedure, select surgical equipment, and act as an educational resource for residents and physicians. Such planning theoretically reduces operative risks associated with the given procedure and reduces operative time.

Despite the advancements in treatment for aortic disease, a significant number of patients remain with complex anatomy that inhibits the use of many of the new surgical devices, such as endovascular aortic repair (EVAR). An abdominal aortic aneurysm with a highly angulated or short aortic neck is a complex situation that requires careful preoperative planning. 3D printing is a tool that the physician can use in order to aid in the preoperative decision-making process. A 3D printed model of an anatomically complex aorta would aid the surgeon by giving a tangible identical representation of the patient's specific anatomy.

Physicians are already using this technology to simulate endovascular repair of thoracic aortic dissections and abdominal aortic aneurysms with complex arch and neck anatomy, respectively [1, 2]. With the 3D printed model, tissue consistency and sites of aortic plaque would be represented, which would allow the surgeon to simulate passing the endograft

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into the aorta and then deploying the device. The practice deployment of an endograft into a patient-specific aorta is an invaluable opportunity that allows the operator to safely determine appropriate positioning and feasibility of such a device creating adequate seal.

Creation of custom fenestrations in a fenestrated endovascular aortic repair (FEVAR) is another utility of 3D printing that can potentially save procedural costs and time and make minimally invasive aortic repair available to more patients. Limitations to FEVAR are long manufacturing and delivery times, which has led to some physicians creating on-site fenestrated grafts using standard commercial stent grafts. Traditionally, physician-modified grafts were made using manual measurements derived from CT imaging. However, this technique is time consuming and can lead to error in fenestration sites. 3D models can serve as patient-specific templates for the placement of fenestrations. This involves creating a 3D printed sleeve of the precise locations of major aortic artery branches specific to the patient's anatomy. The 3D printed sleeve is placed over an aortic endograft and fenestrations are made in the graft, thus creating a custom endograft designed specifically for the patient [3, 4] (Fig. 39.1).

Education

Beyond immediate preoperative planning, 3D modeling may prove to have utility in the training of the next generation of surgeons. Aortic models provide an excellent tool for surgical residents to simulate preoperative planning and deployment of endografts. A recent study comparing the utility of 3D printed models to 3D images for preoperative planning demonstrated that residents using models scored higher on their surgical plans when compared to colleagues using 3D images [5]. This could decrease the need for animal models and increase the variety of aortic anatomy residents would be exposed to before completion of training.

Limitations and Future Directions

In the past decade, reports on patient-specific 3D models have increased exponentially [6]. However, many experts urge cautious optimism with this technology due to several limitations. Accurate modeling requires high-quality CT images. Several factors from body habitus to arterial calcification can make this difficult. Recent studies have

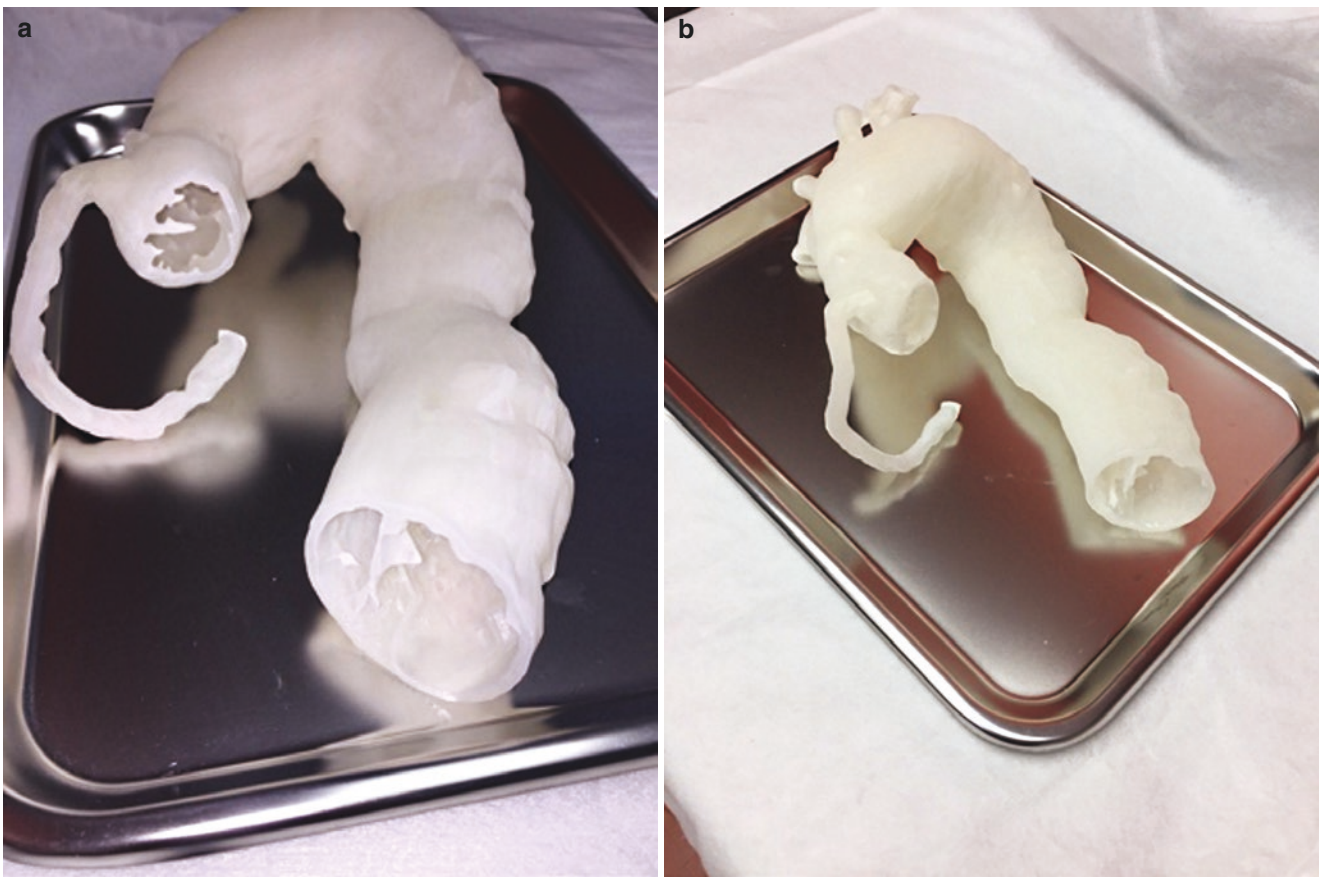

Fig. 39.1 (**a, b**) Examples of 3D printed aortic arches. (Courtesy of Mediprint.us)

found variance of model diameter compared to actual aorta to be greater than 1 mm [7]. While the technology has become more available and efficient, cost of hardware and materials to create models must be examined for long-term feasibility in a clinical setting. A newly arising issue, as the possibility of using these 3D models in vivo gets closer to reality, is finding materials that are nonimmunogenic, durable, and amenable to sterilization.

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Multidisciplinary Aortic Centers

40

Jocelyn K. Ballast, John R. Frederick, and Frank R. Arko III

Introduction

A multidisciplinary aortic center should be created with the goals of providing patients with quality cross-continuum care, advancing research, informing the development of innovative techniques, and contributing to the development of "best practice" standards of care by coordinating a multidisciplinary team of experts. Achieving this goal can be challenging, as it requires strong leadership and effective collaboration between all team members and stakeholders working toward a shared vision. However, it has been shown that there are many benefits (Fig. 40.1) [1]. Over time, as the center's organization, efficiency, capabilities, and quality of care improve, its reputation can be expected to grow. This enhanced reputation will increase the volume of the center and the institution, improving the financial performance of the center, as well as attracting new expertise and talent to join the team [2]. As the addition of expert physicians, researchers, nurses, and administrators contributes to the growth of the program, efficiency and organization will improve, strengthening the capabilities and capacity of the center. With volume increases, the center can also expect to have the opportunity to participate in clinical trials, conduct research, and establish registries, becoming a leader in research and promoting innovation. Protocols and best practice standards and systems will be developed, further improving patient care and spurring regional healthcare improvements. Innovative contributions to the field and the ability to offer high-quality care also build the strength of the institution. While the development of a multidisciplinary aortic center may have its challenges, examining current models and commonalities that lead to success will inform the direction of future centers to bring multidisciplinary, cross-continuum, high-quality care to aortic patients [3, 4].

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Business Model

Modern healthcare is able to provide specialized treatment of a wide range of pathologies. However, current models of healthcare tend to create isolated silos of care which make integrating patient care difficult and often result in redundancy and delay. Coordinating specialists to create an integrated practice unit focused on a particular patient population is a major challenge faced in creating a multidisciplinary center. It has been shown that multidisciplinary teams are capable of providing an improved quality and value of care, but formulating business models and effective strategies to implement the creation of a center can be difficult, as diverse designs can be successful and there is not yet a standard model to emulate [5].

Why Multidisciplinary?

There are many benefits of having a multidisciplinary team involved in patient care [6]. It allows for the holistic treatment of a patient's pathology, identifying contributing factors and caring for related complications. It encourages a cross-continuum of care, providing a streamlined, coordinated approach to treatment that encompasses initial screenings and diagnoses and longitudinal follow-up. A matched, cluster-randomized, controlled trial in Europe found that a multidisciplinary approach to preventative cardiology improved standards of care and outcomes while reducing risk factors for cardiovascular disease [7]. Similarly, Schoenhagen and colleagues recommended a multidisciplinary approach to improve the effectiveness of CT systems,

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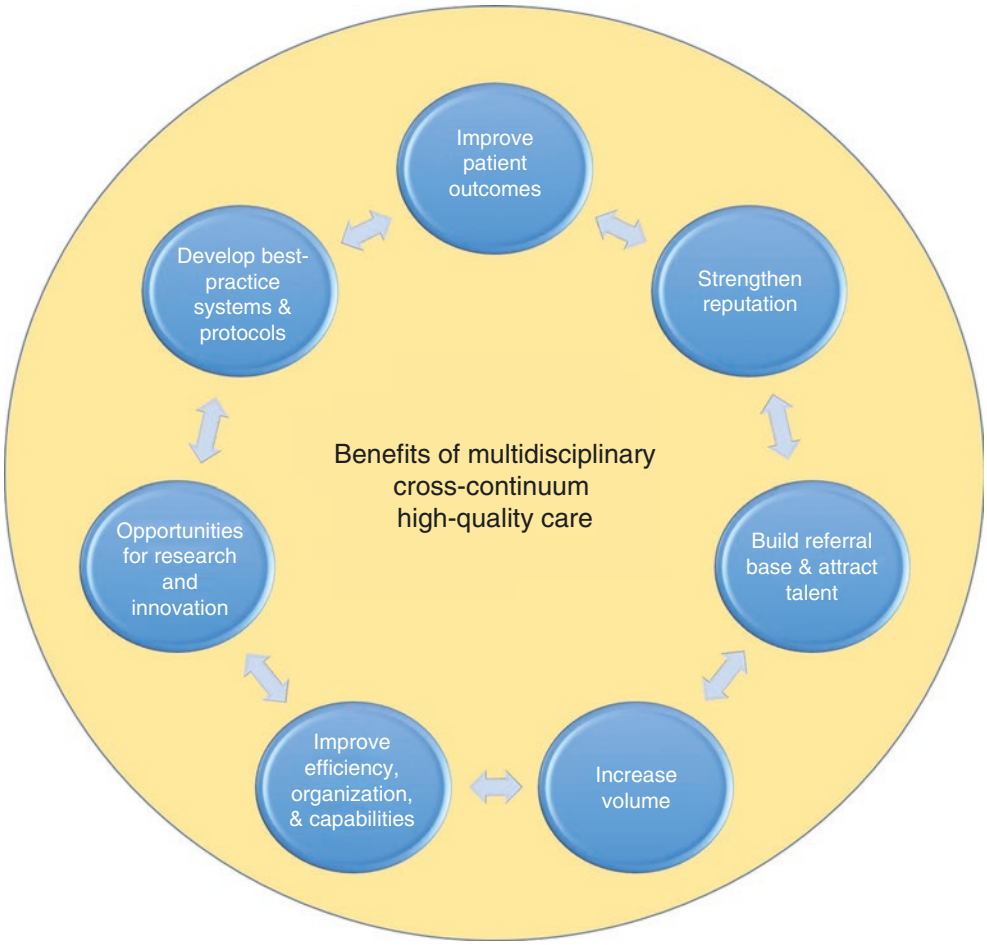

Fig. 40.1 The benefits of developing a multidisciplinary aortic center. Building a multidisciplinary aortic center improves a center's capacity and ability to provide quality care in a multidirectional way. Improving patient outcomes strengthens the center's reputation, increasing volume in such a way that best practice systems and protocols are improved, along with the capacity to provide quality care, thus further improving patient outcomes

improving education and training for physicians and technologists [8]. A study at the Medical College of Wisconsin emphasized that the complexity of hypertension made a multidisciplinary approach a major contributor to improving blood pressure levels in a primary care setting [9]. The Medical College of Wisconsin also found that a multidisciplinary clinical approach lowered risk for heart disease in obese patients with metabolic syndrome [10]. These and other studies have demonstrated that multidisciplinary care increases overall health and has the capacity to improve patient outcomes [11].

Business Models and Strategies

Multidisciplinary aortic centers can have diverse models and be successful. For example, some organizations temporarily convene small teams to redesign specific processes, while others have more permanent design structures to manage multidisciplinary teams [12]. However, several common strategic elements, as outlined by Richard Bohmer of the Nuffield Trust, have shown to be effective in reconfiguring systems and designing multidisciplinary centers to improve healthcare [13]. Bohmer found that effective transition to a multidisciplinary model of care is typically led by clinicians, with an aim to improve quality and efficiency simultaneously and a unifying set of values and norms. Successful models also rely on internal support resources for design, project management, analysis, and organizational development, rather than contracting management consultants. Finally, effective centers have routinized processes for management of patients that are internal and consistent, to enact repetitive, incremental changes that lead to long-term success. However, gradual transformation that builds on existing structure may not be sufficient to create a successful center, as moving toward a system that provides effective value-based healthcare often requires large-scale changes in strategy and organization.

Planning and Buy-in

In developing an aortic center, planning is essential. Conducting a market analysis provides an understanding of epidemiologic trends of aortic disease in the targeted population, patient demographics, and referral patterns. This analysis

will provide vital information about the form that the aortic center should take, along with what services it should consider providing. Identifying current awareness and diagnosis of aortic pathologies, along with identifying existing local clinics and facilities, can inform outreach and inter-facility cooperation and education efforts, along with facilitating future referrals. Such information regarding geography and possible patient volume will allow identification of a need in the community, but should not be the only thing informing the creation of an aortic center. Internally, institutional inventories can anticipate barriers and provide information about the current state of the organization, including individual and team perceptions and expectations. An institution should consider its capacity to provide needed services in all stages of a patient's care and its ability to engage patients. Evaluating the existing institutional strategies and goals will encourage buy-in and support, as it allows for the creation of a business plan and care delivery model that aligns with the system's vision and strategy, providing clear benefits to the system along with positive patient impact and clinical benefits. Further planning will address the center's structure, the extent and range of involvement of clinical specialists, the support staff required, equipment and technology needs, and points of access to the center.

How to Build a Multidisciplinary Aortic Center: Multidisciplinary Team

Developing a multidisciplinary aortic center will require a thoughtful, collaborative design. The design team should follow a multidisciplinary approach to identify resource needs and achieve buy-in from all team members. Stakeholders in various disciplines should be identified in order to integrate their expectations for the center into the design, encouraging more coordinated efforts and collaboration once implementation is underway. In particular, identifying committed vascular and cardiothoracic physicians is of utmost importance, and a multidisciplinary team should be assembled in order to provide cross-continuum of care. Organization of governance and infrastructure should begin with administrative buy-in to establish effective dyad leadership. Achieving buy-in with administration, system leadership, and other team members is essential in the development of the center, as it allows the orchestration of team planning and personnel training, along with facilitating appropriate resource deployment [14].

Governance

The dyad leadership model has been proven effective in healthcare settings and should be implemented in developing an aortic center [15]. As one of the most important intra-organizational relationships, the physician-administrator collaboration allows the merging of core strengths between the two roles to provide a balanced approach to leadership. Physicians contribute to the dyad with their focus on clinical and surgical factors, along with their knowledge of academic research and expertise in specialty systems and strategies. They are also aware of the resources and staff needed to ensure a successful center. Administrators contribute their expertise in business strategies, organizational operation, and awareness of the institution's strategic direction and goals. The collaboration of these two roles allows effective leadership in managing the responsibilities of quality improvement, protocol development, evidence-based practice, resource utilization, cost control, advocating vascular initiatives, and clinical program review, along with management of medical staff relations.

Vascular Team

The vascular team, consisting of experienced vascular and cardiovascular physicians, physician assistants, nurses, and team coordinators, should be the leader in providing quality care and options for patients. Identifying key physicians is especially important in the development of an aortic center, as they hold the main responsibility for clinical decision-making and are instrumental in assisting and training staff to diagnose, treat, and care for patients. Physicians also facilitate the implementation of clinical best practices and ensure appropriate application of novel techniques and treatments. Key physicians should be adept at fostering communication, since they act as a liaison between staff and administration, interface with industry partners, and, of course, collaborate with patients and caregivers.

Services Offered

In order to be a go-to provider, a multidisciplinary aortic center should offer treatment for a range of conditions. They should be able to offer comprehensive evaluation and management of vascular disease, being prepared to provide quality treatment for aortic valve disease, peripheral vascular disease, ischemia and claudication, and a range of other inflammatory, immune, and genetic diseases of the aorta, including aneurysm, dissection, and associated pathologies. In order to provide services for these conditions, appropriate technologies and techniques should be available. The vascular team should be trained in endovascular, open, and minimally invasive approaches, including percutaneous trans-catheter valve therapies. Industry partnership will also be essential, as an aortic center should have access to a range of graft options for endovascular repair, as well as for aortic arch repair. Advanced techniques for cerebral and spinal

cord protection should also be available. Appropriate imaging modalities for pre- and intraoperative needs should be available, including transesophageal echocardiogram (TEE), computerized tomography (CT), computed tomography angiography (CTA), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), 3D reformatting programs, ultrasound, fluoroscopy, and intravenous ultrasound (IVUS). Finally, investment in the creation of a hybrid suite (as discussed in the *Intraoperative Care* section) is recommended. Appropriate staff to provide monitoring and care at all stages of treatment is essential and should involve vascular-specific training.

Elevating Credentials

It is important to elevate credentialing standards for vascular involvement in order to promote quality improvement. Physicians are leaders in aortic centers, with their clinical, surgical, and academic expertise allowing them to direct the development of the center and collaborate with the health care team, referring physicians, industry partners, and administration. Raising standards for physicians ensures that these leaders are highly qualified in vascular initiatives and interventions. Board certification is one essential step to ensuring high standards in vascular involvement. Currently, board certification in the United States is the responsibility of the American Board of Surgery, with certification in vascular surgery overseen by the Vascular Surgery Board and certification in cardiothoracic surgery overseen by the American Board of Thoracic Surgery. Currently, surgeons seeking certification must first complete an Accreditation Council for Graduate Medical Education (ACGME)-accredited residency program in both general surgery and vascular or thoracic surgery. However, board certification paradigms may be shifting to provide several alternatives to the traditional training courses, providing a shorter and more specialized program for both cardiothoracic and vascular surgeons [16]. Further options to consider include certification by the American Board of Internal Medicine and the American Board of Vascular Medicine, both of which assure expertise in medical specialties, thereby raising standards and elevating credentials. Fellowship training is another important consideration for an aortic center. A meta-analysis of 23 studies exploring the structural and surgeon-specific characteristics of fellowship training on patient outcomes found that fellowship training appears to have a positive impact on patient outcomes, with rates of mortality, conversion to open surgery, and complications all reduced in centers with an affiliated fellowship training program [17]. Other strategies to elevate credentials may include case review participation, complex case consultation, and procedure-specific privileging. All these methods increase quality of care by increasing the expertise offered by physicians in the aortic center. The center's standards of excellence and credentialing requirements for vascular involvement should be established as part of the development of a multidisciplinary aortic center.

Equitable Case Distribution

While all physicians in an aortic center should be credentialed and capable of performing surgeries according to their specialization, planning for equitable case distribution is necessary to assure timely, high-quality patient care. Patients requiring uncomplicated standard procedures should be seen in an aortic clinic. If no specific referrals have been made by primary care providers, these cases may be distributed equally to physicians, based on the availability and ease of getting into the clinic. More complex cases may be referred initially to a particular surgeon, or they may be discovered to be more complicated upon complete workup in the clinic. In these situations, aortic case conferences may provide support internally for surgeons to plan complex interventions, while also providing the opportunity for internal referrals to physicians with more expertise.

Specialists and Support Staff

Aortic disease is correlated with a range of comorbidities and complications that extend beyond the scope of surgical vascular intervention. Common comorbidities between vascular disease, coronary artery disease, and cardiovascular disease have long suggested the benefits of integrating cardiovascular tactics [18–20]. While cardiac and vascular surgery play a critical role in an aortic center, collaboration with other clinical specialists can bring further benefits by providing an integration of care addressing all aspects of aortic pathology. In order to provide quality cross-continuum of care for patients, the multidisciplinary approach involves a range of specialists and support staff in a patient's care (Fig. 40.2).

Radiology and Cardiovascular Imaging

Streamlining diagnosis of aortic disease is urgent, as some pathologies involving aortic disease have high morbidity and mortality rates if left untreated [21]. Imaging teams should work closely with vascular teams to identify existence of, location, and severity of the patient's presenting pathology, enabling timely planning of care and treatment. They should be especially adept at distinguishing types of dissections and identifying ruptures and should be able to provide information essential for endovascular planning, such as feasibility of arterial access, landing zones for graft placement, and necessity of debranching. Radiology teams should base their appropriateness criteria on current and relevant data, considering cost, risks, and other factors to determine the proper

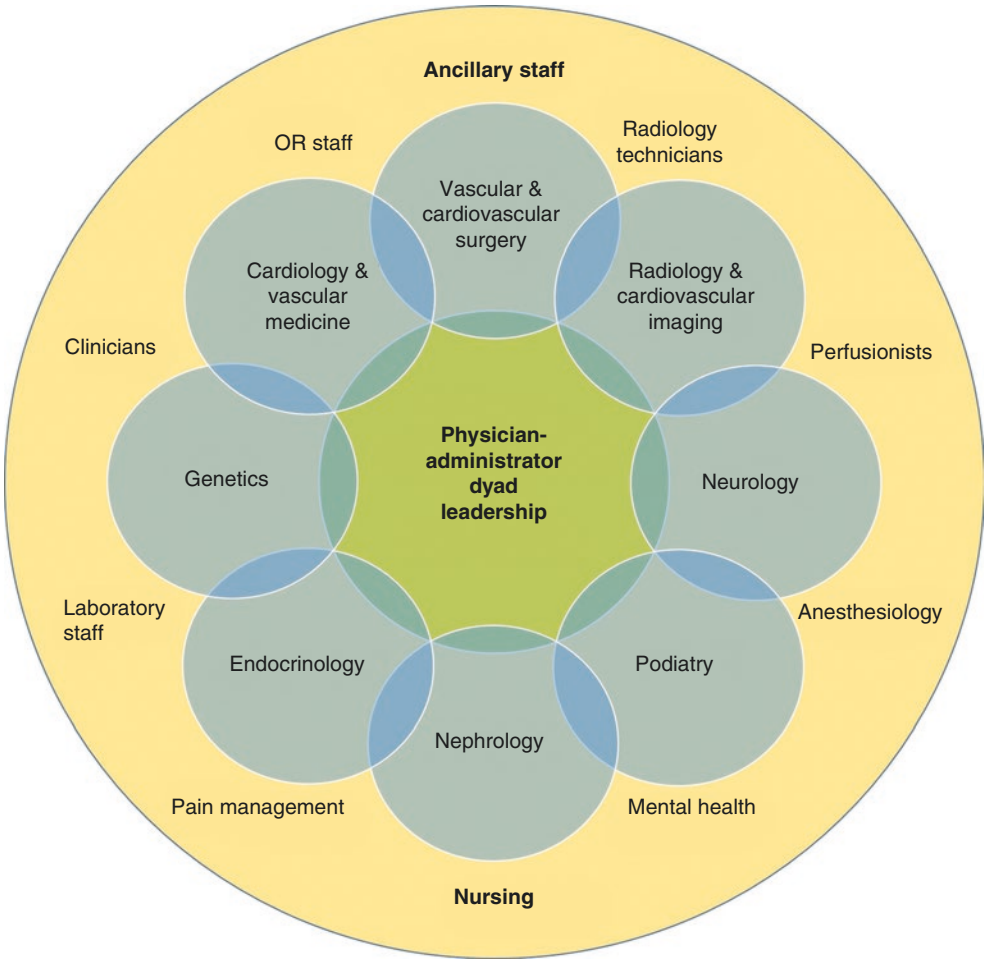

Fig. 40.2 Specialists and support staff. A multidisciplinary center integrates experts in all aspects of patient care under dyad leadership to provide a cross-continuum of care that addresses the often-overlapping needs of aortic patients

indications for each imaging modality [22]. Education and cross-training will ensure that imaging and radiology specialists are able to provide accurate diagnostic imaging to physicians, contributing this essential service to the multidisciplinary team.

Other Specialists and Staff

Cardiology and Vascular Medicine

Integrating cardiology and vascular medicine into the service line should also be addressed in the creation of a multidisciplinary aortic center, as early diagnosis, risk factor modification, and medical management may provide procedural alternatives. Cardiologists and vascular medicine specialists provide cardiac clearance, blood pressure control, cholesterol control, and ongoing surveillance of contributing risk factors, preventing further disease progression along with stabilizing patients to ensure the success of interventions. Medical management is the recommended first line of treatment for some aortic pathologies, further increasing the importance of having vascular medicine and cardiology integrated into the care provided by the aortic center [23].

Geneticists

Genetic testing may improve early diagnosis by identifying genetic risk factors for aortic disease and complications. Genetic connective tissue disorders such as Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, and Turner syndrome increase the risk for dissection and aneurysm [24]. Positive family history of aortic disease also predisposes patients to aortic disease and complications. Involving geneticists in the multidisciplinary team can improve the awareness of genetic disorders and family history, which is critical in informing screening and care plans for at-risk patients. Geneticists should also provide genetic counseling to at-risk patients.

Nephrology

Nephrology specialists should be intimately involved in the multidisciplinary center, as risk for aortic disease is highly associated with complications involving the renin-angiotensin system such as hypertension and kidney disease [25]. Renal insufficiency and kidney disease may also come about secondary to aortic disease causing stenosis or malperfusion, or secondary to complications from aortic intervention, such as coverage of renal arteries or thromboemboli.

Because of the interconnection of these two systems, nephrology experts should encourage preoperative awareness of creatinine levels and be involved in any complex interventions involving visceral arteries. Having nephrology specialists involved also reduces time to postoperative dialysis, should it become necessary. Screening patients with chronic kidney disease or end-stage renal failure for aortic disease may also be beneficial in identifying patients who may require aortic intervention.

Neurology

The involvement of neurology is especially critical intra- and post-operatively, as spinal cord ischemia and stroke are risk factors in many aortic cases. Neurology should be aware of these potential risks and be prepared to advise spinal drain placement or management of stroke secondary to micro-emboli. Because of the neurological symptoms present in pathologies such as dissection or stenosis, neurology may also be called upon to assist in diagnosing and characterizing a case.

Endocrinology

Similarly, involvement of endocrinology specialists in the multidisciplinary team will benefit diabetes patients, along with patients suffering from other endocrine system-related diseases or disorders whose hormonal imbalances contribute to their risk for aortic disease. Because hypertension, cholesterol imbalances, diabetes, and metabolic disorders are so closely associated with cardiovascular disease, a multidisciplinary center whose team involves endocrinology is able to address not only the presenting symptoms and pathologies but also the contributing risk factors.

Support Staff and Nursing

A multidisciplinary aortic team involves more than just clinical specialists and vascular physicians. A multidisciplinary aortic center should provide for adequate and properly trained ancillary staff, along with more specialized support staff. This may include physicians' assistants, anesthesia assistants, radiology technicians, laboratory staff, operating room staff, and perfusionists. Although specialists are leaders in planning and administering treatment and care, providing insight and expertise, having a team of vascular and cardiac-trained nurses is also crucial to the success of the aortic center. Since the nursing staff is involved in the day-to-day care of patients, building and educating a team of nurses with an understanding of aortic disease in particular is necessary in order to provide a cross-continuum of care. Having adequate mental health and pain management support is also necessary. Establishing multidisciplinary rounds will allow all providers involved in a patient's care to remain informed about a patient's case [26].

How to Build a Multidisciplinary Aortic Center: A Cross-Continuum of Care

The staff and equipment involved in multidisciplinary cross-continuum of care should ensure quality care from initial patient contact to full recovery and beyond. Planning of a multidisciplinary center, therefore, should address simple pathways of access to the aortic center, methods of patient identification and attraction, preoperative planning and preparation, intraoperative excellence for successful intervention, postoperative wound care, longitudinal follow-up, and regular surveillance and management of risk factors (Fig. 40.3).

Patient Identification: Community Outreach and Education, Screening, and Referrals

In order to be successful, a multidisciplinary aortic center should put effort into early patient identification. Marketing and outreach efforts, screening, and education opportunities for physicians and communities can improve disease awareness and identify at-risk patients. This early identification provides an opportunity to educate at-risk populations in order to slow or prevent disease progression through self-management. Not only is this beneficial for patients who may be able to prevent vascular disease, it is likely to lead to improved outcomes because of the potential for early diagnosis. As late diagnosis is associated with decreased effectiveness of medical management, a greater need for procedures, higher complication rates, and increased total cost of care, ensuring early diagnosis, may provide higher patient satisfaction as outcomes improve [27].

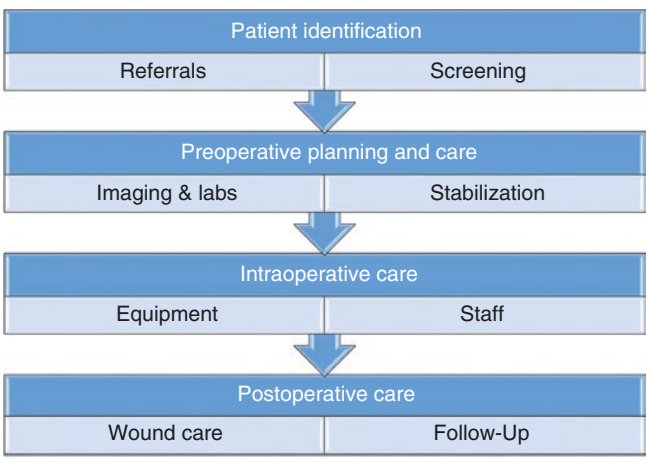

Fig. 40.3 A cross-continuum of care. An aortic center should have the capacity to provide a cross-continuum of care, from patient identification, preoperative planning, intraoperative excellence, and longitudinal follow-up

Marketing and Outreach

Marketing and outreach aim to improve health, increase community and patient awareness, and also attract more patients and referrals to a center, resulting in overall program growth. Internal marketing may also be beneficial in improving patient experience [28]. In-person visits to primary care providers and outside clinics will develop a network of access to the center, while hosting educational seminars can raise community and care-provider awareness of disease. In order to improve patient identification, it may also be beneficial to pursue outreach opportunities with organizations in the community. Connecting with populations identified by the American Diabetes Association, the American Lung Association, the American Heart Association, and the American Association of Retired Persons can provide opportunities to reach patients with comorbidities associated with vascular disease, leading to higher patient identification.

Once target populations have been identified, providing printed reference materials can be a beneficial marketing strategy. Providing primary care providers and outside clinics with materials such as reference cards, brochures, screening vouchers, and preprinted referral forms can be beneficial, as it decreases obstacles to referral and uncertainties about treatment. Printed materials should educate about disease, along with presenting information regarding the services and procedures offered at the center. Other marketing initiatives may include newsletters, digital marketing, and print advertising in publications directed at consumers and physicians. Effective marketing will establish and expand the referral base and improve the regional quality of care as the aortic center becomes an outlet for emergency departments and primary care providers.

Education

Beyond marketing efforts, education will improve community and physician awareness of disease, resulting in increased early identification. Patient education can also play a critical role, as it facilitates behavioral changes necessary to improve outcomes [29]. It has been found that patient literacy levels impact the effectiveness of education materials such as pamphlets, since patients may not have adequate comprehension of the materials, negating their effectiveness [30]. Ensuring that patient education literature is written at an appropriate reading level is thus very important in improving understanding and awareness of disease. Educating and supporting primary care and emergency department physicians in vascular patient identification is also essential. This education can improve the likelihood of prompt and accurate diagnosis of vascular disease since patients often fail to report symptoms and existing symptoms may be attributed to other causes unless patients and care providers are educated on signs and symptoms. While some education may take the form of marketing materials, an effective multidisciplinary center will take advantage of the opportunity to educate at-risk populations in clinics, community screenings, and every patient interaction.

Screening

It is important to establish system-wide high value screening strategies using clinical, behavioral, and social risk factor data to identify patients likely to develop vascular conditions. Untargeted vascular screening is often ineffective, with poor public awareness of vascular risk factors and inefficient resource utilization hindering the identification of asymptomatic patients [31]. Increasing system-wide awareness of available screening options will improve patient identification. In 2006, the Screening Abdominal Aortic Aneurysms Very Efficiently (SAAAVE) Act was passed, qualifying seniors with a family history of AAA or a significant history of cigarette usage to undergo a one-time free AAA screening. However, according to a 2012 study of Medicare enrollees from 2004 to 2008, this preventative benefit was not shown to have any effect on AAA rupture or all-cause mortality [32]. Additionally, Medicare data comparing pre- and post-SAAAVE Act utilization of AAA-related diagnostics and treatment revealed a very low increase in AAA screening, with AAA-related use of abdominal ultrasound decreasing and repair procedure rates remaining constant [33]. Another study evaluating the implementation of SAAAVE found that out of a total of 9788 male smokers who were screened through the Veterans Affairs Healthcare Network over a 5-year period, a total of 2828 patients were inappropriately screened, and 121 patients without aneurysms had multiple screenings [34]. These findings suggest that further education could increase the effectiveness of the SAAAVE initiative, since currently the AAA screening benefit has been under- and inappropriately utilized.

Referrals

Successful marketing of the aortic center will establish and strengthen relationships with potential patients and their other care providers, increasing the visibility of the center and increasing the number of referrals. Incorrect referrals can result in delayed procedures, higher costs, and worse outcomes for patients, while many visits may be unnecessary due to incorrect referrals. Streamlining and simplifying referral processes ensures that access to the aortic center is targeted and effective. Referral strategies may be revised by implementing a protocol to create a single point of referral for all vascular cases through a vascular clinic. Adjusting referral interfaces and arranging the availability of a vascular specialist able to discuss cases with referring physicians may prevent delays in care and ensure that patients are referred to the correct departments for care appropriate to their diagnosed pathology.

Preoperative Planning and Care

Early identification not only allows prevention of aortic disease, but it also allows patients to receive proper preoperative care. Preoperative care in a multidisciplinary center should allow effective stabilization and preparation of patients preparing to undergo surgical intervention. This care may include imaging and laboratories to provide accurate diagnoses and characterization of a patient's condition, blood pressure management, and blood/fluid initiation. Such involvement provides necessary information to physicians about whether intervention is needed and the urgency of such intervention and prepares patients for potential intervention by initiating preoperative procedures, consults, and stabilization. Preoperative care may also include a presurgical pathway for elective repair, addressing behavioral risk factors, improving fitness, and reducing frailty. This type of preoperative care may include physical and medical rehabilitation, pulmonary medicine, and physical and occupational therapy, increasing exercise capacity and improving health to reduce the risk of complications and improve procedural outcomes. Preoperative planning and care should also address initial interactions in emergency situations. ED protocols should be implemented for patients arriving directly to the emergency department or for referrals made from other emergency department facilities. Proper protocols ensure that the aortic team is notified of vascular patients in a timely manner and that the OR team can be activated and prepared for emergent interventions. Planning should be done to implement protocols for nursing and intensive care unit staff to ensure that the appropriate preoperative services are provided to all patients.

Intraoperative Care

Establishing an aortic center requires proper equipment and staff that are available for intraoperative care. The operative team, which includes surgeons, interventionalists, anesthetists, and nurses, should be at hand as well as ancillary staff such as anesthesia assistants, radiology technicians, laboratory staff, and perfusionists. Proper equipment should also be available and necessary training completed for the effective use of such equipment as contrast injectors, IVUS, transesophageal echo, any endovascular devices, open operative instruments, and perfusion services/pump. In the long term, resource investment in developing a hybrid suite may support the goal of efficiently providing patients with all available diagnostic and treatment options [35]. Hybrid suites combine traditional operating room imaging and anesthesia support with angiography, allowing multidisciplinary interventions to occur in a single location. The wide range of procedures accommodated by hybrid suites improves efficiency since a variety of open and endovascular procedures may be performed in parallel, minimizing time and reducing the risk of complications. As part of a multidisciplinary aortic center, the hybrid suite is significant because it allows interdisciplinary efforts to occur in the same room, as specialists are able to collaborate in a patient's care. While costs for a full range of capabilities and technologies in a hybrid suite may be prohibitive, the advantages may lead to improved outcomes and reduced costs per case, resulting in a significant long-term benefit [36–38]. Initial capital investment may be high, but the investment in appropriate technology ensures the high quality of intraoperative care that distinguishes high-volume aortic centers.

Postoperative Care: Longitudinal Follow-Up and Surveillance

Multidisciplinary specialist involvement is essential for effective postoperative care of vascular patients. The multidisciplinary approach ensures that all aspects and complications of a patient's pathology are addressed. Specialists in pulmonology, nephrology, neurology, critical care, general surgery, and other disciplines provide their expertise in planning and assessing rehabilitation needs, establishing a high quality and range of care.

Long-term follow-up and care should be an integral part of a multidisciplinary aortic center. An aortic center should provide ongoing outpatient education to patients and caregivers and maintain communication with primary care providers and referring physicians. Depending on the condition, follow-up may include imaging to determine sizing changes or progression of disease. Post-intervention imaging should identify possible endoleaks, graft migration, and aneurysmal degeneration, along with any ischemic complications. Follow-up labs may also be useful in determining any complications secondary to the intervention. Surveillance of hypertension and high cholesterol, both as contributing factors for aortic disease, should be consistent and include medical management. Other team contributions to long-term care may include coordinating with rehabilitation facilities [39], advising pain management, and encouraging mental health support [40]. Consistent follow-up not only contributes to a true cross-continuum of care but also provides longitudinal data useful for quality control and outcome studies. Postoperative imaging and laboratory evaluation, along with ongoing surveillance and support, will result in improved long-term care, improving outcomes.

Postoperative Care: Longitudinal Follow-Up and Surveillance

Coordination of clinical specialists is one of the most challenging and integral parts of developing a multidisciplinary aortic center. Communication between specialists may be

difficult to facilitate but is essential in developing seamless, cross-continuum of care. Collaboration and interdisciplinary communication may be promoted by the utilization of care coordinators, establishment of an aortic clinic, and the use of case conferences, along with development of protocols standardizing and streamlining pathways of care.

Administration

Administrators have an important role in facilitating collaboration, providing oversight, and supporting program development. In order for the multidisciplinary team to function smoothly, administrators and administrative assistants manage organizational and functional aspects of a center and enable the coordination of specialists in patient care. Traditionally, the relationship between administrative management and physicians has been complicated by differences in fundamental values, strategies, thought patterns, and culture [41]. Interdisciplinary cooperation will require bipartisan investment in creating functional relationships in which there is appreciation of the value of each area of focus. This should start with the development of a dyad leadership relationship, which will model collaborative communication and behaviors. Collaborative leadership encourages cooperation and understanding between different parties to achieve common goals, which should be outlined in the development of the center [42]. In the creation of a multidisciplinary center, it may be helpful to involve administrators with experience in both health science and business to improve health practitioner acceptance rates [43].

Care Coordinators

Care coordinators ensure that patients see the right specialists at the right time, coordinate longitudinal care and follow-up, and embed medical management into patient care plans. They also provide an interpersonal continuity, becoming a touchpoint for patient interaction. Several studies have found that having a patient cared for by the same team over time can increase patient engagement and has been shown to improve long-term outcomes, especially in the management of chronic conditions [44, 45]. To this end, care coordinators should maintain comprehensive knowledge of cases, rounding regularly and interacting with patients to act as liaison and educator between patient and staff. They should also collaborate with nursing leadership to maintain patient satisfaction, along with facilitating communication between various members of the multidisciplinary team. In a multidisciplinary aortic center, with its necessary collaboration between diverse specialists, having a care coordinator to monitor patient progress, streamline care provision, and communicate patient status with all service providers involved can ensure quality of care and efficiency of team members.

Case Conferences

Multidisciplinary collaboration may also be fostered with the establishment of regular case conferences and meetings to represent the needs and perspectives of all stakeholders, involving stakeholders in plans for care and increasing interdisciplinary education and awareness. Case conferences involving representatives from multidisciplinary care teams should be integrated into the care pathway in order to develop a plan of care and should be aimed at complex cases, repeat cases, and new diagnoses. Such conferences provide structure for case management and treatment plans, ensure that a holistic approach is maintained, and promote consistent follow-up and review for long-term care. Discussions may also address logistics, technology and equipment, procedures, and other topics relevant to team mobilization. In chronic care models, attendance to meetings in order to facilitate this type of integration of care has been underfinanced in the past, suggesting that this may be an area to focus on improving in the future [46]. Identifying and anticipating potential barriers to collaboration, then proactively clarifying protocols and best practices while also improving team and patient education, will promote collaborative team interaction, improving patient care [47].

Protocol Development

Developing and implementing standardized protocols for patient treatment facilitate multidisciplinary collaboration and streamline patient care by mapping care pathways. The creation of regional systems that utilize standardized protocols and invest in educating community ED physicians and primary care providers has also been shown to improve patient care by reducing critical time segments by shortening time to diagnosis, medical management, and further treatment [48]. For example, at Carolinas Medical Center in North Carolina, a “code rupture” protocol was implemented in May 2011, utilizing a multidisciplinary team approach to standardize and streamline communication, registration, and rapid initiation of care. Since its initiation, the protocol has achieved a 75–90% reduction in time from OR door to incision time and has increased the education and awareness of ED physicians and key staff [49]. A study from the Minneapolis Heart Institute at Abbott Northwestern Hospital involving 32 community hospitals examined the effects of implementing a standardized acute aortic dissection (AAD) protocol to improve AAD care pathways and processes. The study concluded that creating such standardized

approaches that targeted infrastructure, clinical care, systems, education, and electronic tools did improve patient care by decreasing time to diagnosis and surgical repair and increasing the use of beta blockers and intraoperative TEEE imaging [50]. Multidisciplinary centers should thus develop protocols to standardize and streamline pathways of care.

Protocols may address elective and emergent cases, along with functional aspects of care. An aortic center should develop elective and functional protocols to structure and organize diagnostic processes, basic procedural techniques, OR and ICU care, and postoperative management. Protocols for initial treatment should address radiologic evaluation, initial stabilization, and management. Functional protocols may address ventilation weaning and extubation, along with pain and blood pressure control. Emergent protocols such as "code aorta" or "code rupture" streamline patient transport, imaging, and team mobilization, creating a life-saving reduction in time from presentation to intervention. Emergent protocols should address what tests should be done and what criteria a patient should fulfill in order for a code to be called, along with outlining patient transport and team activation (Fig. 40.4). Once implemented and proven efficient in the setting of the aortic center, emergent protocols should be offered and implemented in surrounding institutions and the community in order to provide rapid diagnosis, transport, and treatment to a wider radius of patients.

Aortic Clinics and Electronic Health Records

Developing an aortic clinic may be beneficial to the center and institution at many levels. An outpatient clinic provides opportunities for outreach and screening initiatives, as well as clinical education programs. A clinic can provide a simple point of contact for referring physicians, emergency departments, and patients while also standardizing pre- and postoperative testing and surveillance. Creation of a clinic within the multidisciplinary aortic center provides an information link with surrounding facilities and within the center itself, allowing the integration of information from referring physicians and multidisciplinary experts. The

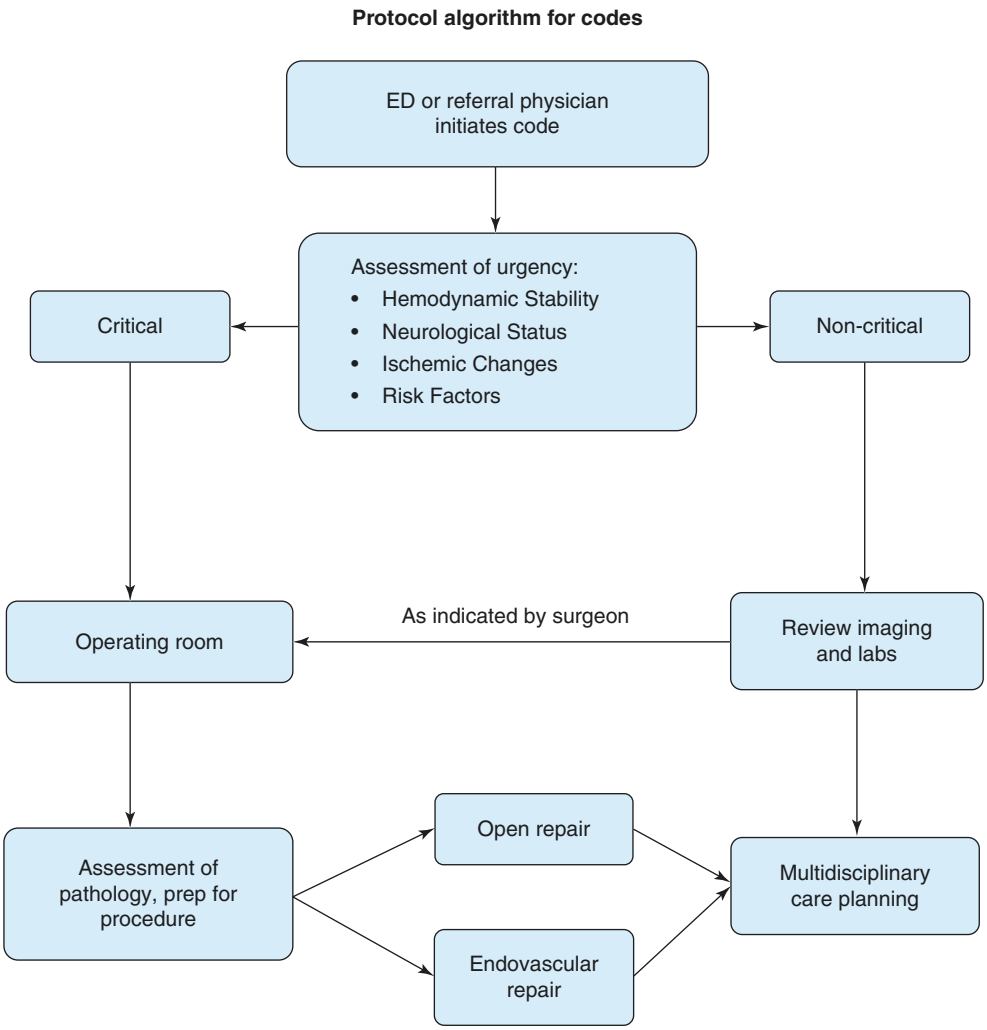

Fig. 40.4 Protocol design. Any protocol or code should standardize and streamline care for patients. In a multidisciplinary center, the importance of effective protocols is increased, as the wider range of specialists involved in patient care necessitates planning for pathways of collaboration

adoption of electronic health records (EHR) may be key in improving communication and collaboration in a multidisciplinary center and its contributing network. In a clinical care setting, EHR allow everyone involved in a patient's care to easily access relevant information, streamlining care by preventing redundancy and ensuring timely and accurate documentation. In 2012, less than half of US hospitals had successfully implemented EHR, suggesting that this may be an area to target in small and rural hospitals, to provide external as well as internal continuity [51]. However, the use of EHR is increasing due to financial incentives for EHR who fulfill "meaningful use" criteria [52]. The creation of a clinic, along with the use of EHR, contributes not only to quality and coordination of care but also to the quality of information provided for research using an aortic database.

Benefits of a Growing Program

There are many benefits in developing a multidisciplinary aortic center. The increase in volume as reputation increases improves patient outcomes and provides research opportunities. Multidisciplinary centers also have the capacity to improve patient satisfaction, an increasingly important consideration in the shift to value-based reimbursement. Despite the high initial capital investment, multidisciplinary centers have the potential to produce returns on investment, providing system-wide benefits for the institution and its contributors.

Volume and Outcomes

Increased physician and hospital volume has been associated with improved patient outcomes, possibly due to the expertise generated by repetition of highly specialized procedures [53–55]. There has been a trend in recent years toward the regionalization of AAA repair, with the percentage of AAA repairs performed at high-volume centers increasing from 12.9% to 30.9% between 1998 and 2004 [56]. In a 2009 study utilizing the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample, McPhee and colleagues found that high-volume centers and teaching institutions were associated with lower mortality rates in patients undergoing endovascular repair for abdominal aortic aneurysms [57]. In 2002, a study using information from the national Medicare claims database and Nationwide Inpatient Sample examined the mortality rates associated with six types of cardiovascular procedures as they related to hospital volume. Although the percentage of mortality rate decrease associated with high-volume hospitals was less than 2% in some procedures, the consistent decrease in hospital mortality rates further supports the trend toward performing complex cardiovascular procedures in high-volume centers to improve outcomes [58]. In fact, a 2014 analysis of Medicare claims mortality data [59] and an analysis conducted by the nonprofit Leapfrog Group [60] both found an inverse relationship between institutional volume and mortality in a range of surgical procedures. Although there is some controversy surrounding this issue [61–63], increased procedural volume does appear to reduce complications and improve patient outcomes [64].

Research, Registries, and Clinical Trials

A center's increased volume and recognition will provide opportunities to participate in and conduct research regarding aortic pathology and treatment. One such opportunity may involve collaborating with industry partners to conduct clinical trials evaluating treatments and technology. Because of the specific requirements establishing criteria for patients to be involved in clinical trials, having a higher surgical volume will increase the likelihood of treating qualifying patients. Participation in trials for stent grafts, medications, and other treatment techniques and technologies can provide valuable information about effectiveness and outcomes, contributing to the field and promoting innovation.

With the increase in volume that is likely to result from the creation of a center, multidisciplinary aortic centers also have the opportunity and responsibility to expand registries and research efforts to improve clinical quality tracking and benchmarking. Creation of registries to drive performance improvement are one of the most challenging areas related to vascular services, and outcomes-based registries for vascular services are under-represented [65]. Barriers to creation of effective registries include the wide range of vascular interventions and unclear quality endpoints. The research potential provided by expanded vascular registries will improve identification and early diagnosis of potential patients, along with informing best practice protocols for technology, procedure, and care strategies. The development of such registries will facilitate performance monitoring and allow data-driven performance improvement, along with providing data to improve outcomes-based research identifying genetic, social, behavioral, and other factors contributing to vascular disease and sources of poor patient outcomes.

Planning how data will be collected and how outcomes will be tracked is important in the development of a multidisciplinary center [66]. Research collected should allow the center to monitor and improve morbidity and mortality rates, present cumulative history and experience, track referral patterns, and provide the ability to present outcomes. Registry design should be undertaken by planning committees involving all stakeholders and should

incorporate comprehensive longitudinal data on disease management, risk modification, and medical treatment as well as procedural interventions. Vascular benchmarks should be established, such as in-hospital mortality rate, length of stay, readmission rate, and financial aspects of care [67]. The use of protocols to standardize pathways of care can facilitate improved collection and monitoring of outcomes data. Patient-tracking capabilities are essential, as providing standardized outcomes data builds institutional knowledge and outcomes and can also contribute to collaborative research initiatives. EHR may thus play a novel role beyond clinical care, providing information for research purposes [68]. The regular generation of patient-specific information results in vast amounts of data with the potential to significantly contribute to research. However, it is important to employ mechanisms to ensure quality of data provided by EHR, as there is potential for incomplete and inaccurate data capture [69]. Ensuring adequate resource support for the creation and management of registries is essential to the collection of quality data, as is the establishment of standardized protocols, staff accountability, and regular committee review.

Patient Satisfaction and Quality of Care

A multidisciplinary center has the capacity to improve quality of care and patient satisfaction. Patient satisfaction is becoming an important consideration in healthcare since pay for performance and value-based reimbursement programs depend partially on patient satisfaction and experiences to determine financial bonuses. It has been shown that patient satisfaction may be a multidimensional concept that may not serve as a valid quality indicator and that the relationship between patient satisfaction and outcomes and cost is not well-defined [70, 71]. However, having patient satisfaction may improve patient outcomes because satisfied patients are more likely to comply with treatment plans, seek advice, maintain a relationship with their physician, and come in for follow-up, all key elements to successful long-term management of disease [72–74]. The use of electronic health records, when there is emphasis on physician dialogue and communication, has been shown to engage patients and allow them to feel more involved and in control of their care, increasing satisfaction [75]. Other factors associated with patient satisfaction include hospital size, surgical volume, low mortality, and hospital stay experience [76]. However, nursing may be the key area to highlight in increasing patient satisfaction, as patient satisfaction has been associated with a variety of nursing factors [77, 78]. In particular, interpersonal care experiences have been shown to influence patient satisfaction and may independently impact outcomes secondary to the therapeutic relationship combining emotional and cognitive care [79]. Overall, while patient satisfaction cannot be undeniably linked to quality of care, it may be associated and is worth examining, especially as healthcare shifts from a focus on the physician and volume toward patient and value focus.

Return on Investment

Development costs and capital investment are notable in the creation of an aortic center. Depending on the initial capacities and capabilities of the institution, operational costs may increase as 24-hour teams are implemented. However, the most costly investments are likely to be equipment required to provide for a range of treatments and care. Hybrid suites and support equipment, along with stocking of stent, wire, and catheter inventory, are necessary for the treatment of various aortic pathologies but represent significant costs which should be addressed in creating a business plan. It is difficult to generalize about institutional gains provided by the development of a multidisciplinary aortic center since models vary significantly between various existing centers. However, initial capital investments are likely to be offset by increased volume as reputation improves. While the initial financial and resource requirements to create a multidisciplinary aortic center involve a significant capital investment, a center can expect to benefit in the long term from quality improvement and associated cost savings. Many hospital systems receive much of their reimbursement from Medicare and Medicaid. With the shifting state of insurance designs and coverage, the health care system must adapt and adjust to transitions to stay solvent [80]. The Affordable Care Act is currently driving the transformation to a value-based insurance design [81–83]. This model emphasizes individual patient care and offers incentives for systems who adopt the guidelines for "Accountable Care Organizations" set forth by Centers for Medicare and Medicaid Services (CMS) [84]. These guidelines also reward the reduction in readmissions secondary to infection, the use of electronic health records, and preventative services, basing incentives on relative improvement as well as reaching CMS-established benchmarks. As health care plans continue to shift with new political leadership, all health care systems, including aortic centers, must be prepared to adapt their strategies to uncertain developments and policies [85]. However, it seems likely that the emphasis on payments tied to quality or value is a trend that will continue, with Health and Human Services having set a goal of tying 90% of all Medicare payments to value or quality by 2018 [86]. Therefore, the development of

multidisciplinary care, which offers a high quality of care and increased value due to its ability to provide a cross-continuum of care, is likely to result in returns on investment, as reimbursement becomes tied to longitudinal efficiency and outcomes.

Conclusions

A multidisciplinary aortic center has the capacity to improve patient outcomes by coordinating a multidisciplinary team of experts and specialists who collaborate to improve diagnosis, treatment, and longitudinal surveillance of aortic pathology, providing a cross-continuum of care. Creation of such a center involves planning to determine organization and structure, the development of vascular and multidisciplinary teams, and the mechanisms for their collaboration, as well as targeted marketing and networking to identify patients and create a strong referral base. Contributions to the field through research and innovation and the ability to offer high-quality care support the move toward a multidisciplinary approach to aortic care. The development of a multidisciplinary aortic center has been shown to have many benefits, and further research will identify even more common features of successful centers in order to inform future models for multidisciplinary aortic centers.

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