Jai Raman
Editor

Management of Heart Failure

Volume 2: Surgical

Second Edition

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ISBN 978-1-4471-4278-2 ISBN 978-1-4471-4279-9 (eBook)
DOI 10.1007/978-1-4471-4279-9

Library of Congress Control Number: 2015949389

Springer London Heidelberg New York Dordrecht

Printed on acid-free paper

Springer-Verlag London Ltd. is part of Springer Science+Business Media (www.springer.com)

This book is dedicated to my family who have supported through times, good and tough. To my wonderful wife, Vandana, who is a tower of strength and a voice of reason, to my boys Aalap, Anoop, and Avik, who keep me grounded in reality and give me a glimpse of the future.

Preface

As I sit here, thinking about the field of heart failure, what springs to mind are the unsung heroes that pervade the arena – right from transplant coordinators to rehabilitation therapists, from heart failure cardiologists to transplant surgeons, critical care physicians to transplant pharmacists, etc. All this becomes more personal, in light of the recent mindless violent shooting death of Dr. Michael Davidson, who was a friend and cardiac surgeon at the Brigham & Women's Hospital. Therefore, this book is dedicated to his memory and many more like him who have not been widely recognized.

Let us start with transplantation of the heart itself. Even though Christiaan Barnard set the world on fire with the successful heart transplant in 1967, it was the hard work of people like Norman Shumway who over the years built the science and many teams that made cardiac transplantation a success. In the same vein, the tireless efforts of Vincent Dor should not go unsung. I remember many meetings when he would get up and present his data on geometric left ventricular reconstruction. The initial skepticism of the audience gave way to credulous acceptance only over a period of two decades. It is remarkable that the patience and persistence of pioneers like him, secure in their clinical and scientific observation, have paved the way for other practitioners to follow. This has helped in the formation of heart failure as a specialty. When one considers that Billroth exhorted in the late 1800s that surgery on the heart was foolhardy and dangerous, it is amazing that coronary artery surgery became the most commonly performed surgical procedure towards the end of the twentieth century. However, as less invasive options of angioplasty and stenting became more widespread, more and more patients were able to survive heart attacks. These patients then had more attention paid to their cardiovascular risks and longevity improved. The cost of all this improved survival is heart failure of varying degrees. So much so, that heart failure is the most common DRG code for hospital admissions in the developed world. The emergence of heart failure as a specialty began with the acceptance of heart transplantation and the use of immunosuppression. However, alternative and delaying techniques to transplantation along with better drug therapy have built this whole specialty into a multidisciplinary behemoth. We have a range of options in the therapy of heart failure, ranging from medications to special techniques of resynchronization, venous ultra-filtration, beating heart surgery, and mechanical assistance of the failing heart. In this regard, let us pay homage to Don Esmore, who passed away in 2013 after a long and protracted illness. He pioneered the implants and promoted the use of continuous flow VADs,

particularly the VentraCor device, which paved the way for an array of newer devices. Dr. Donald Stephen Esmore did this from the Alfred Hospital in Melbourne, and few around the world know about this remarkable surgeon of great energy that pushed through the pain of his illness to forge new ground.

Coronary artery surgery numbers declined, but patients that now present for bypass surgery invariably have some degree of left ventricular dysfunction and more diffuse disease. They are often on aspirin and plavix. As survivors of major and minor cardiac events, these veterans of hospital admissions and multiple interventions pose great management conundrums that require coordination between a multitude of caregivers and practitioners.

As the teams that look after these complex patients grow, so do the number of unsung heroes who perform tirelessly to improve the outcomes of these sick patients. Remember, all this happens while the media is constantly talking about new stem cell therapies, new robotic operations, new drugs for heart failure, etc. Very little mention is made about the nitty-gritty and daily grind of mundane tasks such as cardiac rehabilitation after a heart attack or conventional cardiac surgery that dramatically improves well-being of heart failure patients. Few lay people know about the existence of perfusionists who run the heart-lung machine in open-heart surgery or manage those amazing ventricular assist devices that keep patients alive. The ensemble approach of having a team look after patients for various aspects of care in a coordinated fashion has resulted in many of these patients doing well.

As cardiac surgery and other lifesaving procedures become more commonplace in the developing world, it behooves us to pay attention to the costs of technology. For instance, it is almost criminal that a ventricular assist device, which might extend survival at increased risk of complications, costs over $ 80,000. Also pertinent to note that a lot of the technology that is being utilized is older and not in keeping with modern electronics and communication. We have to work with industry and research laboratories to build affordable and simple devices that can be used reliably at multiple locations around the world. We also have to learn when to say NO, work with hospice care/palliative care, and acknowledge that terminal heart failure is like terminal cancer in its inevitability. When all the medications and machines fail, it is important to develop the concept of a good death.

In addition to thanking the teams that work with us, we have to acknowledge the yeoman service provided by an array of researchers and pioneers who help develop new techniques and technologies. My task here is therefore to acknowledge all those unsung heroes around the world and thank them for their work. I would also like to thank all the contributors to this book, which is the second edition of the first two-volume effort in the realm of heart failure. Grant Weston deserves credit, as the editor from Springer who had the foresight to hang his shingle on a “higher than usual risk” publication. No doubt there are areas of these two volumes that could be improved upon or updated, but our aim was to provide a good overview of the Comprehensive Management of Heart Failure.

Chicago, IL, USA Jai Raman
March 2015

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Surgical Perspectives

1

Arkalgud Sampathkumar and Jaishankar Raman

The earliest mention of heart failure was by Sushruta, in 600 BC, a prominent physician and surgeon of ancient India. There is a good description of what we now describe as heart failure, with patients manifesting with dyspnea, cough, wheezing and edema. In his treatise known as Sushruta Samhita, he saw these as symptoms of a special derangement of a special organ system related to "pittam" or circulating fluids, and prescribed emetics, diuretics and purgatives for its treatment [1].

Western Tradition

Within the western medical tradition, Lancisi (1654–1720) laid the foundation for contemporary understandings of the pathology of heart disease. In particular he described the 'aneurysm of the heart,' which would now be termed dilatation, and recognised the swelling of neck veins as pathognomonic of right heart dilatation.

Albertini (1672–1733) of Bologna, a pupil of the great physician Malphigi, was the first physician to realise the importance of dyspnea as a symptom of heart disease. Morgagni (1682–1771), a professor of anatomy at Padua, recognised and anatomically distinguished between the two chief forms of cardiac enlargement: dilatation and hypertrophy. He also deduced that dyspnea and asthma could have cardiac causes, connecting these symptoms to right heart failure in particular. Senac (1693–1770), a French physician, was the first to write about the importance of inflammation as a cause of heart disease. He described thrills that were associated with valvular insufficiency. Laennec (1781–1826) invented the stethoscope in 1819 and regarded dilatation and hypertrophy to be the most important cardiac lesions. William Stokes (1804–1878) recognised the importance of the myocardium and analysed its relationship to valvular disease [2].

Frank-Starling Relationship

In 1895 Otto Frank, a famous German physician, showed the importance of cardiac filling and size in governing its contractility. In 1915 E H Starling demonstrated conclusively the relationship of pre-load and cardiac filling to cardiac contraction and performance in an experimental heart-lung preparation. This was called 'Starling's law of the heart' and was the basis of the Frank-Starling curve or relationship. The Frank-Starling curve is

Diseases desperate grown by desperate appliance are relieved or not at all. (Shakespeare: Hamlet 4. 3. 9)

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_1

a plot of cardiac size and contractility [3]. ***This curve or law is the very basis of defining the limits of ventricular dilatation and the decompensation that occurs when the heart enlarges beyond a certain size***.

The present emphasis on the medical management of modern heart failure is not that much different. The last few decades has seen great strides in the development of devices and surgical procedures in treatment of heart failure. However, very little of this is known to the wider medical community, let alone the cardiac surgical fraternity. Heart failure has often been called the final surgical frontier. However, this is not quite true as the history of cardiac surgery will attest….

Cardiac surgery is a relatively young surgical specialty that is now in a stage of flux. The heart was always held in great reverence. The great Viennese surgeon Theodor Billroth asserted in the 1880s that it might be dangerous to contemplate surgery on the heart.

In the European tradition, the first surgical treatment of heart failure was drainage of a pericardial effusion that was unresponsive to diuretics, performed by Francisco Romero in Aragon around 1814. Dominique Larrey, surgeon to Napoleon's Imperial Guard drained a traumatic pericardial effusion presenting as tamponade in 1814.

Dr. Daniel Hale Williams, an African American surgeon who set up the Provident Hospital not far from the campus of the University of Chicago, performed the first repair of a cardiac wound in a patient called James Cornish, in 1893. Dr. Daniel Hale Williams called for six of his fellow black physicians to help him get the dying man into an operating room. This was done based on careful clinical evaluation of the patient. Carefully making an incision along the fifth rib, Williams exposed the man's still-beating heart and his near fatal wound. Williams and his surgeons evaluated sewed up a small but ragged gash located on the surface of the heart between two coronary arteries and closed the pericardium. A few days later, when the patient's condition deteriorated, he was taken back to the operating room and the pericardium opened up through a separate incision in the chest. Fluid collected within was drained and the pericardium sewn up again. This patient lived for over 38 years thereafter, ultimately succumbing to the effects of another barroom brawl [4]. This is very pertinent to this book, which was conceived and produced at the University of Chicago, when the first major cardiac procedure was performed in an affiliate hospital. This fact is even more poignant, because one of the authors of this chapter has been on the faculty of this university.

There were two similar instances in Europe around the same time. In 1894, Ansel Cappelen sutured a 2 cm laceration on the surface of the ventricle, at the University of Oslo, Norway. His patient remained gravely ill succumbing 4 days later.

Ludwig Rehn at the University of Frankfurt am Main, in 1896 is credited with having the first successful repair of a large cardiac wound with a surviving patient.

The early decades of the twentieth century set the tone for cardiac surgery, especially in patients with heart failure as a consequence of rheumatic stenosis of the mitral valve.

Pioneers of Heart Surgery

Lauder Brunton wrote a remarkably prescient but restrained paper in 1902, entitled "Preliminary Note on The Possibility of Treating Mitral Stenosis by Surgical Methods". Sir Brunton, working at St Bartholomew's hospital in London, studied a variety of instruments that could be introduced through the ventricle or the auricle. He also proposed that the commissures be divided rather than the leaflets. Despite his great vision, extensive cadaver work, supporting his work, the paper set off a flurry of critical letters. The prevailing view of the cardiologists was skeptical and claimed that the prognosis of the condition depended on the state of the heart muscle rather size of the mitral orifice. Things have not changed that much more than a hundred years later! Unfortunately, Brunton's predictions took almost 50 years to prove.

Elliot Cutler, across the Atlantic at the Peter Bent Brigham Hospital, Boston worked with

many types of cutting instruments. On May 20, 1923, he operated on a bedridden patient who survived for four and a half years, but could not be sure how much relief of mitral stenosis there was. The subsequent experience with the various cutting procedures of the mitral valve failed because the focus was on cutting the leaflets rather than the commissures.

It was 23 years after Brunon's paper, that Henry Souttar introduced a finger through the atrial appendage to ostensibly free up a stenosed mitral valve, on May 6, 1925; to his surprise he found a regurgitant valve, but established the principle of finger fracture.

In 1910, Alexis Carrel reported on experiments performed at the University of Chicago, and at the Rockefeller Institute, New York, at the American Surgical Association. He described a relatively safe period of vena caval occlusion or of cross-clamping of the heart, making it "feasible to cut a mitral or triscuspdian valve, or to perform the curettage of endocardiac vegetations".

Billroth was not alone, for most of history, the human heart has been regarded as an organ forbidden to surgeons. World War II changed a lot of surgical attitudes. Pioneering advances in antibiotics, anesthesia and blood transfusions were made by military doctors, who faced injury and suffering on a massive scale.

Dr. Dwight Harken, as a young U.S. Army surgeon was one of the first surgeons to use these improved techniques to gain access to the heart. Many of Harken's patients were young soldiers evacuated from the European front with shell fragments and bullets lodged inside their hearts. Leaving shrapnel wounds could be very dangerous while removing them could be fatal. Using animal experimentation, he tried to develop a technique that would allow him to cut into the wall of a still beating heart, insert a finger, locate the shrapnel and remove it. All of his first 14 animal subjects died. Of the second group of 14, half died. Of the third group of 14, only 2 died. Harken used these techniques in his patients with no deaths, proving that the human heart could be operated upon.

It wasn't long before surgeons began wondering if Harken's technique might be applied to defective heart valves. In 1947, Harken performed a repeat of the Cutler procedure, which resulted in death of the patient. In 1948, within days of each other, Harken and Dr. Charles Bailey, of Philadelphia independently reported on successful closed mitral commisurotomy using valvulotomes and carefully designed knives. Across the Atlantic, Russell Brock at the Brompton Hospital, London utilized Souttar's approach of finger fracture through the left atrial appendage with very good results. Dubost in Paris devised a reliable mechanical dilator, which was subsequently modified by Oswald Tubbs in South Africa in 1955. This was the early evolution of valvular reparative surgery for heart failure – a truly international effort, which provided dramatic relief to a desperately ill group of patients with mitral stenosis [5].

In the ensuing years, dramatic strides were made in anesthesia, cardiopulmonary support, valve replacement, myocardial protection, etc to facilitate modern cardiac surgery.

Developments in the Twentieth Century

In terms of the development of cardiovascular surgery, Alexis Carrel, a very innovative researcher, pioneered many of the concepts that helped make contemporary heart surgery possible, including cardiac and other solid organ transplantation [6].

Following on from Carrel's pioneering work many groups and stalwarts developed various aspects of heart surgery. In Stanford, California Shumway and co-workers worked tirelessly to help make cardiac transplantation a reality [7]. Eventually, the introduction of Cyclosporin A helped make transplantation viable [8].

In relation to the development of other surgical options for treating CHF Chachques [9] and co-workers, working in Paris in the mid-1980s, used an interesting discovery in skeletal muscle transformation to try to improve the function of the failing heart. The left latissimus dorsi muscle was harvested with its intact neurovascular pedicle, wrapped around the heart and transformed

over a period of 10 weeks to a fatigue resistant state. This technique, known as dynamic cardiomyoplasty, provided some relief to patients with heart failure, but was bedevilled by major morbidity. In addition, the muscle transformation took too long and could impact on the condition of a patient with severe cardiac failure. The mechanism by which this technique worked was probably through containment of the dilating ventricle.

Dr. Randas Batista, a charismatic surgeon from Brazil, first burst on the international scene in 1997 with his ventricular volume reduction surgery [10]. Although his eponymous procedure is not used much any more, he showed the world the value of reducing the size of dilating ventricles to smaller sizes. Batista's technique reduced wall stress and alleviated symptoms in the short term. Unfortunately, the majority of the patients had recurrent ventricular dilatation and either died or proceeded to transplantation.

Another approach that has had some impact on the surgical management of CHF is that of Dr. Steven Bolling and his associates from Ann Arbor, Michigan. They believe that mitral regurgitation is the process by which many patients with heart failure de-compensate and manifest clinically. This group advocates radical mitral annuloplasty and have produced reasonably good results with this technique [11].

Patients with heart failure as a consequence of ischaemic heart disease often have large areas of myocardial scarring, some of which may be dyskinetic or truly aneurysmal. Dr. Vincent Dor of Monaco has long advocated a careful reconstruction of the left ventricle in patients with aneurysmal or dyskinetic segments [12]. These techniques modified linear repairs of ventricular aneurysms advocated by Dr. Denton Cooley [13]. Cooley himself later on employed a patch repair of large aneurysms [14]. Dor's work in the early 1990s demonstrated that excision of these maladaptive scars and implantation of a patch along with a purse-string suture to reduce the size of the neck of the aneurysms, in order to reconstruct the ventricle and reduce its size, has beneficial effects [15]. Jatene's contributions to addressing septal dyskinesis have also contributed to improving outcomes with these reconstructive procedures [16]. At centres in Melbourne, Australia and Chicago, USA we have also had encouraging results using another modification of Dor's technique [17], whereby the purse-string suture is avoided but a small tailored patch is used in an attempt to reconstruct the ventricle in a smaller and more normal shape. Dr. Patrick McCarthy, at the Cleveland Clinic, has had encouraging results using a modification of Dr. Dor's technique [18], whereby he uses a large purse-string but avoids a patch. Yacoub and co-workers have also looked at using left ventricular assistance to aid recovery of the failing heart [19].

The most dramatic and eye-catching development was of course, the first heart transplant. Despite years of work and development by many researchers in the US and Europe, the first implant was carried out in the Southern Hemisphere well away from those crucibles of development and discovery. In December of 1967, Dr. Christiaan Barnard, at the Groote Schuur Hospital, South Africa, transplanted the heart of a 23-year-old woman killed in a motor vehicle accident into the chest of a middle-aged man. He lived for 18 days, until the powerful drugs used to suppress rejection weakened him and he died of pneumonia. The second patient to receive a heart transplant, at the hands of Dr. Adrian Kantrowitz in the United States, lived only 6 h. Dr. Barnard's next heart-transplant patient lived for 18 months.

These surgical triumphs proved short-lived as patients began dying of either rejection or infection. By 1971, 146 of the first 170 heart transplant recipients were dead. Transplantation of the heart received bad press and worse, a bad rap.

Only one surgeon continued – the recently deceased Dr. Norman Shumway persisted in pursuing this high-risk procedure. Throughout the 1970s, he built a team of scientists and doctors to tackle the complex biological problem of tissue rejection in a careful, scientific manner. He developed techniques of endomyocardial biopsies to monitor rejection. It was only fair therefore that Shumway benefited from a chance discovery made in another part of the world.

The soil of Norway's Hardaanger fjord, yielded a fungus which allowed the development

of cyclosporin, a calcineurin inhibitor that revolutionized organ rejection without knocking out all resistance to infection. Hospitals around the world began to re-open their heart transplant units and their patients began to survive and prosper.

Durable mechanical assistance of the heart has become a very cherished dream that may soon be and enduring reality. Attempts by the National Heart Lung and Blood Institute (a division of the National Institutes of Health in the US) to fund long-term mechanical support and artificial heart technology go back over 50 years. The first implant of some kind of artificial heart or ventricular assist device resulted in a very public falling out between two great pioneers – Dr. Michael DeBakey and Dr. Denton Cooley. Little is know about the fate of that first patient, though we know that the relationship between these two former colleagues was destroyed, only to be revived in the dying years of Dr. DeBakey, after he had successfully survived surgery for an aortic dissection at the age of nearly a century. The REMATCH trial in the 1990s devised by Dr. Bud Frazier and reported on by Dr. Eric Rose, showed that in patients with terminal heart failure, mechanical assistance with a Heartmate XVE device actually doubled the likelihood of survival with medical treatment (which was dismal at 8 % at 1 years). In the past years, the late Dr. Esmore from the Alfred Hospital in Melbourne showed the utility of continuous flow or non-pulsatile pumps in reducing adverse events, morbidity and prolonging survival after implantation of the Ventrassist ventricular assist devices. This heralded a new generation of non-pulsatile flow pumps such as Heartmate II, Heartware, etc. Strides have also been made in the Total Artificial Heart technology with the increased application of the CardioWest device.

Congestive Heart Failure

Introduction

Heart failure is a commonly used term that encompasses a wide spectrum of diseases and a range of aetiologies. However, in all these cases, the underlying common feature is the presence of some degree of failure of the musculature of the heart to work efficiently [20]. Heart failure may be defined in clinical as well as physiological terms:

Congestive heart failure (CHF) is a clinical syndrome rather than a specific disease. CHF is characterised by a reduction in exercise tolerance, poor quality of life, and shortened life expectancy. Hypertension and valvular heart disease were at one time the most common causes of progressive heart failure. However, with an ageing population ischaemic heart disease and diastolic dysfunction have become important causes of heart failure. As the heart dilates there is increased wall stress. The Frank-Starling curve becomes inapplicable and the increase in diameter makes the heart expend more energy to pump the same amount of blood to maintain a cardiac output prior to dilatation. Physiologically speaking, failure of the heart as a pump is termed as overall heart failure and differs from myocardial failure, which is a reduction in myocardial contractility [21]. One useful way to define heart failure is to state that it exists when the heart is unable to pump sufficient blood to meet the metabolic needs of the body at normal filling pressures, provided the venous return to the heart is normal.

A Brief Perspective

In general the survival rate of patients with heart failure is related to their degree of myocardial failure, whereas their symptoms are related more to congestive heart failure and its compensatory mechanisms. Most patients with heart failure however, have an ‘enlarged heart’ which, in technical terms, is due to dilatation of the ventricles. Ventricular dilatation usually runs a progressive course that is variable and predisposes the owner of the heart to sudden cardiac death. Indeed, in a landmark paper, White showed that ventricular volume was a major determinant of survival after myocardial infarction. There are numerous possible causes of overall heart pump failure.

Common causes of Heart Failure are [22]

- Coronary artery disease
- Dilated cardiomyopathy of unknown cause
- Dilated cardiomyopathy of know cause,
  - Hypertensive
  - Toxic
  - Viral
  - Parasitic
- Valvular stenosis or regurgitation, with or without left ventricular dysfunction
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy
- Pericardial disease
- Pulmonary hypertension
- Congenital heart disease
- High output states
- Uncontrolled tachycardia
- Iatrogenic causes – post-cardiac surgery, post failed PCI

This large variation in the causes and mechanisms of heart failure has made research into this area difficult. Research has been further hindered by a lack of large animal models that are both appropriate for studying human heart failure and are reproducible, reliable and stable for long-term study.

Congestive heart failure (CHF) is the only cardiovascular disorder that is increasing in prevalence, despite important gains made in other cardiovascular arenas. In the US and other industrialised nations CHF is reported to be the most common cause for medical hospitalisation for patients older than 65 years. It is also distinguished as the leading cause of morbidity and mortality in industrialised nations. Great strides have been made in improving the symptoms of patients and reducing mortality. However, according to noted researchers, patients with congestive heart failure are deemed to be "destined to suffer considerable disability and die from their disease".

The Magnitude of the Problem

The American Heart Association reports that more than 5 million people in the US have congestive heart failure and that at least 550,000 new cases develop on an annual basis. In the US, in 2001, 6.5 million hospital days were associated with CHF admissions. In that year, 53,000 patients died with CHF as their primary diagnosis. Once patients were hospitalised heart failure also accounted for 12–15 million visits to the physician during that same period [23]. In 1995 heart failure accounted for more than $10 billion a year in healthcare costs in the USA. Further analysis of costs revealed that when both federal and non-federal hospital expenditures were examined, the total cost was more like $ 40 billion for 1994, in the USA.

While better treatment has evolved over the past two decades for ischaemic heart disease, only modest improvement has been made in the management of heart failure. The incidence of heart failure is said to double in each decade of life from the age of 45 to 75 years. Thirty-four percent of patients die within the first year of newly diagnosed congestive heart failure. Eighty-two percent of men die within 6 years of the diagnosis. In the second to sixth years of diagnosis, death rates associated with CHF are four to eight times that of the general population. However worsening symptoms are not always a prelude to death. Forty-four percent of deaths in patients with CHF are sudden, with no markers for prediction. The rate of sudden death in this patient group is five times that of the general population.

Incidence and Prevalence

Incidence data on congestive heart failure in Australia is estimated at 300,000 patients or 1–2 % of the population. In the US data on incidence is based on estimates from the study in Framingham, Massachusetts, funded by the National Heart, Lung and Blood Institute. The incidence of CHF is equally frequent in men and women with an annual incidence approaching 10 per 1000 population after 65 years of age. There is an incidence five times greater in patients who have had a myocardial infarction compared to those who have not. **Congestive Heart Failure is the biggest cause of medical admissions in the USA**.

Similarly, prevalence data is not available for Australia but can be roughly extrapolated from figures in the US. However, the Australian Institute of Health and Welfare estimates that heart failure accounts for 5 % of all deaths from cardiovascular disease and 10 % of all hospitalisations for cardiovascular conditions. However, patients over the age of 65 years accounted for 86 % of heart failure admissions [24].

Close to five million Americans have congestive heart failure, with an equal representation of the sexes across this figure. CHF is present in 2 % of people aged 40–59; in more than 5 % of people from 60 to 69, and 10 % of people over the age of 70. The prevalence of CHF has also increased steadily over the past 20 years as the population ages [25]. The aging population has an increased preponderance of diastolic heart failure or heart failure with preserved ejection fraction (HFPEF).

Course of the Disease and Present Treatment Options

Initially, the heart tends to compensate by increasing the heart rate – causing hypertrophy of myocardial cells – and also starts dilating to cope with the load. Eventually, however, these mechanisms fail and the heart continues to dilate. It may enlarge asymptomatically for a variable period of time. As a result the patient may present quite late, with a certain amount of irreversible cardiac dilatation [26]. The extent of symptoms depends on: the clinical phase of the illness, the level of compensation or de-compensation, the underlying cause, and aggravating factors, such as a chest infection or a sudden fluid overload. The majority of patients are managed with medications, which provide symptomatic relief but do nothing to stop the underlying process. Patients are often managed with a combination, or 'cocktail,' of medications that need to be carefully monitored and regularly adjusted. In addition to symptomatic relief some of these drugs may have significant side effects. However, with progressive myocardial dilatation, drugs become ineffective and the only solution maybe surgical therapy of some sort [27].

The gold standard for treatment of end-stage heart failure is orthotopic cardiac transplantation. This is expensive therapy and is limited severely by the lack of availability of donor organs. Patients who undergo transplantation must remain on immuno-suppressive therapy for life, with the consequent risk of infection, rejection and graft atherosclerosis.

A variety of other surgical options, such as biventricular pacing, implantation of implantable cardioverter-defibrillators, coronary artery bypass graft surgery, dynamic cardiomyoplasty, radical mitral annuloplasty, and left ventricular volume reduction surgery, have been tried with inconsistent results and variable success. Left ventricular aneurysm repair or infarct exclusion is a technique that is effective for patients with large infarcted segments that are dyskinetic. The burgeoning and rapidly growing field of mechanical circulatory support has allowed prompt salvage of dying patients and is continuing to change the survival of patients with long-standing heart failure. The field is thus growing and always ripe for the development of new approaches.

The next chapter deals with the pathophysiology, clinical spectrum and management of heart failure. That will set the stage for the evolution of the other chapters in this book.

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2 Pathophysiology: Clinical Spectrum and Current Management

Mahesh P. Gupta and Jaishankar Raman

The noted biological and medical writer Lewis Thomas mused in his 1983 essay, entitled 'The Artificial Heart:

> We do not really understand the underlying mechanism of cardiomyopathies at all, and we are not much better at comprehending the biochemical events that disable the heart muscle or its valves in other more common illnesses. But there are clues enough to raise the spirits of people in a good many basic science disciplines, and any number of engrossing questions are at hand awaiting answers. The trouble is that most of the good questions that may lead, ultimately, to methods for prevention, (for example, the metabolism and intimate pathologic changes in a failing myocardium, the possible roles of nutrition, viral infection, blood-clotting abnormalities, hypertension, life-style, and other unknown factors) are all long-range questions, requiring unguessable periods of time before the research can be completed. Nor can the outcome of research on any particular line be predicted in advance; whatever turns up as the result of science is bound to be new information. There can be no guarantee that the work will turn out to be useful. It can, however, be guaranteed that if such work is not done we will be stuck forever with this insupportably expensive, ethically puzzling, halfway technology, and it is doubtful that we can long afford it. [1]

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Sixteen years later Willerson observed in an editorial on heart failure that: "Not yet clear is what mediates the progression of heart failure after the initial injury, and how it may be influenced" [2].

In order to understand more fully the mechanisms through which the process of ventricular containment is useful for the treatment of CHF, it is crucial to have a thorough knowledge of the pathophysiology of this common heart disease. In this chapter we discuss the disease processes of CHF at a biochemical, molecular or cellular level, and at a more systemic level.

Initiation of Heart Failure

Initial injuries or insults to the myocardium may sometimes be sub-clinical, thus only producing immediate signs of heart failure in a small group of patients. These injuries often initiate a process that leads to chronic congestive heart failure over a period of months or years. Three main forces that initiate the process of CHF are:

- Intrinsic myocardial damage
- Abnormal load on one (particularly the left ventricle) or both ventricles
- Extrinsic forces affecting the heart.

Over half the cases of intrinsic myocardial damage are due to ischaemia and/or infarction caused by ischaemic heart disease [3].

J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_2

Myocardial damage resulting in heart failure may also be caused by auto-immune injury, infections, metabolic insults and toxic conditions [4]. Idiopathic dilated cardiomyopathy may be due to self-directed antibodies to myocyte antigens. Immune modulation may cause improvement in these patients [5]. Toxic and metabolic causes include: alcohol toxicity and hyperthyroidism.

Abnormal loads on the myocardium may due to chronic pressure overload (e.g. systemic arterial hypertension) or volume overload (e.g. aortic and mitral valve regurgitation).

Extrinsic causes of heart failure include constrictive pericardial disease, tachycardia-induced heart failure, and 'high-output' heart failure due to severe anaemia or a large arteriovenous fistula or shunt.

Progression

The underlying mechanism in the development and progression of heart failure involves an initial insult followed by ventricular remodelling. A destructive cycle is set in motion whereby the remaining normal myocardium undergoes changes in cellular metabolism, leading to hypertrophy and fibrosis. This gradually results in changes in the ultra-structure of the ventricles through a process called remodelling. Remodelling occurs initially as an adaptive response to improve cardiac performance. Unfortunately over time this response becomes counterproductive and maladaptive [6].

Molecular and Cellular Basis

There are various factors that impact on the ventricles at a cellular level. For instance systemic arterial hypertension causes a reactivation of embryonic growth factors, which are normally dormant in the adult heart. These factors accelerate protein synthesis and myocyte growth, resulting in hypertrophy of the ventricle [7]. Diastolic dysfunction ensues and progresses to systolic dysfunction, which ends up causing a large, dilated, poorly functioning ventricle.

Myocardial infarction is another trigger for ventricular remodelling. The irreversibly injured myocardium loses contractile function, causing compensatory changes in the remaining myocardium. This functional overload on non-infarcted muscle, as well as intrinsic changes in the infarcted area (such as myocyte filament slippage) lead to remodelling. This process finally results in a dilated heart with severe dysfunction [8].

The contributing mechanisms to ventricular remodelling are complex and not completely understood. Current hypotheses focus on certain cytokines and growth factors, such as Tumour Necrosis Factor (TNF) [9]. Elevated levels of TNF are found in the myocardium of patients with heart failure. Raised levels of TNF may cause myocyte dysfunction through a mechanism involving the induction of nitric oxide synthase (iNOS) [10, 11].

While the maladaptive changes of heart failure can be reversed by successful treatment if instituted early enough [12] further cellular changes result in apoptosis – programmed cell death – and fibrous replacement in normal areas of the heart, causing permanent functional damage [13].

The common end result of chronic congestive failure is systolic dysfunction, which translates as an inability of the left ventricle to eject its contents in systole. Left ventricular ejection fraction while a relatively weak prognostic indicator if used alone [14], is the most frequently used objective estimate of heart failure severity.

Diastolic dysfunction exists when the left ventricle is unable to fill at a normal rate and to a normal extent [15]. Systolic function may be normal in some patients with diastolic dysfunction. This condition can be caused by a variety of conditions including severe left ventricular hypertrophy, restrictive infiltrative myocardial disease, and constrictive pericarditis. There is no accurate way of quantifying diastolic dysfunction. Diastolic dysfunction can be difficult to treat effectively and may progress steadily [16].

Maladaptive Systemic Responses

Chronic congestive heart failure starts off as adaptive cardiac and systemic responses in an attempt to maintain normal perfusion of systemic organs. These responses become counterproductive over time, leading to the progression of heart failure, with worsening symptoms (Fig. 2.1).

Various homeostatic mechanisms are activated in CHF, such as the activation of the renin-angiotensin-aldosterone system. Decreased renal perfusion is detected by receptors in the renal arterioles, leading to renin release from the kidneys. The increased angiotensin II that is formed acts on efferent arterioles increasing glomerular filtration pressure, despite reduction in renal perfusion pressure. Aldosterone synthesis is stimulated by angiotensin II, causing retention of salt and water by the kidney. Initially, this mechanism works to preserve normal systemic and renal perfusion. However, over a longer period this process leads to edema, elevated pulmonary artery pressures, and increased after-load [17]. Figure 2.2 illustrates these mechanisms.

Figure 2.2 shows that there is an increase in sympathetic activity, as well as vasopressin and renin release, in CHF. Neuro-endocrine activation is manifested by the release of norepinephrine, vasopressin and atrial natriuretic peptide [18]. The increased after-load and myocyte damage leads to a repetitive cycle of decreasing cardiac performance. Norepinephrine increases systemic vasoconstriction, chronotropy and inotropy by direct cardiac stimulation [19]. Over time, this increase in tissue norepinephrine activity predisposes to ventricular arrhythmias and sudden cardiac death. Higher circulating levels of plasma norepinephrine have been shown to

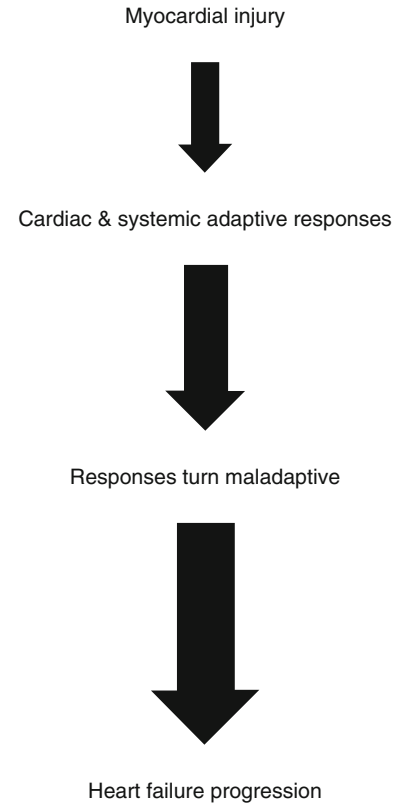

Fig. 2.1 Mechanism of heart failure progression. The steps in the progression of heart failure

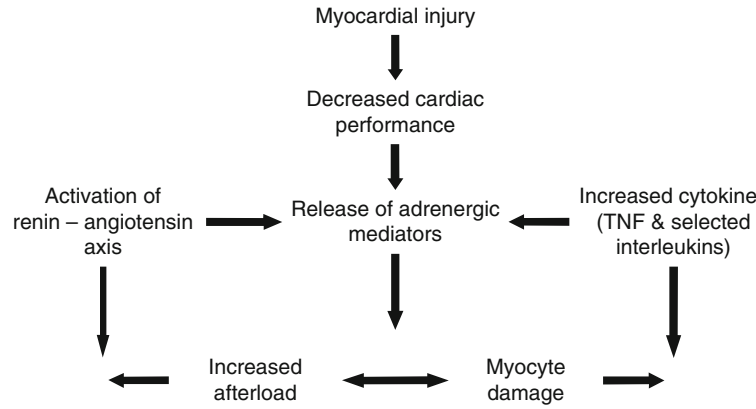

Fig. 2.2 Cycle of HF Progression, interacting with the renin-angiotensin axis, Adrenergic system and cytokines. Injury causing activation of the renin-angiotensin-aldosterone system, release of adrenergic mediators

negatively correlate with the prognosis of heart failure [20]. These values, while a rough guide, can be highly variable and unreliable compared to local concentrations of norepinephrine within the heart. The levels of norepinephrine in the cardiac circulation are measured by norepinephrine spill-over, and are elevated in CHF, providing an accurate prognostic guide [21].

Increased levels of endothelin are also found in CHF, promoting peripheral vasoconstriction, myocyte hypertrophy, and adverse remodelling [22]. Furthermore, atrial and brain natriuretic peptides (ANPs & BNPs) are released by the atria in response to stretch and increased atrial pressure. Neurohormones, cytokines and nitric oxide all interact together in complex ways to create the syndrome of chronic heart failure.

Fetal Gene Activation during Heart Failure

In a hypertrophied heart myocytes are not only big in size, but they also have additional sarcomeres. The manner in which these sarcomeres are added depends upon the type of load being imposed on myocytes. In situation of pressure overload, sarcomeres are added in parallel, leading to increased LV wall thickness, whereas, during volume overload, they are added in series, resulting in dilation of the ventricular cavity. There are also qualitative differences in sarcomeres of hypertrophied myocytes. A great body of evidence suggest that hypertrophy of myocytes is associated with induction of a group of genes, which are usually expressed during fetal heart development. These genes include activation of β-myosin heavy chain (MHC), skeletal-α-actin, atrial natriuretic factor and the repression of α-MHC and SR-CaATPase (SERCA). These changes may be initially salutary for an overloaded heart; however, prolonged hypertrophy leads to myocyte dysfunction, which eventually results into heart failure. Results collected from animal studies have also indicated that, the loss of α-MHC content is a critical determinant of the reduced myocardial contractility during heart failure. Direct evidence in support of a causal link between the loss of α-MHC and the development of heart failure came from experiments in which the α-MHC gene was ablated. Data correlating even small decrements of α-MHC content with changes in the intrinsic contractile characteristics of the myocardium also support the idea that a critical level of α-MHC content is essential for the normal pump function of the heart.

Another possible cause of a decrease in contractile protein-function is an alteration in the expression and/or activity of regulatory proteins. In animal models of heart failure, there are changes in the myosin light chain and the troponin-tropomyosin complex. Changes in myosin light-chain isoforms have been observed in heart samples of patients subjected to increased mechanical stress, and the expression of troponin-T splice variants was found to be altered in failing human myocardium. Changes in the phosphorylation status of Troponin-I have also been suggested to be involved in the loss of contractile activity of myocytes during heart failure. Moreover, defects in sarcoplasmic reticulum Ca2+ATPase and Ca release channels have been suggested to be responsible for the contractile dysfunction of myocytes.

Myocyte Cell-Death during Heart Failure

It has been realized that in addition to muscle gene dys-regulation, cardiomyocyte cell-death significantly contributes to loss of ventricular function in a failing heart. During increased workload, myocytes undergo a hypertrophic growth response to compensate for the increased demand. The initiating events of which are similar to those that drive cell-cycle progression in proliferating cells. A continuous growth signal in myocytes, at some point, causes cells to malfunction and leads to cell-death. As cells die, the workload on the remaining cells increases, which further aggravates this process and eventually leads to organ failure. Both in humans and animals with different cardiac disorders, including

ischemic heart disease, idiopathic dilated cardiomyopathy, hypertensive heart disease, viral myocarditis, pacing-induced cardiomyopathy and different transgenic models of heart failure, myocyte cell-death has been implicated as a common cause of the cardiac pathology. However, the mechanism of cell death in a failing heart remains highly disputed. Some studies have documented a role of caspases in myocyte cell-death, however, other have disputed this notion. The activation of caspases in ischemic heart disease seems fairly accepted, but its participation in non-ischemic diseases remains controversial. Our own studies have shown that in pressure overloaded hearts PARP is not cleaved, a marker of caspase-dependent cell-death, but rather its expression is progressively increased in relation to the degree of cardiac hypertrophy, suggesting that hemodynamic-stress endangers cardiac myocytes through a mechanism that appears different from the conventional caspase-mediated apoptosis. Activation of PARP has been seen during different animal models of heart failure as well as in human failing hearts. Recent evidence suggests that prevention of cardiomyocyte cell-death by PARP-inhibition and/or by changing activity of other cell-death intermediate protects the overloaded heart from going into failure. G-protein coupled beta receptors, which have been implicated in the normal and abnormal functioning of cardiac muscle cells in response to beta-receptor signalling. These receptors and their mechanistic properties have recently been acclaimed by the Nobel committee that saw it fit to award the Nobel Prize in Chemistry for 2012 to Drs Lefkowitz and Kobilka [23].

Genetics of Heart Failure

Before we proceed to a discussion of the complex clinical manifestations of CHF, a brief discussion of the genetic factors at work in CHF is necessary for completion. Almost 20 % of patients with dilated cardiomyopathy are likely to have an inherited genetic defect. For instance, familial hypertrophic cardiomyopathy is caused by a number of gene mutations affecting beta myosin heavy chain, cardiac troponin T & I, alpha tropomyosin, myosin-binding protein C, and myosin light chains 1 and 2 [24]. In certain conditions such as Duchenne muscular dystrophy, there are definite genetic associations of an abnormal gene called dystrophin with abnormal myocardial function [25].

Cytoskeletal Proteins

Discoveries made during the last 20 years have revealed a genetic origin in many cases of dilated cardiomyopathy (DCM). Currently, over 40 genes have been associated with the disease. Mutations in DCM-causing genes induce the condition through a variety of different pathological pathways with complex and not completely understood mechanisms. Genes that encode for sarcomeric, cytoskeletal, nuclear membrane, dystrophin-associated glycoprotein complex and desmosomal proteins are the principal genes involved. In this review we discuss the most frequent DCM-causing genes. A classification has been proposed, in which DCM genes are considered as being major or minor genes according to their mutation frequency and the available supporting evidence [26].

Hypertrophic cardiomyopathy (HCM) is the most common monogenic genetic cardiac disease, with an estimated prevalence of 1:500 in the general population. Clinically, HCM is characterized by hypertrophy of the left ventricle (LV) walls, especially the septum, usually asymmetric, in the absence of any cardiac or systemic disease that leads to a secondary hypertrophy. The clinical course of the disease has a large inter- and intrafamilial heterogeneity, ranging from mild symptoms of heart failure late in life to the onset of sudden cardiac death at a young age and is caused by a mutation in one of the genes that encode a protein from the sarcomere, Z-disc or intracellular calcium modulators. Although many genes and mutations are already known to cause HCM, the molecular pathways that lead to the phenotype are still unclear [27].

Abnormal Lubrication in Diastolic Heart Failure

By regulating migration, proliferation and apoptosis as well as extracellular matrix synthesis and assembly, proteoglycans, integrins and the dystrophin-glycoprotein complex may be of great importance both during development and in vascular disease [28].

Syndecan-1 is a member of the proteoglycan family involved in cell-matrix interactions. In patients with heart failure, syndecan-1 levels correlate with fibrosis biomarkers pointing towards a role in cardiac remodeling. Studies have shown that this proteoglycan is elevated in patients with HF with preserved ejection fraction (diastolic dysfunction) [29].

Clinical Spectrum

Heart failure is usually defined as the inability of the heart to generate an output sufficient to meet the metabolic requirements of the body. The left or right ventricles may fail individually or together. Heart failure may also occur in the face of normal systolic ventricular function.

Left heart failure presents with shortness of breath which, if severe, will occur at rest. Patients are graded on their functional capacity depending on the level of activity that induces shortness of breath. This functional classification, known as the 'New York Heart Association (NYHA) classification,' is widely accepted and used around the world. This functional classification is used in the assessment of patients, prognostication and in tailoring management. The classes are as follows:

NYHA class I	Shortness of breath on unaccustomed exertion. Normal exercise tolerance
NYHA class II	Shortness of breath on accustomed exertion, e.g., Breathlessness on walking uphill or climbing a flight of stairs
NYHA class III	Shortness of breath on mild exertion, e.g., Symptomatic on walking a few metres
NYHA class IV	Symptomatic at rest or on minimal exertion

Minor impairment of cardiac function may remain asymptomatic but, as compensatory mechanisms become maladaptive, the clinical features of heart failure emerge. These relate primarily to the consequences of elevated atrial pressures and reduced cardiac output, expressed as congestion and peripheral hypoperfusion respectively. Manifestations of left and right heart may occur separately, but in reality they often occur together in varying degrees, resulting in the broader syndrome of Congestive Heart Failure (CHF).

Acute Left Heart Failure

This is usually caused by acute myocardial infarction, but may also be due to acute aortic or mitral regurgitation, or fulminant myocarditis. The patient usually presents with sudden onset of breathlessness and may cough up pink, frothy sputum. These clinical features are hallmarks of acute pulmonary edema although, in reality, most patients are now diagnosed on the basis of 'wet lungs' using chest x-ray. Systemic hypoperfusion supervenes, progressing to hypotension, oliguria and, in severe cases, cardiogenic shock.

Chronic Left Heart Failure

Patients usually have varying degrees of dyspnoea on exertion, the causes of which are many. For example, the elevation of left atrial pressure with exertion may be caused by:

- Respiratory muscle fatigue
- Metabolic factors such as acidosis and renal impairment, or
- Muscle fatigue due to low cardiac output and poor muscle conditioning.

Clinical examination may reveal signs of low cardiac output and reflex sympathetic stimulation which include, tachycardia, cool peripheries and, occasionally, cyanosis. Auscultation may reveal inspiratory crackles at lung bases, although this can be unreliable; they are just as likely to be retained secretions within the lungs. Pleural

effusions may be present. A third heart sound may be present producing a gallop rhythm. In severe heart failure, dilatation of the cardiac base and fibroskeleton causes mitral annular dilatation and mitral regurgitation. This is manifested by a pan-systolic murmur at the apex.

Acute Right Heart failure

Acute right heart failure may be caused by pulmonary embolism or right ventricular infarction. Patients usually present with breathlessness, systemic hypotension, cool skin, elevated jugular venous pressure and occasionally an enlarged liver.

Chronic Right Heart Failure

In this condition patients complain more of fatigue, and breathlessness is common. They also complain of a bloated feeling in the abdomen and a loss of appetite. This may be due to ascites, liver congestion, and edema of the gastro-intestinal tract. On examination the jugular venous pulse (JVP) is elevated. Occasionally there may be large 'v' waves in the JVP along with pulsatile hepatomegaly, suggestive of functional tricuspid regurgitation. In such patients a pan-systolic murmur can be heard at the left sternal edge. Peripheral edema and ascites may be present. Occasionally, patients manifest and present with jaundice and impaired protein synthesis, due to chronic impairment of liver function. Right heart failure is more commonly seen in the congenital heart disease population and patients with pulmonary hypertension. The increased use of long term left ventricular assist devices, has uncovered a group of sub-optimally supported failing right ventricles with interesting consequences.

Complications

A variety of cardiac arrhythmias occur in heart failure, especially atrial fibrillation, which causes varying degrees of haemodynamic deterioration. Ventricular arrhythmias occur later in the course of the disease and are more sinister, often causing sudden death. Arrhythmias and cardiac dilatation predispose to thrombus formation within cardiac chambers, which can then embolise into the pulmonary or systemic circulations. Chronic congestion of the lungs also provides a fertile ground for chest infections. Deep vein thromboses as a result of sluggish flow in the veins of the legs and pelvis may progress to pulmonary embolism and sudden death.

Advanced heart failure also causes progressive failure of major organs such as the liver and kidneys.

Diagnosis

As described earlier, CHF can present with a variable clinical picture. However, a variety of investigations can help confirm the diagnosis, such as Electrocardiogram (ECG), Chest X-ray, Echocardiography, Cardiac Catheterization, Radionuclide ventriculography (RNVG), Magnetic Resonance Imaging (MRI), and Cardio Pulmonary Exercise Testing. Great strides have also been made in the use of bio-markers in heart failure, such as BNP (brain related natriuretic peptide), and n-terminal Pro BNP (NT-BNP). Such investigative tools are useful for the mapping the course and progression of the disease. More recently, greater use of monitoring response to therapy with NT-BNP is gaining traction.

Current Treatment Options for CHF

Congestive heart failure is a complex medical condition requiring therapeutic interventions at multiple levels. It is the most common cause of medical admissions in Australia, the United States, Canada and the UK. The biggest advance in the treatment of heart failure has been the establishment of 'Heart Failure Clinics' and heart failure groups in hospitals, serviced by people interested in investigating, understanding and managing heart failure [30].

Multi-disciplinary heart failure programs that run cardiac rehabilitation courses after myocardial infarction or cardiac surgery, have been effective in reducing heart failure related admissions [31]. Symptomatic improvement has also been noticed, along with reduced hospitalisation in patients with cardiomyopathy who attend a specialised clinic [32].

Prevention also plays a very important role. The West of Scotland Study showed that primary prevention, by advocating drug therapy with pravastatin, prevented myocardial infarction and reduced the incidence of heart failure in a population at risk [33]. The 4S Study (Scandinavian Simvastatin Survival Study) followed patients with coronary artery disease, some of whom were randomly assigned to a placebo group and some to a group treated with simvastatin. Secondary prevention in the 4S Study showed that occurrence of heart failure at 5-year follow-up was significantly higher in the placebo than in the simvastatin group [34].

Exercise programs to improve general fitness and the level of exercise tolerance have been shown to significantly improve the functional status of patients with heart failure [35]. Bed rest, which was a cornerstone of traditional therapy for CHF, is therefore no longer advocated for these patients.

Despite these improvements in treatment and prevention the effective management of heart failure continues to be a pressing concern. Before discussing my research into the utility and efficacy of ventricular containment, this next section will review current approaches to the treatment of CHF, both medical and surgical.

Drug Therapy

Inotropic Agents

Digoxin, a drug that exerts a direct inotropic effect on the heart, has been a therapeutic mainstay in CHF for many years. Despite this the DIG trial (Digitalis Investigation Group) found that there was no significant impact on mortality in patients treated with digoxin [36]. However, this study demonstrated that patients treated with digitalis required less hospitalisation for worsening heart failure. The newer inotropic agents have also failed to lower the mortality rate of CHF sufferers. The PROMISE (Prospective Randomised Milrinone Survival Evaluation) trial, for example, did not live up to its name. Indeed there was a 28 % higher all cause mortality in patients randomly treated with 40 mg/day of milrinone compared to the placebo group [37].

Vasodilators

The first Veteran Administration Co-operative Vasodilator-Heart Failure Trial (V-HeFT 1) was published in 1986. The report showed that the addition of the vasodilators hydralazine (300 mg/day) and isosorbide dinitrate (160 mg/day) to a digoxin and diuretic regime resulted in a reduction in mortality of 38 % after 1 year, 25 % after 2 years, and 28 % over the entire follow-up period (a mean of 2.3 years) [38]. In 1991 the V-HeFT II study (conducted by the same group) reported that the ACE inhibitor enalapril was 18 % better than the combination of the two direct vasodilators [39]. However, the hydralazine-isosorbide combination was associated with improved ventricular function and better oxygen consumption at peak exercise.

Calcium Channel Blockers

Calcium channel blockers have been associated with worsening heart failure and a rise in mortality [40] with the exclusion of amlodipine. The PRAISE trial (Prospective Randomised Amlodipine Survival Evaluation) found that while amlodipine had no impact on mortality, it diminished the combined risk of non-fatal and fatal events by 31 % in patients with non-ischaemic cardiomyopathy [41].

Beta-Adrenoceptor Blockade

The sympathetic system is activated in patients with CHF. Another way of dealing with the adverse effects of neurohumoral activation is through beta-adrenoceptor blockage. Carvedilol, for example, is a non-selective beta-receptor antagonist that also blocks alpha-1 receptors and has antioxidant effects. In a recent trial carvedilol reduced mortality, 6–12 months after treatment,

by 65 % in patients with CHF [42]. An Australian trial also showed improvement in ejection fraction, cardiac mortality and morbidity in patients treated with carvedilol [43].

Angiotensin-Converting Enzyme (ACE) Inhibitors

There is now a large volume of work supporting the role of ACE inhibitors in heart failure and these agents have become a cornerstone of first line therapy. Treatment with ACE inhibitors improves haemodynamic profiles as well as functional status, with benefits in exercise performance, dyspnea, fatigue and edema. The Survival and Ventricular Enlargement (SAVE) trial showed improvement in all cause mortality and reduced cardiovascular morbidity in patients with asymptomatic LV dysfunction after MI, who were treated with captopril [44]. The SOLVD (Studies of Left Ventricular Dysfunction) trial showed that enalapril reduced the risk of death and hospitalisation for worsening failure compared to the placebo group [45].

There are many other studies showing the efficacy of various ACE inhibitor drugs in heart failure as a consequence of MI. However, while most of these drugs delay progression of heart failure for a while and provide a solid bedrock of therapy, each of them has a significant incidence of complications. Despite best medical therapy, patients tend to worsen gradually as the ventricle dilates inexorably.

Surgical Therapy

Apart from first-line treatment with drug therapy, a number of surgical techniques have also been developed to treat heart failure. These include:

Ventricular Assist Devices

Mechanical circulatory support has finally come off age. We now have access to easy to deploy pumps such as the CentriMag (Thoratec Corporation) and CardioHelp (Maquet Cardiovascular) that can be used to salvage patients with acute heart failure and decompensation. In the more chronic heart failure patients, the use of left ventricular assist devices such as Heartmate II, Heartware and DuraHeart have made a dramatic difference to outcome. In a small group of patients with cardiomyopathy due to either idiopathic or to reversible causes, ventricular assist devices may be used on a long-term basis until the patients recover [46]. Despite many favourable reports [47] use of these devices were historically bedevilled by a high rate of bleeding, infection and hemolysis [48] as well as thrombo-embolism [49]. The present generation of continuous flow pumps work well in the short and intermediate term to tide patients over until transplantation [50]. However ventricular devices are expensive, require anti-coagulation and careful post-operative monitoring. Due to financial constraints, they are usually reserved for young patients in NYHA Class IV heart failure that are likely to be transplanted. The emerging area of destination therapy addresses patients who have terminal heart failure and are not candidates for transplantation. This field is growing rapidly in the US and almost 40 % of VADs are now for patients who are listed for Destination Therapy. In a sense, this is expensive therapy but is life-saving and prolonging in patients with terminal heart failure.

Cardiomyoplasty

Dynamic cardiomyoplasty was first performed in 1985, utilising the left latissimus dorsi on an intact neurovascular pedicle. The skeletal muscle was transformed to fatigue resistance by long-term electrical stimulation, utilising Pette's elegant finding in muscle physiology [51].

Skeletal muscle transformed in this way was used experimentally in an attempt to augment cardiac function [52] and as an implantable extra-aortic balloon assist device [53]. Despite much enthusiasm for this technique early experiences were marred by high mortality and morbidity rates [54]. A randomised study to demonstrate the efficacy of cardiomyoplasty was commenced quite late; by the time the study was completed the cardiomyostimulators had already been withdrawn from the market. However the results of the randomised study showed that patients with NYHA Class III heart failure who underwent

cardiomyoplasty received symptomatic benefit [55]. Unfortunately, the results of this study came too late to resurrect this procedure.

Mitral Valve Annuloplasty

Bolling and his colleagues from Ann Arbor, Michigan have advocated an aggressive approach to patients with dilated cardiomyopathy and mitral regurgitation. They have shown good intermediate term results with mitral valve repair, usually in the form of a radical annuloplasty to reduce the size of the mitral annulus [56]. This works well only if the mechanism of decompensation is moderate to severe mitral regurgitation. However, long term follow up studies with these patients have not shown significant survival benefit with this procedure.

The Cleveland Clinic heart failure group, headed by Dr McCarthy, had reported good early results with the Alfieri-type edge-to-edge mitral valve repair, along with an annuloplasty, in patients with mitral insufficiency in the setting of a cardiomyopathy [57]. However, these repair techniques had a significant failure rate in the intermediate term.

Partial Left Ventriculectomy (Batista Procedure)

As discussed previously, Dr Randas Batista was one of the first cardiac surgeons to demonstrate the beneficial possibilities of ventricular volume reduction surgery. Batista, working in a relatively impoverished area of Brazil, designed a procedure to reduce the size of dilated ventricles by resecting a portion of the left ventricular myocardium between the papillary muscles. He also advocated an Alfieri-type mitral valve repair. In 1997 he reported good results using this combined procedure [58]. There has been a lot of interest in the procedure with McCarthy, from the Cleveland Clinic, performing a careful evaluation of its efficacy. His findings showed that, in spite of a significant early morbidity and mortality, patients that survived had significant improvement in hemodynamics and ventricular function in the short-term [59]. Unfortunately most patients had recurrent dilatation, which steadily progressed either to death or transplantation [60].

Left Ventricular Aneurysm Repair

Reconstruction of scarred left ventricles in the setting of large left ventricular aneurysms is being performed with increasing frequency. Left ventricular aneurysms may be large saccular thin-walled scars or small dyskinetic and scarred segments. In either case there is usually underlying cardiac dilatation. Early repairs of left ventricular aneurysms were performed in a linear fashion [61] producing distortion of an already abnormal ventricle and often-marginal results [62]. The importance of maintaining a geometric shape similar to that of a ventricle was demonstrated by various groups and resulted in the development of endo-aneurysmorrhaphy [63].

In 1989 Dor [64] showed that endo-ventricular patch repair had physiologic merit and Jatene [65] demonstrated the importance of reducing the size of the defect after aneurysm resection. Late hemodynamic results are also favourable when patch repair of remodelled ventricular segments are performed in association with coronary artery grafting [66].

In 1992 Dor went further and advocated reconstruction of post-ischemic akinetic ventricular dilatation [67]. This was based on the observation that full thickness scarring is prone to a variety of unpleasant sequelae, such as calcification, dykinesis, Dressler syndrome, and progressive dilatation of the remaining ventricular cavity [68]. A modification of this technique has also been developed for treatment of refractory ischemic ventricular tachycardia by endo-ventricular patch plasty [69]. More recently, McCarthy reported on a series of patients undergoing 'cardiac reshaping' (which is akin to the Jatene procedure or the Dor procedure, but without the patch) for ischemic dilated cardiomyopathy. This produced excellent results [70]. Buckberg conducted an international trial called SAVE (Surgical Anterior Ventricular Infarct Exclusion) to evaluate the efficacy of excluding the dyskinetic infarcted anterior segment of hearts in these patients [71] with mixed results. Experience with Geometric Endoventricular Repair [72] has been very satisfactory in repairing anterior and inferior left ventricular scars. This technique incorporates

features of the Cooley and the Dor repair without using a purse-string suture, but utilising a measured pericardial patch.

Results of the much-awaited STICH trial conducted by Jones and sponsored by the NIH, were disappointing. This study, though international. multi-center and randomized, suffered from a few drawbacks. These will be discussed in a separate chapter in detail.

Cardiac transplantation is the accepted gold standard treatment for selected patients with refractory heart failure. Despite a 10-year survival of 65–70 %, a shortage of donors means that it is available only for a very small subset of patients [73].

Other Ancillary Therapies

Pacing

Pacing may be required to treat patients with symptomatic brady-arrhythmias or loss of atrio-ventricular synchrony. These pacemakers should be dual chambered and rate responsive [74].

Biventricular pacing is a promising new approach to re-synchronise cardiac contraction in patients with systolic heart failure and left bundle branch blocks [75]. This approach is the subject of many international trials.

In selected patients with a propensity for ventricular arrhythmias, intra-cardiac cardioverter-defibrillator devices may be implanted reducing the risks of out-of-hospital cardiac arrests [76].

Exercise Training

In the 1990s there were various groups that showed the efficacy of low-intensity exercise training in patients with CHF [77]. Based on this experience, some groups have shown improvement in muscle strength [78] and hemodynamics with resistance training [79]. Whatever the intensity or mode, there is enough body of evidence now suggesting the beneficial effects of exercise in heart failure [80, 81] that most heart failure groups and clinics have an integrated program that includes some form of physical exercise in addition to the general rehabilitative measures as treatment in patients with CHF.

Constraining the Heart: Prevention of Further Cardiac Dilatation

While some of the procedures mentioned so far help to reduce the size of the dilating ventricles (apart from cardiomyoplasty) none of them actually prevent further dilatation of the heart. In CHF the natural tendency is for the heart to gradually enlarge over time. Our interest, then, was in developing a technique for not only reducing but also containing the size of the ventricle. We therefore decided to study the concept of ventricular containment based on what we thought was the presumed mechanism behind cardiomyoplasty. Fortunately there were a couple of papers that supported our premise that the muscle in myoplasty acted as a girdle [82] and that stimulation of the muscle actually gave it a bit of tension that improved the constraint [83]. Furthermore a contemporaneous study reported good results using a goretex sheet wrapped around a dilating heart [84]. Raman and Power, working at the Austin Hospital, Melbourne, Australia, showed that this procedure could be adapted to various stages of progressive ventricular dilatation in an animal model, and this was adapted in human patients with encouraging results [85]. This proved the basis for various devices such as the Acorn cardiac support device, the Paracor device, etc., which will be discussed in Chap. 13.

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Strategies in Surgical Management

3

Irving Kron

Introduction

Heart failure is not a disease but a complex clinical syndrome representing the end-stage of a number of different cardiac diseases. It can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. It has been defined as a reduction in cardiac function such that cardiac output is reduced relative to the metabolic demands of the body and is associated with failure of compensating mechanisms.

Heart failure is one of the leading causes of hospitalization in the United States, with 400,000–700,000 new cases diagnosed yearly. Most current therapeutic strategies are focused toward resolving the acute exacerbation of failure, resulting in a 3-month re-admission rate of 20–50 % and a devastating 2-year mortality of 35–50 % [1, 2]. It currently affects more than five million people causing more than 700,000 deaths annually. Approximately a third of the heart failure patients are in New York Heart Association (NYHA) class III/IV (Table 3.1). The growing cost of caring for these patients approaches $50 billion per year [3].

Table 3.1 New York heart association functional classification of cardiac disability

I	Presence of cardiac disease but without limitations in physical activity. Normal physical activity does not cause fatigue, palpitation, dyspnea or angina
II	Presence of cardiac disease with mild limitation of physical activity. Comfortable at rest but normal physical activity causes fatigue, palpitation, dyspnea or angina
III	Presence of cardiac disease with marked limitation of physical activity. Comfortable at rest but less than normal physical activity causes fatigue, palpitation, dyspnea or angina
IV	Presence of cardiac disease with inability to perform any physical activity without discomfort. Discomfort even at rest with worsening of symptoms if activity is undertaken

Pathophysiology

Heart failure can be categorized by specific mechanisms and manifestations. Two basic classifications are backward failure, first proposed in 1832 by Hope, and forward failure, suggested by Mackenzie about 80 years later. Backward failure refers to accumulation of blood upstream from the failing ventricle. This is represented by pulmonary edema in the face of left ventricular failure or systemic venous congestion in the setting

The heart…moves of itself and does not stop unless forever. – Leonardo da Vinci (1452-1519)

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_3

of right-sided heart failure. Forward failure refers to the inadequacy of blood delivery into the pulmonary or systemic circulation due to the diminished pumping action of the right or left ventricle respectively. Although these two hemodynamic states can be separated in theory, they almost invariably occur together. Both systolic and diastolic dysfunction contribute to the clinical picture. Systolic failure is more familiar and refers to pump failure, whereas diastolic failure is due to the impaired ability of the ventricle to fill properly. Heart failure most commonly refers to left-sided heart failure. Isolated right-sided heart failure can predominate but a mixed picture is usually typical in the clinical setting [4].

Underlying Conditions

Underlying conditions that cause, exacerbate or predispose to the development of heart failure should be identified and treated.

Ischemic Heart Disease

Coronary atherosclerosis is the commonest cause of cardiomyopathy in the United States, comprising 50–75 % of patients with heart failure. In addition, coronary disease may be present in patients with heart failure of other causes, and may sometimes be overlooked as a contributing factor [5]. There are two mechanisms for heart failure in this setting: a prior myocardial infarction (MI) followed by left ventricular dysfunction and remodeling; or hibernating myocardium due to chronic but potentially reversible ischemic dysfunction. Patients with ischemic heart disease may have heart failure from one or both of these mechanisms [6, 7].

Valvular Heart Disease

Valvular heart disease is the primary cause of heart failure in perhaps 10–12 % of patients [8]. Furthermore, valvular dysfunction is a secondary or superimposed phenomenon in many cases of heart failure. An example of this is that there is almost always some degree of mitral or tricuspid regurgitation in patients with severe dilated cardiomyopathy [9].

Valvular dysfunction produces two forms of stress on the heart, volume overload and pressure overload. Both stressors result in increased cardiac afterload. Patients with valvular disease typically exhibit tremendous cardiac reserves. Due to the existence of various compensatory mechanisms, these patients can persist in an asymptomatic, well-compensated state until severe valvular and ventricular dysfunction have developed. In contrast, the patient developing acute valvular dysfunction without a period of gradual adaptation can rapidly succumb to severe heart failure [4].

Other Factors

Other potentially reversible conditions that can impair ventricular function and cause, or worsen, heart failure should also be evaluated. This includes, but is not limited to, hypertension, renovascular disease and drug therapy (a list of these drugs is shown in Table 3.2 [10]).

Evaluation of Patients with Heart Failure

The approach to the patient with heart failure starts with the history and physical examination. Chest x-ray and a series of diagnostic tests are also used to establish the diagnosis, determine etiology, and assess acuity and severity. Recommendations for the evaluation of patients with heart failure were published in 2001 by an ACC/AHA Task Force and are shown in Table 3.3 [11].

As discussed previously, there are two major classes of symptoms in heart failure. First, backward failure leading to excess fluid accumulation results in dyspnea, edema, hepatic congestion and ascites. Secondly, reduced cardiac output that is most pronounced with exertion, due to forward failure, causing fatigue and weakness.

Table 3.2 Drugs associated with increased risk of adverse effects in patients with heart failure

Drug class/drug	Adverse effect(s)
Anti-inflammatory medications	
Corticosteroids	Sodium and fluid retention
Non-steroidal anti-inflammatory drugs	Sodium and fluid retention; blunted response with diuretics; increased systemic vascular resistance
Cardiovascular medications	
Class I antiarrhythmic agents	Negative inotropy; proarrhythmia
Sotalol	Proarrhythmia
Ibutilide	Proarrhythmia
Minoxidil	Fluid retention; neurohumeral activation
Calcium channel blockers	Negative inotropy; neurohumeral activation
Diabetes medications	
Metformin	Lactic acidosis
Thiazolidinediones	Fluid retention
Hematologic medications	
Anagrelide	Phosphodiesterase inhibitor; palpiations; tachycardia; induction or exacerbation of heart failure
Cilostazol	Phosphodiesterase inhibitor; ventricular tachyarrthmias
Neurologic and psychiatric medications	
Amphetamines	Sympathetic agonist activity; hypertension; tachycardia;
Carbamazepine	Negative inotropic effect; bradyarrhythmias
Clozapine	Development of myocarditis and cardiomyopathy
Ergot alkaloids	Sympathetic agonist activity; valve fibrosis
Pergolide	Valve fibrosis
Tricyclic antidepressants	Negative inotropic effect; proarrhythmia
Miscellaneous	
Beta-2 agonists	Sympathetic agonist activity; tachyarrhythmias; hypokalemia

Source: Amabile and Spencer [6]

Table 3.3 Stages in the evolution of heart failure and recommended therapy by stage

Stage A	
At high risk for heart failure but without symptoms or structural heart disease	Treat hypertension
	Encourage smoking cessation
	Treat lipid disorders
	Encourage regular exercise
	Discourage alcohol intake or illicit drug use
	Angiotensin converting enzyme inhibition in appropriate patients
Stage B	
Structural heart disease but without symptoms	Apply all measures used for Stage A
	Beta-blockers in appropriate patients
Stage C	
Structural heart disease with prior or current symptoms of heart failure	Apply all measures used in Stage A
	Drugs for routine use: angiotensin converting enzyme inhibitors
	Beta-blockers
	Digitalis
	Dietary salt restriction
Stage D	
Advanced heart disease and severe symptoms at rest despite maximal therapy. Refractory heart failure requiring specialized interventions	Apply all measures used in Stage A, B and C
	Mechanical assist devices
	Heart transplantation
	Continuous intravenous inotropic infusions for palliation
	Hospice care

Source: Data from Hunt et al. [11]

Preseting Symptoms

The presenting symptoms are important in determining the acuity of heart failure. Acute and subacute presentations (days to weeks) are characterized primarily by dyspnea at rest and/or exertion. Other specialized forms of dyspnea, such as orthopnea and paroxysmal nocturnal dyspnea, are also common. Right heart failure and tachyarryhthmias may be present resulting in symptomotology of hepatic congestion and palpitations respectively.

Chronic presentations (months) differ in that fatigue, anorexia, bowel distention and peripheral edema may be more pronounced than dyspnea. This is because pulmonary venous capacitance adapts to the chronic volume

overload leading to less fluid accumulation in the alveoli, despite the increase in total lung water.

History

Although history alone is insufficient to make the diagnosis of heart failure [12, 13], it remains the single best discriminator to determine the acuity and rate of progression of heart failure. It also often provides important clues to the etiology of heart failure.

Physical Examination

Physical examination can provide important information concerning the degree of volume overload, ventricular enlargement, pulmonary hypertension and reduced cardiac output.

Investigations

A standard workup should include blood tests, a chest x-ray and electrocardiogram on all patients. The presence of pulmonary vascular congestion and cardiomegaly on chest x-ray support the diagnosis of heart failure. Chest x-ray is also useful for ruling out pulmonary disease in patients who present with dyspnea [14–16]. A normal electrocardiogram is unusual in patients with symptomatic systolic dysfunction (98 % negative predictive value) [17].

Echocardiography should be performed on all patients with new onset of heart failure. It is one of the most useful non-invasive tools available in aiding the management of heart failure. In addition to having a high sensitivity and specificity for the diagnosis of heart failure (80 % and 100 % respectively) [18], it can also detect other important findings. Regional wall motion assessment using dobutamine stress echocardiography may increase the ability to distinguish between ischemic and non-ischemic dilated cardiomyopathy [19]. This technique is also useful in predicting recovery of cardiac function [20, 21]. Echocardiography can also detect pericardial thickening, valvular heart disease, presence of thrombi, abnormal myocardial texture, chamber size and function, as well as measuring cardiac output using pulsed-wave Doppler.

Virtually all patients with unexplained heart failure should be evaluated for the presence of ischemic heart disease, as it is not an uncommon cause of dilated cardiomyopathy [5, 22]. This can be done using several techniques.

Non-invasive exercise testing not only provides information about the existence of ischemic heart disease, but can also be used for risk stratification and prognostic purposes. Measurement of the maximal oxygen uptake (VO_2max) provides an objective estimate of the functional severity of the myocardial dysfunction.

Coronary catheterization with angiography is indicated in patients with angina or a positive exercise stress test. However, even patients with a normal exercise stress test, who otherwise have unexplained heart failure, cardiac catheterization should strongly be considered. The ACC/AHA Committee on Coronary Angiography has published recommendations for the use of coronary angiography in patients with heart failure as shown in Table 3.4 [23]. It may also detect and grade underlying valvular heart disease, which may contribute to the symptomotology of heart failure.

The role of endomyocardial biopsy in discovering the etiology of dilated cardiomyopathy is not well defined. The yield for clinically useful information not obtainable without biopsy is low [22, 24, 25]. Hence, it should be reserved for patients with suspected systemic diseases known to affect the myocardium, including hemochromatosis, amyloidosis and sarcoidosis.

Current Management Strategies

Traditionally, heart failure has been thought to be secondary to impaired left ventricular function. This would imply that contractile failure causes systolic dysfunction. However, it is currently thought that systolic dysfunction is secondary to a structural increase in ventricular chamber volume. Hence, instead of chamber dilatation occurring as a result of contractile failure, it happens as

Table 3.4 Recommendations for use of coronary angiography in patients with heart failure (HF)

Class I
1. HF due to systolic dysfunction with angina or with regional wall motion abnormalities and/or scintigraphic evidence or reversible myocardial ischemia when revascularizaiton is being considered
2. Before cardiac transplantation
3. HF secondary to postinfarction ventricular aneurysm or other mechanical complications of myocardial infarction (MI)
Class IIa
1. Systolic dysfunction with unexplained cause despite noninvasive testing
2. Normal systolic function, but episodic heart failure raises suspicion of ischemically mediated left ventricular dysfunction
Class III
1. HF with previous coronary angiograms showing normal coronary arteries, with no new evidence to suggest ischemic heart disease

Source: Data from Scanlon et al. [27]
ACC/AHA classification
Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb: Usefulness/efficacy less well established by evidence/opinion
Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful and in some cases may be harmful

an early response to reduced wall motion, which is necessary to generate a normal stroke volume from a larger end diastolic volume. As a result, alterations in chamber length and shape, which are not related to a preload mandated increase in sarcomere length, occur. This pathologic change is termed remodeling. As the heart remodels and dilates, the radius of curvature increases. According to LaPlace's law, this results in greater wall tension that increases myocardial oxygen consumption, decreases subendocardial blood flow, impairs energetics and increases arrhythmias. Overall, the degree of remodeling correlates directly with poor prognosis [26]. According to this view, remodeling, not contractile failure, is the key to the severity of reduced ejection fraction and poor prognosis. Fortunately, some aspects of the remodeling process have been shown to be reversible [27–32].

Tremendous progress has been made over the past 20 years in the management of heart failure. For many years, medical management has remained the mainstay of therapy. Current pharmacological therapies that improve mortality can inhibit progressive chamber remodeling and improve survival. A number of drugs are commonly used in heart failure for symptom relief and improvement of outcome. There have been several large trials that demonstrated improved mortality, left ventricular function, long-term outcomes and decreased hospitalization rate with the administration of angiotensin-converting enzyme (ACE) inhibitors [33–35] and new generation beta-blockers [36–40]. Further data suggest that the survival benefits can be attributed to the reversed remodeling properties of these drug groups [41–43].

Nevertheless, despite significant advances in the pharmacological support of the failing heart, the results are far from perfect. Mortality remains high and hospitalization costly. Surgical management is still required for patients with end-stage heart failure. Unfortunately, its evolution has occurred in a less structured fashion. Heart transplantation remains the treatment of choice for many patients with end-stage heart failure who remain symptomatic despite optimal medical therapy. Similar to other forms of transplantation, the persistent shortage of donor hearts and strict selection criteria continue to limit the annual growth of this approach. Thus, heart transplantation is not an available option for most patients with heart failure and continues to be performed only at large, highly specialized medical centers.

Surgical Management of Heart Failure

Surgical techniques employed for end-stage heart failure are under active investigation. Although large randomized multi-center trials are unusual in this field, important progress is being made. Specialized strategies considered include implantation of pacemakers, coronary revascularization,

left ventricular reconstruction, mitral valve repair, cardiomyoplasty and mechanical circulatory support.

Pacemaker Implantation

General indications for pacemaker implantation include patients with chronic atrial fibrillation who require atrioventricular nodal ablation for rate control and symptomatic bradycardias. The use of biventricular (BiV) pacemakers, termed resynchronization therapy, can improve symptoms in some patients with moderate to severe heart failure [44, 45]. As a result of this, BiV pacing has been approved by the USFDA as a treatment for moderate to severe heart failure. However, it has not determined when BiV pacing should be used. This is due to potential concerns, which include a small risk of serious complications occurring during implantation [44] and a lack of long-term data [11]. It is also not known if these devices should routinely be used with an implantable defibrillator.

Left Ventricular Reconstruction

In heart failure, both ventricular enlargement, resulting from damaged myocardium, and a ventricular aneurysm, which can develop after a heart attack, can compromise the heart's ability to produce a strong contraction and leads to a decrease in cardiac output. Batista et al. first introduced the concept of surgically reversing this process, partial left ventriculectomy, for patients with NYHA class IV idiopathic dilated cardiomyopathies in 1996. They described a procedure that involved resection of normal muscle between both papillary muscles and extending from the apex to the mitral annulus. The mitral valve was either preserved, repaired or replaced depending on the amount of tissue removed. This restored the ventricle to a more normal volume/mass/diameter relationship [46]. The reduction in ventricular diameter, according to LaPlace's law, results in decreased ventricular wall tension and possibly a more uniform pattern of contraction/relaxation, thus improving systolic performance [47, 48]. Although many patients initially improved markedly [47, 49–55], the perioperative mortality was high and many patients redilated [49, 56] with a high recurrence rate of symptomatic heart failure [51, 55, 57]. As a consequence, overall enthusiasm for the procedure has waned.

The newer surgical modalities for cardiomyopathy have benefited from the lessons learned in the treatment of left ventricular aneurysms. The Dor procedure is an approach to surgical reconstruction in the setting of postinfarction aneurysm formation [58]. Prior to the development of the Dor procedure, surgical treatment for postinfarction aneurysms involved removal of the aneurysmal area and reapproximation of the viable wall (endoaneurysmorraphy) in an attempt to restore left ventricular geometry. However, this approach has not been found to improve left ventricular performance [59]. In the Dor procedure, also called endoventricular circular patch plasty (EVCPP), a purse string stitch is placed around the circumference of the non-viable scarred aneurysm to minimize the excluded area. The size of the scar is more important than whether it is akinetic or dyskinetic. Larger scars may yield a greater improvement in left ventricular ejection fraction (LVEF) but have a significantly higher perioperative mortality rate (12 % versus 2.2 % for a small scar). The residual defect is then covered with a Dacron, pericardium or an autologous tissue flap. This operation shortens the long axis, leaving the short axis length unchanged, producing an increase in ventricular diastolic sphericity while the systolic shape becomes more elliptical [60, 61]. This results in a more normal geometry and improved systolic performance. The overall operative mortality in the first patients who underwent the Dor procedure was 8 %. Operative mortality was higher when surgical repair was performed urgently 16.3 % compared to 6.2 % when it was planned [62]. The overall improvement of LVEF was maintained at 1 year. Also, there was a reduction in the end-diastolic volume index and symptomatic heart failure status improved by 92 % [63].

A modification of the Dor procedure, surgical anterior ventricular endocardial restoration (SAVER), consists of exclusion of non-contracting

segments in the dilated remodeled ventricle after an anterior MI. The efficacy of this approach was evaluated in the multicenter RESTORE trial; 89 % also underwent bypass grafting and 26 % had mitral valve repair or replacement. It revealed a significant reduction of left ventricular end-systolic volume index and an increase in LVEF from 29 to 39 % [62]. Furthermore it has been noted that the Dor procedure ameliorates mitral regurgitation in a majority of cases even in the absence of associated mitral valve procedures, probably due to the reduction in the size of the ventricle and improved orientation if the papillary muscles [64]. The choice of the beating heart approach or continuous aortic cross-clamp plays little to no role in postoperative outcome. Furthermore, the added ischemic time associated with continuous cross-clamp is outweighed by the potential benefits [65]. Cope et al. conducted a cost comparison of heart transplantation versus alternative operations for cardiomyopathy in 2001 [66]. This study compared the cost and survival among patients that have undergone heart transplantation, isolated coronary artery bypass grafting (CABG), mitral valve replacement and the Dor procedure. It was noted that the total cost of heart transplantation, which included the procurement costs, was significantly higher among the heart transplant group. The cost was comparable among the other three groups. The operative survival was similar among the four groups. Thus, ventricular reconstructive surgery is a practical alternative to heart transplantation in the select patients. Recommendations for the indications for ventricular reconstructive surgery have been proposed in a 2002 review as shown in Table 3.5 [64].

Table 3.5 Indications for ventricular reconstructive surgery

1. Anteroseptal myocardial infarction (MI), with dilated left ventricle (end-diastolic volume index >100 ml/m^2), and
2. Depressed left ventricular ejection fraction (even <20 %), and
3. Left ventricular regional dyskinesis or akinesis >30 % of the ventricular perimeter, and
4. At least one of the following
(a) Symptoms of heart failure
(b) Arrhythmias
(c) Ischemia on provocative tests in aymptomatic patients

Source: Data from Kaza et al. [68]

Mitral Valve Repair

Mitral regurgitation (MR) is often a complication of end-stage cardiomyopathy. It can result from dilatation of the mitral annular-ventricular apparatus with altered geometry and ischemic papillary muscle dysfunction [67, 68]. Although the teaching for decades has been that closing off the mitral valve leak removes the "pop-off" valve and is associated with an unacceptable surgical death rate, it is important to keep in mind that the regurgitation of blood into the left atrium leads to a cycle of more volume overload, which can lead to progressive annular dilatation, worsened MR, and more severe symptoms of congestive heart failure [69]. Severe MR in patients with ischemic cardiomyopathy is a difficult management issue. Not only do these patients have worsened symptoms, but they also have an increased death rate. The reported 1-year survival rate for medical therapy in this subset of patients is less than 20 % [70]. Among patients with significant (>2+) secondary MR, mitral valve repair should be considered in NYHA class III/IV patients with dilated cardiomyopathies [3]. Several studies have shown that mitral valve repair in patients with end-stage cardiomyopathy is not only feasible but also improves ventricular function and overall survival [70–75]. If mitral valve repair is not possible, it is essential that mitral valve replacement be performed with retention of the subchordal attachments. Preservation of both the anterior and posterior chordal attachments to the papillary muscles helps to maintain normal ventricular geometry and function following mitral valve replacement [76–79]. Most of these studies, however, have dealt with mitral valve repairs in patients with non-ischemic dilated cardiomyopathy.

Ischemic MR seems to be more complex. Often the posterior leaflet becomes functionally restricted owing to ventricular enlargement. Patients with severe MR secondary to ischemic cardiomyopathy have two separate pathophysiologies that not only augment pump failure, but also need to be each dealt with separately surgically. The surgical man-

agement of these patients, particularly those requiring both mitral valve surgery and concomitant CABG, has traditionally been associated with an increased surgical risk [80]. Clearly these patients represent a substantial increased surgical risk compared with patients undergoing either CABG or mitral valve surgery alone [72]. Fortunately, with the advances in myocardial protection and surgical techniques, some of these more difficult patients are now not only at a lower surgical risk, but also are experiencing improvements in their symptomatic status. A more recent study concluded that concomitant CABG and mitral valve repair compare favorably to both CABG alone and cardiac transplantation, thus offering a reasonable alternative for this patient population [81].

Surgical Revascularization

Heart failure resulting from coronary artery disease (CAD) is usually due to MI and subsequent ventricular remodeling. When the ischemia is chronic, the recoverable or viable myocardium is termed "hibernating" but when the insult is transient, that myocardium is described as "stunned". The impaired left ventricular function in these patients is not entirely an irreversible process, if hibernating myocardium is in part responsible to the decline in myocardial function. About 40 % of segments involved in MI may subsequently recover, either spontaneously or after revascularization. Also, LVEF may improve markedly, and even normalize, in subsets of patients following successful revascularization [82, 83]. Patients with documented viability by thallium perfusion imaging, PET scanning or dobutamine echocardiography had significant 80 % reduction in annual mortality with revascularization. There was a direct relationship between severity of left ventricular dysfunction and magnitude of benefit. In contrast, there was no difference in outcome with revascularization or medical therapy in patients without viability [7].

Surgical revascularization for patients with ejection fractions of <20 % to recruit hibernating myocardium is now becoming commonplace [84]. These patients are generally sicker with more preoperative risk factors. However, despite increased hospital mortality of about 4–6 %, they enjoy 90 % 1-year survival and 64 % 5-year survival [85]. Patients with ischemic cardiomyopathy, evidenced by viable myocardium, and bypassable vessels can be revascularized with permissible risk, achieving 88 % perioperative survival with 72 % of patients alive at 1 year. These results are reproducible and have been reported by different authors [86–89].

It is commonly believed that patients with both ischemic cardiomyopathy and significant left ventricular dilatation should undergo transplantation secondary to poor outcome after CABG [90]. However, Aziz and associates [91] addressed this issue by comparing the outcomes of cardiac transplantation between patients with ischemic cardiomyopathy and those with idiopathic cardiomyopathy. Although the operative mortality between the two groups was essentially the same (11.2 % and 10.6 % respectively), the 10-year survival was remarkably different (39 % and 80 % respectively). Hence, the decision to operate on patients with severely depressed left ventricular function is not straightforward. There are excellent short-term results with CABG alone but inferior mid-term results compared with CABG plus ventricular remodeling [92].

PTCA Versus CABG

The usefulness of angioplasty depends upon the pattern and extent of arterial narrowing. Angioplasty is often recommended over bypass surgery when arterial narrowing is mild or moderate and when only one or two coronary arteries are narrowed. It is more effective in patients who do not have diabetes mellitus. Patients with diabetes appear to have a greater benefit from CABG, especially in the setting of multivessel, multilesion or severe CAD [93].

Recommendations for revascularization for patients with native-vessel CAD by the ACC/AHA/ACP-ASIM are shown in Table 3.6 [94]. These recommendations were ratified again in the 2002 update.

Table 3.6 Recommendations for revascularization with percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG) in patients with stable angina

Class I
1. CABG for patients with significant left main coronary disease
2. CABG for patients with 3-vessel disease. The survival benefit is greater in patients with abnormal left ventricular (LV) function (ejection fraction <50 %)
3. CABG for patients with 2-vessel disease with significant proximal left anterior descending coronary artery disease (CAD) and either abnormal LV function (ejection fraction <50 %) or demonstrable ischemia on noninvasive testing
4. PTCA for patients with 2- or 3-vessel disease with significant proximal left anterior descending CAD, who have anatomy suitable for catheter-based therapy, normal LV function, and who do not have treated diabetes
5. PTCA or CABG for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing
6. CABG for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD who have survived sudden cardiac death or sustained ventricular tachycardia
7. In patients with prior PTCA, CABG or PTCA for recurrent stenosis associated with a large area of viable myocardium and/or high-risk criteria on noninvasive testing
8. PTCA or CABG for patients who have not been successfully treated by medical therapy and can undergo revascularization with acceptable risk
Class IIa
1. Repeat CABG for patients with multiple saphenous vein graft stenoses, especially when there is significant stenosis of a graft supplying the left anterior descending coronary artery. PTCA may be appropriate for focal saphenous vein graft lesions or multiple stenoses in poor candidates for reoperative surgery
2. PTCA or CABG for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD but with a moderate area of viable myocardium and demonstrable ischemia on noninvasive testing
3. PTCA or CABG for patients with 1-vessel disease with significant proximal left anterior descending CAD
Class IIb
1. Compared with CABG, PTCA for patients with 3- or 2-vessel disease with significant proximal left anterior descending CAD who have anatomy suitable for catheter-based therapy and who have treated diabetes or abnormal LV function
2. PTCA for patients with significant left main coronary disease who are not candidates for CABG
3. PTCA for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD who have survived sudden cardiac death or sustained ventricular tachycardia
Class III
1. PTCA or CABG for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD who have mild symptoms that are unlikely due to myocardial ischemia or have not received an adequate trial of medical therapy and
(a) Have only a small area of viable myocardium or
(b) Have no demonstrable ischemia on noninvasive testing
2. PTCA or CABG for patients with borderline coronary stenoses (50–60 % diameter in locations other than the left main) and no demonstrable ischemia on noninvasive testing
3. PTCA or CABG for patients with insignificant coronary stenosis (<50 % diameter)
4. PTCA in patients with significant left main CAD who are candidates for CABG

Source: Gibbons et al. [98]
PTCA is used in these recommendations to indicate PTCA and/or other catheter-based techniques such as stents, atherectomy, and laser therapy
ACC/AHA Classification
Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb: Usefulness/efficacy less well established by evidence/opinion
Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful and in some cases may be harmful

The randomised trials of initial medical treatment versus initial surgery showed that patients with left main stenosis >69 % and those with multivessel CAD with a proximal left anterior descending artery stenosis >69 % have a better late survival rate if they have coronary bypass surgery. Because the randomised trials of PTCA versus bypass surgery included an inadequate number of patients in these high-risk subsets, it cannot be assumed that the alternative strategy of PTCA produces equivalent late survival in such patients.

Meta-analysis of the randomised trials of medical management versus CABG have further indicated that patients without severe symptoms but with a proximal left anterior descending artery lesion have a better survival rate with surgery, even if they have normal left ventricular function and only 1-vessel disease. For these patients, data from the PTCA versus CABG trials appear to show that, at least for the first 5 years, the alternative revascularization strategy of PTCA does not compromise survival for patients who are good angiographic candidates for PTCA [94].

The recent publication of the 5 year results of the Syntax trial, which was a multi-center, randomized trial comparing outcomes in patients with triple vessel coronary artery disease undergoing CABG versus PTCA are very interesting. The survival for patients undergoing CABG surgery was significantly better than those of patients undergoing PTCA. [Syntax trial references]

Mechanical Circulatory Support

Circulatory assist devices were initially designed to support patients in hemodynamic collapse. Currently, they can be used in a wide range of clinical conditions including refractory heart failure. It is an established therapy as a bridge to transplantation with 70 % of patients successfully transplanted after implantation of a left ventricular assist device [3]. These devices allow patients to be sent home while awaiting a suitable donor heart. They also allow these patients to be mobile and rehabilitated prior to their transplantation.

Ventricular assist devices have many beneficial effects on myocardial function, which includes improvement in contractile performance, reversal of the downregulation of beta-receptors seen in heart failure and normalisation of chamber geometry with a reduction in myocardial fibrosis [95–98].

These devices can be divided into four main categories.

Counterpulsation Devices (Intra-aortic Balloon Pump)

This is the commonest used mechanical support that has had a long record of success. It is simple in design, easy to use and least expensive. This type of device is of limited use however, in patients with significant peripheral vascular disease, those with aortic dissections and significant aortic regurgitation.

Cardiopulmonary Assist Device

This has limited use outside the cardiac catheterisation laboratory. It provides full cardiopulmonary support analogous to that provided by bypass during cardiac surgery.

Left Ventricular Assist Devices

These can be further divided into intermediate and long-term devices. The intermediate-term devices can be thought of as true bridges to transplantation. They are intended to be removed during transplantation and are not designed for chronic, permanent support [99].

Long-term devices were designed as replacement therapy for patients with heart failure. Although they are FDA approved as a bridge to transplantation, patients with severe disease who are not eligible for transplantation have improved survival with long-term left ventricular assist devices compared to optimal medical therapy alone [100].

Total Artificial Heart

Another type of mechanical device is the total artificial heart. It is inserted orthotopically accompanied by the removal of the patient's own ventricles. A study in 2004 [101] found that patients supported with the total artificial

heart, compared to controls, had a significantly higher rate of survival to transplantation (79 % versus 46 %) and of overall survival at 1 year (70 % versus 31 %). Complications, which include infection, thromboembolism and bleeding, were frequent but deemed to have only affected the outcome in a minority of patients.

Mechanical devices with increased longevity are currently in trial or development that may obviate the need for heart transplantation in the future for a significant number of patients.

Cardiomyoplasty

Dynamic cardiomyoplasty is a procedure in which skeletal muscles are taken from a patient's back or abdomen, wrapped around an ailing heart and paced during ventricular systole. This procedure is experimental and performed only in limited numbers. Some studies have shown that in patients undergoing this procedure, the operative mortality decreased and there was an improvement in symptoms [102]. However, long-term outcome data with cardiomyoplasty is limited and its future for chronic heart failure remains uncertain [103].

Mechanical Inhibition of Dilatation

The Acorn CorCap cardiac support device is a simple, yet profound, new investigational strategy for treating moderate heart failure. It is intended to be an adjunctive therapy with standard medical and surgical heart failure management for patients with dilated cardiomyopathy. The biocompatible, mesh-like jacket is drawn up and anchored around the ventricles. By supporting the heart and reducing stress-mediated myocardial stretch, left ventricular dilatation is limited with improvement in LVEF. Preliminary data suggest that the device produces an improvement in heart failure symptoms, LVEF, end-diastolic and end-systolic dimensions, and quality of life [104].

Cardiac Transplantation

Cardiac transplantation is the treatment of choice for many patients with end-stage heart failure who remain symptomatic despite optimal medical therapy. It can improve both survival and quality of life in this patient population. In 1999, the International Society for Heart and Lung Transplantation reported that there was annual mortality rate of approximately 4 % after the first year of heart transplantation. The survival rate was 79 % at 1 year and 50 % at 8.8 years overall [105].

Patients who should be considered for heart transplantation are listed in Table 3.7 [106]. The main indications are to improve survival and to enhance the quality of life. This benefit is easy to demonstrate in the moribund, hospitalised

Table 3.7 Criteria for patients with heart disease considered for cardiac transplantation who do not respond to maximal medical therapy

A. Systolic heart failure as defined by left ventricular ejection fraction (LVEF) <35 %
Excluded etiologies
1. Amyloid
2. Human immunodeficiency virus (HIV)
3. Cardiac sarcoma
B. Ischemic heart disease with intractable angina
1. Not amenable to coronary artery bypass graft (CABG) or percutaneous coronary intervention
2. Maximal tolerated medical therapy not effective
3. Rejected for direct myocardial revascularization or transmyocardial revascularization or the procedure attempted was unsuccessful
C. Intractable arrhythmia that is uncontrolled with implantable cardioverter-defibrilattor
1. Not amenable to electrophysiologic guided single or combination medical therapy
2. Not a candidate for ablative therapy
D. Hypertrophic cardiomyopathy with NYHA class IV symptoms that persist despite maximal therapy
1. Alcohol injection
2. Myomectomy
3. Mitral valve replacement
4. Pacemaker therapy
E. Congenital heart disease in which fixed pulmonary hypertension is not a complication

Source: Data from Steinman et al. [106]

patients, but is less clear in many ambulatory patients. In keeping with the recommendations from the ACC/AHA task force [11], the minimum requirements for consideration for cardiac transplantation are as follows:

A history of repeated hospitalisations for heart failure
Escalation of intensity for medical therapy
A reproducible VO_2max of less than 14 ml/kg/min is a relative indication, while a VO_2max of less than 10 ml/kg/min is an absolute indication in otherwise appropriate candidates

Other indications recommended by the ACC/AHA tack force include:

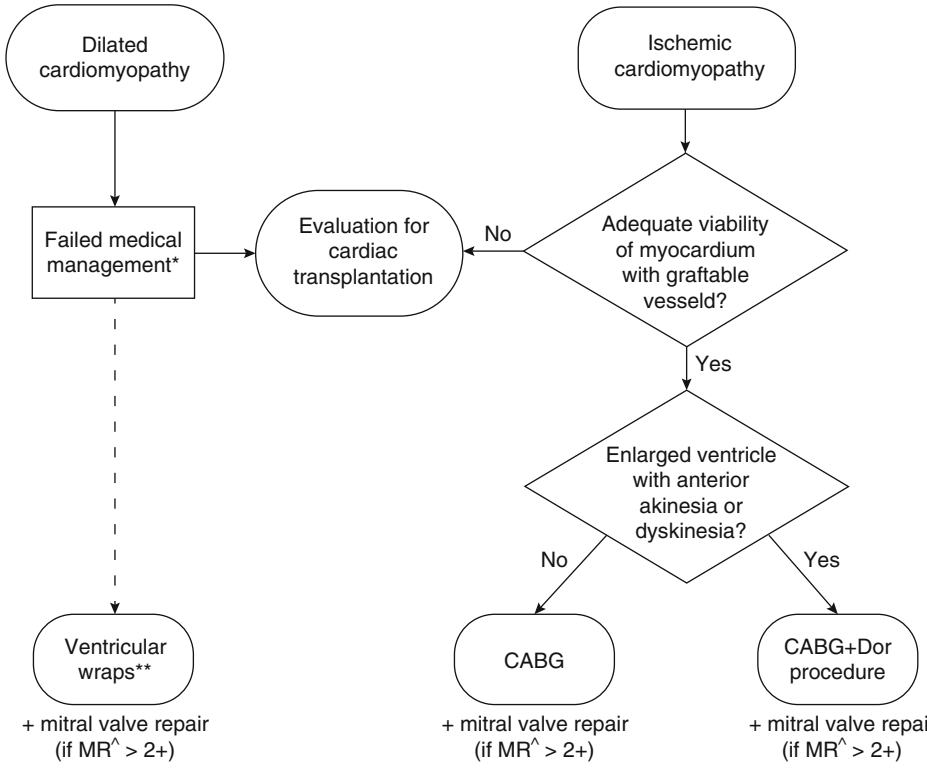
Refractory cardiogenic shock
Continued dependence on intravenous inotropes to maintain adequate organ perfusion
Severe symptoms of ischemia that limit routine activity and are not amenable to revascularization (absolute indication) or recurrent unstable angina not amenable to other intervention (relative indication)
Severe symptomatic ventricular arrhythmias refractory to all therapies

Summary

To summarize, the surgical management for patients with heart failure can be divided into two broad categories based on the type of underlying cardiomyopathy. Hence, care must be taken to accurately diagnose these patients as either having dilated cardiomyopathy or ischemic cardiomyopathy. There are not many surgical options available for dilated cardiomyopathy. If maximal medical therapy, which includes BiV pacing for a widened QRS complex, has failed, these patients are usually referred for cardiac transplant evaluation. Mitral valve repair is performed in these patients, for MR of 2+ or greater, if they are appropriate surgical candidates. The role of the various cardiac wraps still remains unclear. Ventricular assist devices can be used here as a bridge to transplantation if the patient becomes unstable.

The surgical management of heart failure due to ischemic cardiomyopathy is more complex. Treatment options depend on the size of the ventricles and the presence or absence of MR. As in patients with dilated cardiomyopathy, mitral valve repair is warranted for patients with MR of 2+ or greater. Patients with ischemic cardiomyopathy who have no valve pathology should have a CABG, if there is viable myocardium and graftable vessels. However, the Dor procedure should be performed concurrently with CABG if these patients also have enlarged ventricles with anterior akinesia or dyskinesia. Cardiac transplantation is reserved for failure of the above strategies or if there is insufficient viable myocardium (Fig. 3.1).

Heart failure is a major cause of mortality and morbidity in the United States. Although medical treatment in improving, a substantially large proportion of patients with heart failure should be considered for more advanced therapies. An aggressive approach to surgical revascularization, correction of mitral insufficiency, or reversal of left ventricular remodelling should be considered in any patient who has exhausted pharmacologic therapy. Such procedures should be performed in large dedicated centres that have specialized expertise with these therapies in patients with end-stage heart failure.



* Includes biventricular pacing in presence of widened QRS complex

** Insufficient data presently to support this approach

^ Mitral regurgitation

Refer for cardiac transplant evaluation if failure of surgical strategy

Fig. 3.1 Algorithm for surgical management of heart failure

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Transplantation for End-Stage Heart Disease

4

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The history of cardiac transplantation is an intriguing story which started as a clinical experiment over four decades ago resulting in depressingly poor results to the point that the procedure risked abandonment as futile therapy. An era of renaissance emerged coincident with the introduction of cyclosporine-based immunosuppression evolving into an era where cardiac transplantation was regarded as the primary and "gold standard" therapy for end-stage heart disease. No doubt other factors and experience played into this development. Cardiac transplantation now, however, has entered quite a different era as a result of the considerable imbalance between the number of available donor hearts and the much greater number of potential recipients. Although long-term survival after cardiac transplantation has improved dramatically, the imperfections of current immunosuppression and the consequence of chronic rejection manifesting as coronary allograft vasculopathy continue to limit the long-term effectiveness of this therapy. In this present time, cardiac transplantation is but one of many surgical and nonsurgical alternatives for patients with end-stage heart disease. The challenge in this era is the accurate assignment of one or more therapies for an individual patient to produce the maximal benefit in terms of life expectancy and quality of life. The appropriate assignment of therapy for an individual patient is predicated upon the generation of patient-specific (which implies risk adjusted) time-related survival estimates for these various therapies, but currently the widespread application of this process remains elusive.

Although the concept of *survival benefit margin* [1] may not necessarily be articulated, it is embodied in the decision-making processes throughout transplantation for an individual patient. It permeates decision making regarding

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_4

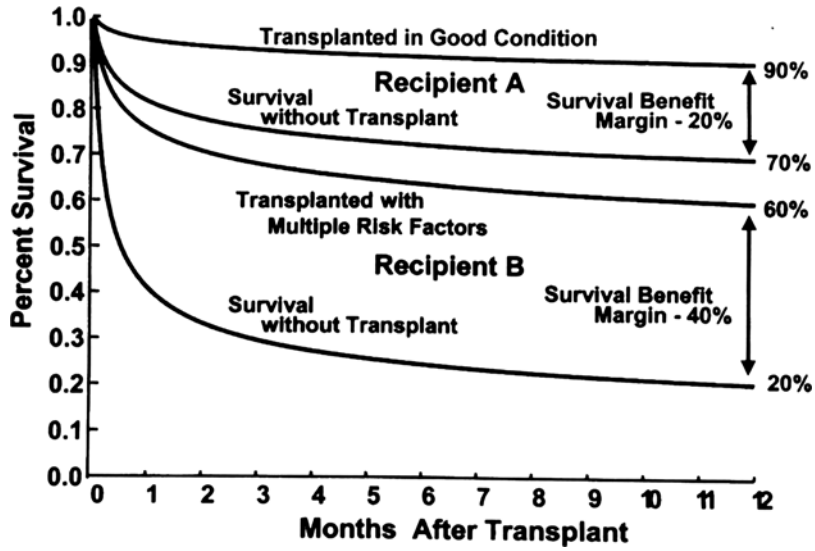

Fig. 4.1 Hypothetical depiction of survival benefit margin for a stable recipient in good condition (Recipient *A*) and a seriously ill recipient with multiple risk factors (Recipient *B*) (Kirklin et al. [1] with permission)

alternative surgical and nonsurgical therapies, listing for transplantation, donor selection, and donor-recipient matching. In essence, the concept of survival benefit margin refers to the difference in predicted survival for an individual patient between the natural history without transplantation and that of cardiac transplantation. Ultimately, decision making for an individual patient represents a very difficult balance between maximizing survival benefit margin (such as recipient B in Fig. 4.1), but with the potential for inferior survival compared with a recipient whose survival benefit margin is not as great (recipient A in Fig. 4.1), even though long-term survival is superior. It is the improving results of cardiac transplantation, the results of surgical and nonsurgical alternatives to transplantation, and the changing landscape of donor organ availability (such as the use of "marginal" donor hearts) that makes application of these important allocation principles so challenging.

Recipient Evaluation, Indications and Listing for Transplantation

The *evaluation* process for patients with end-stage heart disease integrates the goals of avoiding cardiac transplantation either prematurely or too late in the natural history of the disease, considering alternative therapies to cardiac transplantation, and detecting comorbidity that would contraindicate transplantation. Therefore, the approach to patients with end-stage heart disease [1] is to (a) detect potentially reversible causes of heart failure, (b) evaluate severity of heart failure and functional capacity, (c) tailor medical therapy to relieve symptoms, (d) assess risks of rapid progression of heart failure or sudden death, (e) identify indications for transplantation, (f) exclude contraindications to transplantation, (g) and throughout the evaluation and listing process, continue to manage heart failure and regularly reevaluate the patient to ensure appropriateness of the therapeutic strategy.

A critical part of the evaluation process is the identification of processes for which there may be an alternative to transplantation. For example, it is important in patients with ischemic heart disease to determine the extent of myocardial viability since the disease may be amenable to percutaneous or surgical options. Similarly in patients with end stage valvular heart disease an assessment must be made of the likelihood that the patient may achieve equivalent or better survival with conventional valvular surgery as compared with cardiac transplantation. Non-surgical therapy [2] involves a number of possible

strategies. Pharmacologic therapy with vasodilator agents, diuretics and beta blockers must be optimized and it is important that the results of maximal medical therapy should be observed for several months if possible before proceeding with consideration of cardiac transplantation. Control of arrhythmias [2] is an important issue – ventricular arrhythmias should be managed with anti-arrhythmic therapy, catheter ablation and device implantation or some combination of these treatments. In patients with atrial fibrillation, restoration of sinus rhythm or rate control is required. It is important that counterproductive agents be discontinued such as alcohol, illicit drugs and non-steroidal anti-inflammatory agents. Biventricular pacing should be considered in patients with prolonged QRS [2].

Implicit in the timing for listing for cardiac transplantation is the assumption that the natural history of end-stage heart disease can be predicted, but unfortunately this information is still quite imperfect. There have been a number of attempts made to develop predictive equations for survival with advanced heart failure, and this information is important to incorporate into the decision-making process; for example, the Heart Failure Survival Score (HFSS) from Columbia-Presbyterian Medical Center [3, 4]. This score was developed using multivariable methods to determine both noninvasive and invasively derived variables that predict either death without transplantation or the need for urgent cardiac transplantation.

The Seattle Heart Failure Model [5] is a widely used prediction model of survival of heart failure patients with the advantage that it uses clinical characteristics that are available in essentially all patients (as opposed to models that require invasively derived variables). An attractive feature of the Seattle Heart Failure Model is its ability to predict survival and the impact on survival of adding medications and/or devices in an individual patient (Fig. 4.2), although it has been suggested that this model overestimates survival in patients with implanted devices [6]. Other models (such as the MUSIC Risk Score) [7] incorporate biomarkers, in this case troponin and amino-terminal pro-brain natriuretic peptide. A predictive model of heart failure mortality [8] that incorporates multiple time related cytokine (tumor necrosis factor and interleukin-6) levels as well as "ensemble modeling", a technique developed from statistical machine learning that combines the results of multiple statistical models, (by adjusting for the biological variability inherent in clinical studies) has improved the accuracy of these predictive models.

A protocol for potential recipient evaluation is outlined in Table 4.1. Part of the evaluation includes determination of the immunologic status for the purpose of recipient-donor matching and assessment of the adequacy of the patient's social support and financial resources since deficiencies in these areas may be just as threatening to survival and quality of life as any comorbid medical condition.

It is important to remember that advanced heart failure may result in organ injury that may become irreversible and either compromise survival after cardiac transplantation or may contraindicate cardiac transplantation. It is implicit that consideration be given to cardiac transplantation before irreversible secondary changes become established.

General guidelines have been established as *indications* for cardiac transplantation [1] (Table 4.2) although increasing knowledge of the results of alternative therapies for patients with heart failure, improving results of cardiac transplantation with the seemingly immutable shortage of donor hearts, and the specific criteria that precipitates listing for transplantation are still very much in flux. However, it is generally accepted that patients should be considered for cardiac transplantation when they have New York Heart Association (NYHA) class III-IV heart failure, severe reduction in the quality of life due to their symptoms, and a predicted 2-year survival of less than approximately 60 %.

There are a number of *contraindications* to cardiac transplantation [2] (Table 4.3). Although there would be general agreement that many of these contraindications are absolute, some would be regarded as relative, based on programmatic experiential reasons or risk/benefit considerations in an individual patient. For example, in many programs renal dysfunction (due to intrinsic renal disease or associated with heart failure)

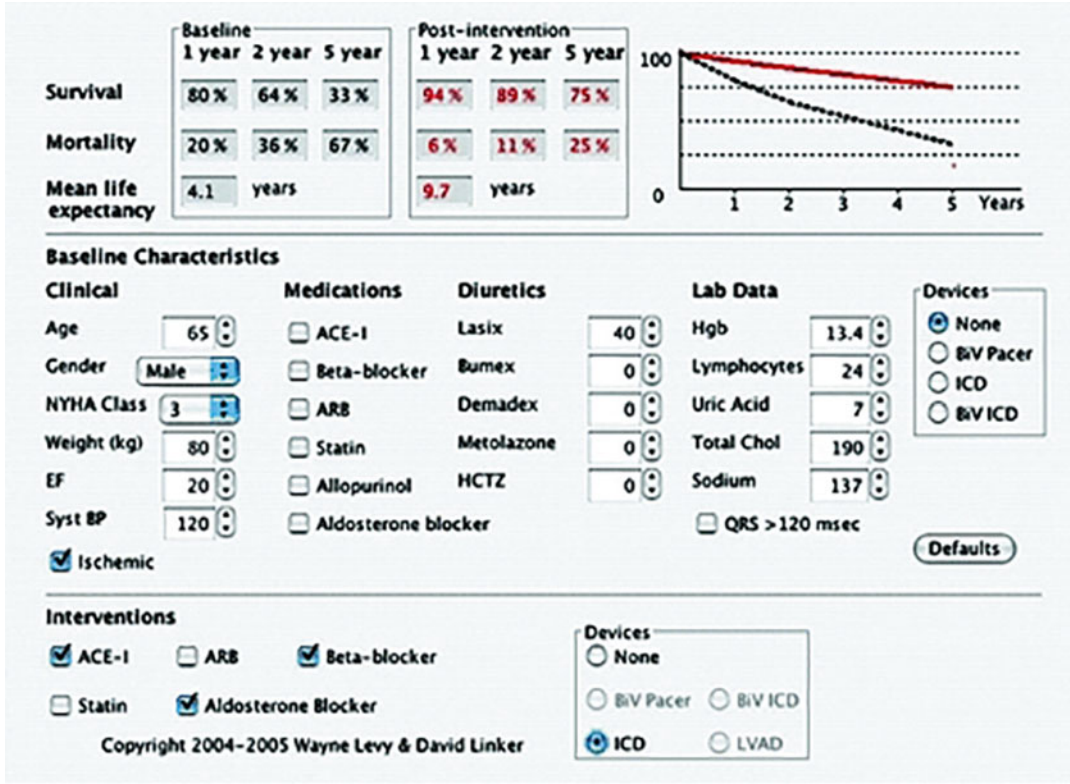

Fig. 4.2 An example of the output from the Seattle Heart Failure Model for a patient with the specified characteristics with the predicted survival before and after the listed interventions. The baseline survival curve is the *straight line* and the *dotted line* is the survival after intervention (Levy et al. [5] with permission. Copyright 2004–2005 Wayne Levy & David Linker)

would not be regarded as a contraindication as excellent results can be achieved with combined heart-kidney transplantation.

The etiologies of heart failure most frequently considered for transplantation are ischemic heart disease and dilated cardiomyopathy. A much smaller proportion of adult patients undergo transplantation for heart failure associated with previous correction of congenital heart disease such as a failing Fontan procedure, end-stage valvular heart disease, and retransplantation.

There are disease processes that were previously regarded as absolute contraindications to cardiac transplantation that are now being considered under experimental protocols. For example, amyloidosis has previously been regarded as an absolute contraindication to cardiac transplantation, but a protocol of orthotopic cardiac transplantation using extended-donor organs followed by high dose chemotherapy and stem cell transplantation in patients with primary amyloidosis, reported by Maurer and colleagues resulted in survival that was significantly better than medical treatment alone (75 % versus 23 % $p<0.0006$). Furthermore the survival of these patients was similar to that of patients receiving cardiac transplantation on the alternate as well as the standard list [9].

Information [10] from the registry of the International Society for Heart and Lung Transplantation illustrates the dramatic impact that *mechanical circulatory support* has had on the management of heart failure in cardiac transplantation. The proportion of patients receiving heart transplantation who were bridged with mechanical circulatory support (left ventricular assist device, right ventricular assist device, biventricular assist device support or total

Table 4.1 Evaluation protocol for cardiac transplantation

General
Complete history and physical examination
Nutritional status evaluation[a]
Blood chemistries including liver and renal profiles (bilirubin, SGOT[AST], alkaline phosphatase, BUN, creatinine, calcium, phosphorus, magnesium)
Hematology and coagulation profile (complete blood cell count, differential, platelet count, prothrombin time [or International Normalized Ratio], partial thromboplastin time, fibrinogen)
Serum electrolytes
Lipid profile[a]
Urinalysis
24-h urine for creatinine clearance (and protein if diabetic or urinalysis positive for protein[a]
Nuclear renal scan with measurement of effective renal plasma flow[a] (ERPF)
Pulmonary function testing with arterial blood gases
Ventilation-perfusion scan[a]
Stool for heme
Mammography[a]
Prostate-specific antibody (PSA)[a]
Abdominal ultrasound study (liver, pancreas, gall bladder, and kidney evaluation)
Carotid ultrasound
Social evaluation
Psychiatric evaluation
Neuropsychiatric evaluation (neurocognitive evaluation)[a]
Dental evaluation
Sinus films[a]
Cardiovascular
Electrocardiogram
Chest radiograph, (PA and lateral)
Two-dimensional echocardiogram with Doppler study
Exercise test with oxygen consumption (peak Vo_2)
Right-heart catheterization with detailed hemodynamic evaluation
Shunt series[a]
Left-heart catheterization with coronary angiography[a]
Myocardial biopsy[a]
Radionuclide angiogram (gated blood pool study)[a]
Nuclear imaging study for myocardial viability (thallium-201 or positron emission tomography)[a]
Holter monitor for arrhythmias (if ischemic cardiomyopathy)[a]
Immunology
ABO blood type and antibody screen
Panel reactive antibody (PRA) screen
Human leukocyte antigen (HLA) typing (if to be listed for transplantation)
Infectious disease screening
Serologies for hepatitis A, B, and C; Herpes virus, human immunodeficiency virus (HIV), cytomegalovirus (CMV), toxoplasmosis, varicella, rubella, Epstein-Barr virus, veneral disease research laboratory (VDRL), Lyme titers[a], histoplasmosis and coccidioidomycosis complement-fixing antibodies[a]
Throat swab for viral cultures (CMV, adenovirus, Herpes simplex virus)[a]
Urine culture and sensitivity[a]
Stool for ova and parasites[a]

Kirklin et al. [1] with permission
[a]Only performed if appropriate or indicated

Table 4.2 General indications for cardiac transplantation

Criteria for consideration of heart transplantation in advanced heart failure
Significant functional limitation (NYHA Class III-IV heart failure) despite maximum medical therapy that includes digitalis, diuretics, and vasodilators, preferably angiotensin-converting enzyme inhibitors, at maximum tolerated doses
Refractory angina or refractory life-threatening arrhythmia
Exclusion of all surgical alternatives to transplantation, such as the following:
Revascularization for significant reversible ischemia
Valve replacement for severe aortic valve disease
Valve replacement or repair for severe mitral regurgitation
Appropriate ventricular remodeling procedures
Indications for cardiac transplantation determined by severity of heart failure despite optimal therapy
Definite indications
Vo_2 max <10 ml/kg/min
NYHA Class IV
History of recurrent hospitalization for congestive heart failure
Refractory ischemia with inoperable coronary artery disease and left ventricular ejection fraction <20 %
Recurrent symptomatic ventricular arrhythmias
Probable indications
Vo_2 max <14 mg/kg/min (or higher with multiple other risk factors)
NYHA Class III–IV
Recent hospitalizations for congestive heart failure
Unstable angina not amenable to coronary artery bypass grafting, percutaneous transluminal coronary angioplasty with left ventricular ejection fraction <0.25

Kirklin et al. [1] with permission

Table 4.3 Contraindications to heart transplantation

Absolute contraindications
Systemic illness with a life expectancy of less than 2 years despite heart transplant, including
Active or recent solid organ or blood malignancy within 5 years (e.g. Leukemia, low-grade neoplasms of prostate with persistently elevated prostate-specific antigen)
AIDS with frequent opportunistic infections
Systemic lupus erythematosus, sarcoid, or amyloidosis that has multisystem involvement and is still active
Irreversible renal or hepatic dysfunction in patients considered for only HT
Significant obstructive pulmonary disease (FEV_1 <1 L/min)
Fixed pulmonary hypertension
Pulmonary artery systolic pressure >60 mmHg
Mean transpulmonary gradient >15 mmHg
Pulmonary vascular resistance >6 Wood units
Relative contraindications
Age >72 years
Any active infection (with exception of device-related infection in VAD recipients)
Active peptic ulcer disease
Severe diabetes mellitus with end-organ damage (neuropathy, nephropathy, or retinopathy)
Severe peripheral vascular or cerebrovascular disease
Peripheral vascular disease not amenable to surgical or percutaneous therapy
Symptomatic carotid stenosis

(continued)

Table 4.3 (continued)

Ankle brachial index <0.7
Uncorrected abdominal aortic aneurysm >6 cm
Morbid obesity (body mass index >35 kg/m^2) or cachexia (body mass index <18 kg/m^2)
Creatinine >2.5 mg/dL or creatinine clearance <25 mL/min[a]
Bilirubin >2.5 mg/dL, serum transaminases >3× normal, INR >1.5 off warfarin
Severe pulmonary dysfunction with FEV_1 <40 % normal
Recent pulmonary infarction within 6–8 weeks
Difficult-to-control hypertension
Irreversible neurological or neuromuscular disorder
Active mental illness or psychosocial instability
Drug, tobacco, or alcohol abuse within 6 months
Heparin-induced thrombocytopenia within 100 day

Mancini et al. [2] with permission
INR indicates international normalized ration
[a]May be suitable for HT if inotropic support and hemodynamic management produce a creatinine <2 mg/dL and creatine clearance >50 mL/min. Transplantation may also be advisable as combined heart-kidney transplantation

artificial heart) is now just over 30 %. The landscape of mechanical circulatory support is continually changing with improvements in the engineering aspects of the devices, evolution from pulsatile to continuous flow devices and the improvement in their reliability, as well as increasing clinical information that is providing some clarity to the appropriate situations where mechanical circulatory support may be of benefit. The use of mechanical circulatory support, particularly as a bridge to transplantation, represents a balance between the probability of survival to transplantation versus the serious potential complications associated with implantation of a mechanical circulatory support device including operative risk, infection, sensitization with allo-antibodies, stroke, acute and chronic bleeding episodes and device failure. In order to better refine the indications for mechanical circulatory support as a bridge to transplantation the NIH-funded Interagency Registry for Mechanical Assist Devices (INTERMACS) was initiated [11]. An important component of the appropriate application of mechanical circulatory support is a system of classification based on the severity of heart failure (Table 4.4). It is the application of mechanical circulatory support to patients with the highest acuity of illness (INTERMACS level 1 and 2) where the greatest amount of controversy exists, but current opinion is that in patients in cardiogenic shock, their best chance of survival is a temporary support device with stabilization and recovery of the inevitable organ dysfunction before proceeding with a more definitive device to bridge the patient to transplantation [12].

Table 4.4 INTERMACS levels of limitation at the time of implantation and the time frame of need for consideration of MCS

INTERMACS profile level	Status	Time frame
1	Critical cardiogenic Shock	Hours
2	Progressive decline	Days to week
3	Stable but inotrope Dependent	Weeks
4	Recurrent advanced HF	Weeks to few months if baseline restored
5	Exertion intolerant	Weeks to months
6	Exertion limited	Months, if nutrition and activity maintained
7	Advanced NYHA class III	

Mancini [2] based on reference [11], with permission
NYHA indicates New York Heart Association

It is important to be aware of the time course of events after implantation of mechanical circulatory support devices as a bridge to transplantation (Fig. 4.3). By 12 months after implantation of a device as a bridge to transplantation 32 % have undergone transplantation and 48 % still have the device, so durability of the device is essential.

It has been well demonstrated that *cardiac retransplantatio*n for early graft failure or intractable acute cardiac rejection has poor survival (Fig. 4.4) [13] and has been mostly discouraged. However, retransplantation for the indications of non-specific graft failure or coronary allograft vasculopathy has survival that is very similar to that of patients undergoing primary cardiac transplantation (Fig. 4.5) [14], although contrary information has suggested [15] that long-term survival after retransplantation may not be universally similar to that of primary transplantation.

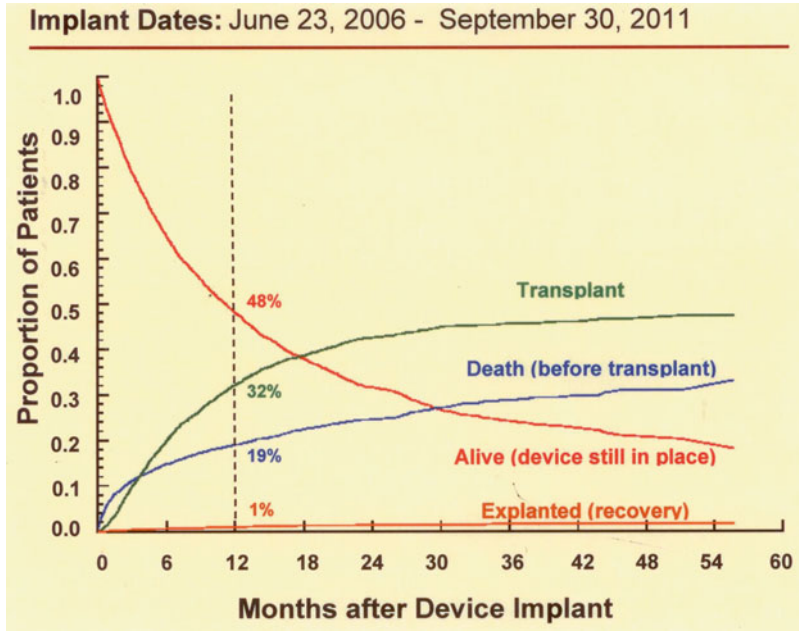

Fig. 4.3 Competing outcomes depiction for primary continuous flow device implant as a bridge to transplantation. The sum of the percentages of any time point equals 100 %. The depicted percentage is referred to the 12-month time point (Permission from: Interagency Registry for Mechanically Assisted Circulatory Support, National Heart Lung and Blood Institute. Contract Award HHSN268201100025C. http://www.uab.edu/intermacs. 5/12/15)

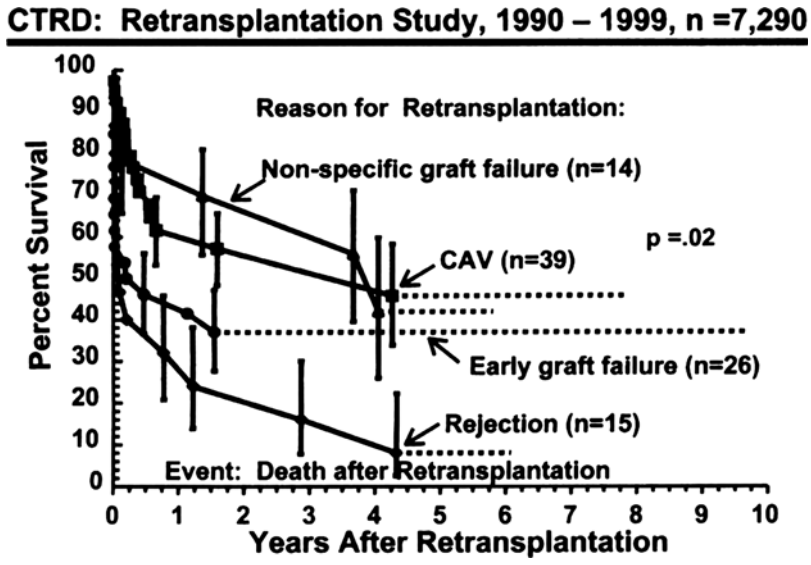

Fig. 4.4 Actuarial survival (Kaplan-Meier) stratified by reason for cardiac retransplantation. *Vertical bars* represent the standard error (Radovancevic et al. [13] with permission)

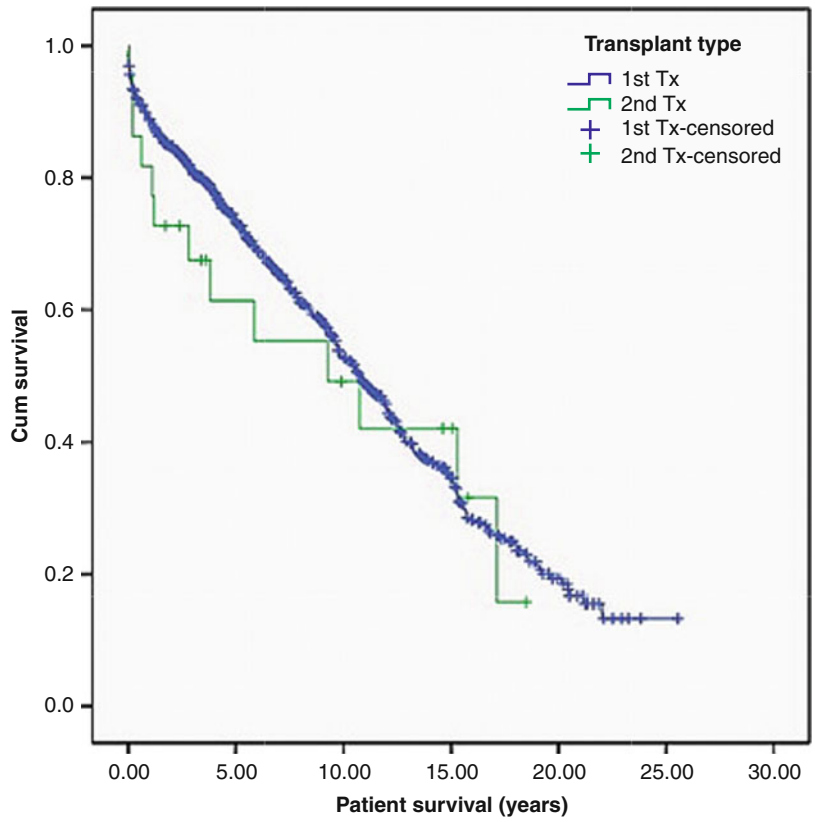

Fig. 4.5 Patient survival: 818 patients undergoing primary transplantation are shown in *blue*, and 23 patients undergoing elective retransplantation are shown in *green*. *Tx* transplantation (Copeland et al. [14] with permission)

In the United States, patients are *listed for cardiac transplantation* with United Network for Organ Sharing (UNOS) which is responsible for the donor organ distribution system. The algorithm for allocation of donor hearts is based on the severity of illness and medical urgency reflected by the need for interventions such as mechanical circulatory support, intra-aortic balloon pump, extracorporeal membrane oxygenation, mechanical ventilation and high dose inotropic drugs. A similar allocation system exists for pediatric patients with the inclusion of the presence in patients less than 6 months of age who are demonstrating reactive pulmonary hypertension [16]. Similar organ allocation systems exist around the world.

Cardiac Donor Evaluation

Cardiac transplantation is possible only through unselfish organ donation by families at the worst possible time of their lives. The procurement of hearts from heart-beating donors is predicated upon the worldwide acceptance of brain death criteria. The volume of cardiac transplantation is limited by donor heart availability and there will never be enough donor hearts available to fill the need that currently exists. The immutable shortage persists despite intensive educational programs, "presumed consent" laws in some European countries and "required request" protocols in the United States which mandate that hospitals approach families of brain dead patients regarding organ donation.

Effects of Brain Death on Cardiac Function

Brain death is a hostile environment for the heart and consequent donor heart dysfunction may preclude use of the donor heart or contribute to the 20 % incidence of primary graft failure following cardiac transplantation. The causes of donor

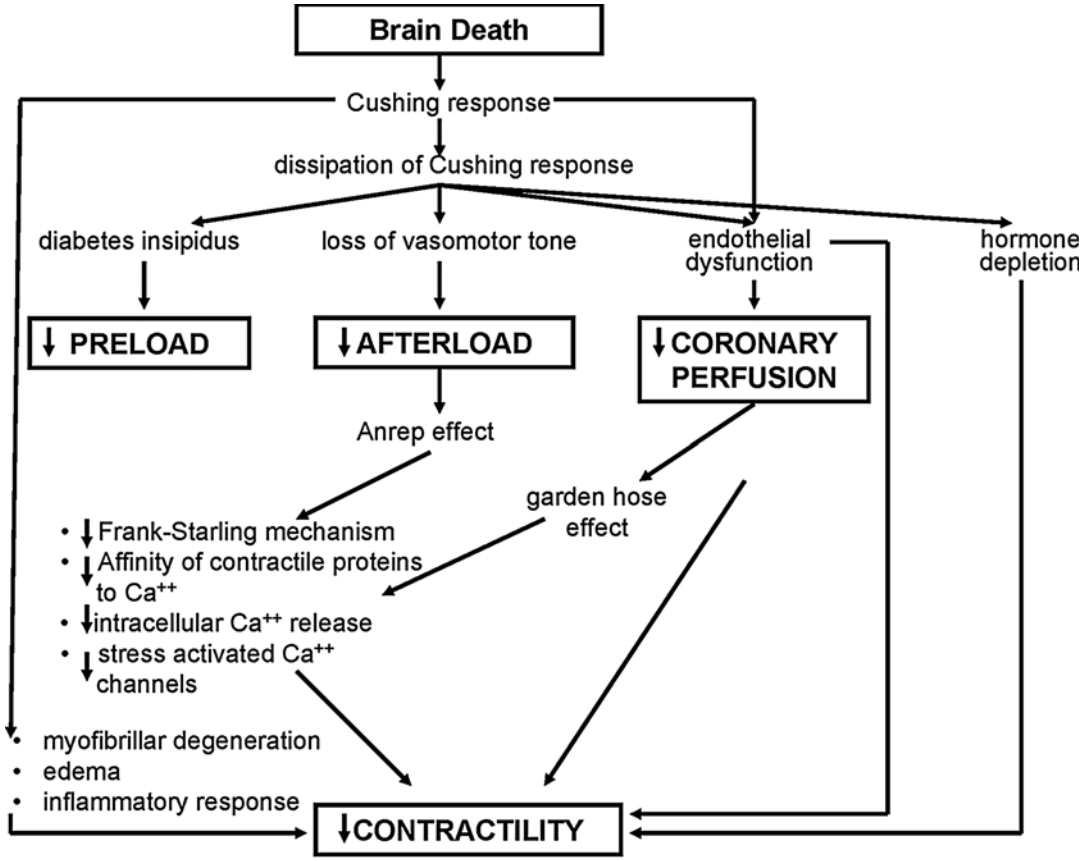

Fig. 4.6 Pathophysiological effects of brain death on the cardiovascular system following brain death (Based in part on Szabo) [17]

heart dysfunction can be conceptualized into two phases: those occurring with the Cushing response and those following dissipation of the Cushing response (Fig. 4.6).

The Cushing response is a "catecholamine storm" inducing hypertension, tachycardia, intense vasoconstriction, and an increase in myocardial oxygen demand, resulting in myocardial ischemia. The injury to the myocardium results in a phenomenon known as myofibrillar degeneration (which is also known as contraction band necrosis or coagulative myocytolysis) which is distinct from the coagulation necrosis seen in acute myocardial infarction. Myofibrillar degeneration is characterized histologically by the death of myofibers in a hypercontracted state with obvious contraction bands. The other important histological feature that may be seen is a mononuclear cellular infiltrate, which is evidence of the intense inflammatory response known to be activated with brain death. There are experimental studies [18, 19] that have detected upregulation of cytokines, chemokines, adhesion molecules and immunoregulatory molecules after brain death, which occur along with leukocyte activation. All of these likely have a role in endothelial cell injury and activation. When this period of intense sympathetic activity is dissipated, there is loss of sympathetic tone with a massive reduction in systemic vascular resistance contributing to the second phase of potential myocardial injury. This phase of injury can be conceptualized as abnormal loading conditions and coronary perfusion [20]. Intervention and donor management in this phase, offers some hope of retrieving donor hearts that would

ordinarily have been lost. There is experimental evidence that if coronary perfusion pressure is decoupled from aortic pressure and returned to pre-brain death levels, coronary blood flow and myocardial contractility can also be restored [20]. The exact mechanisms of how the loading conditions and coronary perfusion down-regulate myocardial contractility are not completely clarified, but may occur through the Frank-Starling mechanism or other less well-characterized mechanisms such as the Anrep effect [21, 22] (maintenance of optimal stroke work over a range of afterload conditions controlled through cellular mechanism) and the garden hose effect [23, 24], which has been described in isolated heart preparations. This effect refers to the relationship between increased coronary perfusion pressure and increased contractility by direct intramyocardial vessel stretch and this mechanism may possibly come into play at a level of coronary perfusion pressure below which autoregulation is no longer operational.

Table 4.5 Screening criteria for cardiac donation

General organ donation screening
Absence of infection
Hepatitis B and C and HIV
Negative blood cultures
Psychosocial/lifestyle screening
Absence of malignancy (exluding primary CNS tumors)
Screening for coronary disease
Age usually less than 55
Coronary angiography if possible:
Men >40 years
Women >45 years
No pathologic Q waves on ECG
No history of insulin-requiring diabetes
No other prior cardiac history
Screening for cardiac function
No requirement for high-dose inotropic support (after volume replacement)
No prolonged resuscitation
Normal echocardiogram (mild segmental wall motion or mitral prolapse not a contraindication, expanded criteria using moderate wall motion abnormalities if normal *coronaries*)

Modified from Hosenpud [25] with permission
CNS central nervous system

Screening for Cardiac Donation

Following declaration of brain death and obtaining consent, the process of determining suitability for cardiac donation is allowed to proceed. The screening process [25] (Table 4.5) has a number of goals. The general organ donation screening is to prevent the transmission of malignancies or the transmission of viral disease such as hepatitis B and C and HIV infection. Although it is generally considered that transplantation of hearts from donors who have died of primary brain tumors is safe (based on the very low incidence of extra neural spread of these tumors), transmission of primary brain tumors to a recipient has indeed been reported and for that reason organs from donors with CNS tumors of high grade malignancy should probably not be used [26]. The current recommendation [27] for the use of hearts from donors with *severe infection* is that they can be used provided [1] the donor infection is community acquired and death occurs within 96 h of the onset of the infection [2], repeat blood culture before organ procurement are negative [3], pathogen-specific antimicrobial therapy is administered to the donor [4], donor myocardial function is normal [5], there is no evidence of endocarditis by direct inspection of the donor heart. Exclusion of *coronary artery disease* (CAD) is necessary in cardiac donor males older than 40 years and females older that 45 years, although these age criteria may vary depending on the presence or absence of risk factors for CAD.

The determination of the adequacy of cardiac function should be delayed until hemodynamic stability has been obtained. Many donors have deranged loading conditions due to the very low systemic vascular resistance together with a low preload associated with the aggressive diuresis often used to control cerebral edema prior to progression to brain death and/or diabetes insipidus following brain death. As a consequence, these donor are often on high-dose adrenergic support, which, with optimization of loading conditions,

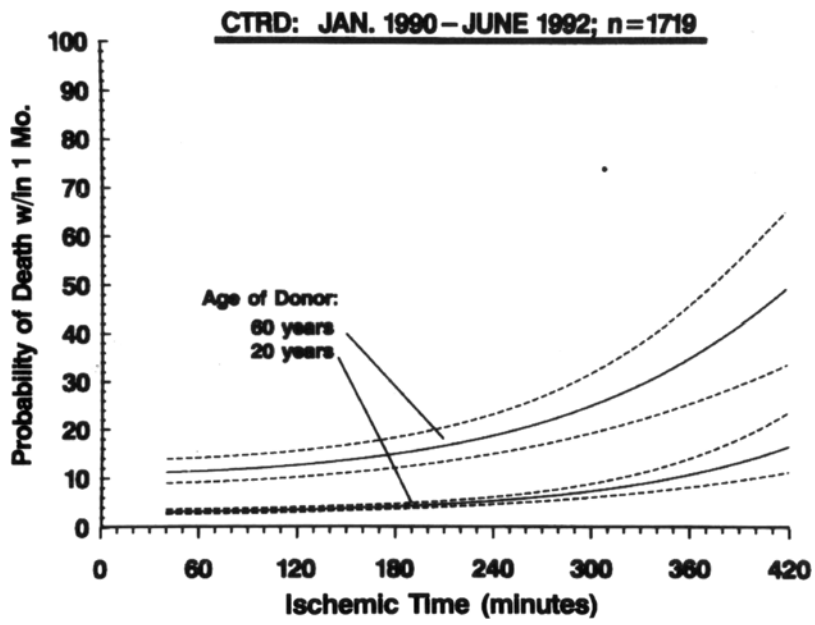

Fig. 4.7 Nomogram from donor/recipient multivariable analysis in hazard function domain depicts varying ischemic time for two donors, age 20 and 60 years. Equation is solved for 50-year-old male recipient who is not on a ventilator, not on a ventricular assist device, has not undergone previous sternotomy, and has a pulmonary vascular resistance of 2.2 Wood Units and male donor who is not diabetic, not receiving inotropic support, did not die of a cardiac arrest, and has no diffuse wall motion abnormalities. *Dashed lines* represent 70 % confidence limits around parametric curves (Young et al. [29] with permission)

can be rapidly weaned. At that stage, the echocardiogram has become the most useful test to evaluate left and right ventricular systolic function.

A number of biomarkers have been investigated as a means of discriminating donor hearts that should or should not be used for transplantation because of the possibility of post-transplant graft failure. Biomarkers that have been investigated include cardiac-specific troponins (cTnI and cTnT), TNF-α, IL-6, procalcitonin and B-Type naturetic peptide. These molecules reflect different aspects of the impact of brain death such as myocardial injury, myocardial wall stress and the pro-inflammatory environment of brain death but none have been found to be sensitive or specific enough to be useful [28].

Factors Effecting Post-transplant Donor Heart Function

Early graft failure represents an important cause of morbidity and mortality after cardiac transplantation and is impacted by a number of donor heart factors. However, when making a decision about the suitability of a particular donor these factors cannot be considered in isolation since they are all inextricably interrelated. Furthermore, the use of a donor heart with factors that may impair post-transplant function must always be considered in the context of the condition of the recipient and the urgency of transplantation.

A relationship exists between older *donor age* and the probability of graft failure and this risk is further exacerbated by increasing *ischemic time* (Fig. 4.7) [29]. This effect is no doubt related to the overall decline in myocardial reserves associated with increase in age. Even though this information is from an earlier era in transplantation, the same relationship between ischemic time and donor age and it's impact on survival after cardiac transplantation has been consistently demonstrated [30]. In general, the ischemic time should be less than 5.5 h. *Excessive inotropic support* (dopamine at a dose of 20 mcg/kg/min or

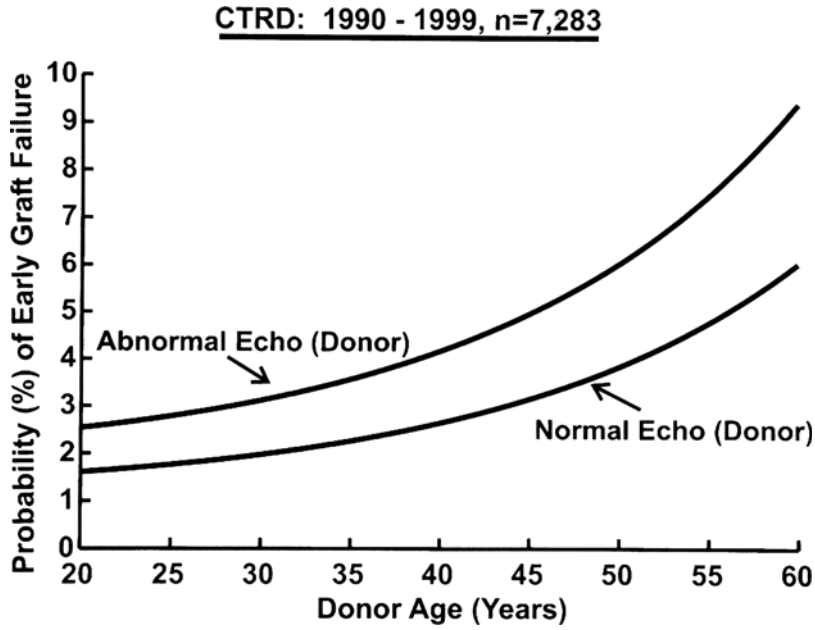

Fig. 4.8 Nomogram from Cardiac Transplant Research Database (CTRD) multivariable analysis depicting the effect of donor age and left ventricular function by echocardiography (echo) on fatal early graft failure (Young et al. [31] with permission)

similar doses of other adrenergic agents) contraindicates the use of the heart if these inotropic drugs are required despite optimization of filling pressures. *A discrete wall motion abnormality* on echocardiography increases the risk of early graft failure and such a donor heart should not be used [31]. The effect of discrete wall motion abnormalities becomes increasingly pronounced with older donor age (Fig. 4.8) [31]. The development of severe concentric *left ventricular hypertrophy* following cardiac transplantation is a clear independent risk factor for cardiovascular and all cause mortality [32, 33], and this hypertrophy may develop for a number of reasons including post-transplant hypertension and immunosuppression. There is compelling evidence that commencing the post-transplant course with a hypertrophied donor heart also negatively impacts survival. A donor heart left ventricular wall thickness of greater than 1.4 cm is associated with reduced survival and this has been demonstrated both in a univariate analysis (Fig. 4.9) and in a multivariable model [34]. Furthermore, the impact of donor left ventricular hypertrophy on survival worsens with increasing donor age and increasing ischemic time [35].

Donor hearts with potential toxicity have been considered for transplantation. *Cocaine abuse* has direct effects on the heart, which include vasoconstriction, endothelial dysfunction, and myocardial toxicity. These effects have been principally related to the intravenous use of cocaine and hearts from such donors are currently regarded as unsuitable for transplantation. However, donors with a history of non-intravenous cocaine abuse who have normal left ventricular systolic function with no evidence of left ventricular hypertrophy are currently considered suitable [36].

There are direct toxic effects of *alcohol* on the myocardium and recipients who have received hearts from donors with a history of significant alcohol abuse have inferior survival. Hence, if a strong history of chronic alcohol abuse can be elicited, currently hearts from these donors are not used for cardiac transplantation [37]. However, it should be mentioned that there is not unanimity in the information on this issue and there is evidence [38] that suggests the exact opposite, that donor chronic alcoholism may, in fact, have a protective effect on donor hearts. Because of the finding that this protective effect may translate into superior recipient survival to that over recipients receiving hearts from non-alcoholic donors, it has been suggested that it is safe to use donor hearts regardless of a history of alcoholism.

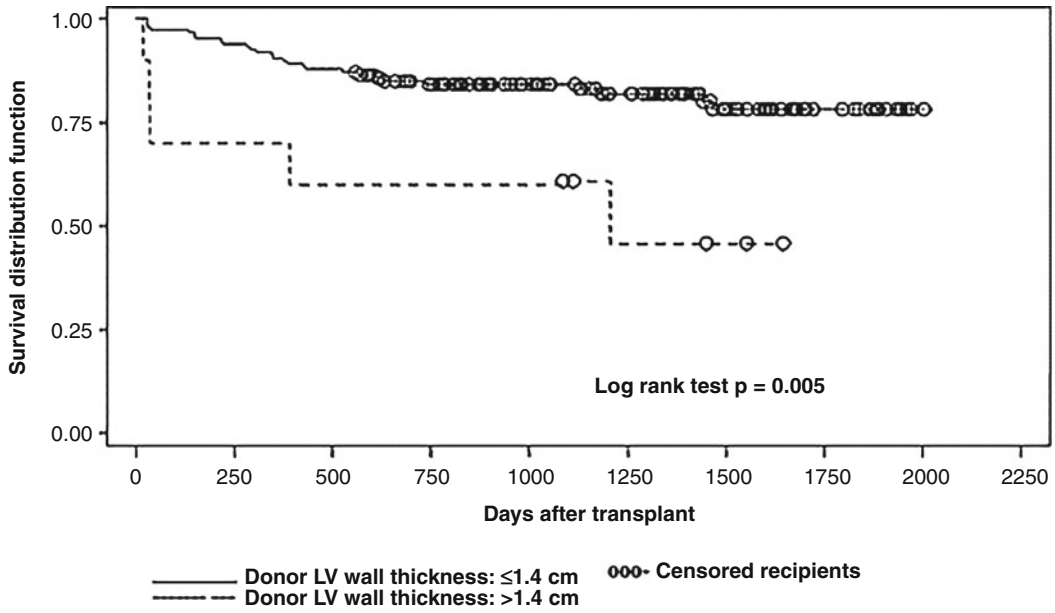

Fig. 4.9 Comparison of survival in recipients of donor hearts with left ventricular wall thickness of <1.4 cm versus >1.4 cm (log-rank test) (Kuppahally et al. [34] with permission)

Use of hearts from donors dying from *carbon monoxide poisoning* is still contentious [39]. However, use of hearts from such donors is probably safe, provided the electrocardiogram and echocardiogram are normal with minimal elevation of cardiac markers, and minimal inotropic requirements.

Transplantation of hearts from hepatitis C positive donors to hepatitis C negative recipients is associated with substantially inferior survival and this strategy cannot be recommended. However, transplantation of hearts from hepatitis C positive donors to hepatitis C recipients may be considered.

Special Situations

In order to increase the number of available donor hearts, a number of donor conditions may still be considered compatible with successful transplantation.

Donor *CAD* is not necessarily a contraindication to transplantation and coronary bypass surgery has been utilized on donor hearts. This concept of matching "recipients who would not ordinarily meet criteria for cardiac transplantation or retransplantation" to "marginal" donor hearts has given rise to the concept of the "alternate list" [40]. Survival of recipients with donors hearts that have undergone coronary bypass surgery appears to be very acceptable [41].

Although supplying only a very small number of donor hearts, the "*domino procedure*" (the use of a heart from a heart/lung transplant recipient) appears to provide just as good survival as the use of cadaveric donors [42].

Donor-Recipient Matching

Donor-recipient size matching should not be considered in isolation from other factors such as donor age and acuity of the transplant procedure. The use of hearts from donors whose body weight is no greater that 30 % below that of the recipient is generally considered safe. The heart from a male donor of average weight (70 kg) may be considered for any recipient of equivalent or greater weight, provided donor age is taken into account. Undersizing with older donors age is clearly associated with an increased risk [43], and certainly this information would argue

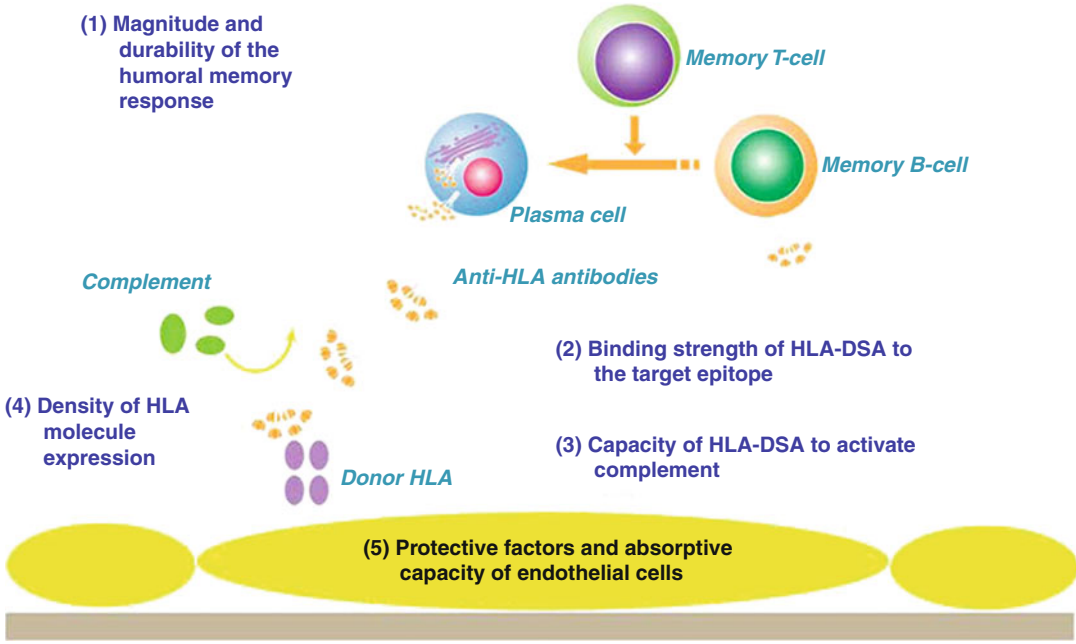

Fig. 4.10 Many factors on different levels might contribute to the pathogenicity of donor-specific HLA antibodies (*HLA-DSAs*): (1) the magnitude and durability of the humoral memory response upon rechallenge; (2) the binding strength of the HLA-DSA to the recognized epitope. Potentially, there might be a link between the immunogenicity of HLA epitopes evoking an antibody response and the magnitude of the immunologic memory response upon rechallenge; (3) the capacity of the HLA-DSA to activate the complement system; (4) the density of HLA molecules on the endothelial cell surface; (5) protective factors and the 'absorptive capacity' of endothelial cells that might modulate the clinical impact of HLA-DSA (i.e. accommodation) (Amico et al. [44] with permission)

against the use of small hearts from an older donor to "rescue" a critically ill recipient.

Sensitization due to the development of antibodies directed against human leukocyte antigens (HLA) is a major problem for heart transplantation and is associated with an increased risk for hyperacute rejection, acute rejection (cellular and antibody mediated), graft dysfunction, graft loss and development of coronary allograft vasculopathy. Sensitization may occur because of previous pregnancy, transfusion, previous transplantation and the use of homograft tissue that may be employed in correction of, for example, congenital heart disease. Desensitization strategies have been used with mixed results and the removal of donor specific antibodies at the time of transplantation does not necessarily prevent a memory immune response. There are a number of factors that dictate the impact of donor specific HLA antibodies on the transplanted heart (Fig. 4.10). However, there seems to be little doubt that if HLA donor specific antibodies activate complement that it is potentially very damaging to the transplanted heart. There are a number of ways of avoiding a cardiac transplant in the presence of donor specific antibodies. The complement-dependent cytotoxicity (CDC) crossmatch is the classic test which involves mixing potential recipient serum with donor T and B lymphocytes together in the presence of complement. The T-cell crossmatch generally reflects antibodies to HLA class I (expressed on all nucleated cells) and the B-cell crossmatch reflects HLA class I and II (class II expression is restricted to dendritic cells, macrophages and B-cells). There has been a move away from the CDC crossmatch to flow cytometry crossmatching which is more sensitive for detecting donor specific antibodies compared with the CDC crossmatch. A positive flow crossmatch in the presence of a negative CDC crossmatch suggests a non-complement fixing antibody, a non-HLA antibody or a low level antibody [45]. The development of solid phase matrices (beads)

coated with HLA antigens has allowed the detection and identification of HLA-specific antibodies in a potential recipient. These HLA-specific antibodies can then be compared with the HLA typing of the prospective donor, a strategy known as the *virtual crossmatch*. Virtual crossmatching is of particular importance to cardiac transplantation where donor lymphocytes may not be available for a CDC or flow crossmatch because of time constraints and the donor being at a remote location. The accuracy of virtual crossmatching and its ability to increase the access of sensitized patients awaiting heart transplantation to potential donors has been demonstrated [46–48].

Cardiac Transplant Procedure

Myocardial Preservation

Myocardial preservation during cardiac transplantation is vitally important. Biochemical derangements induced during the ischemic process may contribute to primary graft failure, and preservation strategies that improve post-transplant graft function may allow longer ischemic times and the use of marginal donor hearts, with greater confidence that post-transplant function will be satisfactory. Biochemical processes involved in myocardial preservation are complex, but the primary methods of achieving cellular and functional integrity of the myocardium are through hypothermia and mechanical arrest of the heart. The role of hypothermia is based on the observation that in mammalian enzyme systems there is an approximately 50 % reduction in enzymatic reactions for every 10 °C decline in cardiac temperature, which decreases but does not eliminate cellular activity completely [49]. Even though the heart is mechanically arrested, ATP is still being consumed at a low level to allow breaking of actin-myosin cross-brides. If ATP depletion continues below a threshold level, irreversible contracture will occur. Although the myocardium can use stored glycogen to produce ATP by anaerobic glycolysis to maintain an ATP level above the critical threshold, once contracture commences ATP consumption markedly increases. The maintenance of ion homeostasis is also an important requirement of preservation. Even though with hypothermia Na^+/K^+ ATPase activity is markedly reduced, passive ion movement will still occur down a concentration gradient. As a result, intracellular H^+ ions are exchanged for extracellular Na^+ ions, and Ca^{2+} ions are also exchanged for Na^+. This produces an increased intracellular solute accumulation with water entering the cell down an osmotic gradient, and this intracellular edema may result in disruption of structural integrity. It is the accumulation of Ca^{2+} in the cytoplasm that may, on reperfusion, result in hypercontracture [50].

Preservation solutions are distinguished by their ionic composition as either "extracellular" or "intracellular". Clinical experience with University of Wisconsin (UW) Solution (an intracellular solution) demonstrates excellent myocardial preservation out to approximately 6 h. UW solution also contains oxygen-derived free-radical scavenger molecules in an endeavor to ameliorate the ischemia/reperfusion injury that may be in part related to oxygen-derived free radical production. Preservation solutions may contain a variety of agents including impermeants (such as raffinose and lactobionate) and oncotic molecules (such as hydroxyethyl starch), metabolic substrates as well as molecules that inhibit the consumption of ATP and inhibit the Na^+/H^+ exchange, and Mg^{2+} as a Ca^{2+} antagonist [51].

An alternative to the current preservation method of cardioplegic arrest and cold storage is continuous perfusion of an empty beating heart with an oxygenated nutrient-rich blood perfusate. There is experimental evidence [52–54] that a continuous perfusion method results in improved cardiac performance, reduced ischemic-reperfusion injury and improved preservation of myocardial ultrastructure. This experimental information has resulted in the development of the TransMedics[1] device which is a perfusion system that is being used clinically for transport of donor hearts. This system

[1] TransMedics, Inc., Andover, MA.

does have the potential to increase the distance over which hearts are transported without incurring an ischemic injury, the possibility of metabolically "resuscitating" hearts that may have been regarded as unsuitable for transplantation and provide a mechanism by which donor hearts can be functionally evaluated prior to transplantation.

Technique of Orthotopic Cardiac Transplantation

The biatrial orthotopic cardiac transplant procedure that was developed by Lower and Shumway [55] has remained unchanged for approximately 30 years. The bicaval orthotopic technique is now the recommended technique. The bicaval technique appears to be free of geometric distortion and as a consequence has superior left and right atrial function, better right and left atrial emptying, less tricuspid regurgitation and lower probability of postoperative permanent pacemaker implantation compared with the biatrial technique [56–59] and it appears that these benefits may possibly translate into a survival benefit in favor of the bicaval technique [60, 61]. The donor heart procurement procedure involves an incision in the left atrium to decompress the left ventricle and division of the inferior vena cava to decompress the heart, cross-clamping of the ascending aorta, and commencement of the infusion of preservation solution together with topical cooling. The heart is excised by transecting the inferior vena cava, superior vena cava (at the confluence of the innominate and right interval jugular vein), ascending aorta, and the main pulmonary artery (or pulmonary artery branches if the lungs are not being procured), and transection of the left atrium above the atrioventricular groove (or pulmonary veins if the lungs are not being procured) (Fig. 4.11). The heart is triple bagged with preservation solution and ice slush.

In the recipient operating room a median sternotomy is performed and cardiopulmonary bypass is established with separate caval cannulation. Following aortic cross-clamping and snaring of the caval tapes, cardiectomy is performed by entering the left atrium anterior to the right pulmonary veins and carrying this incision superiorly and inferiorly under the cavae. The right atrium is divided well above the right atrial-inferior vena cava junction and also on the atrial side of the superior vena caval-right atrial junction. The ascending aorta and main pulmonary artery are divided (Fig. 4.12).

Bicaval Technique

The left atrial anastomosis is constructed using 3-0 polypropylene as for biatrial orthotopic cardiac transplantation (Fig. 4.13). The inferior vena cava anastomosis is performed with continuous 4-0 polypropylene and the superior vena caval anastomosis is performed with continuous 5-0 polypropylene. The pulmonary artery anastomosis is then performed with continuous 5-0 polypropylene following which the aortic anastomosis

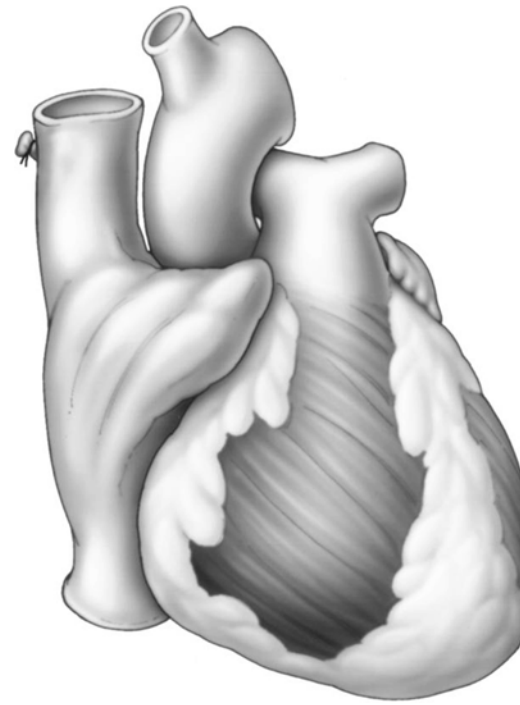

Fig. 4.11 Completed excision of donor heart. Additional length of superior vena cava has been obtained in preparation for a bicaval implantation (Kirklin et al. [36] with permission)

is performed with continuous 3-0 polypropylene (Fig. 4.14). Following deairing the aortic cross-clamp is removed from the heart and reperfused. An alternative sequence is to perform both the superior vena cava and pulmonary artery anastomoses following cross-clamp removal with the heart in a beating, perfused state. When rewarming is complete and cardiac function is satisfactory, the patient is weaned from cardiopulmonary bypass.

Post-transplant Immunosuppression

The distinction between acute cellular cardiac rejection and antibody mediated rejection is somewhat artificial as both the T-cell and B-cell responses are interlinked. Post-transplant immunosuppression is primarily directed against the T-cell activation but it also has consequent B-cell line effects. The mechanism of action of the immunosuppressive agents that are used for post-transplant immunosuppression is depicted in Fig. 4.15.

Immunosuppressive Modalities

Corticosteroids have a long history in transplant immunosuppression and are still regarded as an essential component of the perioperative immu-

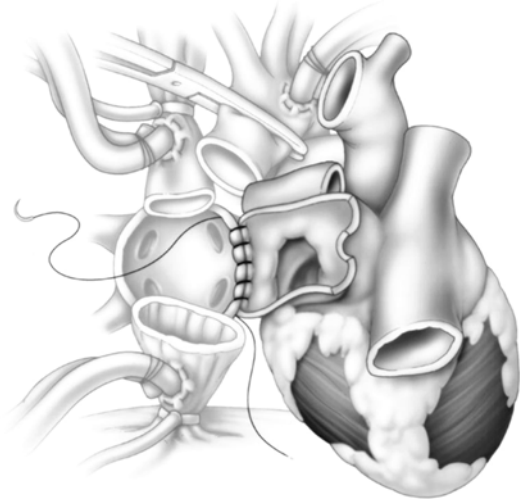

Fig. 4.13 Commencement of left atrial anastomosis in the bicaval technique (same as for biatrial orthotopic cardiac transplantation) (Kirklin et al. [36] with permission)

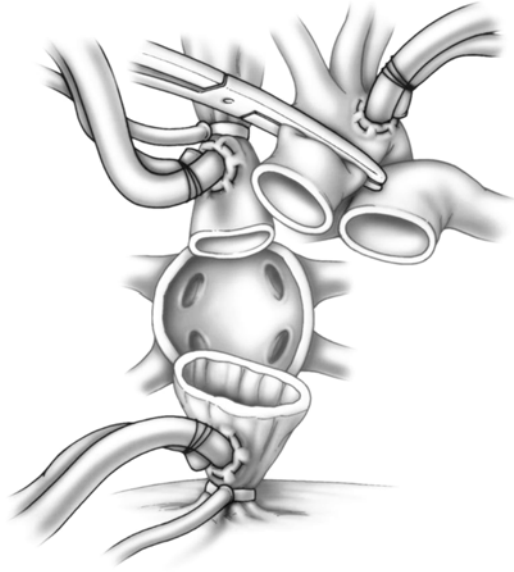

Fig. 4.12 Division of the right atrium to create superior and inferior vena cava cuffs for bicaval technique. The great vessels are divided as in the standard orthotopic method (Kirklin et al. [36] with permission)

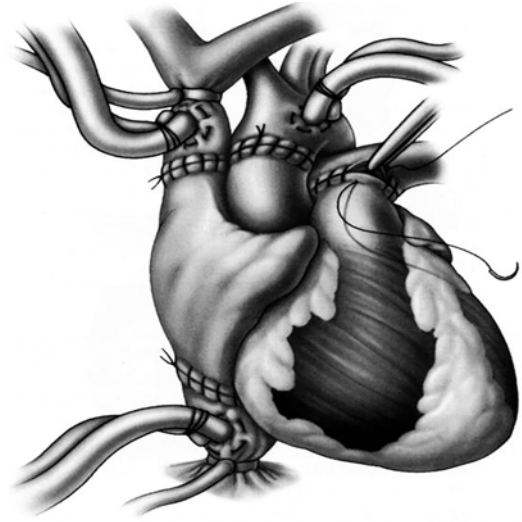

Fig. 4.14 Completion of bicaval transplant technique, showing the inferior vena cava, superior vena cava, aortic and pulmonary artery anastomoses (Kirklin et al. [36] with permission)

nosuppression protocol in cardiac transplantation. The benefit of corticosteroids is based on both their immunosuppressive and anti-inflammatory properties. The quite nonspecific immunosuppression properties of steroids related to their effect at a number of levels of T-cell activation, including suppression of antigen presentation to the T-cell and suppression of gene transcription in the nucleus to inhibit the expression cytokine such as interleukin-2 (IL-2) as well as a number of other cytokines. Corticosteroids also suppress macrophage function and B-cell proliferation, inhibit transmigration of leukocytes through blood vessels and reduce adhesion molecule expression. The anti-inflammatory properties of corticosteroids are due to inhibition of inflammatory mediators such as leukotrienes and prostaglandins and, probably through this mechanism, promote rapid reversal of symptoms of clinical rejection. However, it is the toxicity of corticosteroids that is responsible for much of the morbidity associated with immunosuppression, such as diabetes, obesity, impaired wound healing, avascular necrosis of the femoral head,

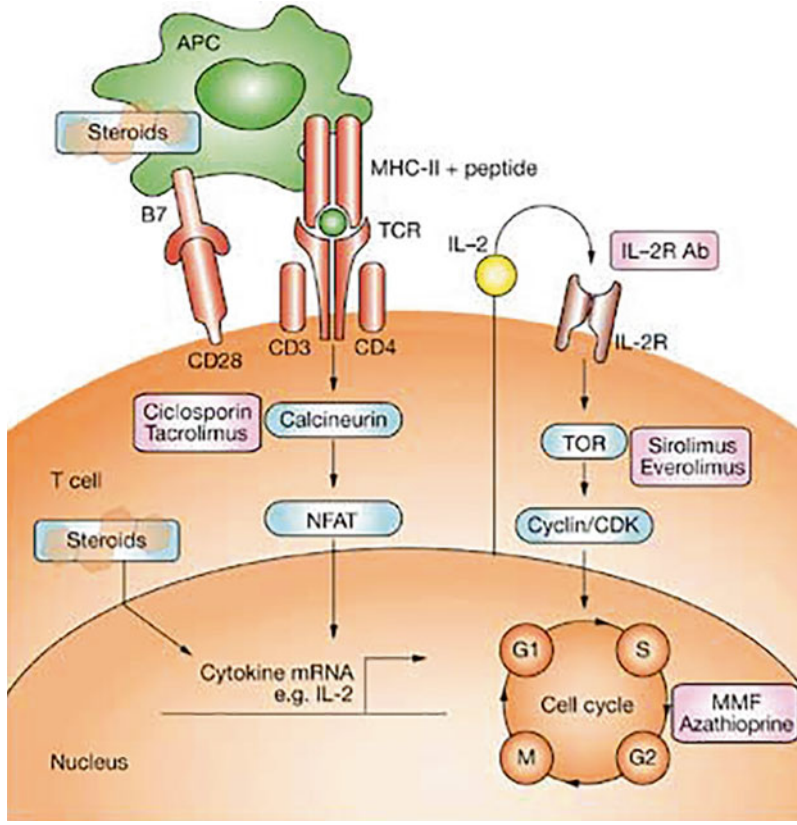

Fig. 4.15 Schematic of mechanisms of action of immunosuppressive drugs. T-cell proliferation results from activation after presentation of donor antigen (peptide) by antigen-presenting cells in conjunction with the major histocompatibility complex class II and B7 complex. This mechanism results in activation of calcineurin, which leads to production of interleukin-2. Autocrine stimulation by interleukin-2 results in cell proliferation by a pathway involving target of rapamycin and cyclin/cyclin – dependent kinase. Immunosuppressive agents (shown in *pink boxes*) exert their effects at a number of different targets to prevent T-cell proliferation. G1 (first growth phase), S (synthesis of DNA), G2 (second growth phase) and M (cell division) represent the phases of the cell cycle. *APC* antigen-presenting cell, *CDK* cyclin-dependent kinase, *IL-2* interleukin-2, *IL-2R* interleukin-2 receptor, *IL-2R Ab* interleukin-2-receptor antibody, *MHC* major histocompatibility complex, *MMF* mycophenolate mofetil, *mRNA* messenger RNA, *NFAT* nuclear factor of activated T cells, *TCR* T-cell receptor, *TOR* target of rapamycin protein (Kobashigawa et al. [62] with permission)

osteoporosis, cataracts, pancreatitis, and gastrointestinal complications such as peptic ulcer disease and colonic perforation. Because of this important toxicity, eliminating corticosteroids from the immunosuppression protocol is a goal that has been variably achieved. Patients most likely to benefit from steroid-free immunosuppression are pediatric cardiac transplant patients, postmenopausal females, patients with severe osteoporosis, insulin-dependent diabetes, and marked obesity.

The availability of *calcineurin inhibitor* (CNI) based immunosuppression (*cyclosporine or tacrolimus*) was one of the advances that marked the turning point in cardiac transplantation from an era of poor results to one of a mature effective therapy. The mechanism of action of cyclosporine is blockade of the calcineurin pathway, hence blocking the transcription of IL-2 and other cytokines. Cyclosporine, however, is associated with a number of toxic effects, including nephrotoxicity, hypertension, hepatotoxicity, neurologic problems including hand tremors and seizures, gingival hyperplasia, and hypertrichosis. The nephrotoxicity may manifest early after transplantation and appears to be mediated through renal arteriolar vasoconstriction. Chronic cyclosporine nephrotoxicity, which is associated with prolonged use of the drug, is characterized by patchy glomerular sclerosis and interstitial fibrosis within the renal parenchyma. The original cyclosporine formulation was oil based and its gastrointestinal absorption was rather variable. The development of a microemulsion formulation of cyclosporine has reduced the variability in absorption with more reliable blood levels.

Tacrolimus inhibits T-cell activation and proliferation through the blockade of calcineurin, but by a mechanism entirely different from that of cyclosporine. The place of tacrolimus was initially as "rescue therapy" for cardiac transplant patients with resistant rejection but is now used as a primary agent because of the demonstration of lower rejection rates (but not superior survival) compared with cyclosporine. The toxicity of tacrolimus includes nephrotoxicity (although there is some evidence that it may be less nephrotoxic than cyclosporine), neurologic side effects including tremor, headache, confusion (which are dose related), glucose intolerance, and hyperkalemia. There is some evidence that hypertension may be less prevalent than with cyclosporine.

Azathioprine has been a component of immunosuppression since the earliest days of transplantation. It is a purine analogue which inhibits purine synthesis and therefore interferes with DNA and RNA synthesis, consequently suppressing T- and B-cell proliferation. The most important toxicity of azathioprine is myelosuppression, which is dose dependent. Other toxicity includes hepatotoxicity and pancreatitis. Azathioprine may also predispose to malignant transformation, particularly development of cutaneous squamous cell carcinoma.

Mycophenolate mofetil (*MMF*) inhibits the de novo purine synthesis pathway and since human lymphocytes are able to synthesize purine DNA only through the de novo pathway, they are particularly susceptible to the action of this drug. As a result, MMF inhibits the proliferation of both T- and B-cells. The most frequent toxicity of MMF is gastrointestinal, including nausea, vomiting, and diarrhea, which may be severe enough to require discontinuation. Although evidence for the superiority of immunosuppression provided by MMF compared to azathioprine is sparse, the suggestion [63] that MMF may result in lower mortality (decreased rejection and incidence of rejection and infection) and reduction in the incidence of grade 3A or greater rejection and the requirement for rejection treatment has resulted in MMF largely replacing azathioprine as primary immunosuppression.

Cytolytic therapy with anti-lymphocyte globulins was originally developed for use as induction therapy. Polyclonal antibodies are produced by inoculation of animals with human lymphocytes, thymocytes, and lymphoblasts, and hence their mechanism of action is directed against a number of T-cell molecules as well as B-cells. There may also be antibodies in the preparation that react against monocytes, macrophages, platelets, and neutrophils. On the other hand, monoclonal antibody preparations

are directed against a specific cell surface molecule or they can block a specific receptor ligand and hence have the advantage of specificity. For example, OKT3 is directed against CD3 antigen and campath is directed against the CD52 antigen. Both monoclonal and polyclonal antibodies are associated with an increased risk of viral infection (particularly cytomegalovirus) due to suppression of cell-mediated immunity against viruses. They are also associated with the development of post-transplant lymphoproliferative disorder (PTLD) as a result of reactivation of latent Epstein-Barr virus (EBV), which can induce transformation of an EBV-dependent polyclonal B-cell population into a malignant monoclonal B-cell lymphoma. The use of cytolytic therapy is now usually limited to specific situations: (1) to delay the introduction of a CNI immediately after transplantation because of nephrotoxicity or hepatotoxicity, (2) in patients at increased risk of rejection because of sensitization or a positive cross-match, and (3) treatment of recurrent or persistent rejection that is not responsive to pulse steroid therapy.

IL-2 receptor inhibition (anti-CD25) is mediated by a monoclonal antibody that binds to the CD25 molecule which is present on activated (but not resting) T-cells. Basiliximab is a chimeric antibody that still retains some of the murine components of the immunoglobulin chain whereas daclizumab is a humanized antibody. Studies in cardiac transplantation suggest [64] that time to first rejection is increased, and that overall rejection severity is decreased with induction daclizumab therapy.

The proliferation signal inhibitors (PSI)/mammalian *target of rapamycin* (*mTOR*) *inhibitors* (sirolimus and everolimus) are drugs that block the proliferation signals that connect the autocrine stimulation by IL-2 on the cell surface to the cell nucleus for proliferation of T-cells. In addition to suppression of interleukin-driven T-cell proliferation, these drugs have antiproliferative effects including growth factor-induced proliferation and migration of vascular smooth muscle cells (potentially reducing the development and/or progression of coronary allograft vasculopathy), and inhibition of a number of enzymes along signaling pathways that play a role in the development of the progression of different cancers (potentially inhibiting the development and/or progression of post-transplant malignancies). The toxicity of sirolimus includes renal dysfunction (when combined with a CNI), hypertension, hyperlipidemia, thrombocytopenia and pneumonitis. In addition, a particularly concerning side effect is delayed wound healing, and for that reason these drugs should probably not be used in the first 3 months after transplantation. The use of sirolimus or everolimus may reduce the incidence of coronary allograft vasculopathy and the rate of progression in patients with already established coronary allograft vasculopathy [65, 66].

Plasmapheresis is a process that involves separation of the plasma containing macromolecules including immunoglobulins from whole blood. Plasmapheresis (usually the plasma exchange technique) is used in patients with acute cardiac rejection associated with donor specific antibodies, a positive crossmatch, evidence of antibody mediated rejection and acute rejection with hemodynamic compromise. *Photopheresis* is an immunomodulatory therapy that is effective in the treatment of a number of conditions such as cutaneous T-cell lymphoma and chronic graft versus host disease. This therapy involves separation of the buffy coat from whole blood, exposure of the buffy coat to a photo active compound (8-methoxypsoralen) and exposure to ultraviolet light and then return of the buffy coat to the patient. The T-cells are irreversibly damaged but the mechanism of immune modulation is more complicated than just damaging T-cells. It also likely involves increased production of regulatory T-cells that have an inhibitory action on the immune response. Photopheresis is frequently used in cardiac transplantation as an adjunct therapy for patients with recalcitrant rejection or following reversal of an episode of hemodynamically compromising rejection to prevent recurrence.

When commencing immunosuppression in an individual patient it is important to tailor the immunosuppression in the context of prevailing risk fac-

tors for rejection (under immunosuppression) and infection (over immunosuppression). As an example the relationship between rejection and infection for the risk factors of age and race is depicted in Fig. 4.16. The most commonly used immunosuppression protocols involves steroids, a CNI, MMF and induction therapy with an IL-2 receptor inhibitor. Currently a PSI agent is used when there is CNI induced nephrotoxicity and the CNI is being withdrawn. A concerted effort is made to withdraw corticosteroids and successful weaning of corticosteroids can be achieved in 50–80 % of patients when on a CNI based immunosuppression [68–73]. In order to achieve the lowest necessary immunosuppression novel therapies are being pursued such as tacrolimus mono therapy [74].

Acute Cardiac Rejection

Traditionally, immunosuppression and the diagnosis and treatment of acute cardiac rejection has focused on cell-mediated acute cardiac rejection. Antibody-mediated rejection has long been suspected to occur but there is now compelling evidence that antibody-mediated rejection (AMR) mediated through B-cells, plasma cells and their antibodies may play an important role in heart transplant rejection, particularly when it involves hemodynamic compromise which is associated with a high mortality.

Acute Cellular Rejection

The risk of acute cardiac rejection has a well-defined time pattern (Fig. 4.17) with the risk being highest within the first 3 months after transplantation, then falling to a low level by approximately 6 months after transplantation, although the risk of acute rejection never completely disappears. This time course dictates that immunosuppression and the surveillance for acute rejection should be intensified in the first 6 months after transplantation and thereafter may be reduced. Most patients with acute cardiac rejection are asymptomatic, and it is usually detected on routine endomyocardial biopsy. By the time a patient becomes symptomatic with acute cardiac rejection, the injury to the myocardium from the rejection process may be quite advanced.

The gold standard test for diagnosing acute cardiac rejection is endomyocardial biopsy. There have been many attempts to find non-invasive tests including biochemical, immunological, electrophysiological and echocardiographic (alone or in

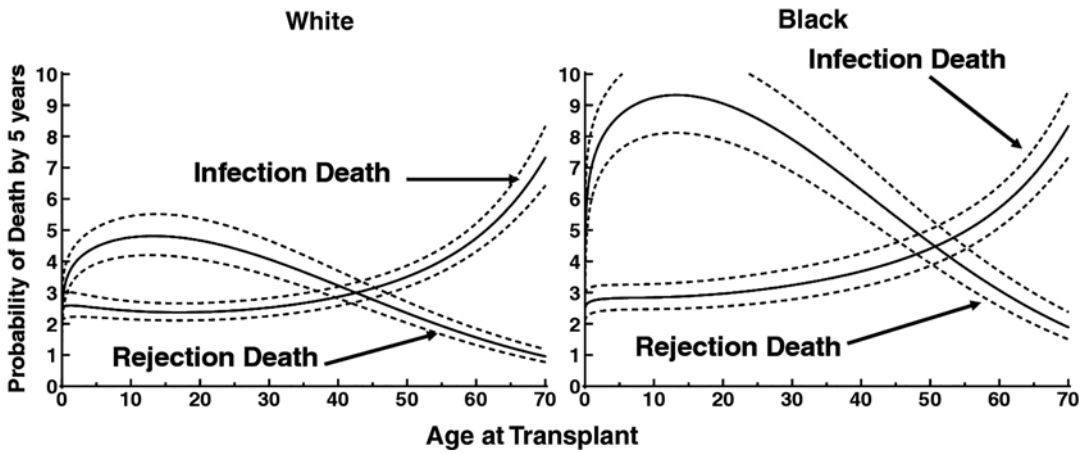

Fig. 4.16 The solution of multivariate equations depicting the probability of death due to rejection or infection at 5 years post-transplantation with respect to age at the time of transplantation in black or white female recipients transplanted in January 1, 2006, as indicated in the plots. The *dashed lines* represent 70 % confidence intervals (George et al. [67] with permission)

combination) to replace endomyocardial biopsy, but none have been found to be sensitive or specific enough to be considered a screening test for acute cardiac rejection. More recently gene expression profiling has been investigated, employing a gene expression panel representing a number of biological pathways including T-cell activation, T-cell migration and mobilization of hemopoetic precursors. However, the strategy of gene expression profiling is still in its infancy [76].

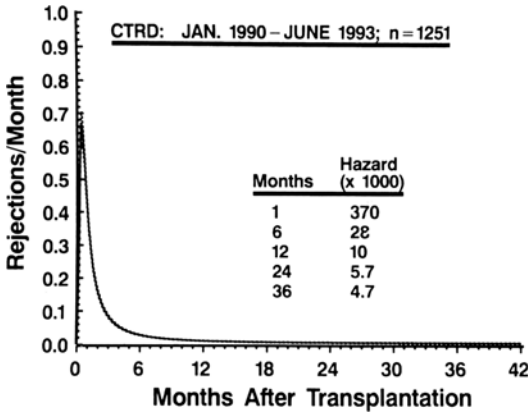

Fig. 4.17 Hazard function for initial rejection episode after heart transplantation. *Dashed lines* indicate the enclosed 70% confidence limits. *CTRD* Cardiac Transplant Research Database (Kubo et al. [75] with permission)

A standardized grading system for the histological diagnosis of acute cardiac rejection in cardiac biopsies was used for many years [77]. However, because of points of contention in the grading system such as the controversial grade 2 rejection, the ISHLT biopsy grading scale was revised in 2005 [78]. The revised classification system reduced the number of grades from four to three, likely improving the reproducibility of the interpretations. The ISHLT standardized cardiac biopsy grading for acute cellular rejection, both the revised 2004 scheme and the 1990 scheme for comparison is in Table 4.6. The 2004 grading scheme recognizes a grade 1R (mild) which describes an interstitial and/or perivascular infiltrate with up to one focus of myocyte damage (Figs. 4.18 and 4.19). Grade 2R (moderate) describes two or more foci infiltrate with associated myocyte damage (Fig. 4.20). Grade 3R (severe) has a diffuse infiltrate with multifocal myocyte damage with or without edema, hemorrhage or vasculitis (Fig. 4.21).

The treatment of acute or persistent cellular rejection varies between programs. However, the general principles are the following. Mild and moderate grades of rejection are treated with intravenous pulse corticosteroids within the first

Table 4.6 ISHLT standardized cardiac biopsy grading: acute cellular rejection

2004		1990	
Grade 0 R[a]	No rejection	Grade 0	No rejection
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage	Grade 1, mild A-Focal B-Diffuse	Focal perivascular and/or interstitial infiltrate without myocyte damage Diffuse infiltrate without myocyte damage
		Grade 2 moderate (focal)	One focus of infiltrate with associated myocyte damage
Grade 2 R, moderate	Two or more foci of infiltrate with associated myocyte damage	Grade 3, moderate A-Focal	Multifocal infiltrate with myocyte damage
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis	B-Diffuse Grade 4, severe	Diffuse infiltrate with myocyte damage Diffuse, polymorphous infiltrate with extensive myocyte damage ± edema, ± hemorrhage + vasculitis

The presence or absence of acute antibody-mediated rejection (AMR) may be recorded as AMR 0 or AMR 1, as required

Stewart et al. [78] with permission

[a]Where "R" denotes revised grade to avoid confusion with 1990 scheme

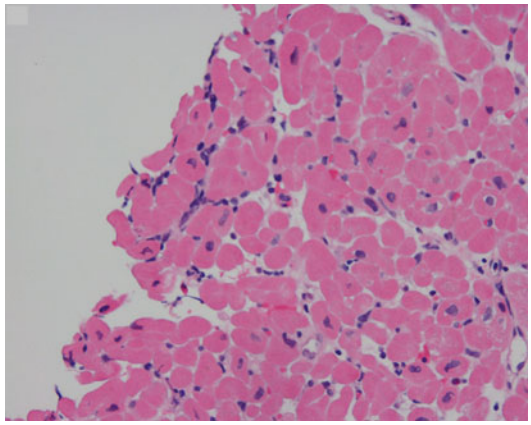

Fig. 4.18 Grade 1R, mild acute cellular rejection (Grade 1A under the 1990 classification)

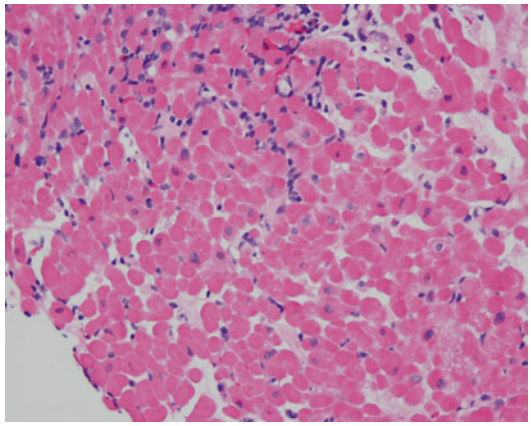

Fig. 4.19 Grade 1R, mild acute cellular rejection (Grade 1B under the 1990 classification)

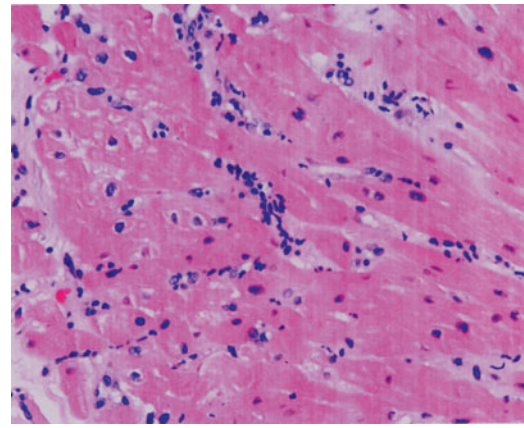

Fig. 4.20 Grade 2R, moderate acute cellular rejection (Grade 3A under the 1990 classification)

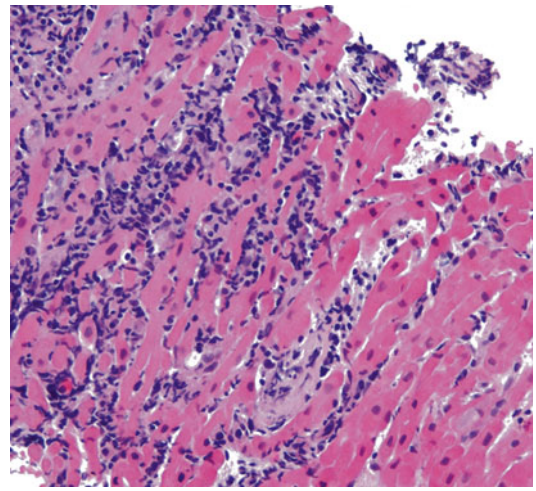

Fig. 4.21 Grade 3R, severe acute cellular rejection (Grade 3B under the 1990 classification)

6 months after transplantation or oral prednisone (beyond 6 months after transplantation). Severe rejection if occurring early after transplantation, is treated with intravenous corticosteroids together with cytolytic therapy. Persistent high-grade rejection may also require consideration of other strategies such as augmentation of baseline immunosuppression, photopheresis, or addition of another agent such as a PSI.

Antibody Mediated Rejection

Antibody mediated rejection (AMR) was first described in 1987 [79] with a picture of an arteriolar vasculitis associated with poor outcome after transplantation. The mechanism of AMR is the production of antibodies which fix and activate the complement cascade resulting in the generation of split products such as C3a, C4a and C5a which not only have vasoactive effects but also are powerful attractors of neutrophils, monocytes and macrophages [80]. The end result is activation of the coagulation cascade and consequent tissue injury [81]. A number of risk factors for AMR have been identified [82–87] and include female gender, elevated pretransplant panel reactive antibodies, development of de novo donor specific antibodies late after transplantation, positive donor specific crossmatch, prior sensitization to OKT3, cytomegalovirus

(CMV) seropositivity, prior implantation of a ventricular assist device and retransplantation. AMR is suspected when a patient following cardiac transplantation develops heart failure, low cardiac output or evidence of left ventricular dysfunction on echocardiography associated with an endomyocardial biopsy that lacks a cellular infiltrate [87].

The histological diagnosis of AMR is based on some combination of histopathologic findings (myocardial capillary injury associated with endothelial cell swelling and intravascular macrophage accumulation) and immunostaining of immunoglobulin (IgG, IgM and/or IgA) and complement C3d, C4d and/or C1q deposition in capillaries and staining of intravascular macrophages in capillaries (CD68 staining) [88]. An example of AMR characterized by C4d deposition is illustrated in Fig. 4.22. Routine monitoring for AMR is currently recommended at the time of all protocol endomyocardial biopsies noting specific histological features and immunostaining for C4d at 2 weeks and 1, 3, 6 and 12 months after transplantation and when AMR is clinically suspected. If a C4d positive biopsy is detected then C4d staining must continue on all subsequent biopsies until positivity has cleared. Surveillance for AMR also includes monitoring of circulating donor specific antibodies [87].

There are a number of current and possible future therapies that may be used for the treatment of AMR after solid organ transplantation through the mechanisms of B-cell depletion/inhibition, plasma cell depletion, antibody depletion or inhibition of antibody function (Fig. 4.23). A variety of strategies that have been used in treating AMR after cardiac transplantation but there is certainly no consensus [87]. Currently the primary therapy for treating AMR is high dose corticosteroids, plasma exchange and IVIG with secondary therapies including rituximab, bortezomib and the anti-complement antibodies.

Late Surveillance for Acute Cardiac Rejection

The usefulness of continuing routine endomyocardial biopsies beyond the first year after cardiac transplantation (in the absence of any other evidence of rejection) has now been called into question [90, 91]. The yield of biopsy proven severe rejection on routine surveillance endomyocardial biopsies is extremely low and in the absence of any other compelling reason routine endomyocardial biopsies could probably be discontinued beyond 5 years. Furthermore, biopsy proven severe rejection beyond 2 years after cardiac transplantation may not have the same sinister outlook as early severe rejection because of the demonstration [92] that such episodes may resolve spontaneously.

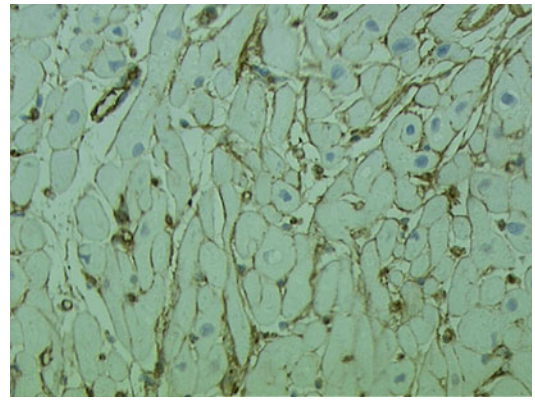

Fig. 4.22 Acute antibody mediated rejection with C4d deposition in the walls of capillaries

Survival after Cardiac Transplantation

Survival of adult patients undergoing cardiac transplantation has progressively improved across the eras (Fig. 4.24a) and most of the improvement in survival is associated with decreased mortality during the first year. Beyond 1 year after transplantation the improvement in survival is minimal (Fig. 4.24b). The median survival or half-life for adult and pediatric heart transplant recipients in the International Society of Heart and Lung Transplantation Registry since its initiation in 1982 is 11 years and is 14 years for patients who have survived the first year after transplantation [10].

Causes of Mortality and Morbidity after Cardiac Transplantation

The leading causes of death after cardiac transplantation are depicted in Fig. 4.25. Graft failure is

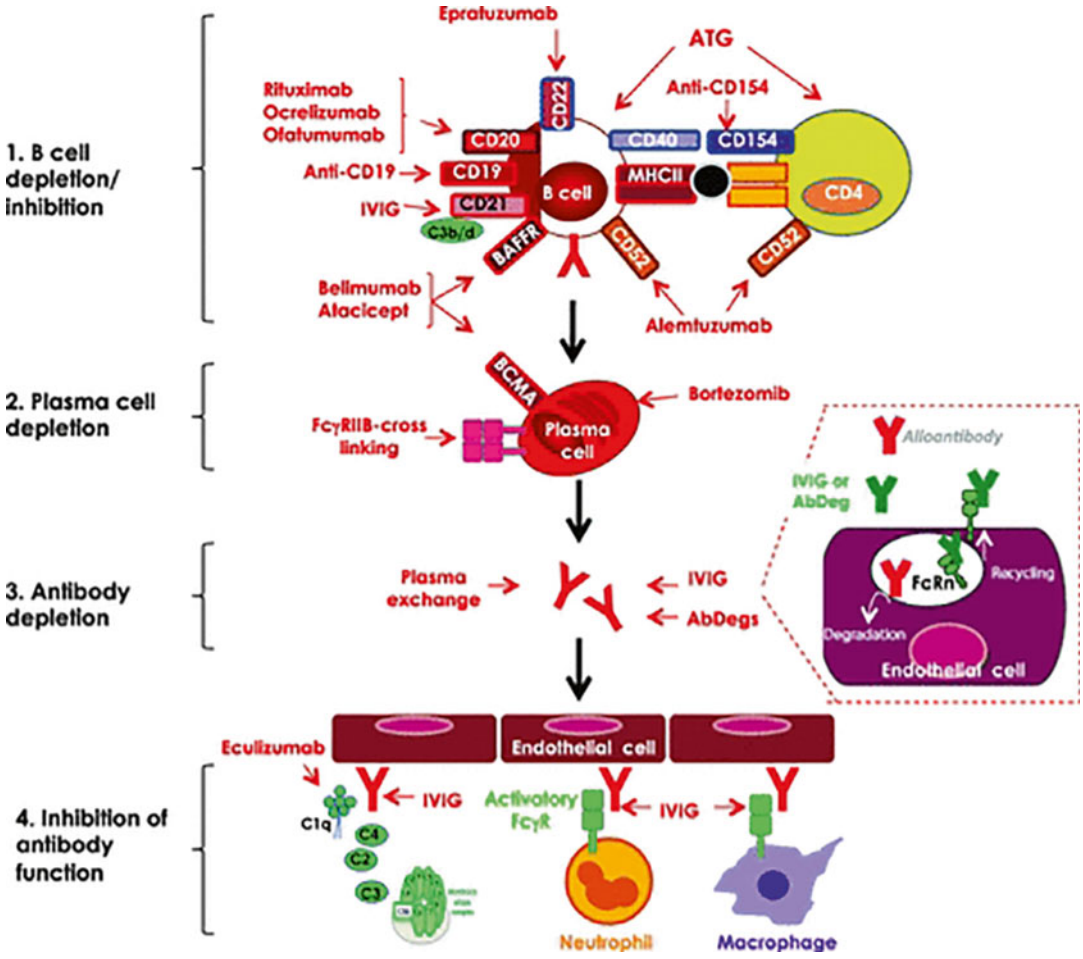

Fig. 4.23 Current and potential B-cell therapy in transplantation. The main mechanisms of action of agents are: (1) B-cell depletion or inhibition of B-cell activation; (2) plasma cell depletion; (3) antibody removal; (4) inhibition of antibody effector function. B-cell depleting agents currently in use in transplantion are ATG, alemtuzumab, rituximab. Those with future potential include the CD20 antibodies ocrelizumab and ofatumumab and the CD19 antibody MDX1342. Agents which may reduce B-cell activation or limit survival include those targeting the BAFF pathway (belimumab and atacicept) and apratuzumab. ATG and alemtuzumab may also limit B-cell survival through removal of T-cell help. The proteosome inhibitor bortezomib has been used to deplete plasma cells, other potential strategies include blockade of BAFF and APRIL (e.g. with atacicept) or cross-linking of Fc_y RIIB to induce apoptosis. Plasmapharesis allows the removal of antibody, but is a short-term solution, as titers usually rebound. IVIG can also modulate IgG titers, probably by blocking FcRn-mediated salvage of circulating IgG. AbDegs (IgG modified to increase affinity for FcRn) might also be useful to reduce alloantibody. IVIG may also act to block the effector functions of antibody, including activatory Fc_y R ligation on neutrophils and macrophages (Fc mediated) as well as neutralizing complement components (F(ab)2 mediated). BAFF (B-cell activating factor belonging to the tumor necrosis family factor) BAFF is a costimulator of B-cell survival and expansion and may play a role in acute and chronic AMR. APRIL (a proliferation inducing lygan) – both BAFF and APRIL promote B-cell and plasma cell survival and therefore blockade of these molecules may be a useful therapeutic strategy. BCMA (B-cell maturation antigen) (Clatworthy [89] with permission)

the major cause of death in the first 30 days after transplantation and remains an ongoing problem. Graft failure late after cardiac transplantation is most likely related to myocardial injury from processes such as coronary allograft vasculopathy or antibody mediated rejection [93]. Acute cardiac

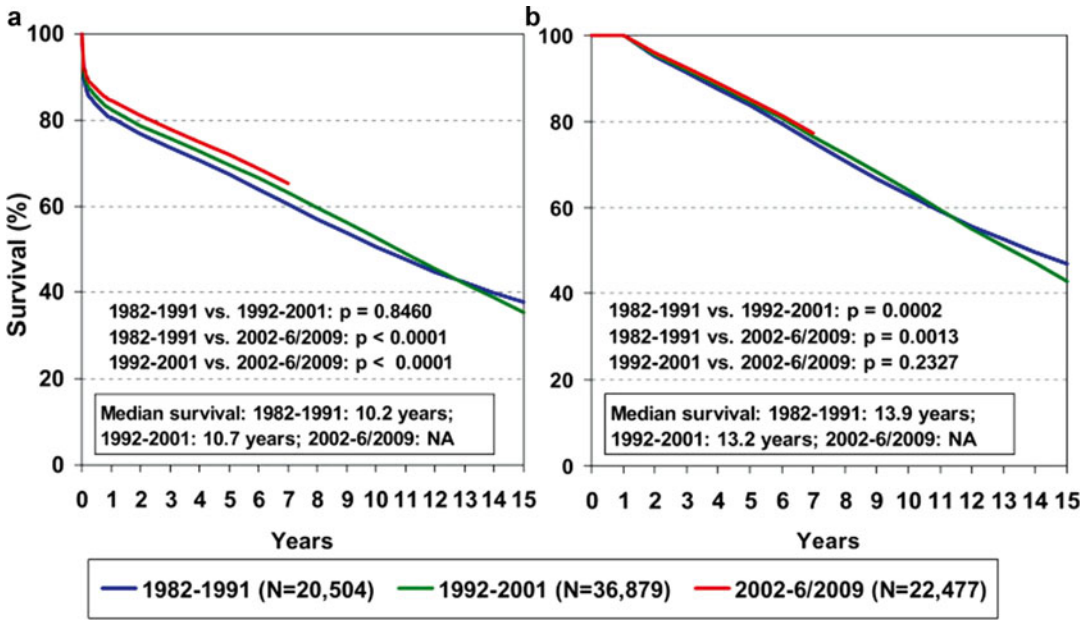

Fig. 4.24 (**a**) Survival and (**b**) survival conditional on surviving to 1 year after transplant for adult heart transplants performed between January 1982 and June 2009, stratified by era of transplant (Stehlik et al. [10] with permission)

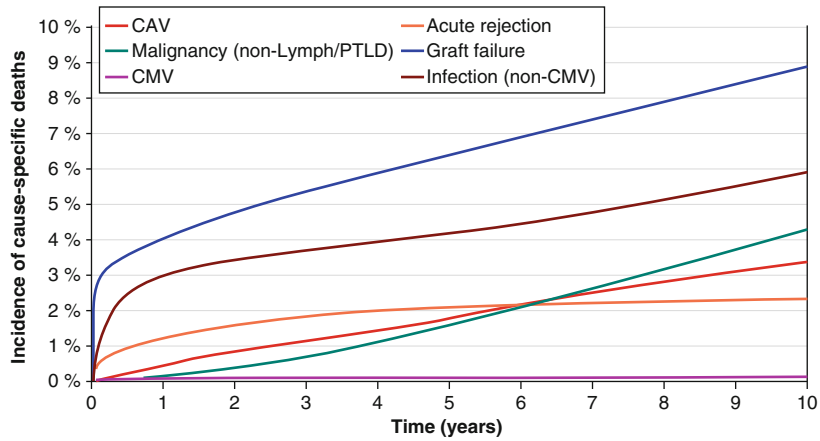

Fig. 4.25 Cumulative incidence of the leading causes of death for adult heart transplants performed between January 1992 and June 2008. *CAV* coronary allograft vasculopathy, *CMV* cytomegalovirus, *lumph/PTLD* lymphoma or post-transplant lymphoproliferative disease (Stehlik et al. [93] with permission)

rejection is now a relatively infrequent cause of death. Infection, malignancy and coronary allograft vasculopathy all have distinctive patterns of prevalence.

Infection

The prevention and management of infection constitutes a significant part of patient management after transplantation. A broad range of organisms may be involved including the usual pathogenic organisms, as well as organisms that are not normally pathogenic except in immunocompromised hosts, endogenous organisms, and organisms transmitted from the donor. Presentation of infectious disease in immunocompromised patients may be quite different from that in non-immunocompromised patients with blunting of signs and symptoms because of the effect of immunosuppression

on the inflammatory response. Infection may directly injure the transplanted heart through immune modulation (coronary allograft vasculopathy) or cause malignant transformation (EBV and CMV). Infection and rejection may coexist since treatment of rejection may precipitate infectious complications and certain immunomodulating viruses may precipitate rejection.

The term "immunocompromised host" refers to patients where host defenses are impaired because of immunosuppression. These patients are susceptible to infection caused by true pathogens (organisms that are able to overwhelm the natural defense mechanisms of a non-immunocompromised host), which may colonize a mucocutaneous surface and cause infection when there is a breach in that surface, and nonpathogens that do not present a risk to a normal host, but to which immunocompromised patients are susceptible. The term opportunistic infection refers to infection in immunocompromised patients that may be caused by true pathogens, nonpathogens, or sometime pathogens that may produce an illness that clinically may be quite different from that produced in a host with normal defense mechanisms.

Normal host defense mechanisms are usually highly successful in minimizing the risk of infectious disease. The first line of defense is epithelial/mucosal barriers that defend against micobiological penetration. The skin, epithelial surface of the lung, and mucosal surface of the gastrointestinal tract are surfaces that can be readily breached and represent portals of micobiological entry and invasion after cardiac transplantation. Immunological mechanisms are the second line of defense and the components are humoral, cellular, and phagocytic. All of these components may be seriously compromised by the variety of immunosuppressive modalities that may be used after cardiac transplantation.

The susceptibility to infection of a patient after heart transplantation is a function of a complex interplay of multiple factors which contribute to the "net state of immunosuppression". These factors include recipient comorbid disease such as diabetes, malnutrition, hepatic dysfunction, renal dysfunction, age, the nature and dose of immunosuppressive agents, compromise of the epithelial and mucosal defenses, and the presence of infection with immunomodulatory viruses, such as CMV and EBV. Immunosuppressive agents contribute in a major way to the development of infection. Corticosteroids increase susceptibility in infection through a number of mechanisms (both immunosuppressive and anti-inflammatory), including reduced accumulation of neutrophils at the site of inflammation, impairment of the mononuclear-phagocytic system, blunting of the T-cell activation cascade, inhibiting the function of alveolar macrophages, and impairment of wound healing. Cytolytic therapy, due to its effect of depleting circulating lymphocytes, is associated with an increased incidence of CMV infection and PTLD through EBV infection. Azathioprine reduces antibody production (by inhibiting B-cells), decreased cytotoxic T-cell proliferation, and impairs natural killer cell activity. Cyclosporine predisposes to infection through its blocking action on antigen-induced T-cell expression, although the risk of infection is less likely than with azathioprine/prednisone-based immunosuppression.

Infection has a predictable time-related probability. It is highest in the first month after transplantation at a time when immunosuppression is at its most intense, when epithelial and mucosal barriers are at their most vulnerable because of surgical wounds and instrumentation. The time course for different infectious agents after cardiac transplantation is quite distinct (Fig. 4.26).

From a numerical perspective, CMV infection is an important infection after cardiac transplantation. As a member of the herpesvirus family, CMV has the characteristic of latency and hence CMV infection may occur by transmission from donor to recipient (primary infection), or a recipient who is a reservoir of CMV because of previous infection may develop reactivation infection following commencement of immunosuppression following transplantation. The term reinfection (superinfection) is used when a CMV seropositive recipient receives a heart from a seropositive donor with a CMV strain that is different from the recipient latent CMV strain.

CMV has a number of direct and indirect effects. The direct effects include (1) CMV

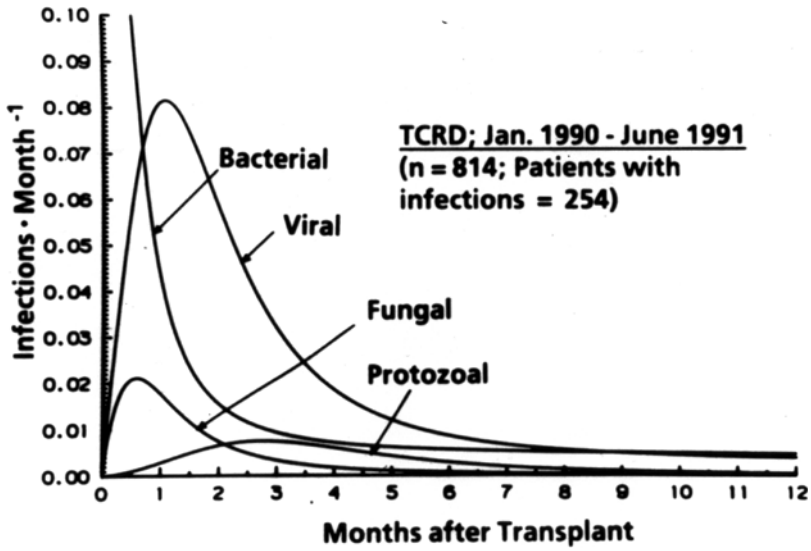

Fig. 4.26 Hazard function (instantaneous risk over time) for first infection of each major category of infectious agent. *TCRD* transplant cardiologist research database (Miller et al. [94] with permission)

syndrome (a flu-like illness with fever, chills, malaise, leucopenia, and thrombocytopenia accompanied by CMV viremia), (2) CMV disease (CMV syndrome or tissue invasive disease accompanied by detection of CMV in tissue), (3) CMV infection (asymptomatic viremia, CMV syndrome, and CMV disease).

There are a number of potential indirect effects of CMV after cardiac transplantation. CMV infection, either symptomatic or asymptomatic, has been implicated in the pathogenesis of coronary allograft vasculopathy [95–97]. Asymptomatic CMV reactivation has been linked with the development of acute allograft rejection [98].

The most important factor that determines the occurrence of CMV infection and disease after cardiac transplantation is the serological status of the donor and recipient, the highest risk being in CMV-negative recipients receiving hearts from CMV-positive donors [99].

The clinical manifestations of invasive disease depend on the organ involved and the type of infection (patients with primary CMV infection as opposed to reactivation infection are more likely to be symptomatic with greater severity of symptoms). CMV infection can be highly variable, manifesting as gastritis, duodenitis, hemorrhagic colitis, retinitis, pneumonitis (a severe form of CMV disease that has a poor prognosis, more likely to occur in lung transplant patients), hepatitis (a rare event in cardiac transplant recipients), and encephalitis.

The standard treatment for CMV infection is ganciclovir, with strategies that include intravenous ganciclovir, oral valganciclovir, or sequential intravenous ganciclovir followed by valganciclovir.

Prevention of CMV infection is now the primary method employed to reduce its incidence, and two general strategies are used: prophylaxis and preemptive therapy. The most widely used strategy is universal prophylaxis (except for donor negative/recipient negative in most centers) and a variety of regimens are currently used including intravenous ganciclovir, valganciclovir, and a combination of CMV immune globulin and intravenous ganciclovir in the highest risk group. Preemptive therapy, which involves administration of anti-CMV treatment to patients who have objective evidence of CMV infection, does have the advantage that fewer patients are exposed to the risks of antiviral drugs. Tests most frequently used for the diagnosis of CMV infection are detection of antigen (pp65 antigenemia assay), CMV DNA or mRNA.

There is evidence [100] that with selective antimicrobial prophylaxis, aggressive steroid weaning, selective use of induction therapy and the use of more targeted immunosuppression that the incidence of CMV disease, pneumocystis and fungal infection is decreasing.

Coronary Allograft Vasculopathy

Coronary allograft vasculopathy (CAV) is the manifestation of chronic cardiac rejection, and this process is one of the major factors limiting survival after cardiac transplantation. The fundamental morphology of the lesion of CAV is progressive intimal thickening involving both epicardial and intramyocardial coronary arteries. One of the characteristics of this process is its diffuse nature and concentric obliterative lesions, which is distinct from typical atherosclerotic native CAD, that tends to produce focal, proximal, eccentric lesions, sparing intramyocardial branches.

A number of immunologic and nonimmunologic factors are believed to be responsible for CAV. Donor/recipient immunological disparity, cellular and antibody mediated rejection, repeated episodes, and higher grades of acute cardiac rejection likely predispose to this process. Nonimmunologic factors include the traditional atherosclerotic risk factors such as donor and recipient age, hypertension, smoking, hyperlipidemia, diabetes, and obesity, but additional factors may have a role. These include CMV infection (perhaps due to the impact of CMV on endothelial cells), impaired fibronolysis, and ischemia/reperfusion injury at the time of the transplant.

The incidence of CAV is substantial. From the ISHLT registry [94] the incidence of coronary allograft vasculopathy is 8 % at 1 year, 20 % at 3 years, 30 % at 5 years and more than 50 % at 10 years. The diagnosis of CAV also carries the risk of short term mortality, approximately 10 % of patients dying in the 12 months after diagnosis of CAV [94].

The standard method of diagnosing CAV is by coronary angiography (Fig. 4.27) as part of the post-transplant surveillance protocol. However the severity and extensiveness of CAV is usually underestimated by angiography. Intracoronary ultrasound provides a more sensitive means of detecting coronary allograft vasculopathy because it actually images the arterial wall. Treatment of established coronary allograft vasculopathy is largely ineffective. Percutaneous intervention may offer some hope for focal stenoses. Drug eluting stents appear to have a significant local benefit but this is offset by the appearance of CAV at remote sites due to the progression of the disease [101]. However, for diffuse CAV the only effective therapy is retransplantation. Prevention of the development and progression of CAV is the focus of multiple treatment strategies. In addition to the usual strategies for control of typical atherosclerotic risk factors, measures that have shown some efficacy include statin drugs, calcium channel blockers, angiotensin-converting enzyme inhibitors, antiplatelet therapy, immunosuppressive agents with antiproliferative action (myocophenolate mofetil and sirolimus), photopheresis, and possibly anti-CMV therapy.

Malignancy

Malignancy after cardiac transplantation occurs in three major settings [36]: (1) transplantation in patients with preexisting malignancy, (2) transmission of a malignancy from donor to recipient, and (3) de novo malignancy developing in a recipient following cardiac transplantation.

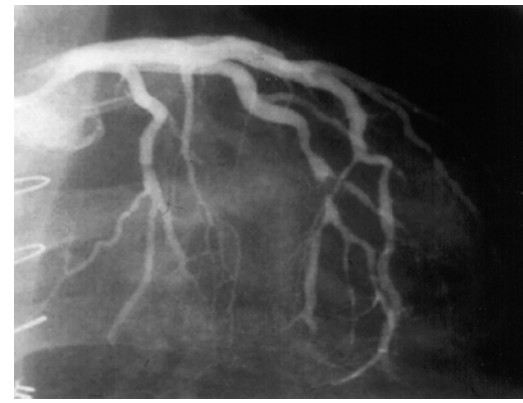

Fig. 4.27 Coronary angiogram demonstrating severe allograft arteriopathy of large epicardial, smaller secondary branches, and distal vessels (note the abrupt cutoff of several arteries) in a patient who was 5 years post-transplant and died suddenly (Kirklin et al. [36] with permission)

Defining a mandatory waiting time from treatment of the malignancy to cardiac transplantation that would ensure the lowest risk of recurrence has not proven possible and furthermore, an excessively long waiting time may result in a potential recipient dying from heart failure. Rarely, an unrecognized donor malignancy may be transmitted to a recipient. Potential mechanisms involved in the development of de novo recipient malignancy include disordered immune surveillance, principally as a result of the burden of immunosuppression, and oncogenic viral infections caused by EBV (implicated in the development of PTLD which can transform into a malignant monoclonal line), herpes simplex virus, and human papillomavirus.

The incidence of malignancy after cardiac transplantation is approximately three to four times that of the general population. The most common malignancies after cardiac transplantation are skin cancer followed by lymphoproliferative disorders, and less commonly carcinomas of the prostate, lung, bladder, kidney, breast and colon [94]. Cardiac transplant recipients at greatest risk for fatal malignancy include those with a history of a malignancy prior to transplantation, older age and a history of treated rejection.

Other Long-Term Complications after Cardiac Transplantation

Numerous important long-term complications after cardiac transplantation may contribute to morbidity and mortality. Gastrointestinal complications include peptic ulcer disease (due to such causes as invasive CMV disease and *Helicobacter pylori* infection, and the use of corticorsteroids), diverticular disease (perforation is likely increased by the use of corticosteroids), pancreatitis (due to invasive CMV disease, azathioprine toxicity, hyperlipidemia), and cholelithiasis. Ocular complications (cataracts and glaucoma both related to corticosteroid use), hypertension, CNI induced nephrotoxicity, hyperlipidemia, and bone complications (osteoporosis and avascular necrosis) assume increasing significance with improvement in post-transplant survival.

Final Thoughts

Cardiac transplantation is a mature therapy for end-stage heart disease, but is currently constrained by the tremendous imbalance between the number of potential recipients and the number of available donor hearts. One of the challenges for the future is to utilize the extraordinary amount of data that is available to classify patients with end-stage heart disease into those who are likely to experience the best results from cardiac transplantation and those who have risk factors that portend significantly inferior results (where other therapies such as chronic mechanical circulatory support may be an option). Only in this way will the assignment of appropriate therapy for patients in end-stage heart disease be rational.

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Coronary Artery Bypass Grafting in the Treatment of Heart Failure

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Heart failure remains a major medical burden with an estimated six million people affected in the United States of America alone making it the most common diagnosis in all hospital admissions [1, 2]. Coronary artery disease (CAD) with subsequent ischemic cardiomyopathy is the underlying cause of heart failure in roughly 70 % of all heart failure patients [3]. Indeed, myocardial infarctions (MI) are responsible for 750,000 deaths annually with an estimated 60,000 of the survivors developing congestive heart failure [4]. Transplantation has traditionally been the only surgical treatment for end stage heart failure but the scarcity of donor organs, the recipient suitability for organ transplantation as well as the rapid rise of heart failure have made this less than an ideal solution for all. Increasingly, surgical intervention has concentrated on coronary revascularization, valvular repair/replacement, ventricular restoration/remodeling, ventricular assist devices, stem cell therapy and external restraint devices [4, 5]. In this chapter, we aim to highlight the utility and selection of offering revascularization to the subgroup of heart failure patients who will benefit from this intervention.

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Role of Coronary Arterial Bypass Grafting (CABG) in Patients with Heart Failure

Patients with heart failure should be referred to tertiary care centers for the possibility of definitive surgical therapy. A comprehensive multidisciplinary team approach with discussions of the possibility of ventricular assist device and heart transplantation should be anticipated as both immediate and long-term treatment options in patients with ischemic heart failure. The initial goal in treating patients with heart failure is to determine whether or not there is any benefit to be gained from coronary arterial revascularization.

Assessment of Myocardial Viability

In order to assess whether these ischemic hearts benefit from surgical and/or hybrid revascularization, it is important to differentiate between hibernating myocardium and scarred

J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_5

non-functional muscle. In patients with ischemic hibernating myocardium, coronary revascularization will result in improved function. However, when the majority of the myocardium is necrotic and akinetic, coronary revascularization may be of no benefit with an unsurprisingly higher risk of mortality. Unfortunately, assessment of these patients is not straight forward as there is a mixed pattern of scar interspersed with viable tissue. This has led to some considerable debate over the utility of myocardial viability testing prior to any contemplated intervention without definitive answers from the much-anticipated STICH trial [6]. There are currently several available techniques to assess myocardial viability. Dobutamine stress echocardiography has mostly fallen out of favor given its higher false negative rates. The favored approach for viability testing includes nuclear imaging utilizing technetium-labeled radioisotopes or positron emission tomography (PET) tracers in both rest and stress conditions, single-photon-emission computed tomography (SPECT) myocardial perfusion imaging as well as cardiovascular magnetic resonance (CMR).

Nuclear imaging utilizing labeled tracers (PET) or photon-emission (SPECT) relies on the uptake of radiotracer by the cardiac myocyte and is by definition dependent on regional myocardial blood flow to show myocardial viability. Images can be obtained at both rest and stress to show perfusion defects correlating with myocardial ischemia, which are then classified as being either a reversible or fixed perfusion defect. CMR as an imaging modality has gained considerable traction within the last several years because of its ability to provide cine CMR showing segmental and global ventricular function in addition to perfusion imaging both at rest and at a delayed time to show myocardial viability and scar.

These advanced imaging techniques are useful screening tools to detect the presence of, as well as the extent of myocardial ischemia, further elucidating patients with ventricular dysfunction who have the greatest potential of benefit from revascularization. Indeed there is a consistent relationship between the amount of viable myocardium and the improvement of the left ventricular function following revascularization [7]. Some studies have suggested that the minimum viability of myocardium needs to be at least 50 % to show unequivocal evidence for myocardial improvement following reperfusion [8].

Benefits of Revascularization of Viable Myocardium

The risk of myocardial damage at the time of CABG, must be weighed against the benefit of revascularizing hibernating myocardium when deciding to operate on patients with heart failure – defined as on with an ejection fraction <35 %. Although mortality as high as 15 % has been reported, with appropriately selected and managed patients, mortality can be as low as 2–6 % [4]. In addition to a mortality benefit, revascularization has shown reverse cardiac remodeling with improved left ventricular function and quality of life [4]. It is thought that CABG mitigates the affects of maladaptive cardiac remodeling by preventing the distortion and enlargement of the left ventricular and hence keeping a smaller, more efficient LV geometry.

Technique of Surgical Revascularization

Perioperative Management

Coronary revascularization has emerged as a successful therapy for high-risk patients with heart failure. Medical optimization with beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, after load reducers and nitrates along with ionotropic support and optimal end organ function prior to coronary revascularization are key components on having a successful outcome. Liberal use of Perioperative intra aortic balloon pump (IABP), right ventricular support with phosphodiesterase inhibitors and inhaled prostaglandins has led to improved biventricular contractility and improved hemodynamics. Additionally, vasopressin to combat the chronic depleted stores of vasopressin levels and resultant perioperative vasodilatory state of these patients

has been beneficial. Some subset of patients may need an early trial of hemodynamic improvement via initiation of intra aortic balloon pump support and if necessary the early ventricular assist device to support end organ perfusion while allowing the ischemic myocardium the required 2–3 days to regenerate depleted adenosine triphostate (ATP) stores. Although ischemic heart disease is the most common cause of heart failure, optimal treatment sometimes still is unclear.

Despite our improved knowledge of medical management, this remains limited in its effectiveness with a resultantly high mortality and morbidity. Revascularization should be the procedure of choice in this high risk group of patients with ischemic heart disease in the presence of impaired left ventricular function with special attention to factors affecting outcome such as: status of the patient, acuteness of presentation, right ventricular failure, and presence of good surgical targets. The keys to a successful operation requires a coordinated team approach with an experienced anesthesiologist and a cardiac surgeon comfortable with performing high-risk surgery with ventricular assist device backup.

In these high-risk patients, a Swan Ganz catheter and a transoesophogeal echocardiography (TEE) are important adjuncts in maintaining normal hemodynamic performance. A thorough TEE should be used to assess left ventricular wall motion, the presence and degree of valvular regurgitation, severity of atheroma of the aorta, and right ventricular function. Presence of more than moderate mitral regurgitation can aid in the decision to perform off pump versus on pump coronary revascularization. In view of the emerging data supporting mitral repair in the presence of ischemic cardiomyopathy repair of the mitral valve should be considered in patients with moderate or greater regurgitation.

Off Pump Coronary Arterial Bypass (OPCAB) Grafting

There have been many efforts to decrease the risk of surgical revascularization, especially in these high-risk patients. The challenge has been to offer complete revascularization to these patients while minimizing post procedure morbidity and mortality. Even though these high risk patients can be successfully revascularized with conventional cardio pulmonary by pass techniques, with CABG, there has been an interest in revascularizing these high risk patients off pump (OPCAB) in an effort to limit the myocardial injury associated with aortic cross clamping, ensuing global myocardial ischemia and cardioplegia related dysfunction. Off-pump surgery also aims to eliminate the ischemic inflammatory response elicited by cardiopulmonary bypass (CPB) [9].

Even though these high-risk heart failure patients can be successfully revascularized with conventional coronary artery bypass (CABG) techniques, there has been interest in performing this surgery off pump or without the aid of cardiopulmonary bypass. This is somewhat controversial; however, given to an improvement in techniques of myocardial protection and hemodynamic management.

In evaluating patients who would benefit from avoiding the “pump” or extracorporeal circulation, the primary indications are often:

1. Older age
2. Atherosclerotic burden in the ascending aorta and aortic arch
3. Renal dysfunction
4. Patients with significant myocardial dysfunction
5. Patients with poor pulmonary function
6. Patients with severe liver dysfunction
7. Patients with underlying disorders that may preclude anticoagulation required for CPB

Preoperative planning is also very important in successful off pump surgery. It is necessary for the surgical team to know the patient’s anatomy, the vessels to be bypassed and other diseased coronary vessels that may be involved. There should be a clear plan for the choice and type of conduit, the vessels to be revascularized as well as alternatives.

It seems clear that revascularization is indicated in the management of heart failure and ischemic coronary disease [10]. Particularly in this high group risk of patients, OPCAB seems

the preferable approach. A recently published study from The Society of Thoracic Surgeons National Database showed decreased risk of death, stroke, major adverse cardiac events, prolonged intubation and transfusion rates [11]. We cannot; however, underscore the importance of complete revascularization in these patients with heart failure. Complete revascularization is vital in achieving good results in patients with severe left ventricular dysfunction [12]. Completeness of revascularization has been shown to improve early survival in young and elderly patients and is a critical factor in patients with left ventricular dysfunction. The liberal use of balloon pump support, appropriate ionotropic support, hemodynamic monitoring, and perioperative analgesia are all important in the multi-disciplinary approach to these patients. The importance of preoperative optimization allows for a successful coronary revascularization in patients with heart failure and has been shown to improve survival in this cohort of patients with low ejection fraction [13]. It has also been shown in a large database that CABG reduced the likelihood of additional readmissions in the ensuing year over either medical management or percutaneous intervention [14]. A comparison of a small sub-group of patients with ejection fraction <35 % showed that OPCAB patients had similar results in providing this benefit to patients undergoing conventional CABG. OPCAB mortality in patients with unfavorable characteristics such as dysfunctional left ventricle and left main coronary disease can be safely performed with a mortality rate near 2.5 % [15]. Another large series looked at a high-risk group of patients (low ejection fraction, advanced age, left main disease, and an acute myocardial function and re-do coronary artery surgery) undergoing OPCAB and compared them to a similar cohort of patients undergoing conventional CABG on CPB. The results showed that that average number of grafts were comparable (3.0 in the OPCAB group and 3.2 for the on-pump group, the hospital mortality was 3.2 % for OPCAB and 4.5 % for the conventional CABG group respectively) [16]. Additionally, patients undergoing OPCAB surgery with a depressed ejection fraction (<40 %) showed significant improvement in their post-operative ejection fraction. Another study looking at a group of high risk patients (defined as a EuroSCORE ≥6) undergoing isolated coronary revascularization with and without cardiopulmonary bypass was compared with propensity score matching. This showed that in a propensity matched group of 510 OPCAB with 510 conventional CABG, that the OPCAB group had better early outcomes with similar clinical results [17]. The 30-day mortality was higher in the conventional CABG group, 5.9 versus 3.1 %. There was also a significantly lower evidence of cerebrovascular accidents (CVAs). A multivariate logistic regression analysis, confirmed that the use of cardiopulmonary bypass was an independent predictor for a higher early mortality, (odds ratio of 2.0) as were CVAs and early major recurrence of chest pain. Five-year freedom from major events (myocardial infarction in a grafted area, need for myocardial coronary re-intervention and any cause mortality) were similar in both groups.

Heart failure patients tend to have more than just one co-morbidities and are thus a set up for post-operative morbidity and mortality. Patients with this degree of systemic disease along with advanced left ventricular dysfunction do not tolerate super imposed bypass with resultant post-inflammatory injuries to their organs [18]. An early report comparing the techniques of OPCAB to conventional CABG in patients with ejection fraction <35 % showed that there was a higher prevalence of lower ejection fraction (defined as <20 %) in the OPCAB group. Additionally, the average number of grafts was similar with a similar percentage of internal thoracic or mammary arteries being used (see Figs. 5.1 and 5.2). There seemed to be a trend towards lower operative risk in the OPCAB group with better long term survival in these patients done off pump versus the on pump patients [19].

Special Considerations in Choice and Technique of OPCAB

There are certain instances when OPCAB should not be the preferred method for revascularization

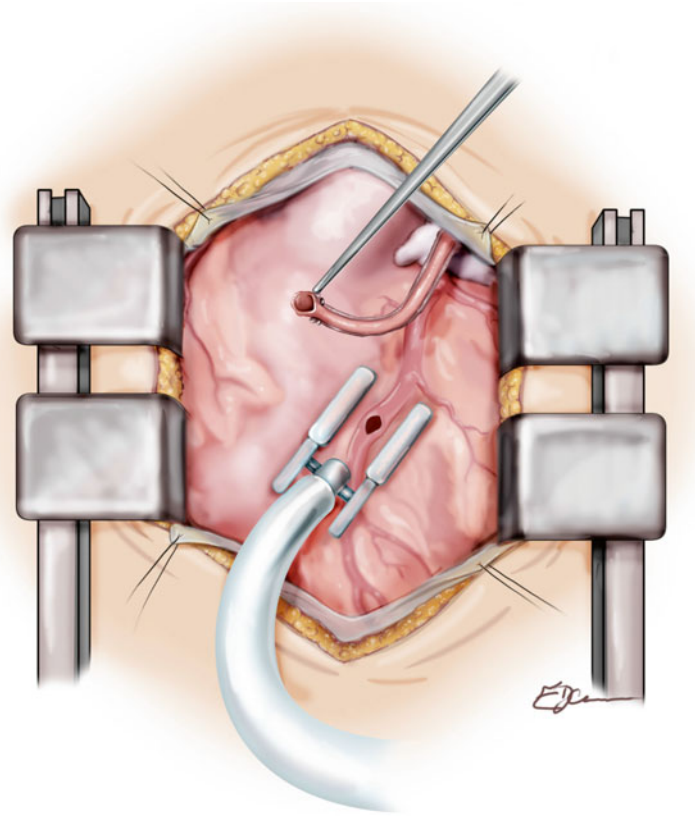

Fig. 5.1 Schematic showing a left internal mammary artery (LIMA) being readied for anastomoses to the left anterior descending (LAD) artery. The myocardium is being stabilized by a suction based stabilizing device to facilitate the LIMA to LAD anastomosis

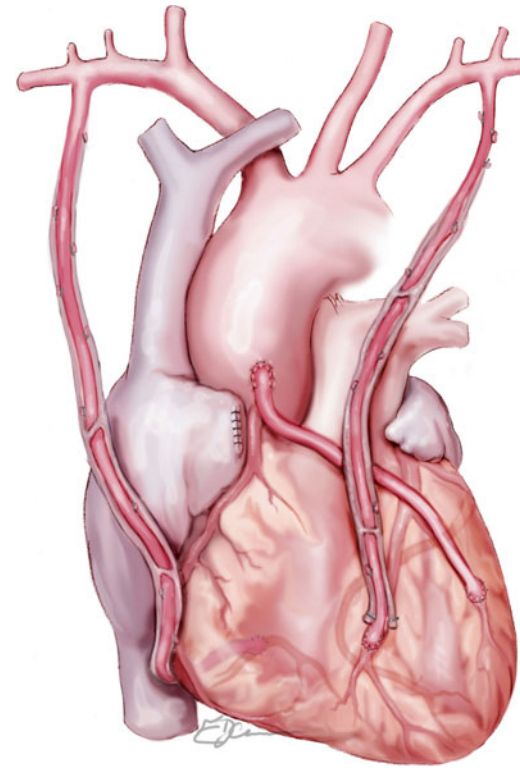

Fig. 5.2 Schematic showing the use of the left internal mammary artery as a bypass conduit to the left anterior descending artery as well as the right internal mammary artery to the posterior descending coronary artery. Additionally, an aortocoronary graft to a diagonal coronary artery is shown

[20]. Particular attention should be paid to the presence of and degree of mitral regurgitation. In the presence of greater than moderate mitral regurgitation, patients should have the mitral valve repaired or replaced [21]. A retrospective study compared 45 OPCAB versus 102 conventional CABG recipients with ejection fractions <30 % and although there were comparable incidence of adverse events, there were fewer grafts performed in the OPCAB group [22]. Similarly, another large study of 355 patients undergoing revascularization with an ejection fraction of ≤30 % showed that the number of grafts in the OPCAB group was 2.8, compared with 3.3 for the on pump group [15]. Once again, the importance of the completeness of revascularization cannot be understated.

A major deterrent to OPCAB surgery is the tolerance of patients to undergo the degree of cardiac manipulation and displacement that is necessary to perform total revascularization. Continual communication between the surgeon, anesthesiologist, nursing staff and perfusionist are vital to ensure smooth conduct and success of the operation. By nature, there will be alterations and swings in hemodynamics as the position of the heart is manipulated; however, careful alterations in position combined with cooperation and active participation of the anesthesiologist can minimize any systemic effect. There are some surgical tenants to adhere to in the performance of OCPAB surgery:

1. Ensure effective and clear communication with the team of anesthesiologists, nurses and perfusionists as to the planned procedure, vessels to be grafted, alternate conduits and potential exit or bail-out strategies before the procedure.
2. Try to minimize large manipulation of the heart by lifting the heart. Rather, use deep pericardial stay sutures allowing immediate assessment to whether or not the patient will tolerate off-pump surgery. If not, convert to early on-pump surgery as a strategy.
3. Decide on the availability and suitability of conduits to be harvested and ensure the LIMA is the first graft for the LAD graft. Thereafter, proceed with a sequence to effect revascularization to the next most ischemic area. If another pedicle graft is used, such as the RIMA, perform this next. If aorto-coronary grafts are planned, try to perform the aortic anastomosis first so that when the distal anastomoses are completed, there is instant revascularization of that territory.
4. If there are issues with rhythm, use atrial pacing or dual chamber pacing with ventricular pacing wires placed on both ventricles for hemodynamic stability (see Fig. 5.3).

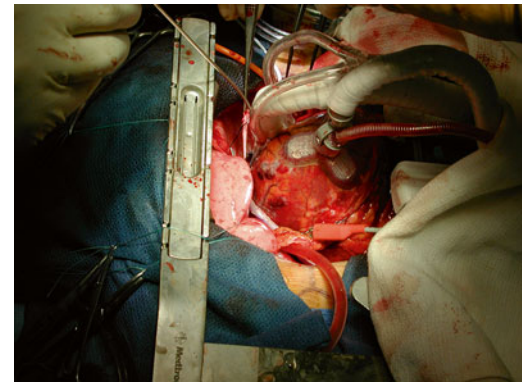

Fig. 5.3 Operative photograph showing facilitation of coronary grafting with heart stabilization with a suction device along with pacing. Note the pacing cable at the bottom of the picture

In patients with severe heart failure particularly with left main coronary disease, a useful technique of positioning the heart is by gently putting a glove filled with warm saline behind the heart positioning the LAD into the center of the surgical field and allowing easier access for grafting. The advantages of grafting the LAD first is establishing coronary flow through the septal perforators into the septum and providing better tolerance of the myocardium to further manipulation. There are certain instances when off-pump surgery may not be possible. These are encountered in patients with very stiff myopathic hearts that do not tolerate manipulation. In these cases, there are two options possible; either leaving the lateral wall revascularization to percutaneous intervention or using pump assisted, beating heart CABG (so called "pump assisted") method. Discounting the inflammatory cascade from use

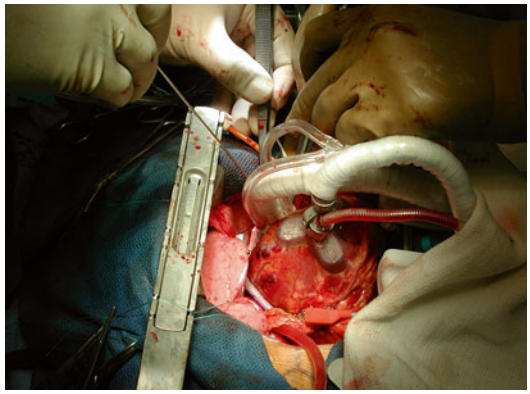

Fig. 5.4 Operative photograph showing an apical positioning device and a stabilizer (both suction based) used to expose the circumflex artery along the lateral wall of the left ventricle

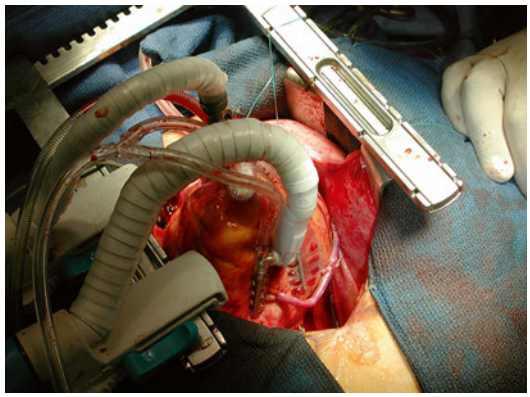

Fig. 5.5 Operative photograph showing a completed distal anastomosis to an artery on the inferolateral wall of the left ventricle

of cardiopulmonary bypass, this may be the safest approach in sick patients with very low ejection fractions and profound left ventricular dysfunction. Another helpful alternative may be to use intra-aortic balloon counter pulsation to provide circulatory support for tolerance of OPCAB manipulation. In some studies of patients with an EF $\leq$25 %, one predictive factor of better outcome was pre-operative balloon pump insertion as compared to those who did not receive counter pulsation support. That being said, there is no doubt that the use of positioning and stabilizing devices has made a huge difference in the ability of surgeons to operate on vessels on the lateral and inferior wall (see Figs. 5.4 and 5.5). These suction, traction or pressure-based devices allow for stabilization of regions of the heart to allow for an operation. The most successful of these is the Medtronic Octopus, which is a suction based device initially developed at the University of Utrecht, Netherlands. Most off-pump procedures require a combination of a positioner and a stabilizer for each of the distal coronary anastomoses.

In general the OPCAB sequence of the operation follows a philosophy as outlined in the above tips. The goal should be for complete revascularization. In some instances positioning of the heart can be performed by opening of the pleura and allowing the right heart to be displaced into the right chest. This allows easy access to the circumflex vessels with minimal hemodynamic disturbance. However, this can be of concern if the LIMA has been grafted to the LAD as there may be too much tension to allow distraction of the heart and as such this needs to be considered in the pre-operative graft sequence planning. The proximal anastamoses can be performed to the aorta with a single partial clamp or by avoiding the clamp with the Heart String (which is a clampless way of providing a safe aortotomy) as depicted in Fig. 5.6.

In summary, OPCAB revascularization has been shown to be as effective and as safe as conventional coronary arterial bypass in experienced hands [23]. In fact, in patients with multiple risk factors, particularly those with heart failure with a low EF, OPCAB with complete revascularization can be more beneficial. To provide for reproducible and successful outcomes; however, the procedure needs to be performed by an experienced team. There needs to be a vigilant and responsive anesthesia team along with seamless communication between all team members. It is essential for the surgeons to inform the anesthesiologists about the number of grafts required, the sequence of grafting, the nature of the occlusion of the target vessel among other details of the proposed procedure.

Another useful technique, which is less invasive and mostly performed off-pump is the MICS (Minimally Invasive Cardiac Surgery) CABG. This involves a left minithoracotomy,

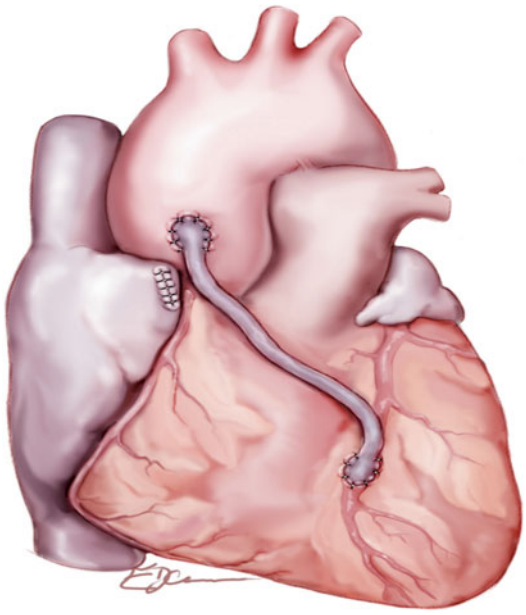

Fig. 5.6 An illustration depicting a single saphenous vein graft to the left anterior descending artery using the proximal anastomotic technique of interrupted U-clips. This can be a particularly useful strategy in re-operative surgery where the proximal anastomosis can be performed without a clamp

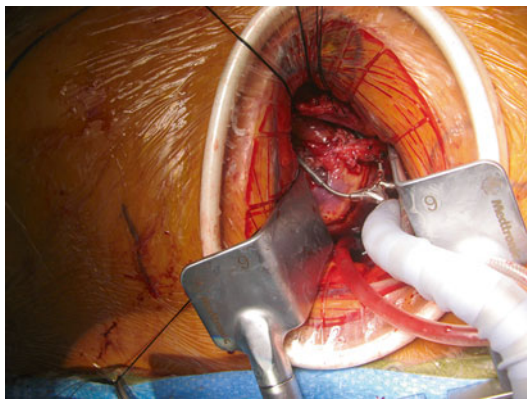

Fig. 5.7 Shows a LIMA to LAD anastomosis complete through this approach

with harvest of the left internal mammary artery through the lateral incision. The completion of the distal anastomoses, especially LIMA to LAD can be performed safely through this incision.

Figure 5.7 shows a LIMA to LAD anastomosis complete through this approach.

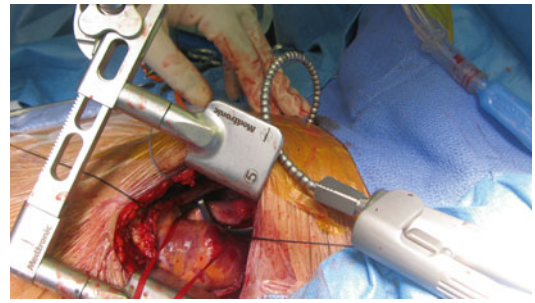

Fig. 5.8 Shows a trans-thoracic partially occluding Cygnet clamp used on the ascending aorta, in preparation for a proximal anastomosis of a vein graft

An experience of over 100 patients with this technique in high risk patients over the past 3 years (personal experience of JR), showed satisfactory results with an acceptably low mortality of 2 % and low risk of peri-operative complications. This technique is technically more demanding and needs special equipment such as a specific retractor to facilitate LIMA harvest, custom made partial occluding clamps for the ascending aorta, long single shafted instruments to allow handling of the grafts, etc.

Figure 5.8 shows a trans-thoracic partially occluding Cygnet clamp used on the ascending aorta, in preparation for a proximal anastomosis of a vein graft.

Anesthesiologists have to continuously be conscious of the hemodynamic monitoring, filling pressures and ventricular wall motion assessment with trans-esophageal echocardiography to facilitate an expeditious and safe operation. One lung anesthesia has to be available to facilitate the left mini-thoracotomy MICS CABG approach.

Hybrid Revascularization

In a subset of patients with severe heart failure who may not be able to recover from a sternotomy or partial sternotomy, a hybrid approach is a very attractive option. Usually the LIMA is grafted to the LAD in a minimally invasive fashion. This can be performed by a thoracotomy or sub-xyphoid minimally invasive directed coronary artery bypass (MIDCAB) approach [24].

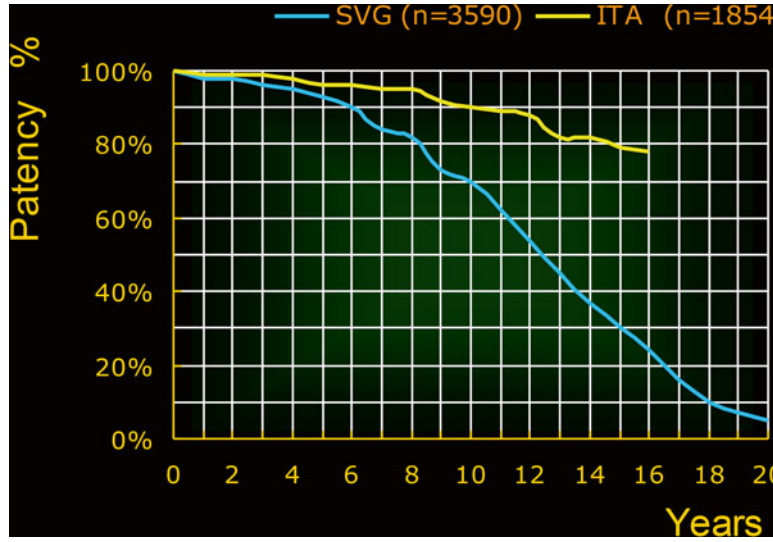

Fig. 5.9 Cumulative patency of saphenous vein grafts compared to the internal thoracic (mammary) artery (Kind courtesy of Prof Brian Buxton, University of Melbourne and Epworth Hospital Databases – maintained by Prof Buxton and Dr J Fuller)

The other less important vessels can be staged with percutaneous stenting thereafter. In general, the sequence is to perform the LIMA-LAD bypassing followed by a percutaneous intervention – either in the same setting or within 48 h. This two-stage sequence of revascularization has the major benefits of providing the mortality benefits of an LAD protected by a surgical LIMA graft as well as the ability to evaluate this anastomosis and potentially intervene with angiography. In view of the improving stent technology, this may become the future of revascularization. Hybrid revascularization entails surgical revascularization combined with trans-catheter therapy. This hybrid approach allows for a less invasive approach to provide complete revascularization. It can also be used in the reoperative setting where the back wall vessels can be grafted through a thoracotomy with inflow from the descending aorta with stenting of the other vessels.

Choice of Bypass Conduits

The perceived notion that all-arterial grafts should be used for all bypass grafting stems from the long-term patency data comparing the internal mammary (or thoracic) artery patency rates with that of saphenous vein grafts (SVG). A large database utilizing data over two decades shows a widening gap between the patency rate of SVG as compared to ITA (internal thoracic (or mammary) grafts). The patency of the ITA remains excellent throughout the follow-up period (Fig. 5.9).

This data, along with others, has made the use of the left internal mammary artery graft to the LAD the standard of care [25, 26]. This finding spawned the idea that two arteries are better than one and three better than two (see Figs. 5.10 and 5.11). Some have argued that this may lead to a lower prevalence of heart failure in patients who have previously received multiple arterial bypass grafts [27].

Despite these arguments, the standard coronary artery bypass procedure in the United States utilizes a single left IMA and saphenous vein conduits from the thigh. Surprisingly, coronary artery surgery in emerging markets such as India and China show a great deal more sophistication, with over 60 % of patients in India receiving at least two arterial grafts. In addition to the use of bilateral internal mammary artery use as conduits of choice, a great deal of interest has emerged in the use of a patient's radial artery from the non-dominant arm. Despite success at some institutions, other centers have not been as apt at employing this as a bypass conduit. In the early mid-term results of the RAPCO (Radial Artery Patency and Cumulative Outcomes) study, there

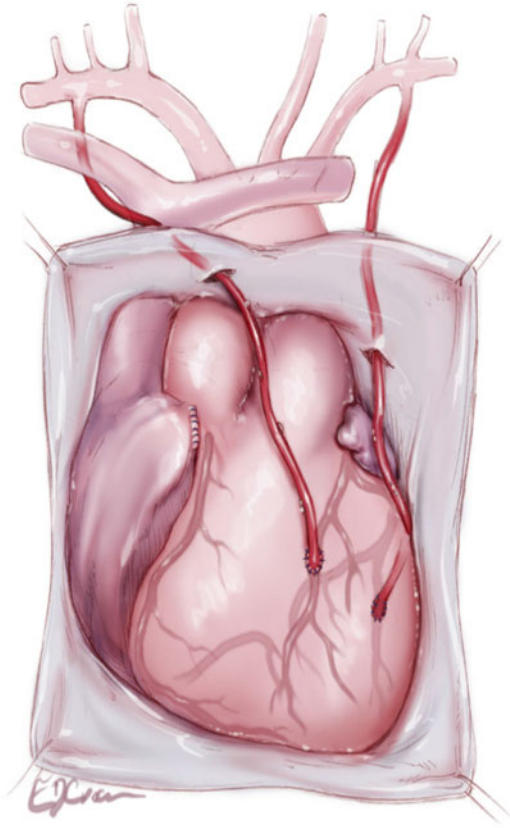

Fig. 5.10 Illustration depicting bilateral pedicled skeletonized internal mammary arterial (IMA) grafts. The left IMA to an obtuse marginal of the circumflex and the right IMA to the left anterior descending coronary artery

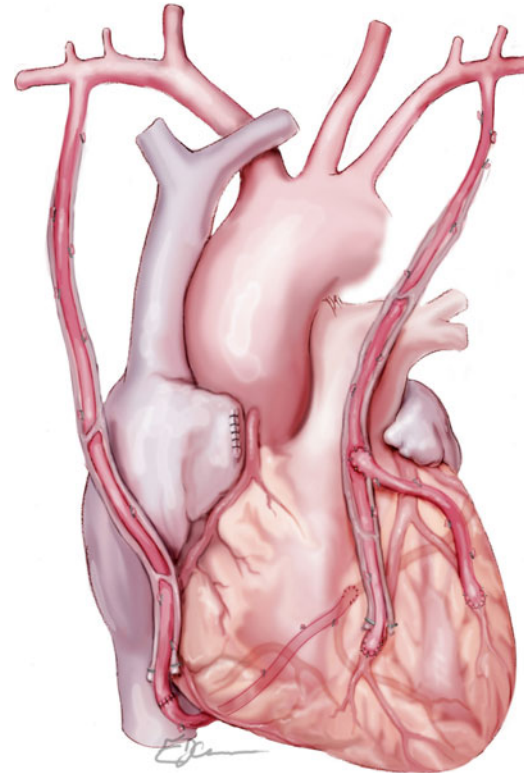

Fig. 5.11 All arterial grafting with no aortic manipulation. Two pedicled IMA grafts with one radial artery segment extending the RIMA and the other radial artery segment hooked up to LIMA as inflow. Figure 5.5 shows all arterial grafts performed without any aortic manipulation, which truly provides the full benefits of off-pump surgery. Note that one limb of radial artery has been used to prolong the RIMA, providing a composite graft that can revascularize the inferior wall. The other segment of radial artery is anastomosed to the mid-portion of the LIMA, end-to-side to allow grafting of the lateral wall

seems to be a hint at equivalent survival and graft patency between the radial artery and the right internal mammary artery – however, the primary end points and final results will not be available until 2014 [28].

Discussion

Off-pump CABG with complete revascularization has been shown to be as effective and safe as conventional coronary artery bypass grafting. In patients with heart failure and severe ventricular dysfunction with an ejection fraction of ≤35 %), complete revascularization can also be performed using OPCAB. This technique can minimize the inflammatory cascade that results from the cardiopulmonary bypass circuit and has the potential of being more beneficial in this high-risk population. In order to have a successful and complete revascularization; however, these patients need to be medically optimized prior to the intervention and have the procedure performed by an experienced team to be successful. The experienced heart failure surgeon needs to have the entire armamentarium to coronary revascularization and be readily apt at dealing with the various clinical scenarios that can arise.

Key Points

- Complete revascularization via coronary arterial bypass grafting surgery provides the definitive primary modality in the treatment of ischemic heart failure as a consequence of coronary artery disease.
- Off-pump coronary artery bypass surgery may have particular advantages in this high-risk patient population.
- Appropriate choice and use of arterial conduits may confer protection against future episodes of heart failure.
- Coronary artery surgery remains the cornerstone for the prevention and treatment of ischemic heart failure.

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Acute Mechanical Circulatory Support: Bridge to Recovery or to Decision

6

Bryan A. Whitson, Katarzyna Hryniewicz, and Ranjit John

Mechanical circulatory support (MCS) is, as the name implies, the use of electro-mechanical devices to support the circulatory system. This support may be uni-ventricular, bi-ventricular, pulmonary, percutaneous, central, or any combination of these, depending on the clinical scenario. A large component of MCS use is in a more permanent fashion in the bridge-to-transplant (BTT) or destination therapy (DT) patient. The other scenario where MCS is used is in the acute setting as a means of supporting the patient as a bridge-to-recovery or a bridge-to-decision about long-term MCS.

For the clinician, being presented with treating a patient in acute heart failure, either as a de novo presentation or as a decompensation of chronic congestive heart failure, is daunting. Similarly, the management and treatment of a patient with acute, refractory cardiogenic shock is similarly difficult. While there are many pharmacologic approaches, which are employed in the treatment of the patient with acute decompensation, when they are exhausted, there are few options left available to the clinician. In many instances, the only tool in the armamentarium is MCS. In this chapter we will discuss the management of the patient with acute decompensation and heart failure, the types and role of acute MCS, and the approach to determination of candidacy for acute MCS.

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Acute Decompensated Heart Failure

In the general population, chronic, congestive heart failure is relatively common and in the United States almost 200,000 deaths annually are attributed to it [1]. While acute decompensations of chronic heart failure are more difficult to track, it is estimated that approximately one million annual United States admissions are attributed to acute heart failure. In patients with acute decompensated heart failure, the median age of admission is 75 years of age and more than 50 % have significant coronary artery disease, diabetes, or other stigmata of chronic comorbidities (Table 6.1) [2]. The hemodynamic status and renal function of the patient are strong predictors of patient mortality. For example, those patients

J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_6

Table 6.1 Characteristics of patients with acute decompensated heart failure [52–54]

Characteristic	Incidence (percent)
Median age	75 years
Female	More than 50 %
Coronary artery disease	60 %
Hypertension	70 %
Diabetes	40 %
Atrial fibrillation	30 %
Renal insufficiency	30 %

Adapted from Greenberg, Acute Decompensated Heart Failure [2]

with a blood urea nitrogen (BUN) greater than 43 g/dL, with a systolic blood pressure (SBP) of less than 115 mmHg, and a creatinine (Cr) greater than 2.75 mg/dL, the risk of death is 22 %. This is in stark contrast to the patient with a BUN below 43 g/dL, with a SBP above 115 mmHg whose risk of death is 2 % [3].

Cardiogenic shock associated with an acute coronary syndrome (ACS) is associated with a much worse prognosis. In an analysis of the Global Registry of Acute Coronary Events (GRACE) the presence of cardiogenic shock in patient with ACS was associated with a 59 % in-hospital mortality rate. For those patients with ACS who did not develop cardiogenic shock, the in-hospital mortality rate was only 2.3 % [4]. What the GRACE registry also tells us is that cardiogenic shock associated with ACS is relatively occurs at a relatively low rate, 4.6 %. Of those patients with ACS, 57 % underwent cardiac catheterization and 47 % had revascularization. The presence of cardiogenic shock did cause the patients treatment with recommended medication to be changed [4]. So while developing cardiogenic shock after ACS is uncommon, the risk of death when it does occur is significant.

Medical Management and Referral

Often times, acute cardiogenic shock treatment begins with the use of single the multiple inotropes and vasopressors. This escalation often then leads to the placement of an intra-aortic balloon pump (IABP). While a recent article of the results of the IABP-SHOCK II trial call into question the benefit of IABP use in patients with cardiogenic shock from ACS who are planned for early revascularization [5], its use is currently in the algorithm.

For those patients with refractory cardiogenic shock, the associated early mortality rate is more than 50 %. This is even in the setting of being adequately revascularized [6, 7]. In those patients who are refractory to medical management, acute MCS is often the only means of survival. However, these patients are exceedingly ill and prone to a high degree of liability. This compromise extends to the hemodynamic blood pressure regulation, coagulation, hepatic and renal perfusion, and any subsequent multi-system organ failure [8].

There is a role for aggressive, early use of MCS. In a series of 41 patients with refractory shock treated at the University of Minnesota with placement of central, centrifugal flow pump MCS, 68 % of patients were able to be discharged from hospital with only 19.5 % dying while being supported on MCS [8]. This approach allows for a bridge to recovery or decision and will be the basis for the remainder of our discussion.

Technology and Approaches

As previously mentioned, MCS is often the only option for survival in those patient with cardiogenic shock from ACS or in those with acute decompensated heart failure. This treatment algorithm is a short-term, temporary cardiopulmonary support that enables time for clinical decisions on long-term management to be made (Fig. 6.1). The use of MCS as a bridge to recovery or decision is, just that. The use of these technologies allow for improvement of end organ perfusion facilitate any recovery that would then enable explant of the MCS. The use of permanent left ventricular assist device (VAD) placement in the setting of multi-system organ failure and hemodynamic instability has a prohibitively poor outcome [9].

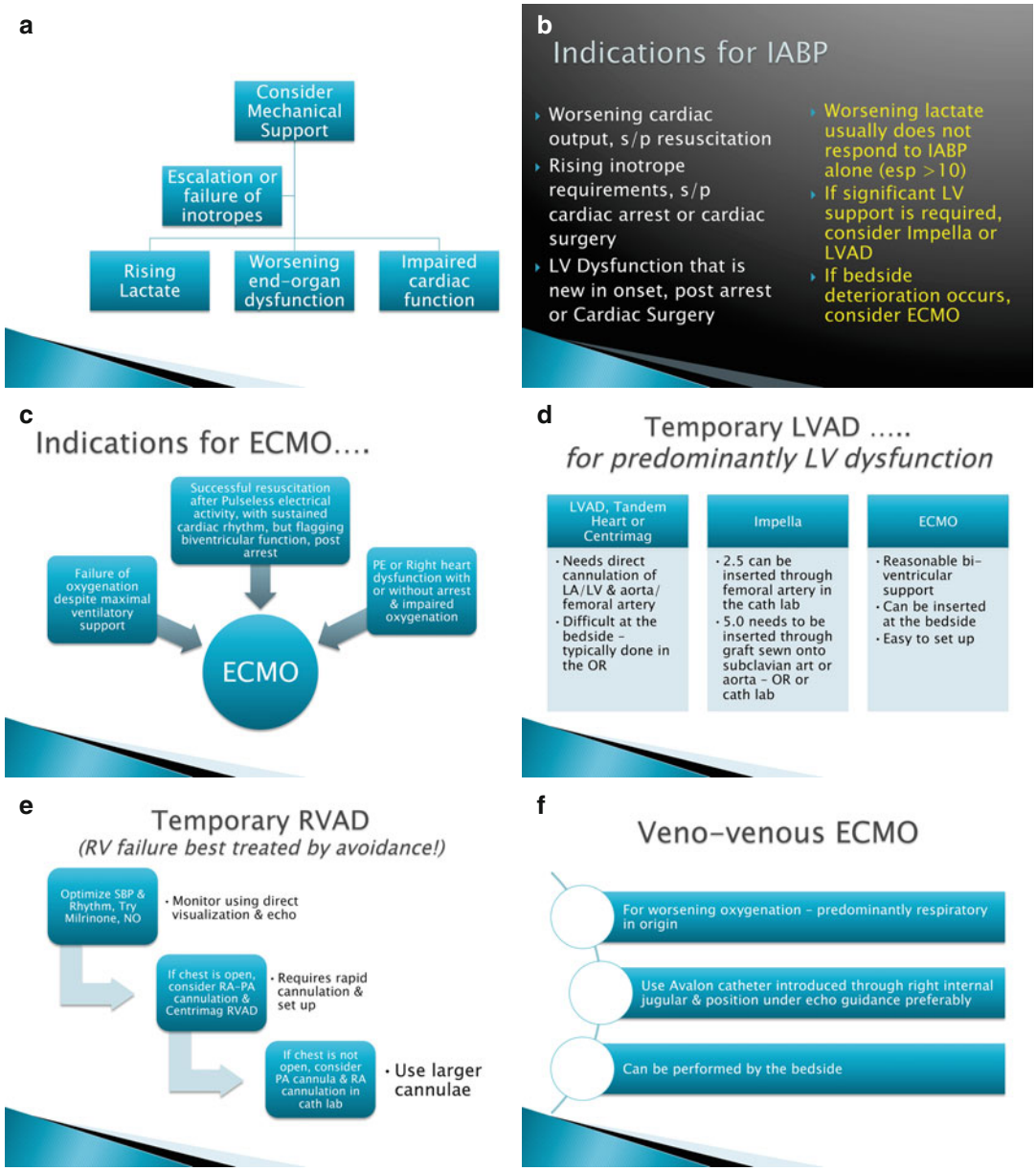

Fig. 6.1 (**a**–**f**) Algorithm for acute MCS

Therefore, the use of MCS to improve end-organ perfusion and more thoroughly resuscitate the patient allows the physicians, treatment team, support services, the patient and their family to discuss long-term options. If the patient does not recover end organ or neurologic function then plans for end of life care can be made. There are many options for short-term or acute MCS. There are surgically and percutaneously placed technologies. For clarity of nomenclature, either isolated uni- or bi-ventricular support is termed a VAD. The placement of an in-line membrane oxygenator, in either central or peripheral VAD, then is termed extra-corporeal membrane

oxygenation (ECMO) or extra-corporeal life support (ECLS).

Surgically Placed Ventricular Assist Devices

Thoratec CentriMag

The Thoratec CentriMag (Thoratec, Pleasanton, CA, USA) pump system (Fig. 6.2a) is an extracorporeal centrifugal blood pump. The system, initially introduced and provided by Levitronix (Wiltham, MA, USA) and subsequently acquired by Thoratec, contains a centrifugal blood pump, a motor, a controller console, and a flow probe [8, 10, 11]. A key advantage of the CentriMag pump, as compared to other centrifugal pumps on the market, is that has a low risk of hemolysis and thrombosis formation. This risk is ameliorated through the magnetically levitated impellar and a lack of bearings or seals. These features also produce minimal wear. A flow rate of up to 10 L/min can be obtained over pump speeds that range from 500 to 5,500 rpm [8, 9, 12].

There is a great deal of versatility in the implantation technique of the CentriMag which allows the surgeon to tailor the approach to best fit each patient's clinical situation. It may be implanted centrally or peripherally and has the ability to provide single or biventricular support. The ventricular support can be either right (RVAD) or left (LVAD). Biventricular support (BIVAD) can be obtained by utilizing two pumps, one for each ventricle. An oxygenator can easily be spliced in-line to convert to ECMO at any time, either intraoperatively or postoperatively.

For central cannulation (Fig. 6.2b), a median sternotomy is performed. Cardiopulmonary bypass (CPB) may or may not be utilized. In the patient with a large body habitus or intolerance of holding

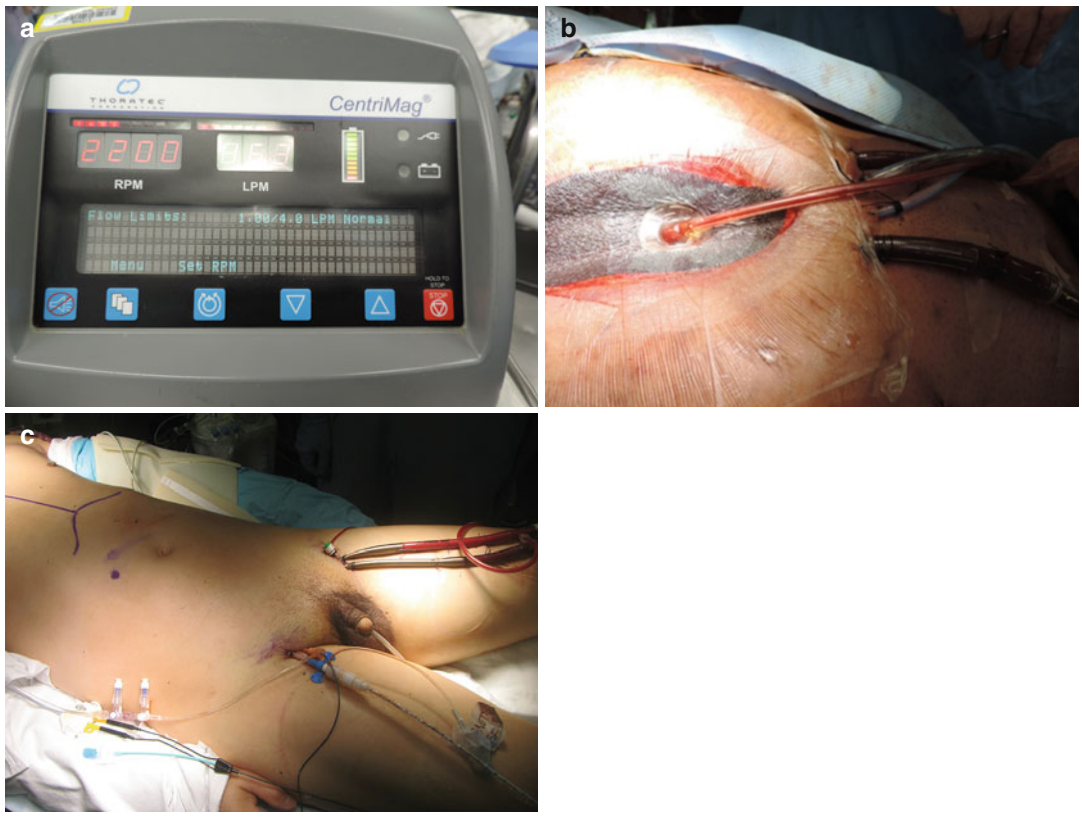

Fig. 6.2 (**a**) Schematic picture of CentriMag. (**b**) Central Cannulation with CentriMag. (**c**) Peripheral cannulation with CentriMag

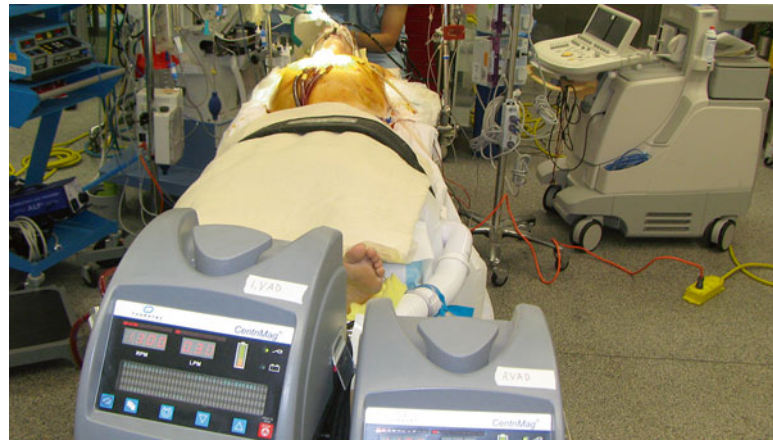

Fig. 6.3 Centrimag central – LVAD, RVAD, and BIVAD

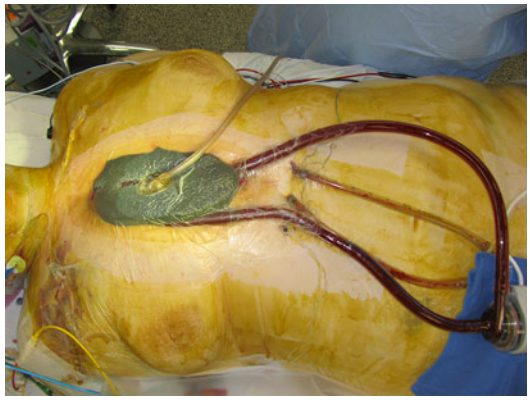

Fig. 6.4 RVAD with diagram of pledgets for cannulation

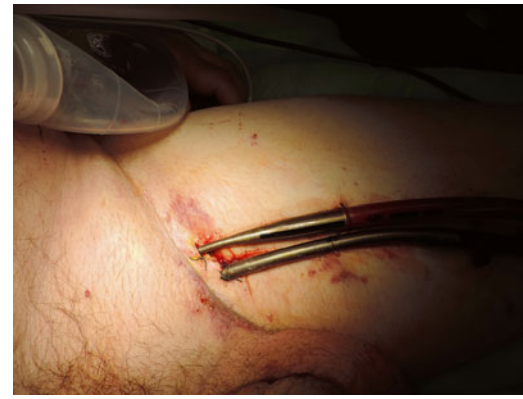

Fig. 6.5 Centrimag peripheral cannulation picture; inset showing peripheral cannulation via direct cannulation and chimney graft

respiration, CPB may add a degree of safety to the cannulation operation. Peripheral cannulation with cannulae inserted percutaneously through the femoral artery and vein (Fig. 6.2c) provide a very satisfactory method of supporting these sick patients emergently. This can be performed by the bedside.

For LVAD implantation (Fig. 6.3), the inflow cannula is placed into the left atrium through the right superior pulmonary vein at the interatrial septal groove. The outflow cannula is placed into the ascending aorta via direct cannulation as one would do for CPB. When used as an RVAD, the inflow cannula is placed in the right atrium, typically through the right atrial appendage. The outflow cannula is placed into the main pulmonary artery in a fashion similar to standard aortic cannulation. All cannula are secured with pledgeted purse string stitches (Fig. 6.4) and tourniquet. The purse strings are secured to the cannula. Of note, the cannula are ideally tunneled, as one would a chest tube, prior to insertion or connecting to the CentriMag circuit. Placement is characterized via trans-esophageal echocardiography [8].

For peripheral cannulation, only a LVAD approach can be utilized. The peripheral cannulation is typically via the femoral vessels (Fig. 6.5). The femoral artery and vein can be accessed directly. If the femoral artery has the arterial cannula placed into it, the distal limb perfusion should be assessed and if necessary distal limb perfusion implemented. Alternatively, the femoral artery may be accessed via placement of a 8-mm "chimney" graft onto the femoral artery and the arterial inflow cannula placed into

it. The use of a chimney graft, while a slightly longer operation, provides antegrade distal limb perfusion.

The CentriMag pump allows for the support to be weaned over time or intermittently to assess for function as an evaluation of recovery, the need for long-term MCS, or transplantation. Reports have described use of a CentriMag system for over 100 days without pump failure or thromboembolic complications [13, 14]. The modular nature of the CentriMag, and/or membrane oxygenator, in this setting allow for relatively easy exchange at bedside, whether in the intensive care unit or the operating theater [8, 14].

After ensuring hemostasis, heparin is used to anti-coagulate the patient with a goal activated clotting time (ACT) of 180–220 s. If mediastinal bleeding occurs, the heparin can be held for up to 48 h if the flow is maintained at 4 L/min or more and there are no concerns for pump malfunction, thrombosis, or emboli [8, 9].

In the group at the University of Minnesota's published series, the mean duration of CentriMag support in acute, refractory cardiogenic shock, was 12.2 days. The mortality rate with this device, in that series was 19.5 %. Of the 41 patients in the series, 68.3 % were able to be discharged from hospital. Sixteen of the patients were bridged to long-term MCS [8].

Abiomed BVS5000

The Abiomed BVS5000 (Abiomed, Inc., Danvers, MA, USA) is an external, pulsatile VAD. The BVS5000 is pneumatically controlled [15–17]. An external pneumatic drive console controls the system's single use blood pump (Fig. 6.6). In the Abiomed system, there are dual chambers that reflect those in a heart; an atrial chamber to "fill" and a ventricular chamber to "pump". The atrial chamber is passively filled throughout the cardiac cycle. The ventricular chamber then pumps extracorporeal blood back to the patient through ventricular chamber systole. The atrial chamber's continuous drainage allows for continuous drainage of the heart. There are two versions of the pneumatic controller that enables up to 5 L/min, or 6 L/min of flow in the high flow version. The pneumatic pump empties

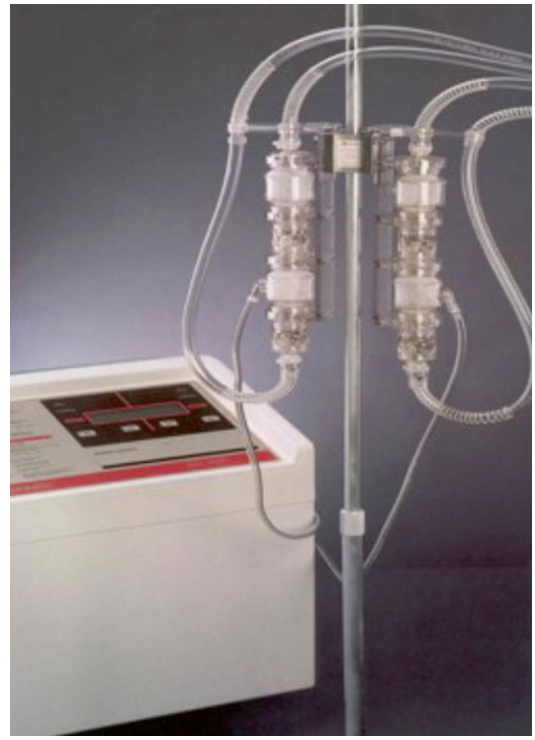

Fig. 6.6 Abiomed BVS 5000 – pump

when the chamber is sensed to be full so there is asynchrony between the pump and the patient's cardiac cycle. This feature is potentially advantageous in patients with unfavorable ventricular rhythms [8].

The typical insertion of the Abiomed BVS5000 is via median sternotomy. As with the CentriMag, there is option of implantation on or off CPB and for the ability for uni-ventricular or BIVAD support [8]. There have been descriptions of alternative implantation strategies (posterolateral thoracotomy) [18]. In this system, the inflow cannula for LVAD and RVAD are placed similarly with cannula placed into the atrium. The outflow cannula utilize a graft sewn to the artery. For the LVAD application, the inflow cannula is placed into the left atrium via the superior pulmonary vein at the intraatrial groove, the left dome of the atrium, or the left atrial appendage. The cannula is secured again with double purse string sutures [17]. For the RVAD application, the inflow cannula is placed into the right atrium, typically via right atrial

appendage. For the outflow in both LVAD and RVAD applications, a woven graft (10–14 mm) is anastomosed to the aorta (LVAD) or main pulmonary artery (RVAD) in an end-to-side fashion with running non-absorbable mono-filament suture [8, 16, 17, 19]. If need be, an oxygenator can be attached to the system for pulmonary support. As an alternative cannulation strategy, femoral access has been described [15, 20].

Anticoagulation should be initiated as soon as it is safe and the patient is free from ongoing bleeding (within 24 h). The anastomosis of the graft conduit to the artery is a potential source of bleeding and should be considered if there is a change in hemodynamic, chest tube output, or concern for trauma from traction on the pneumatic pump. The pump head needs to be monitored for fibrin build up or clot. If there is thrombus, the pump should be exchanged. The pump may go up to a week without needing to be exchanged [8]. In a series of BVS5000 patients, almost 50 % were able to be weaned from the pump and approximately 30 % of those patients were subsequently able to be discharged from the hospital [18].

Medtronic Bio-Medicus Bio-Pump

The Medtronic Bio-Medicus Bio-Pump (Medtronic, Inc, Eden Prairie, MN, USA) is a centrifugal pump. The Bio-Medicus pump is available in most cardiac surgery centers and has been used for femoral-femoral bypass, CPB, VAD, and ECMO [21, 22]. The BPX-80 biopump is the version which has seen the most clinical use. The newer generation Affinity biopump has been modified to have a lower priming volume, a modified impeller to minimize hemolysis, and two different types of biocompatible surfaces (Fig. 6.7).

The cannula are typically placed either centrally via sternotomy (LVAD, RVAD, or BIVAD) or peripherally via the femoral vessels (LVAD). The cannulation and cannula securing strategies are essentially identical to those employed with CentriMag placement. LVAD inflow cannula into the superior pulmonary vein or left atrium and outflow cannula into the ascending aorta. RVAD inflow cannula is from the right atrium with outflow cannula into the main pulmonary artery.

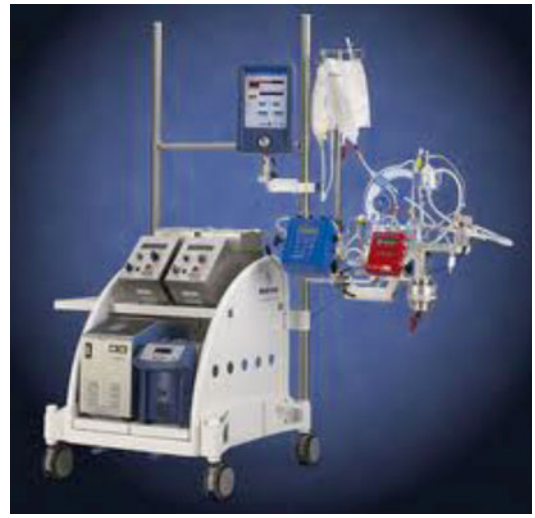

Fig. 6.7 Medtronic Biomedicus pump

If the bioactive coatings are used (Carmeda BioActive Surface, Trillium Biosurface, or Balance Biosurface, Medtronics Cardiopulmonary, Anaheim, CA, USA) minimal to no heparinization can theoretically be used. As a practical point, heparinization is often used though however. In the setting where non-heparin bonded lines are utilized, heparin drip systemic heparinization should be used to minimize the risk of thrombosis/thromboembolic events with a goal ACT of 150–200 s. Additional anticoagulation is needed for weaning trials to avoid the risk of clot. When the patient demonstrates an ability to be successfully weaned from temporary MCS, the cannula can be removed and pledgeted purse-strings sutures secured in the standard fashion [21, 22]. This approach is similar to that described for the CentriMag decannulation [8].

The Bio-Medicus pump is available at many cardiac centers in the United States. Due to its duration of service, it is a “tried and true” workhorse biopump of many centers. The use of the Bio-Medicus pump for weaning of post-cardiotomy failure is reported to be 45–70%. The survival of those patients who are able to be weaned from the temporary pump is on the order of 40–60 % [8, 21–24].

Percutaneously Placed Ventricular Assist Devices

Intra-aortic Balloon Pump

When Moulopolous and colleagues published their seminal article on intra-aortic balloon pump (IABP) placement in 1962 [25], it is unlikely that they could have estimated the extent of its adoption. The initial clinical use inpatients was in 1968 by Kantrowitz [26]. The IABP has become the archetype for bedside, percutaneously placed cardiac augmentation.

The IABP is inexpensive, simple to place, portable, and has been effective in treating those patients with cardiogenic shock. The IABP has two functions to improve hemodynamic stability. The first is, through its inflation during diastole, it provides improved coronary arterial perfusion. Secondly, through the synchronized deflation with the cardiac cycle, there is afterload reduction. This afterload reduction has the potential to improve cardiac output. Augmentation should be timed such that deflation occurs immediately prior to aortic valve opening. Insufflation should be timed with aortic valve closure. The timing can be synchronized with the electrocardiogram tracing or with the aortic pressure tracing. An advantage of the IABP is its ease of placement. Through percutaneous access or direct femoral arterial cut-down, the IABP may be placed with a sterile Seldinger technique. Fluoroscopy, plain chest Xray, or trans-esophageal echocardiography are able to be used to visualize correct placement. The proximal tip of the IABP should be place distal to the left subclavian artery. If a protracted duration of IABP use occurs, or if balloon inflation ratios of 1:2 or greater are used, anticoagulation with heparin should be considered.

There are potential complications of IABP use, however. The can be distal limb ischemia. The balloon can rupture and inattention to removal could lead to thromboembolic sequelae. At the entry site, infection, neuropathy, fistula (arteriovenous or lymphatic), pseudo aneurysm formation, aorto-iliac dissection, and arterial rupture. If the IABP is not appropriately placed, there is a potential for mesenteric or renal arterial occlusion.

For decades, IABP has been used as the treatment of choice to initially stabilize patients with cardiogenic shock after myocardial infarction. This has been especially true in the setting of patients who are to undergo revascularization. The role of the IABP in the treatment of cardiogenic shock in the setting of myocardial infarction is being called into question however. In 2012, Theile and colleagues from the IABP-SHOCK II investigators published on a prospective registry of 600 patients who were randomized to IABP or no IABP use, in the setting of patients with myocardial infarction and cardiogenic shock who were expected to undergo early (percutaneous or coronary artery bypass grafting) revascularization. In this study, there was no significant reduction in 30-day mortality, short term outcome metrics, or complications [5].

Subclavian IABP

In patients with contra-indications to easy implantation of a conventional LVAD or percutaneous peripheral cannulation, en emerging experience from Chicago with intra-aortic balloon pumps inserted through a graft sewn to the left or right subclavian artery shows great promise [27] (Fig. 6.8).

Abiomed Impella 2.5, 5.0 and LD

The ability to actively pump blood and increase cardiac output to improve end organ perfusion from a percutaneous delivery platform is an ideal bridge to recovery or decision option. The Abiomed Impella 2.5 (Abiomed Inc., Danvers, MA, USA) is a micro axial blood pump. It pumps blood from the ventricle to the ascending aorta, across the aortic valve, at flow rates up to 2.5 L/min [27]. The 12-french pump motor is placed though a 13-french introducer catheter is placed in to the femoral artery. Care should be taken in those patients with extensive aorto-iliac calcifications or tortuosity. Under fluoroscopic guidance, the Impella is placed across the aortic valve. (Figure 6.9 shows a schematic overview of the Impella 2.5 inserted through the femoral approach

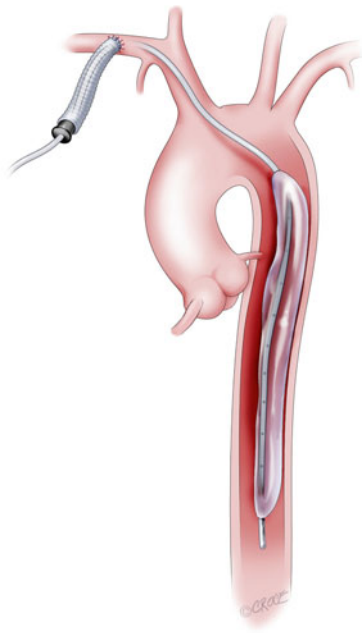

Fig. 6.8 Sublavian artery balloon pump

with the tip in the LV). There are nine variations on pump speed control that are able to be adjusted via and external control/monitoring console [8]. These variations are from 25,000 to 51,000 revolutions per minute (rpm). At 25,000 rpm, the flow is 0–0.5 L/min. At 51,000, the flow is 2.1–2.6 L/min. The maximum recommended rpm is 50,000 rpm with a flow of up to 2.5 L/min. The pump requires systemic anticoagulation, typically via a heparin drip to maintain a partial thromboplastin time (PTT) of 50–56 s [27–29] or ACT above 250 s. The Impella 2.5 has been used as support during high-risk percutaneous coronary intervention inpatient with cardiogenic shock after myocardial infarction [30, 31]. When compared to IABP, the Impella 2.5 demonstrated better hemodynamics. There was no difference between IABP and the Impella 2.5 is 30-day mortality though [30].

For higher flow rates, up to 5 L/min, the Impella 5.0 pump is an option [32]. The Impella

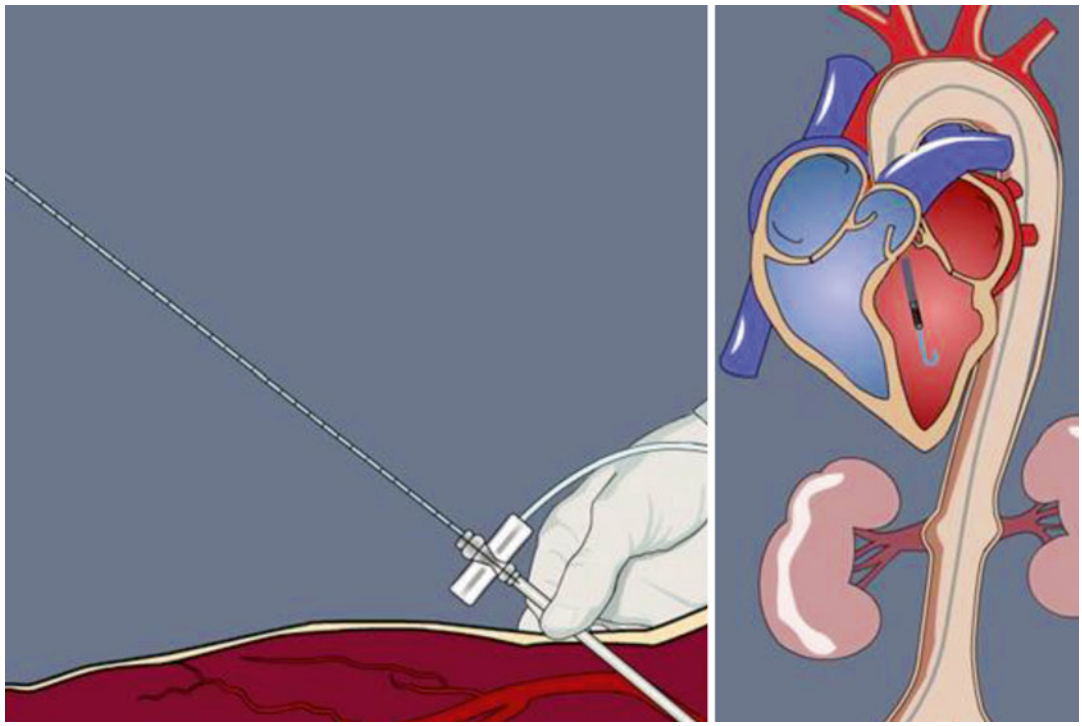

Fig. 6.9 Abiomed Impella 2.5

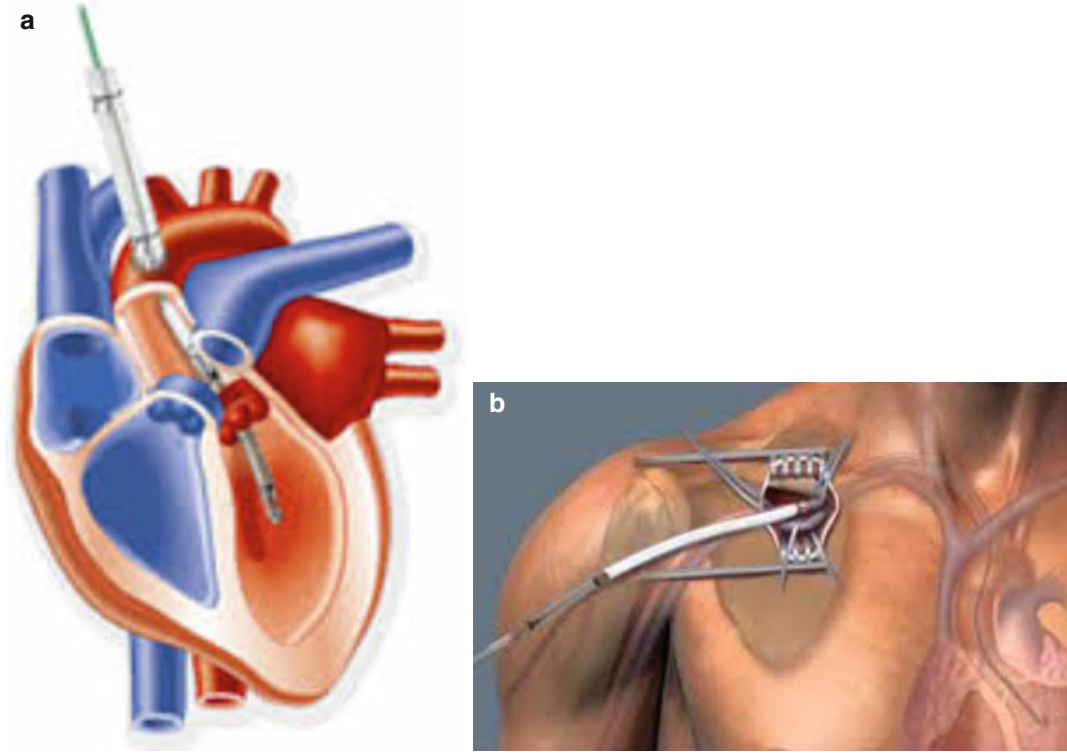

Fig. 6.10 (**a**) Trans-aortic Impella 5.0 LD, (**b**). Impella 5.0 LD through graft in the subclavian artery

5.0 can be placed into the femoral artery [32–34] or the axillary artery, via direct cut-down for either. The 5.0 device utilizes a pump motor that is 21-french in diameter. A variant on the Impella 5.0 is the Impella LD. The LD is placed into the ascending aorta, through a 10-mm graft that has been anastomosed to the ascending aorta. The Impella LD is again placed across the aortic valve in order to provide support and off-loading of the ventricle. It has been used for the treatment of post-cardiotomy heart failure and can achieve flows of up to 5 L/min [34].

The Impella devices have the ability to provide percutaneous short term ventricular support. The Impella 2.5 device has the ability to be place percutaneously. The adequacy of 2.5 L/min of flow in a patient with severe shock or elevated BMI and the ability to provide adequate end organ perfusion in that setting is a concern. The percutaneous nature make the placement easier in a cardiac catheterization lab. The 5.0 and LD devices provide a more adequate flow but have the disadvantage of needing either a direct vascular cut-down or a sternotomy, respectively. (Figure 6.10a shows an Impella 5.0 device inserted directly through the aorta and Fig. 6.10a shows the Impella 5.0 device inserted through a graft sewn through the subclavian artery). With the percutaneous devices, there is the limitation of limited availability, short duration for support, possibility for cannula dislodgement, lower extremity ischemia, and the difficulty for transport to a tertiary care facility [8, 12].

TandemHeart R

Another option for percutaneous VAD support is the TandemHeart R (Cardiac Assist, Inc., Pittsburgh, PA, USA). The TandemHeart is a percutaneous system that has intra cardiac drainage cannula and an extracorporeal blood pump. The system requires fluoroscopic guidance for placement and has the ability to deliver flow rates of up to 5 L/min. Via the femoral vein, the inflow cannula is placed into the left atrium through a trans-

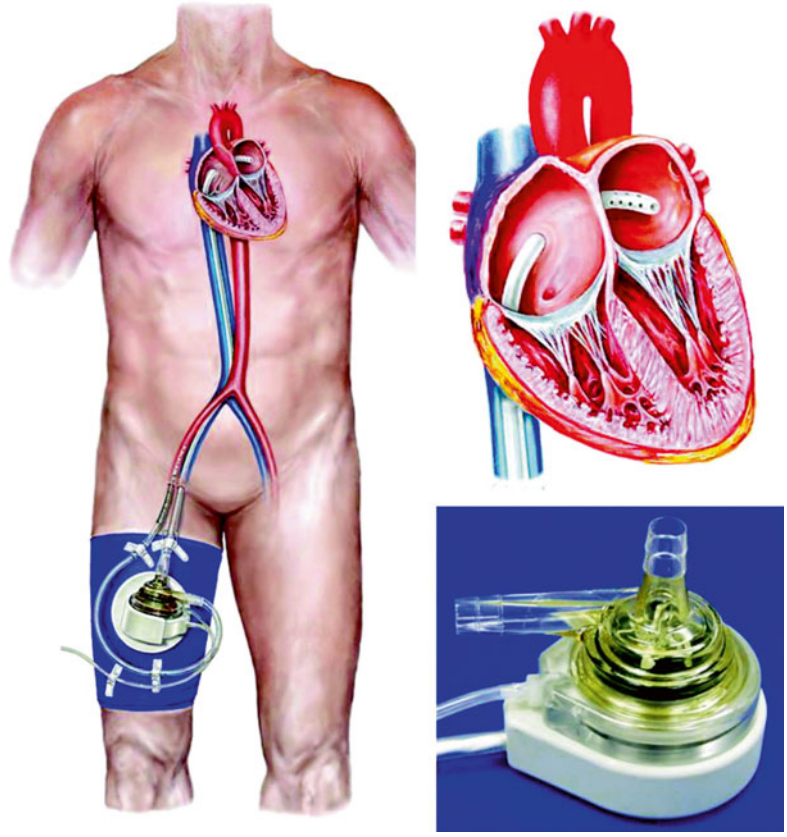

Fig. 6.11 Tandem heart schematic

septal atrial approach. The return outflow cannula is then placed into the femoral artery, as in peripheral cardiopulmonary bypass. The extracorporeal pump utilizes a centrifugal pump. (Figure 6.11 shows a TandemHeart pump with console). With this device, there is a need for systemic anticoagulation. Typically a heparin drip is utilized to maintain an activated clotting time of more than 200 s [8, 35–37]. The pump is able to be removed at the bedside or at the time of cardiac surgery. If there is no residual left to right shunt, then the atrial septal defect does not mandate closure. If the temporary device is being exchanged for a permanent VAD, then the atrial septal defect made during inflow cannula placement is closed at the time of implant via sternotomy [38, 39]. The etiology of the reason for TandemHeart placement has spanned from high-risk percutaneous interventions to post-cardiotomy heart failure, to bridge to decision to bridge to transplantation [35–40].

Surgical Approaches and Adjuncts to Care

Extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) has taken the short term VAD and added the ability to support the lungs to it. In the typical ECMO setting, an oxygenator is placed in line of the circuit. The support has multiple permutations. On one end, there is veno-venous ECMO. This is either via a jugular and femoral venous cannula where the femoral cannula is used for drainage and the jugular is for return. The alternative is the bi-cavil dual lumen (BCDL) catheter (Avalon Laboratories, LLC, Rancho Dominguez, CA, and USA). The BCDL catheter is placed into the right jugular vein and contains two inflow ports and one outflow port. The inflow ports are used to drain the superior and inferior vena cava, respectively. The outflow port is positioned so that the flow is directed through the tricuspid valve. For

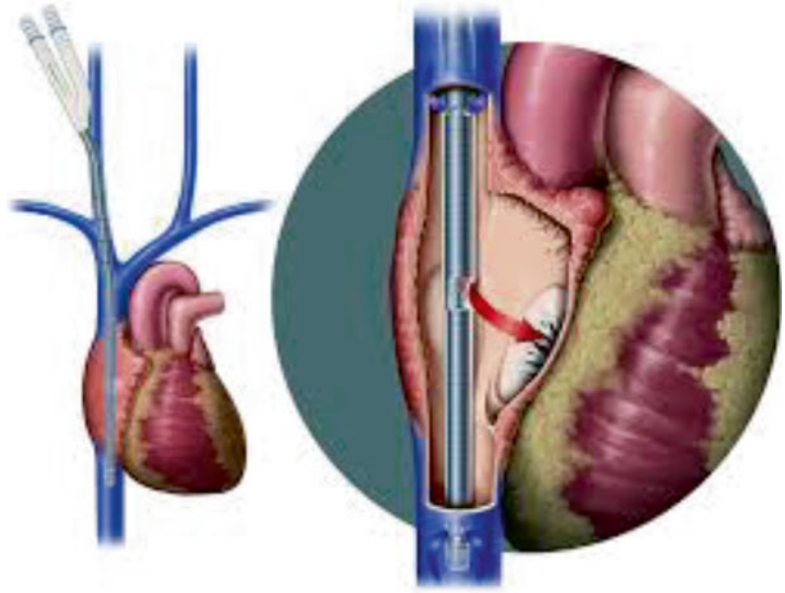

Fig. 6.12 Avalon catheter

veno-arterial or arterio-venous, there are multiple permutations [41, 42] (Fig. 6.12).

ECMO has been used to support cardiogenic shock and requires the use of an oxygenator to be differentiated form a VAD [41, 43]. In the adult patient after surgical bleeding has been controlled, there is a need for full anticoagulation. Typically this is with heparin to a goal ACT of 160–180 s [8]. A typical goal is to keep platelet counts above 100,000/dL and a hemoglobin above 10 g/dL.[41–43]. Of note, there are adverse events associated with the use of transfusion and the use of point of care measurements have been advocated [44, 45]. It is unknown if lower transfusion thresholds can be beneficial.

Complications of ECMO

Bleeding is a major complication associated with ECMO. This bleeding tendency is due to the platelet destruction on the circuit and associated with the oxygenator and the need for anticoagulation [8]. In those patients with respiratory failure, the hemoglobin is kept at a high level so that ventilator support can be decreased.

In the patient with peripheral cannulation, distal limb ischemia is a concern. The peripheral arterial cannula can cause inadequate flow due to the size of the cannula needed to get appropriately adequate flow rates and the size of the native peripheral artery [41–43, 46]. Duplex ultrasonography can be a simple bedside test to confirm the diagnosis and the need for distal perfusion. The distal perfusion can be attained percutaneously or by cannulating a "chimney" graft sewn to the vessel.

In general, there are reasonable rates for weaning of ECMO. There is a significant concern for infection, sepsis, and multisystem organ failure. In a series of patients who were successfully weaned from ECMO and bridged to a permanent VAD, there is an approximate 50 % mortality rate, due to sepsis [8, 47]. Ensuring resolution of end organ dysfunction may be an important step in increasing the success of permanent VAD placement [9].

Candidacy

There are many options available for temporary, acute mechanical circulatory support as we have discussed. They each have their advantages and disadvantages. The current or next generation centrifugal pumps will undoubtedly mark an

improvement of outcomes of acute MCS in the patient with shock. The role of percutaneously placed cannulas will evolve and their role is not completely defined. One limitation of the percutaneous VADs is their durability. In general their support is limited to less than 7 days [8]. The centrifugal pumps have the ability to be left in place for prolonged periods of time [8, 14] and reports of durable use up to 105 days have been reported [14].

Bridge-to-Decision Patient Identification

It is these authors belief that there is no role for a permanent or long-term MCS device to be placed in an emergent situation. The technologies described above allow for a bridge to decision in the emergent situation. This approach allows for the ability to stabilize the situation, regain end organ perfusion, evaluate neurologic function, and more thoroughly assess the patient's and family's wishes. This approach enables a more appropriate use of the permanent long-term VAD.

A team approach is needed to optimize the patient care and give the best chance for success. Having an open and honest communication discussion with the family is best [8]. There is an increasing role for palliative care in the management of heart failure patients and MCS. Palliative care in long-term or destination VAD is evolving [48–51]. Their involvement in the acute setting will undoubtedly be valuable as well.

At our institution, we find the CentriMag support system to be safe and cost-effective while allowing for maximal use of limited resources and excellent short-term survival. It is therefore, our choice for temporary circulatory support in patients with acute cardiogenic shock refractory to medical treatment as a bridge to decision device. In the near future, we do not know what the interplay will be between surgical and percutaneous devices, including ECMO. Until then, it remains imperative that we continue to be innovative, open-minded, and aggressive, continually striving to improve outcomes in this critically ill group of patients.

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Left Ventricular Reconstruction in Ischemic Cardiomyopathy

7

Salim Aziz and Jaishankar Raman

Introduction

Repair of left ventricular aneurysms was reported as early as the late 1950s by Likoff and Bailey [1]. Cooley reported on the success of linear closure of these aneurysms [2].

Josephson and Harken described blind endocardial resection for VT with poor functional results [3]. Gorlin was among the first to show that the ventricular wall after myocardial infarct could be akinetic or dyskinetic [4]. Dor and co-workers described a technique [5] which is illustrated in Fig. 7.1 to close the left ventricle reorganizing a neo left ventricular apex, in an attempt to recreate the normal conical shape in 1985. Jatene also described a plication technique in the same year using an external circular set of sutures [6]. However, it was Batista's bold experiments in dilated cardiomyopathy with heart failure and very public presentations of his "successes" that made people in the heart failure arena consider left ventricular reconstruction seriously [7].

Despite all this intuitive work on preserving left ventricular geometry, there was little interest in adopting these techniques into widespread clinical practice.

The 1980s were marked by two important steps in the knowledge of evolution and prevalence of ischemic failing ventricles:

1. The mechanism of progressive ventricular dilatation following transmural myocardial infarction, also known as remodeling, was well analysed and characterized [8]. The role of neurohormonal activation was established and this helped to provide therapeutic targets [9]. Ischemic remodelling lead to progressive ventricular dilatation which then sets in motion the cascade of heart failure [10].
2. Aggressive treatment of acute myocardial infarction, by revascularization of the occluded artery, has resulted in improved the survival rates. However, even after successful recanalization, the left ventricular wall of survivors, remains affected by scar in 80–100 % of cases; the infarct size varying from 6 to 60 % of the ventricular surface area as indicated by Christian [11].

Various imaging modalities such as cardiac magnetic resonance (CMR) developed as accurate, reliable and reproducible tools [12] to assess

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_7

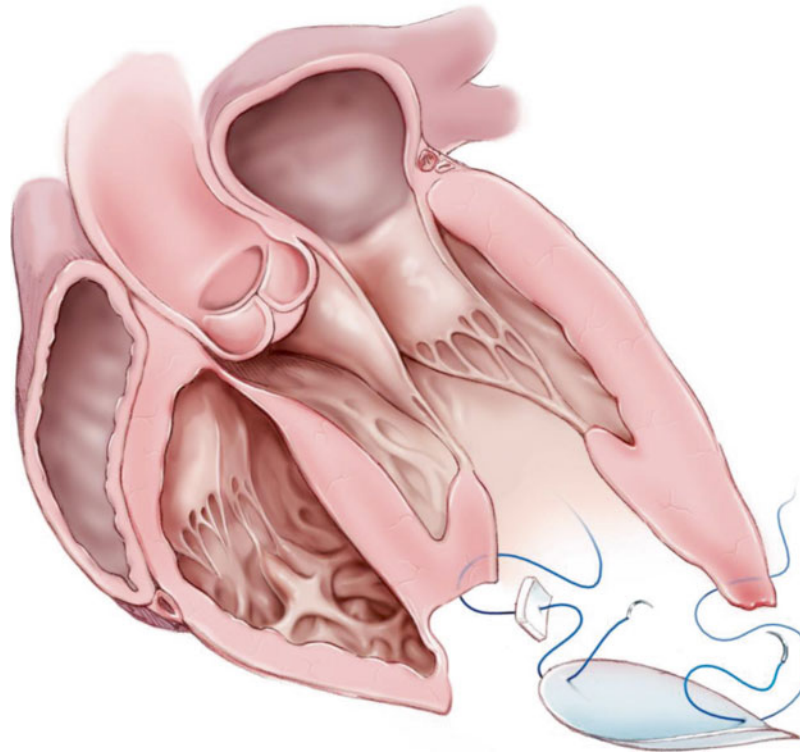

Fig. 7.1 Schematic of the principles of Left ventricular reconstruction (As proposed by Dor in 1985)

both anatomy and performance of the ventricles after infarction. Use of contrast MRI further enhanced the utility of this imaging modality [13].

More recently, three dimensional echocardiography and volume rendered images with multi-detector CT scanning have shown particular promise in this arena.

Fate of the Left Ventricle after Infarction

Gorlin in 1967 observed that:

> when 20 % to 25 % of LV area is asynergic, contraction of the myofibers to maintain stroke volume exceeds pathophysiological limits and cardiac enlargement (by the Frank-Starling mechanism) must ensue to maintain cardiac output.
>
> There are two types of asynergy seen as consequence of ventricular aneurysms: regional akinesis (total lack of wall motion), and regional dyskinesis (paradoxical systolic expansive wall motion.

In spite of revascularization of the culprit artery altering the immediate prognosis, the left ventricular wall may remain diseased [14].

(A) Evolution of the Infarcted Area: The infarcted wall undergoes changes that start with necrosis, progress to fibrosis and, eventually to calcification

1. The typical left ventricular aneurysm is characterized by a transmural infarct (Fig. 7.2).
2. The use of thrombolysis and/or revascularization in the acute phase may prevent transmural necrosis (Fig. 7.2b). Ventricular muscle adjacent to the epicardial artery is salvaged by recanalization, but the subendocardial muscle is necrotic, as described by Bogaert in 1997 [14]. The resultant ventricular wall may have viable myocardium which maybe evident at surgery (or during Thallium test) surrounding an akinetic, necrotic zone. The scarred asynergic ventricular wall may result in dyskinesia or akinesia. In both morphologies, it is important to know the extent of ventricular wall is abnormal, since this determines the indications and prognosis of surgical intervention.
3. Location: The **antero-apical and septal** regions are most commonly involved in

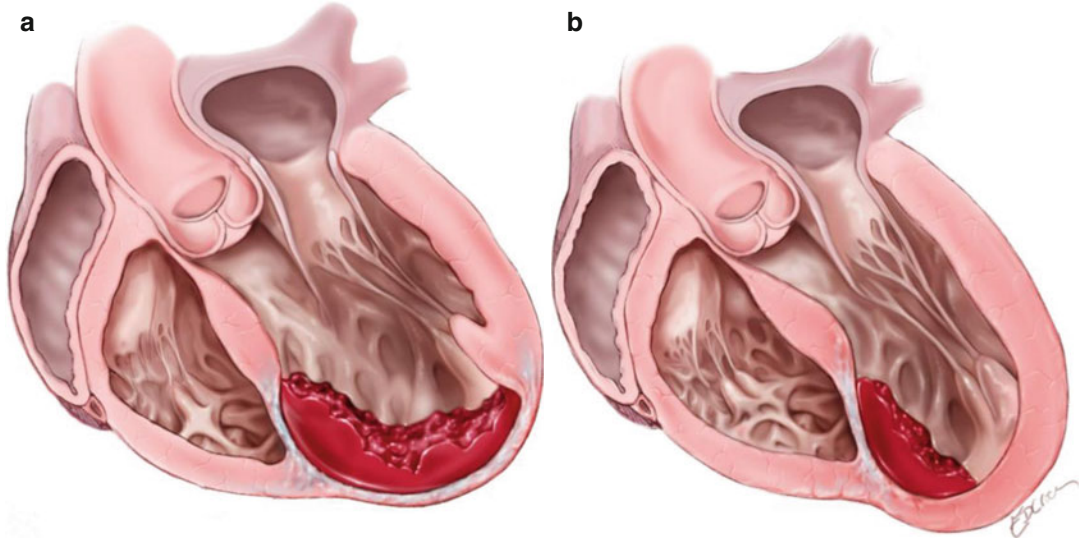

Fig. 7.2 Anteroseptal infarcts with extensive apical and septal involvement (**a**), Anterior infarct with predominantly septal involvement (**b**). Note adjacent mural thrombus formation

anterior infarctions caused by left anterior descending artery occlusion. Involvement of the septum is difficult to assess on ventriculography. The septum is best assessed by biplane angiography, echocardiography or cardiac MRI.

4. The extent of asynery or abnormality governs the prognosis of the left ventricle after infartion. This can be assessed by a variety of imaging techniques. Traditionally angiography using the centerline method in the right oblique projection has been used. However, increasingly, other techniques such as contrast echocardiography, radionuclide ventriculography, multi-slice CT Scan, cardiac magnetic resonance (MRI), provide more information. Analysing the LV wall and the presence of a necrotic scar is very important. The extent of asynergy can be expressed as the ratio between the length of necrotic wall and the total length of the LV circumference. The progression towards severe heart failure is likely when this ratio reaches 50 %.

(B) Fate of the Non-Infarcted Myocardium:

While normal at first, the undamaged myocardium undergoes hypertrophy to compensate for the lack of contractility of the necrotic wall, and finally dilates by a combination of mechanical forces and neurohormonal signaling. The Frank-Starling mechanism explains the early dilatation that temporarily improves the cardiac output and function. LaPlace's Law described increased wall stress and this is the fundamental reason behind the deleterious effects on myocardial contractility due to increased wall tension. Left ventricular remodeling is the term used to describe the progressive dilatation of the heart, and is based on a set of complex inflammatory and neurohormonal processes. Gaudron suggested that the culmination of this process is progressive dilatation of the non-infarcted area with an ensuing spherical shape and akinesia, which occurs, in 20 % of patients treated for myocardial infarction [15].

Harvey White was an early proponent of using left ventricular volume as a sensitive marker of post-infarction ventricular dysfunction [16]. Yamaguchi used left ventricular end-systolic volume as an important predictor for prognosis after surgical repair [17]. Doubling of indices can be considered markers of severe dilatation (normal values are 25–30 ml/m^2

for end-systolic volume index (ESVI) and 50/60 ml/m^2 for end-diastolic volume index (EDVI).

Who Should Be Considered for Surgical Ventricular Restoration (SVR) or Left Ventricular Reconstruction (LVR)?

Currently SVR is largely established for patients with ischemic cardiomyopathy after myocardial infarction, although some have advocated a variant of the technique for patients with idiopathic dilated cardiomyopathy.

Presently, the "ideal" patient should have a dilated ventricle and NYHA class III to IV heart failure symptoms following infarction. As for patients with LV aneurysms, totally asymptomatic patients should not be considered. The SVR/LVR is advocated for patients with a prior left anterior descending artery territory infarct (anterior wall, septum region). Patients with both LAD and circumflex artery occlusions may not be suitable candidates. The infarcted segment can either be akinetic or dyskinetic.

The timing of surgery is also important. Conventional wisdom states that 6 weeks following infarction should elapse before SVR is considered. There is, however, one small series of seven patients that underwent surgery soon after a large anterior infarction with encouraging results [18]. Anecdoctal cases have been performed in the early post-infaction period (2–14 days), particularly in the setting of low cardiac output as salvage therapy.

Preparation for Surgery

1. **Pre-operative preparation**: Patients that have been inpatients in cardiology for recurrent episodes of CHF and titration of medical therapy, often need tuning up. A variety of tests may be of benefit:
   - Measurement of pulmonary arterial pressure (PAP) by right heart catheterisation and the response to vasodilator therapy, and/or oxygen administration helps in stratifying patients.
   - Detailed echocardiographic assessment including three-dimensional echocardiography is of great benefit. Mitral regurgitation has to be assessed by pre-operative echocardiography or trans-esophageal echocardiography if necessary.
   - The extent of the scar and its location are important in planning the operation. Establishing viability of the remote non-infarcted segments is crucial because often there are regional wall motion abnormalities in these areas. Gadolinium enhanced magnetic resonance imaging is a good test of viability. Segments that are hypokinetic predictably improve if there is no hyperenhancement. If MRA is contraindicated due to implantation of a defibrillator or pacemaker, multi slice CT scan or 3-D echocardiography may be used. However, these tests may only assess contractility of the remote segments.
   - A coronary angiogram is mandatory to delineate the coronary anatomy.
2. **Preoperative medical treatment is continued** except for cessation of anti-platelet and anticoagulant therapy.
   - The intra-aortic balloon pump (IABP) should be used whenever there is hemodynamic compromise, such as evolving infarction without remission, CHF not improved by medical therapy, patients with a mechanical complication of myocardial infarction, or incipient renal failure. Some have found it useful in all SVR procedures as adjuvant therapy.
3. **Specific operative procedures**: A femoral arterial line is inserted for monitoring purposes and to allow quick access for insertion of a balloon pump if required. The patient is prepared for saphenous vein harvest if required. Cannulation for cardiopulmonary bypass is routine, utilizing an aortic cannula and a dual stage right atrial cannula. Monitoring includes arterial line, central venous pressure and Swan Ganz catheter.

Trans-esophageal echocardiography is used routinely.

- For the management of cardiopulmonary bypass, we minimize crystalloid use. Retrograde autologous priming of the circuit helps remove the crystalloid that is added to prime the circuit. Hemofiltration during bypass in helpful in reducing myocardial edema.

Left ventricular reconstruction (LVR): (Fig. 7.3)

Sequence of surgical steps may depend on the acuity of the patient, the extent of ischemia, presence or absence of left ventricular thrombus, etc.

1. The repair may be conducted utilizing the open-beating or cardioplegic arrest methods of myocardial protection (Fig. 7.4).
2. Grafting all coronary arteries with meticulous myocardial protective strategies is important. Retrograde cardioplegia preserves septal contractility as is crucial in preventing low output states postoperatively. Particular care is taken to revascularize the LAD, or diagonal if possible, thereby increasing septal blood flow.

What is the best resultant shape/volume of the operated left ventricle? What sort of patch should be used? These are interesting questions that are yet to be resolved conclusively. Although some authors have suggested that the LV can be "tailored" without a patch, this can be difficult, especially for the novice surgeon. This technique promoted by McCarthy is described in the next chapter. The size of the patch and the stiffness of the patch also may have a bearing on the outcome long-term, and these matters are addressed in the next chapter.

Management of Associated Mitral Regurgitation

Mitral regurgitation is found often in these patients, either due to the nature of the remodeling or due to involvement of the infero-basal wall of the left ventricle. Our personal preference to correct any degree of mitral regurgitation that is greater than moderate or 2+. Typically, this is done by utilizing a flexible posterior band or a remodeling annuloplasty ring. At times a simple Alferi stitch maybe resorted to as well. The mitral valve can be accessed and repaired through the ventriculotomy or via a separate incision in the left atrium or a trans-septal approach. The limitation of the ventricular approach is that access to the valve may be suitable only in very large scars that are more apico-septal in orientation (Fig. 7.5).

1. **The LVR technique**: Dor reported the technique of endo-ventricular patch patch plasty in 1989 [19]. In this classic technique, the ventricular wall is opened at the center of the scarred area, which often appears as a dimpled area once a left ventricular vent is placed after aortic cross clamping (Fig. 7.3b). Any clots present are removed. It is important to note that some fragmented and friable small clots may not be seen on trans-esophageal or epicardial echocardiography, especially if the thrombus is non-homogenous or small. The endocardial scar is dissected and resected if the scar is calcified (Fig. 7.3e) or if there is evidence of ventricular tachycardia (VT). Ablative treatment at the edge of scar usually at the borderzone, with radio-frequency energy or cyoablation is a short adjunctive procedure shown to limit postoperative dysrrhythmias.

   The reconstruction of the left ventricular cavity is started using a continuous suture 2-0 monofilament purse-string suture (Fig. 7.3d) with bites going into the muscle at the borderzone (the junction between the scar and normal myocardium). Typically, this suture is run as a continuous purse-string suture is tightened over a rubber balloon inflated within the cavity at the theoretical diastolic left ventricular volume (50–60 ml per sq.m. of BSA). This technique was introduced to avoid making the residual cavity too small [20]. This is a good guide to surgeons with limited experience. The endoventricular circular suture is also known as the "Fontan stitch" (Fig. 7.3d)

and helps optimize orientation of the patch while selecting its shape and size.

The septum and apex are more involved than the lateral wall in the antero-septo-apical type of scarring. In these cases, the suture, thus placed deeply in the septum, totally excludes the apex and the posterior wall below the base of the posterior papillary muscle, and only a small portion of lateral wall above the base of the antero-lateral papillary muscle. Therefore, the orientation of this new neck (and of the patch) roughly follows the axis of the septum.

Dor described the use of a Dacron patch that is sutured to the Fontan Stitch. The excluded, redundant bits of scar are then sutured over the patch to aide in hemostasis. The traditional Dacron patch is quite stiff, and various modifications of the technique include use of Gortex, bovine pericardium or no patch at all.

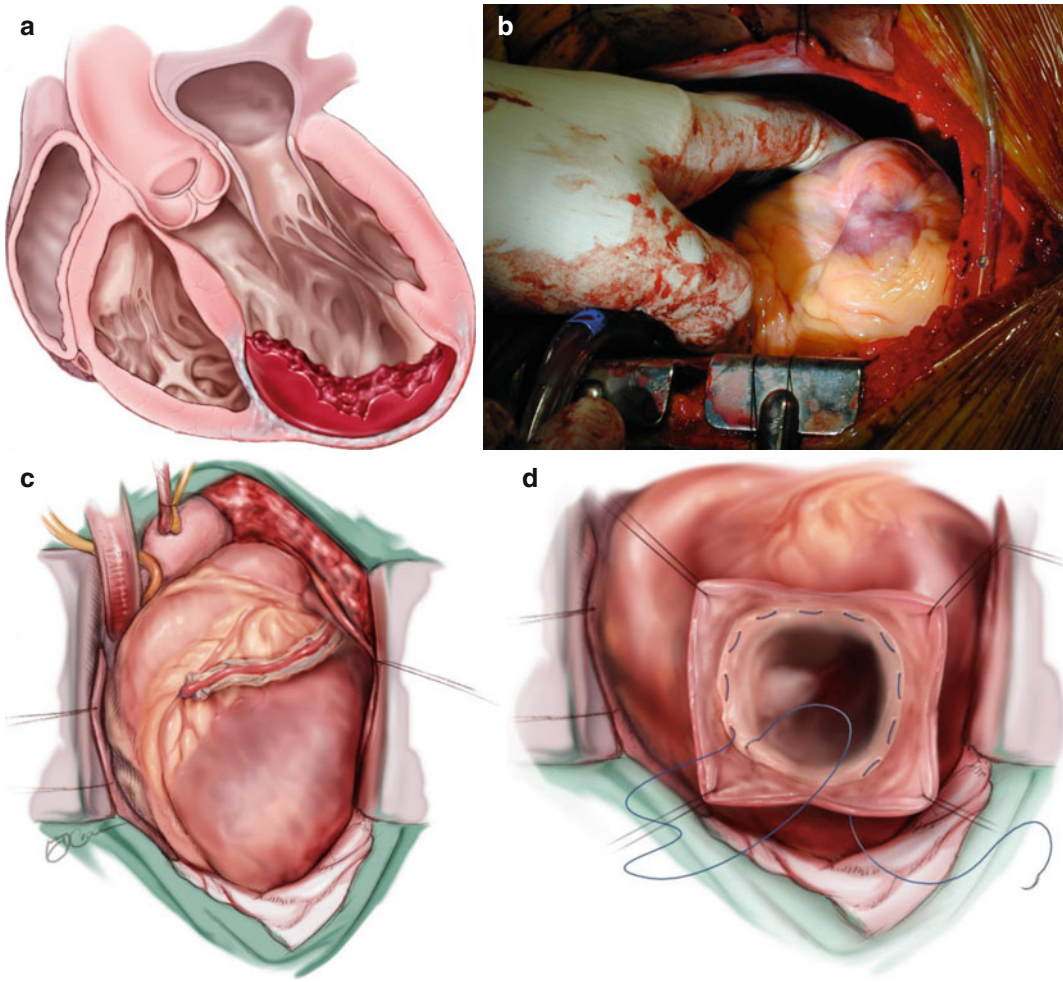

Fig. 7.3 Steps of surgery for Left Ventricular Reconstruction (LVR): Left Ventricular Reconstruction: (**a**) The antero septo apical aneurysm with mural thrombi: the dilatation also affects the non-scarred myocardium on septum (S) and lateral wall (L). (**b**) Intra-operative photograph showing dimpling of Left ventricular scar with use of vent. (**c**) Coronary revascularization accomplished first on arrested heart. (**d**) The continuous purse-string suture at the limit between fibrous and normal myocardium (Fontan "Trick"). (**e**) possible endocardectomy if needed. (**f**) The suture is tied on a rubber balloon inflated to 50 mm per square meter of the body surface area (normal diastolic volume). The shortening of the SL length illustrates the reorganization of the curvature. (**g**) The Dacron patch anchored on the suture. The right ventricle apex projects beyond the new LV apex

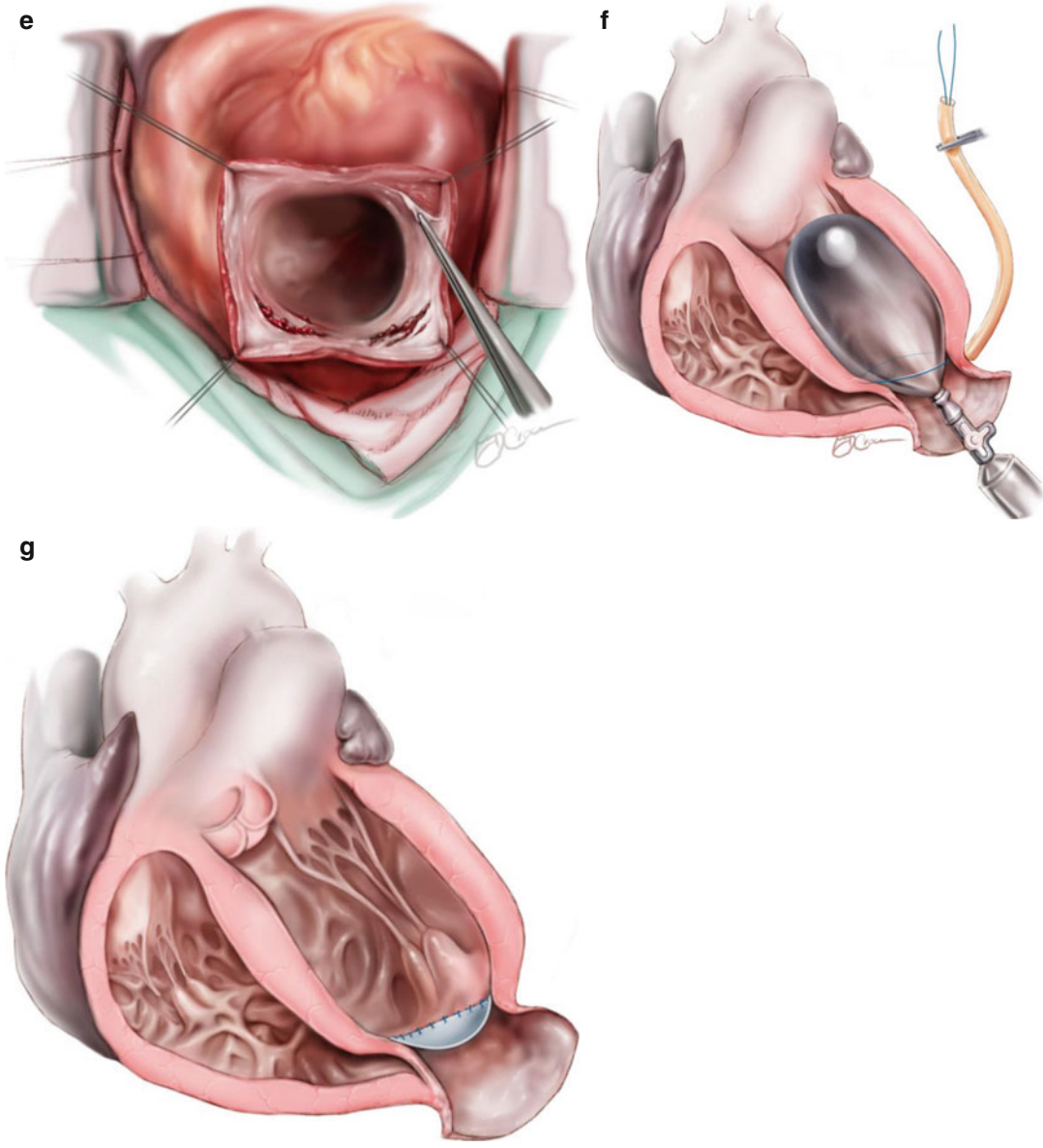

Fig. 7.3 (continued)

2. **Wean off CPB**: Typically, weaning from bypass is slow and gentle to allow complete recovery of both ventricles. Frequent use of antegrade and retrograde blood cardioplegia every 8–10 min helps preserve biventricular function and allows quicker recovery of the heart. Our choice of inotrope typically involves milrinone and dobutamine. Often, norepinephrine and/or vasopressin are required as an adjunct to counter the hypotension that is seen due to the effect of milrinone. Liberal use of the balloon pump has been found to be very useful. Prophylactic atrial and ventricular pacing wires are used to ensure a regular rhythm. If there is a history of atrial fibrillation or ventricular arrhythmia, prophylactic use of amiodarone helps reduce the risk of lethal arrhythmias.

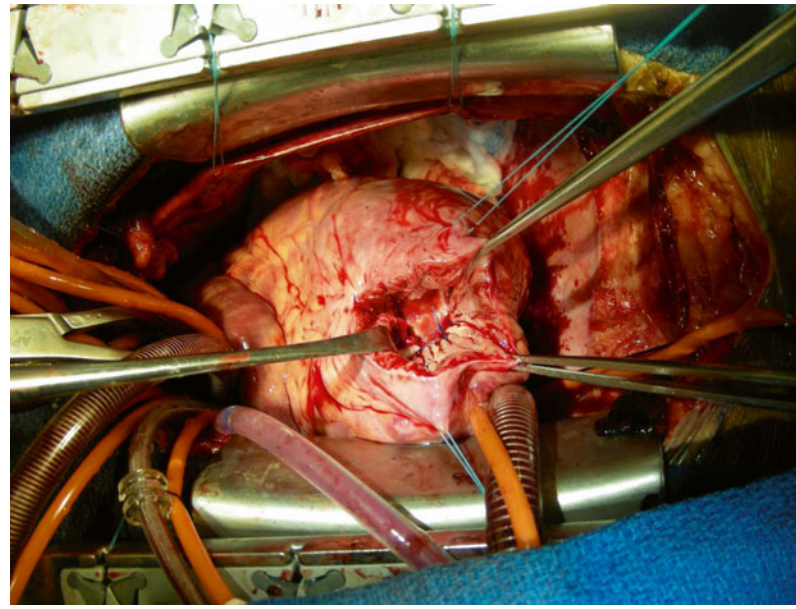

Fig. 7.4 Completed patch implant

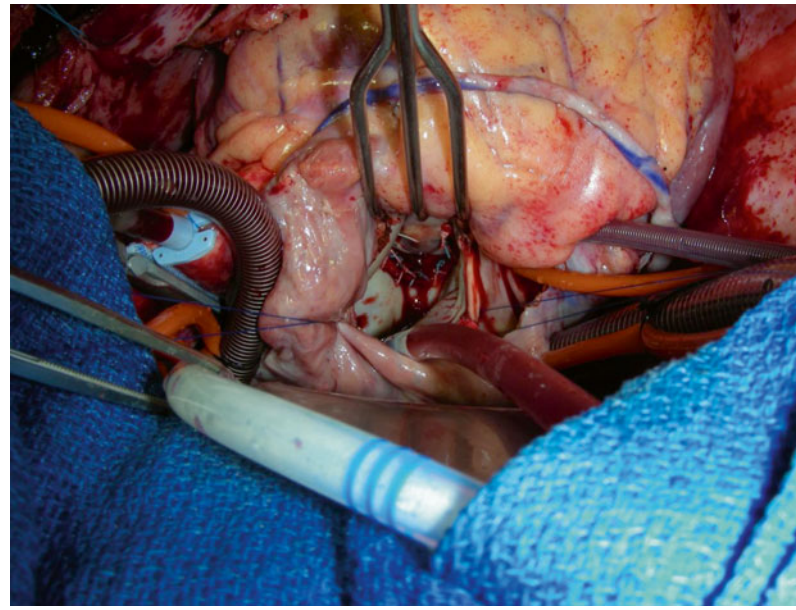

Fig. 7.5 Completed mitral valve repair. Note vein graft to inferior to a branch of the RCA and trans-septal approach to mitral valve

3. Specific modifications: (Fig. 7.6)
   (a) Changes based on alterations of the ventricular wall
      • Autologous tissue has been used for the patch: either a semicircle of the fibrous endocardial scar mobilized with a septal hinge if this scar is strong, or autologous pericardium. Figure 7.7a, b show a septal hinge being used to patch the defect.
      • When the tissues are soft and necrotic, during the repair of an acute mechanical complication of myocardial infarction (exclusion of septal rupture or treatment of free wall fissures), the patch has to be inserted into healthy tissue by deep stitches

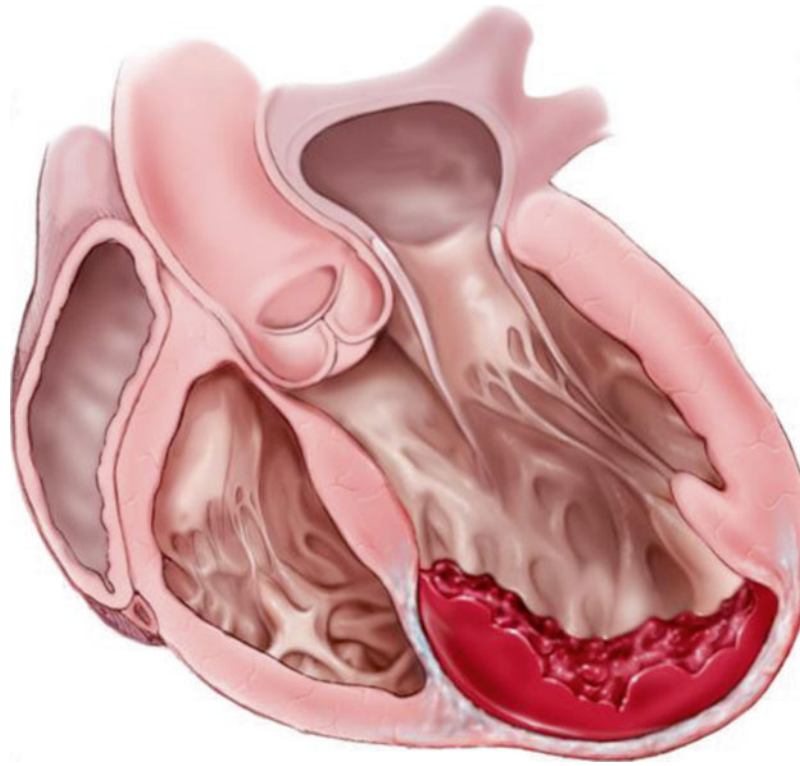

Fig. 7.6 This shows the left ventricle in longitudinal section with mural thrombus along the septum and antero-apical wall

reinforced with Teflon pledgets. The patch is anchored above the septal rupture which is excluded from the LV cavity (Fig. 7.7d).

Figure 7.7c, d show a septal infarct that has been excluded with a pledgetted plicating suture and subsequent implantation of a patch to exclude the septal infarct.

(b) Amount of Scar Exclusion: In cases of a large amount of asynergy (above 50 % of LV cavity) surgery is accomplished with some modifications. These patients typically are in Class III or IV heart failure and on inotropes. Mean pulmonary artery pressure is often above 25 mmHg, ejection fraction (EF) below 30 %, EDVI above 150 ml/m^2, and ESVI above 60 ml/m^2. Ventricular tachycardia may be present in nearly 50 % of cases and this should preferably be addressed by ablative strategies and/or endocardectomy. Mitral insufficiency has to be repaired in the majority of cases. Mitral valve repair in this instance is performed as a remodelling annuloplasty, with Bolling and his followers advocating rigid, shaped rings. David and his group have shown good results with flexible posterior bands. If the presentation is acute or if there is difficulty in repairing the valve, a valve replacement with chordal preservation should be considered. Theoretically, the exclusion of all scarred areas may lead to a very small LV cavity with a high risk of immediate or delayed diastolic dysfunction. The Fontan stitch is placed slightly beyond the edge of healthy muscle at the transitional area. The use of a mandril or balloon inside the LV, inflated at the theoretical diastolic volume of the patient is a useful guide to optimize tension on the suture. The patch can be slightly more redundant (3–4 cm in diameter) than in the usual technique.

If the septum cannot be excluded easily, the redundant septum can be plicated or imbricated separately or at the edge of the patch as described by Jatene.

(c) **Inferior and posterior scars** (Fig. 7.8b): An oblong or triangular patch, with its base aligned along the posterior or postero-lateral mitral

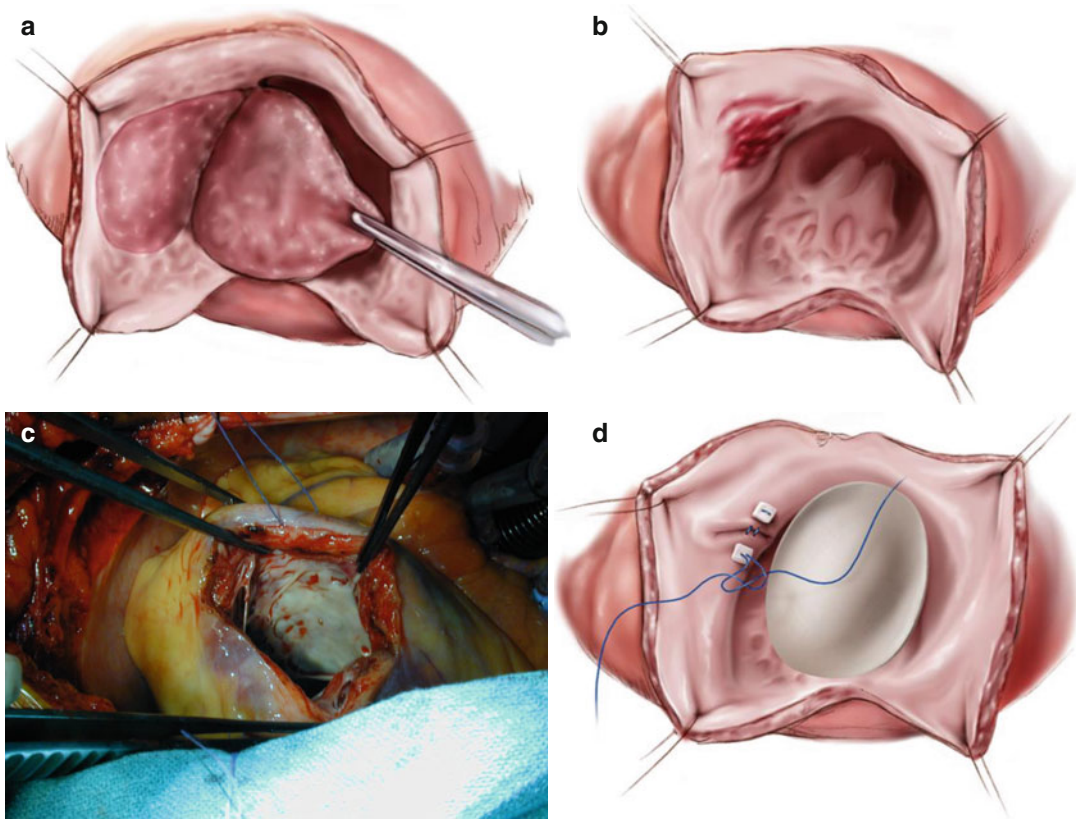

Fig. 7.7 Particular cases of Endoventricular patch reconstruction: (**a**) utilization of the septal scar as an autologous patch. A semicircular portion of the scar mobilized from the septum with a septal hinge is sutured on contractile muscle inside the left ventricle. (**b**) Septal Involvement after opening up the left ventricular scar. (**c**) Operative photograph of septal infarct and scar. (**d**) Septal Involvement. The patch is anchored above the septal repair, which is excluded from the left ventricular cavity

annulus and its apex close to the base of the posterior or antero-lateral papillary muscle is the typical orientation. This allows the reconstruction to follow a geometric pattern restoring shape to normal. If the posterior papillary muscle is totally involved in the resected scar, the mitral valve can be replaced by a prosthesis, implanted through the ventriculotomy.

Figure 7.8 a–c show repair of a postero-inferior scar with replacement of the mitral valve and implant of a triangular patch.

Early Results

Early results with simple linear closure were variable and often suboptimal. Left ventricular reconstruction is a complex procedure performed on patients with significantly impaired ventricular function and is frequently associated with an operative mortality risk of about 7 %. The risk profile is dependant on the extent of scarring, the degree of heart failure, the amount of remaining normal ventricle, the presence of arrhythmias and the amount of mitral régurgitation. Hospital mortality can be stratified into three categories:

- Very severely depressed EF <30 %: mortality of 12–15 %.
- EF of 30–40 %: mortality of 7 %
- EF >40 %: mortality of 1.3 %

LVR Outcomes (Restore Group)

Dor's contributions inspired a multinational study of ventricular restoration. A collaborative

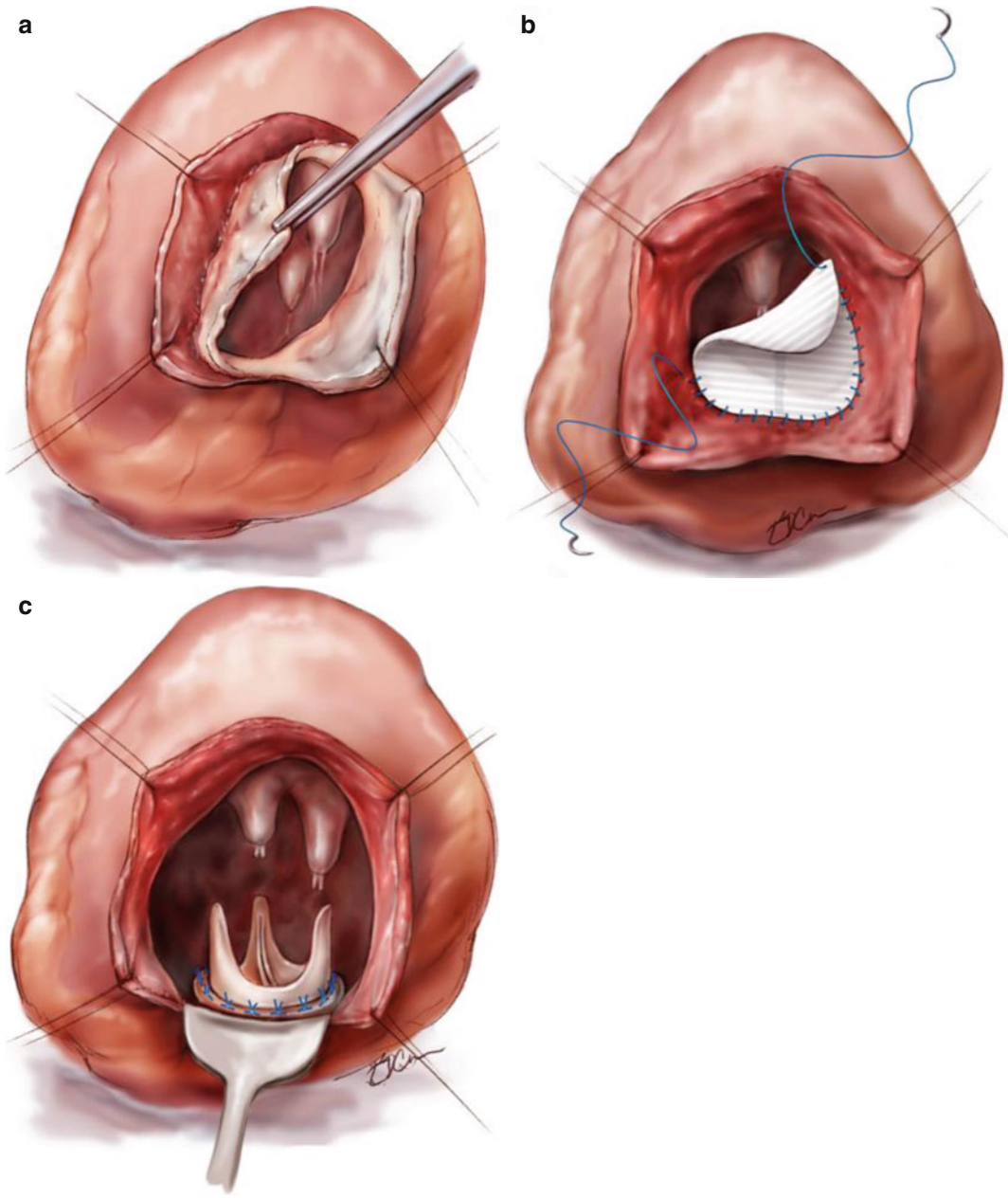

Fig. 7.8 (**a**) LVR for posterior aneurysm: positioned for posterior incision and endocardectomy. (**b**) Triangular patch closure of the posterior left ventricular scar. (**c**) Mitral valve replacement through a posterior scar

group of cardiologists and cardiac surgeons (the RESTORE Group) from four continents (US, Europe, Asia, South America) applied SVR in 1,198 patients between 1998 and 2003 [21]. Patients were included in the registry if SVR was performed with the following criteria: prior anterior myocardial infarction, significant ventricular dilation (LVESVI ≥60 ml/m^2), and a regional asynergic (non-contractile) area of ≥35 %. SVR was most often done as a concomitant procedure: 90 % received coronary bypass grafting and mitral valve repair was required in about 20 %.

In the RESTORE registry, 86 % of patients had NYHA class III/IV symptoms of CHF preoperatively. Such patients have a high mortality with medical therapy, or with surgical revascularization without left ventricular restoration, where late deaths are attributable to CHF. Echocardiography,

ventriculography or magnetic resonance angiography (MRA) was used to confirm the asynergic area and calculate the ejection fraction (EF). LVESVI was determined by ventriculography or MRA.

Hospital mortality after SVR was 5.3 %, and increased as preoperative ventricular volume rose: 2.3 % if LVESVI was <60 ml/m^2, 5.7 % if LVESVI was 60–90 ml/m^2, 8.1 % if LVESVI was 90–120 ml/m^2 and 8.4 % if LVESVI was >120 ml/m^2. These findings are comparable to recently reported mortality rates (5.5–11 %) in ischemic patients with left ventricular dysfunction (EF <35 %) undergoing coronary artery bypass grafting alone. The addition of mitral valve repair influenced early outcome. Hospital mortality was 8.7 % with mitral repair vs. 4.0 % without repair ($p<0.001$). Perioperative mechanical support with intra-aortic balloon pumping was uncommon (<9 %). Global systolic function improved postoperatively as EF increased from 29.6 ± 11.0 % preoperatively to 39.5 ± 12.3 % postoperatively ($p<0.001$). LVESVI decreased from 80.4 ± 51.4 ml/m^2 preoperatively to 56.6 ± 34.3 ml/m^2 postoperatively ($p<0.001$).

The overall 5-year probability of survival after SVR was 68.6 ± 2.8 % and confirms Dor's extensive experience and is unprecedented in the treatment of advanced ischemic cardiomyopathy. The multivariate analysis of SVR demonstrated that major risk factors were age, preoperative EF, LVESVI, and NYHA functional class.

The RESTORE data further emphasized the importance of measuring LVEVI as a surrogate marker of left ventricular function. EF and LVESVI are not directly related, as there is a wide variation in volume for a given EF. Patients with preoperative LVESVI ≤80 ml/m^2 had long-term survival of 79.4 ± 3.3 % as compared to 67.2 ± 3.2 % for those with larger hearts. Preoperative NYHA functional class was also predictive of outcome with decreased 5-year survival in patients with preoperative class IV symptoms (49.7 ± 5.8 % vs. 69.9 ± 4.7 % in class III). These predictors of long-term outcome after SVR are similar to those previously reported. A small number of patients (9 %) in functional Class I underwent SVR as an adjunct to CABG because ventricular dilation (LVESVI >60 ml/m2) has been shown to be a precursor of late development of CHF and early death.

1. **Cardiac morphology and performance**:
   - The most striking findings on imaging are the relative normalcy of ventricular shape and function postoperatively. If a localized scar is effectively excluded with restoration of normal shape, the heart failure symptoms are dramatically ameliorated. **Improvement in Systolic function**: Often, the mean increase in ejection fraction early after reconstruction is between 10 to 20 %. Improvement is similar for dyskinetic as well as akinetic lesions [22].
   - **Improvement in Diastolic function**: The peak filling pressures and filling pressures in the left atrium as surrogate markers of left ventricular diastolic function are relatively normal a few months after operation.
   - **Efficiency**: The elimination of the dead space of the scar helps improve the efficiency of ventricular contraction by:
   – Elimination of the asynergic scar.
   – Restoration of the curvature of the ventricular wall: Analysis of pressure-volume curves has shown reduction in wall stress [23].
   – Mechanical synchrony is restored.

Intermediate and Long Term Results

1. Despite acceptable early morbidity and mortality, the intermediate and long-term results are not uniform. They are based on a variety of comorbidities and factors. Late mitral regurgitation has been noted to recur in some series [24]. We could speculate that this might be related to the stiffness and size of the patch. This may also occur in very large ventricles where there has been a delay of more than 40 months between infarction and surgical repair. Progression in remodeling may depend on mechanical causes or neuro-hormonal activation [25]. Continued medical therapy with diuretics, vasodilators, beta-blockers and ACE inhibitors are vital in ensuring good long-term outcomes.

2. **Improved left ventricular function and dimensions**.

Our experience along with those of others, have shown that there is reverse remodelling of the reconstructed left ventricle over a period of weeks and months. There is a steady improvement in functional status and exercise tolerance in the majority of patients. However, there is a small group of patients where the results may be mediocre, with functional status remaining static or with some deterioration. These are usually patients with diastolic dysfunction or a significant amount of myocardial fibrosis. Occasionally, the underlying cause may be the use of too large a patch or residual mitral regurgitation.

McCarthy reported on the Cleveland Clinic's experience with a variation of the technique whereby the left ventricle was reconstructed without a patch, where they analysed the first data for the first postoperative year [26]. These patients had a mean EF 23.9 % and mean EDVI 140 ml/m^2, that changed to 36 % and 90 ml/m^2 respectively. The levels of norepinephrine, plasma rennin activity, angiotensin and brain natriuretic peptide decrease significantly, confirming the regression of neurohormonal activation.

3. **Long-term results**

Global life expectancy at 5 years, in a series of 207 surviving patients analysed from 1991 to 1998, was 82 %. In another consecutive series of 245 patients from 1998 to 2003 (analysed to assess the impact of diastolic balloon sizing), the life expectancy at 5 years, hospital death included, is 85 % for the global series and 70 % for patients with very poor ventricular function (ESVI >120 ml/m^2). At 10 years, in the last category of very largely dilated failing ventricle, the percentage of survivors is 50 %, while it is 80 % for patients with ESVI <90 ml/m^2.

The Surgical Treatment for Ischemic Heart Failure (STICH) trial was designed to define the role of cardiac surgery in the treatment of patients with heart failure and coronary artery disease. One of the two major hypotheses of this trial (Hypothesis 2) was that surgical ventricular reconstruction, when added to CABG, would decrease the rate of death or hospitalization for a cardiac event, as compared with CABG alone.

This was conducted as a multicenter, nonblinded, randomized trial at 127 clinical sites in 26 countries. The trial was sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health.

Between September 2002 and January 2006, a total of 1,000 patients with an ejection fraction of 35 % or less, coronary artery disease that was amenable to CABG, and dominant anterior left ventricular dysfunction that was amenable to surgical ventricular reconstruction were randomly assigned to undergo either CABG alone (499 patients) or CABG with surgical ventricular reconstruction (501 patients). The primary outcome was a composite of death from any cause and hospitalization for cardiac causes. The median follow-up was 48 months.

Surgical ventricular reconstruction reduced the end-systolic volume index by 19 %, as compared with a reduction of 6 % with CABG alone. Cardiac symptoms and exercise tolerance improved from baseline to a similar degree in the two study groups. However, no significant difference was observed in the primary outcome, which occurred in 292 patients (59 %) who were assigned to undergo CABG alone and in 289 patients (58 %) who were assigned to undergo CABG with surgical ventricular reconstruction (hazard ratio for the combined approach, 0.99; 95 % confidence interval, 0.84–1.17; P = 0.90).

Adding surgical ventricular reconstruction to CABG reduced the left ventricular volume, as compared with CABG alone. However, this anatomical change was not associated with a greater improvement in symptoms or exercise tolerance or with a reduction in the rate of death or hospitalization for cardiac causes. (ClinicalTrials.gov number, NCT00023595.) [27]

The results of the STICH trial while not reflective of the experience or practice of many skilled heart failure surgeons, was a body blow to the

whole field of left ventricular reconstruction. There were many flaws in this study, which are addressed below.

Firstly, that there was great reliance on imaging using SPECT nuclear scans and dobutamine stress echocardiography. These techniques have their limitations, as alluded to in the publications in the New England Journal.

Second, there was a range of techniques used and residual volumes accepted as part of the study.

Third, the surgical strategy was different in various centers, with little standardization.

Fourth, there was a selection bias in that many centers that were experienced in left ventricular reconstruction tended to randomize patients who were in the grey zone. These patients who often ended up having that procedure, may not have been representative of the patients with actual akinetic left ventricles that would have benefited from LVR,.

Discussion

(A) **Other surgical techniques**: Beck first described a technique for repair of ventricular aneurysm before the age of the heart-lung machine [28]. This early technique utilized a clamp for resection and repair of aneurysms. Thereafter, the technique evolved to linear closure with use of cardiopulmonary bypass. Eventually, the techniques evolved into a variety of geometric repairs to recreate the conical shape of the left ventricle.

It is difficult to compare linear suture and circular repair, as these techniques can be utilized for the following good indications:

- A distal anterior and apical bulging true dyskinetic aneurysm can be repaired by resection of fibrous exteriorised scar followed by direct suture of the "neck" of the aneurysm.
- When the septum is widely involved, geometric reconstruction is the best solution in a great majority of cases. Linear repair produced poor physiological results [29]. Jakob et al. [30], Grossi [31], and Lundblad [32] are among authors that have reported positive experiences with endoventricular plasty and geometric repair over the past 15 years. Interestingly, Shapira [33], Kesler [34], and Tavakoli [35], showed no difference in the results between linear suture and patch repair. The reasons for equivocal results between two distinctly different techniques might be due to
- The retrospective nature of the comparisons,
- Small number patients in each series,
- The procedure being used only on dyskinetic bulging aneurysms.
- The series often spanning a long time period
- Left ventricular ejection fraction is used to report the data, without detailed information on the technique of assessment (angiography, radioisotope, or echocardiography) or ventricular volume measurements. The imaging techniques are often not consistent and, therefore, not comparable.
- Some suggestions have been made to improve poor results of linear suture. Stoney described a sandwich technique [36], for repairs of septal scars. Cooley described plication of the free ventricular wall in his original publication and this technique is still a very useful but fails to address the issue of the akinetic or dyskinetic septum. Mickelborough uses reinforcement of the septum with a patch [37] and also advocates a tailored "convergent suture" from outside to inside to reduce the length of the vertical suture.
- Athanasuleas and Buckberg promoted beating heart repair during the ventricular repair phase of the operation in an attempt to better preserve ventricular function and to also assess areas of potentially viable myocardium by palpation [38]. There are many advantages and disadvantages of beating heart repair. The theoretically benefits of a perfused myocardium over cardioplegic arrest, may not be clinically obvious in the majority of patients [39].

Some of the contentious discussion points are:

1. The exact location and the extent of the asynergic area cannot be reliably and reproducibly identified by palpation alone. The extent of scar should be carefully analysed preoperatively on imaging studies with multiple projections and a plan formed as to the actual areas that need to be excluded.
2. Diastolic balloon sizing of the residual left ventricle is more cumbersome when performed on a beating heart. This may be an important step for inexperienced or occasional surgeons, to ensure good early and intermediate results.

Adjunctive Therapies in Ischemic Cardiomyopathy

- Medical treatment with the appropriate medications form the cornerstone of chronic management [40]. Many of the drugs have a positive impact on controlling symptoms and reducing the metabolic demand on the heart, thereby allowing greater efficiency of cardiac function. Newer approaches such cardiac resynchronization or bi-ventricular pacing may be effective in about one third of ischemic patients, with a potential improvement of 1.5–5 % in EF without any effect on 1 year mortality [41].
- Improving blood flow to the ischemic areas with percutaneous intervention or surgical revascularisation, without addressing the enlarged heart, does not significantly improve dilated ischemic myocardium [42].
- There is much promise in the arena of cellular therapy, during acute, healing and the chronic phases after myocardial infarction. The hope is that this will reduce the extension of the scar, and prevent remodelling. None of the trials of regenerative therapy have been significant clinically [43].
- There is a revolution in the realm of mechanical assistance with a variety of small pumps that show great promise. For the moment, these devices are building on the promise shown by the Heartmate in the REMATCH trial [44].
- Ventricular containment or passive constraint maybe of interest in the treatment of dilated cardiomyopathies [45]. Containment of a reconstructed scar with the addition of cellular regenerative therapy maybe a future therapy to watch. This may even be applied early after a myocardial infarction to reduce remodelling and improve borderzone function [46].

Key Points to Remember

Left ventricular volume, not ejection fraction determines prognosis in dilated ventricles after myocardial infarction.

Left ventricular reconstruction began with repair of left ventricular aneurysms in the 1950s by the linear closure technique.

The contributions of Dor and Jatene suggested that the best approach would be to attempt to recreate the conical shape of the left ventricle.

Jatene's proposed imbrication of the septum to eliminate dyskinesia of this segment.

Geometric principles essentially utilize small patches of various kinds or purse string sutures to get reshape the ventricle into a conical form.

Reconstruction of scarred ventricles should be advocated soon after the ventricle dilates without waiting for symptoms of heart failure and decompensation.

Reconstructive therapies owe their success to a combination of modification of the anatomical deformation of the dilated ventricle, physiologic improvement of geometric efficiency and appropriate medical therapies.

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Ventricular Containment, Shape Change, Infarct Restraint

8

George C. Christensen III, Jaishankar Raman, Ahmet Kilic, and Bryan A. Whitson

Introduction

This chapter describes the concepts, historical perspective, and evidence behind the shaping of the ventricle to prevent heart failure progression. The techniques described range from ventricular containment, infarct restraint, and stabilization in so that to modify the ventricle to reduce wall stress, including updated studies since the prior edition.

Ventricular remodeling to prevent the progression of heart failure has been the mainstay, targeted goal for generations. Cardiologists and cardiac surgeons have placed great emphasis towards medical and surgical management of severe cardiomyopathy. Since the twentieth century, namely, devices have been introduced to facilitate ventricular containment, infarct restraint, and stabilization. This chapter will discuss the techniques, historical perspectives, and evidence behind this novel approach reshaping the ventricles. However, as you will encounter, many of these devices and companies are no longer in existence.

A three dimensional cone, the left ventricle has an elaborated rugose and trabeculated endocardial surface. The right ventricle, on the other hand, is crescent shaped in cross-section and wraps around the right side of the left ventricle. In systolic heart failure, as the ventricles dilate, the normal shape and size of the ventricles become distorted. On transverse section, its concavity presents an oval or nearly circular outline, with left ventricular wall size ratio of 3:1 to its counterpart. Histologically, the nucleus of the myocytes in dilated cardiomyopathy frankly enlarge as the spindles lengthen versus widen such as in hypertrophic cardiomyopathy.

Physiologically, the Frank-Starling mechanism of the heart is affected [1], which was described initially by Frank in 1895 and further elaborated in 1914 by Patterson and Starling [2]. This describes the pressure-volume relationship of the left ventricle and the importance of preload in driving the mechanical properties of the heart as a pump. Unfortunately, most studies on cardiac physiology have been with them in the isolated heart preparation and are limited as being in one or two dimensions.

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_8

The left ventricle is best described in physical terms as a prolate spheroid with an equatorial region that can be approximated as a thick walled cylinder. Guccione et al. focused on this equatorial region to yield an analytically tractable boundary value [3] and the application of various laws such as the infamous Law of Laplace *(Tension = Pressure * Radius)*.

The model behind cardiomyoplasty and passive ventricular constraint stemmed from pressure-volume data collected by Freeman et al. [4]. Intact pericardia from dogs revealed the pericardium to be an effective constraint to ventricular deformation.

The concept of shape change to alter wall stress in larger hearts is based on the application of Laplace's Law to the left ventricle. There are limitations to simple interpretation of this law and this maybe the reason behind sub-optimal results with the devices that advocate shape change as a means of controlling heart failure, even to a cellular level. Perhaps cardiac Computed Tomography and Magnetic Resonance Imaging will be added to the armamentarium for the clinician in determining ventricular matrices, various types of cardiomyopathy, and the effects of passive ventricular devices.

Ventricular Containment

Ventricular Containment, Constraint, or Restraint is a concept that arose from the experiences with dynamic cardiomyoplasty. The positive outcomes with this procedure in the 1980s were shown to be due to constraint provided by the latissimus dorsi muscle wrap of the ventricles [5]. We then proposed, based on suggestions by prominent surgeons including Stuart Jamieson that we might dispense with the muscle and attempt passive constraint with a prosthetic mesh. Our early proof of concept experiments performed at the Austin Hospital, Melbourne in 1997 showed that passive ventricular constraint prevented progression of heart failure [6].

Drs. John Power and Raman then proceeded to study a large group of sheep in various stages of heart failure to establish the role of passive ventricular constraint in halting the progression of heart failure [7]. Based on our animal work and similar experiments with another model of heart failure in Detroit, MI [8], the concept of ventricular constraint was studied in human patients by a start-up Company called Acorn Cardiovascular Inc. (Fig. 8.1). The first human procedure was performed at the Austin Hospital in Melbourne on April 19th, 1999 by Raman and colleagues. Thereafter, a phase 1 study was performed in Berlin and Melbourne. Resulting from this early experience, a pivotal trial was conducted in the US with 15 participating centers, with a primary endpoint of improved, unchanged, or worsening composite classification (NYHA classification, need for cardiac intervention, or death). The results of this study were presented at the 2004 Annual Scientific sessions of the AHA. Figure 8.2 shows an operative figure of a patient undergoing ventricular containment along with CABG.

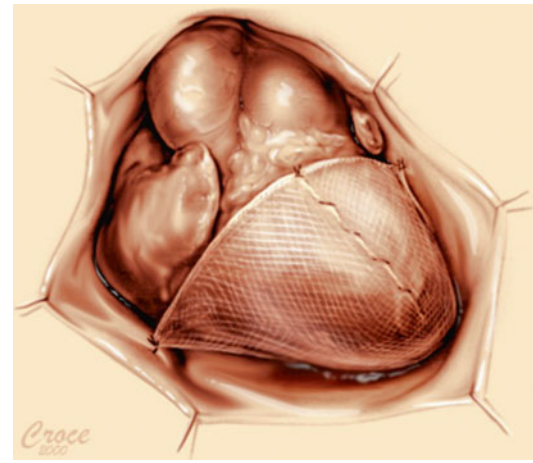

Fig. 8.1 An artist rendition of the polyester implant, a concept of the Acorn cardiac support device

Salient findings in the Acorn Trial in the US were identified. For instance, among patients with heart failure and dilated CMP, the CorCap cardiac support device was associated with a significantly improved primary composite endpoint viz. Clinical status based on rates of death, major cardiac procedures indicative of HF progression, or changes in NYHA class.

The primary endpoint has been largely driven by significant reduction in major cardiac

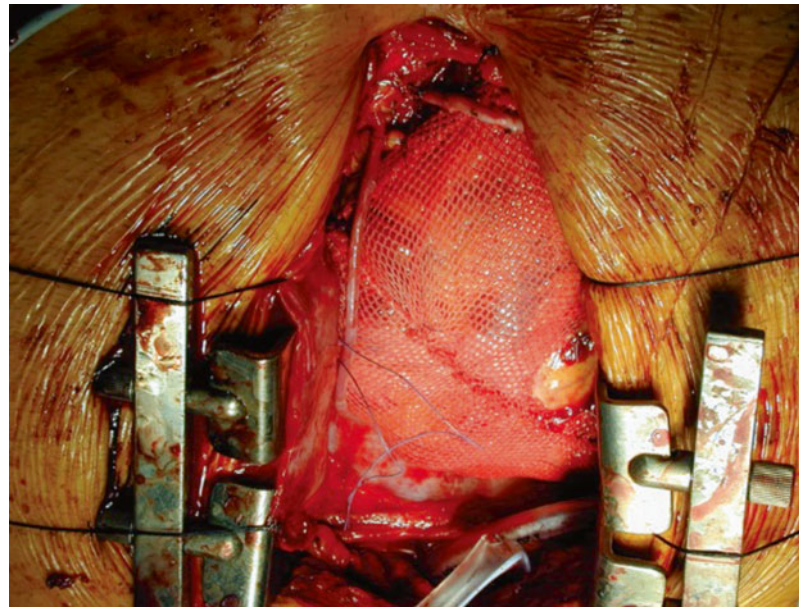

Fig. 8.2 Operative photograph of one of the first implants of the Acorn cardiac support device. Operative photograph of a contained ventricle in the setting of CABG (1999). Note the window in the mesh cut away for a distal anastomosis of a graft

procedures and a trend toward improvement in NYHA in the CSD group. No difference between the two groups in mortality.

The CSD group had significantly lower left ventricular ESV/EDV, greater enhancement in sphericity index, noteworthy improvements in measures of quality-of-life than the control group. However, the groups had similar LV ejection fractions and comparable rates of adverse events, including repeat hospitalizations.

The Acorn device was deliberated by the FDA panel three times. The panel voted overwhelmingly on all three occasions to deny approval for human use. Acorn eventually asked for a further review through the FDA ombudsman. Finally, a recommendation was made that asked for another 50 patient study to be performed. The Acorn CSD was then re-engineered to be implanted in a minimally invasive fashion through a left mini-thoracotomy. This was after many iterations of the implant tool were developed at the Texas Heart Institute by Dr. William "Billy" Cohn. Unfortunately, the company ran out of money and is now defunct.

Interestingly, a 2012 publication from Journal of Thoracic and Cardiovascular Surgery, Mann et al. probed the 5-year results of the CorCap and the non-MR stratum. Conclusively, the CSD demonstrated no long-term adverse effects on mortality, concurrently illustrating a reduction in the LV remodeling. Moreover, results of a study involving the implant of the CorCap device utilizing minimal invasive conditions are pending [9].

In order to make this approach worthy of clinical application, the device has to be dramatically modified to allow subsequent interventions safe. In addition it would be preferable to use smart materials that are actively promote reverse remodeling of the ventricles.

Unfortunately, drawbacks were identified and the trial, though painted as positive in media releases, was turned down by the FDA panel multiple times. Their reasons were many fold and make thought-provoking reading:

- Lack of complete follow up
- Data not validated by a core lab
- Composite end point was significant, but no single factor achieved significance of its own
- No change in left ventricular ejection fraction between the groups
- No differences in heart failure admissions or mortality between the two groups.
- The need for clear and definite end points to be delineated before the study was started.

The decreased need for new cardiac procedures in the study group was perceived as reluctance on the part of implanting surgeons to re-operate on a patient with an increased risk of severe adhesions.

Another motivating lesson was the Hawthorne effect within each group that displayed continued care and repeated follow-up *actually* benefited patients and reduced heart failure symptoms and subsequently admissions.

Long-term follow-up of patients undergoing mitral valve repair along with containment with the Acorn Cardiac Support Device demonstrated some benefit at 5 years (Acker et al.).

Nevertheless, the areas that showed significant difference were those concerned with left ventricular dimensions and size, with the study group validating that the ventricles were contained at the smaller size. Our own work in animals illustrated that the best results were obtained when sheep were contained in a moderate phase of heart failure (akin to class II heart failure) [10]. Containment late in the cycle of dilatation and heart failure provided marginal benefit with improved survival in sheep with contained ventricles [11].

At a molecular and cellular level, a 2003 study in dogs showed long-term benefit of CSD in the attenuation of the LV remodeling process by investigating various gene expression molecules, cardiac myocytes, and stretch response proteins [8].

Alteration of Left Ventricular Wall Stress by Shape Change

Myocor Approach

Myocor was a company that founded in 1996 to utilize the theory of ventricular shape alteration to reduce wall stress (Fig. 8.3). They presupposed the left ventricle to be a cylinder or a sphere. If Laplace's law were applied, wall stress increases proportionate to the radius of curvature. To alter and diminish this, Myocor proposed skewering the heart with a tensioning chord or splint that would change the left ventricle in cross section from a large circle to two small circles or a bi-lobed ventricle (Fig. 8.3). Preliminary studies with the Myosplint in human patients were performed in Munich with poor results. McCarthy implanted a few of the Myosplint devices acutely in patients undergoing transplantation prior to explant of the heart with equally poor results. Myocor had mixed clinical success with the CoApsys device which utilized a portion of these elements, but this worked predominantly to correct functional MR. The Myocor experience in correcting functional mitral regurgitation was promising. Myocor was not able to express clinical significance of any of their approaches during the operation of the trial and depleted of funds. This company has been defunct for over 4 years now.

Fig. 8.3 The concept behind the Myocor Myosplint is by altering the short axis of the left ventricle into two bilobed spheres, thereby reducing wall stress

Cardioclasp

In keeping with the shape change and altering the stresses on the myocardium, Dr. David Melvin, from Cincinnati developed another device that looked and behaved like a vice around the ventricle (Fig. 8.4). Although conceptually interesting, the animal studies led only to mildly promising results, halting progression to clinical evaluation.

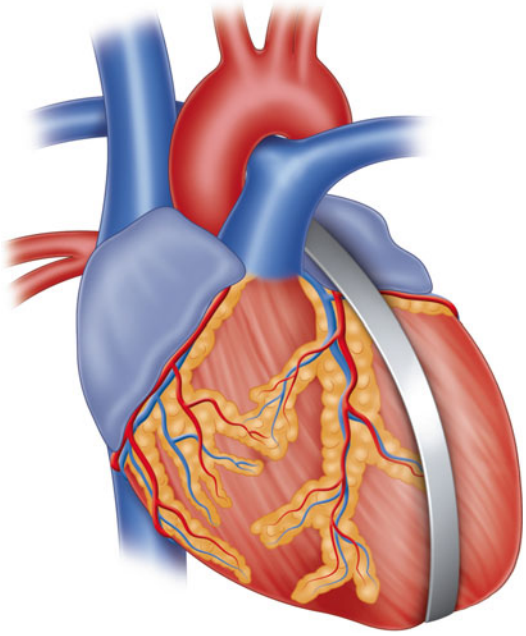

Fig. 8.4 Illustration of the Cardioclasp device. The anterior and posterior bars are aligned to the long axis of the left ventricle, adjacent to the left anterior descending and posterior descending coronary arteries. While this concept is interesting, the animal studies showed only mild promise and this concept did not progress to clinical evaluation [21]

Dynamic Ventricular Restraint (by Corset)

The concept of dynamic ventricular restraint was developed by a group of researchers at the Cedars Sinai Medical Center. The notion was tested in animals in Melbourne, Australia by Raman and colleagues with a prototype restraint device that had inflatable balloon panels along its length, linked to a portacath type device. The plan was to gradually infuse saline into the portacath so as to slowly increase the constraint over time. Unfortunately, the tubing connecting to the balloons often leaked and there was no indication that the balloons actually inflated enough to cause significant reduction in ventricular size. This device did not proceed beyond initial proof of concept studies in animals. This is quite relevant to the development of other devices by various startup groups that have touted the benefits of inflatable balloon panels within the pericardium.

Quantitative Ventricular Restraint (QVR)

Brigham and Women's developed a quantitative, adjustable ventricular restraint device that is a double layered, semi-elliptical, polyurethane balloon connected to a portacath line (Fig. 8.5). The QVR balloon is placed below the atria, around both ventricles, and secured to the heart along the arteriovenous groove. The portacath is tunneled through the left anterior chest wall. Contrast to prior static devices, measurable restraint levels can be quantified and experimented in the ovine model, distinguishing reverse remodeling at a given extrinsic balloon pressure. Additionally, short-term changes were declared as primary endpoints including decreased transmural pressures (Ptm) and oxygenation consumption of the myocardium. Moreover, they noticed that a decrease in device pressure from lessened Ptm slowed the reverse remodeling process. Limitations to this study were acknowledged as small sample size and long-term effects, suggesting the aid of cardiac imaging, including magnetic resonance [12].

Paracor

The concept of dynamic ventricular restraint has been spoken about and developed initially by another startup company called Paracor (Figs. 8.6 and 8.7). This device, the *HeartNet*, utilizes a meshwork of nitinol coated with silicone that can be laid around the ventricles to ensure dynamic restraint of the dilating ventricles. There is very little published data about the efficacy of this approach in experimental animals. The first human implant was performed at the Ohio State University on May 19, 2005. The clinical results of the pivotal study were equivocal and this halted the study. As with prior passive ventricular devices, heart failure symptoms in conjunction

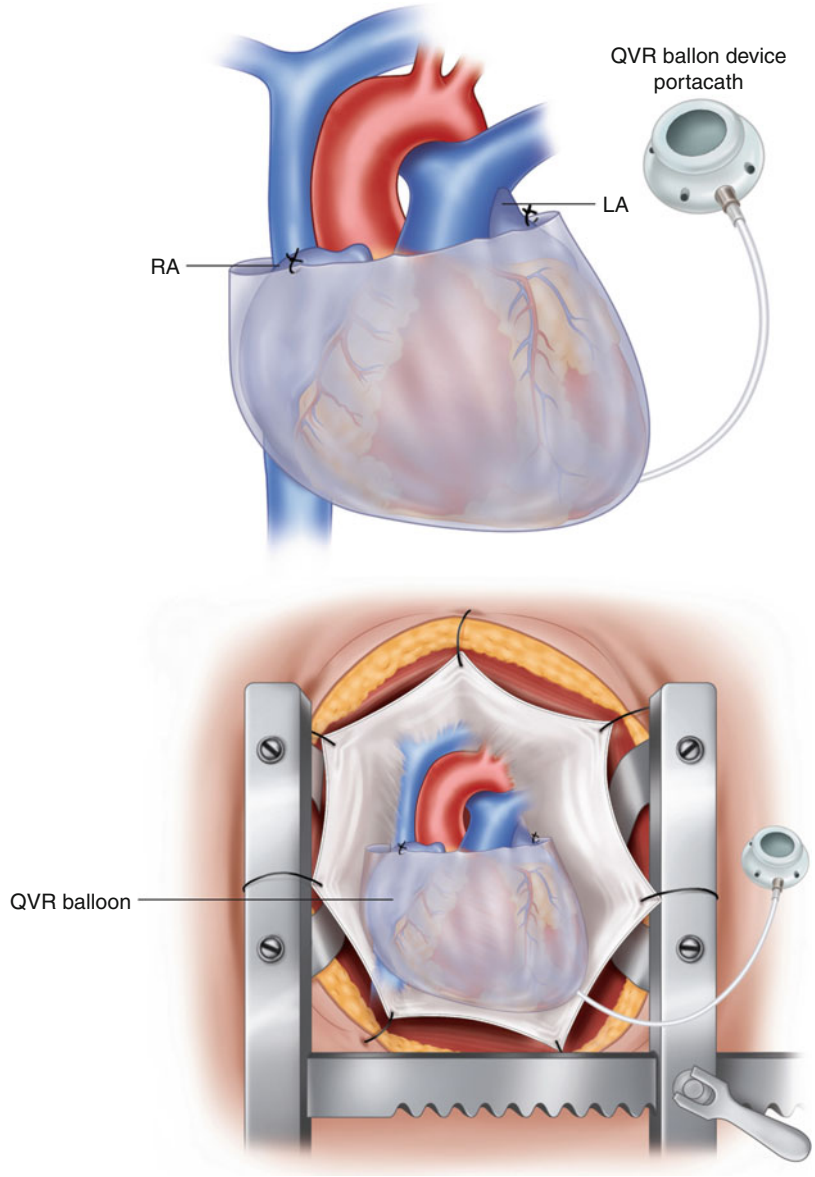

Fig. 8.5 (**a**, **b**) Photographs of the semi-ellipsoidal QVR Balloon Device with its portacath (Modified from Ghanta et al. [12])

with measurements in chamber physiology revealed noticeable improvements including dimensions, end-diastolic and end-systolic volumes. Further analyses showed that there might be some benefit in patients who also had biventricular pacing therapy.

Infarct Restraint and/or Constraint

Extensive studies have been performed by the Edmunds' laboratory at the University of Pennsylvania focusing on localized constraint or restraint upon dyskinetic or akinetic areas of the ventricles. They revealed that a certain type of a non-absorbable material that is applied and secured to the epicardial surface of the ventricle in an area of akinetic or dyskinetic scar helps reduce infarct expansion [13].

Our own adoption of this principle has been in the use of Teflon strips in reinforcing the scar over a reconstructed ventricle in the setting of a modified Dor procedure or a Left ventricular reconstructive procedure.

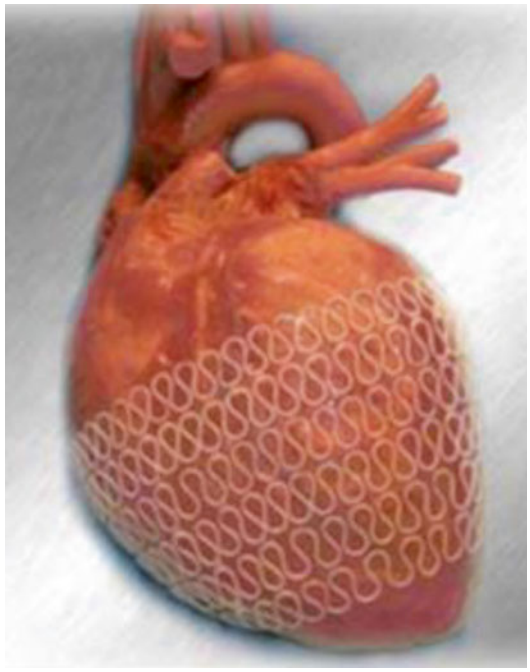

Fig. 8.6 The Paracor device, which is a nitinol mesh coated with polyurethane; this is slipped over the heart preventing progressive dilatation

Devices in the Minimally Invasive Treatment of Mitral Regurgitation

Percutaneous Mitral Valve Approaches

Several minimally invasive percutaneous devices have developed utilizing the coronary sinus as the fulcrum for tensioning rods to correct mitral regurgitation. Several companies have introduced these devices through both animal and phase I/II human trials.

Edwards Monarch Device

Edwards Lifesciences (Irvine, CA) developed a percutaneous coronary sinus (CS) annuloplasty device (Fig. 8.8) in which most recently was followed with a publication of the 1-year results (EVOLUTION trial). A phase one human trial, largest of its kind to date, has shown improvement in mitral regurgitation in 50 % of its sample size at the 6-month mark, an 86 % reduction in heart failure symptomatology. There were no in-hospital deaths.

However, sample size was small, assessments for quality of life and 6-min walks were not assessed, and patient follow-up was suboptimal.

When considering percutaneous CS annuloplasty devices, major adverse outcomes have been documented including CS perforation, coronary artery compression or occlusion (MI), device malfunction or migration, and arrhythmias [14].

Coapsys

Myocor then developed a device called Coapsys, which is explicitly designed to address the subannular component in ischemic mitral regurgitation (Figs. 8.9 and 8.10). This device is deployed using the technology developed by Myocor in skewering the heart and passing Gore-Tex chord/chords through the ventricle below the level of the mitral annulus with pads on either side. Preliminary data from the Escorts Heart Institute in India suggested that this approach of skewering the left ventricle below the annulus of the mitral annulus may be effective in some patients with ischemic mitral regurgitation [15].

Thereafter, a randomized study of 165 patients was completed in the US, called the RESTOR-MV trial and showed significant benefits in the treatment of functional MR by the Coapsys device, including LV dimensions and survival advantage [16]. The study was halted due to lack of funds.

Similarly, the TRACE trial randomized 30 patients in the off-pump CABG setting and who were followed 3 months postoperatively. NYHA classification and MR Grading improved in the early follow up time period, with survival at 100 %.

The VIVID (Valvular and Ventricular Improvement Via Coapsys Delivery) feasibility study in humans was withdrawn prematurely because of further technical difficulties during device implantation and suboptimal patient applicability [20].

Viacor

Viacor was a startup company founded by Drs. William Cohn, Marc Gillinov, and John Liddicoat. It used the principle of straightening the coronary sinus to improve mitral valve patency (Figs. 8.11 and 8.12). In experimental animals, especially

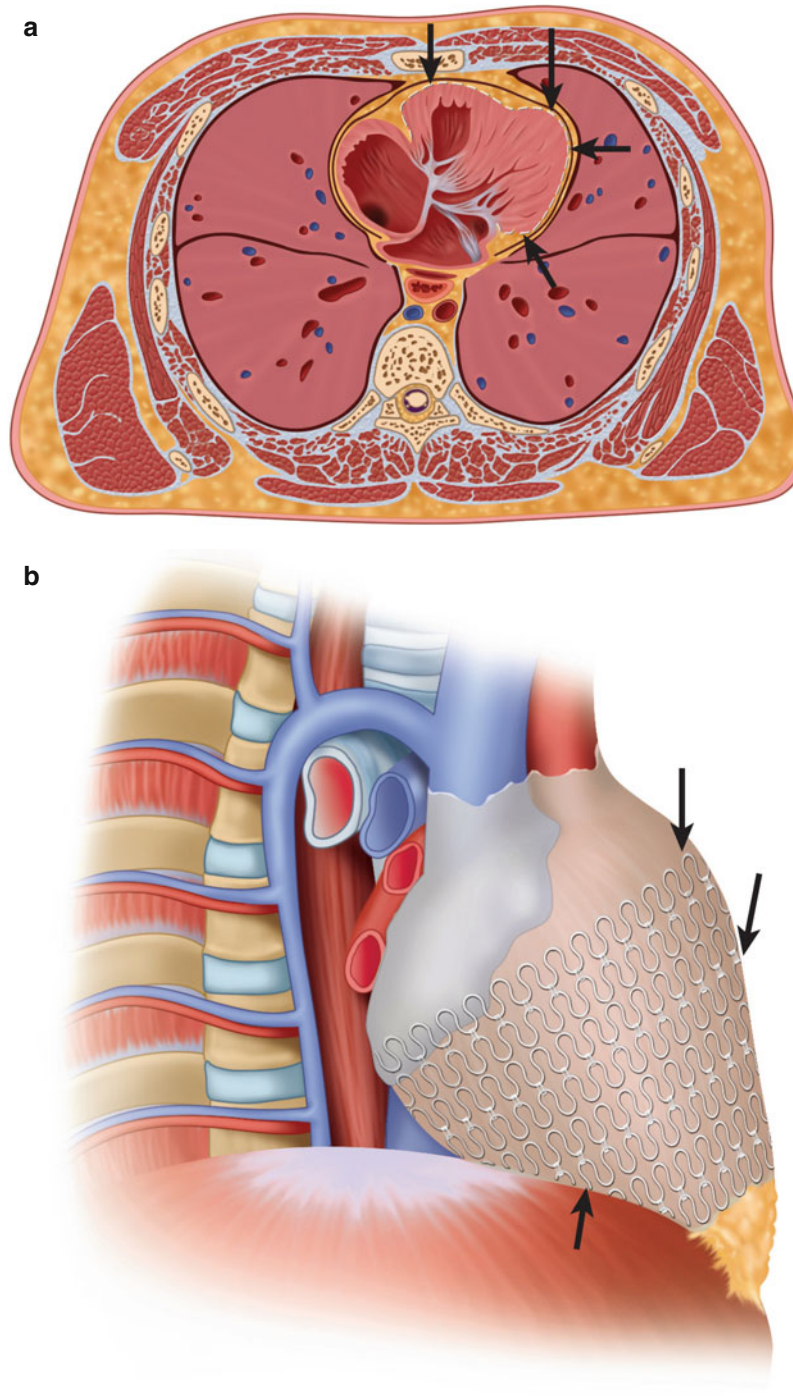

Fig. 8.7 (**a**, **b**) Axial and Coronal CT images of a Paracor device in a 61-year-old male with heart failure. Further analyses showed that there might be some benefit in patients who also had bi-ventricular pacing therapy (Modified from [22])

sheep and pigs, the coronary sinus is large and is more closely applied to the posterior mitral annulus than in humans. In human patients, the coronary sinus is variable in size and in its relationship to the mitral annulus. Hence, the sinus may subtend varying amounts of the muscular portion of the mitral valve annulus. So, a tensioning system or rod in this location has an unpredictable amount of correction of the mitral valve. This approach is flawed for a few reasons:

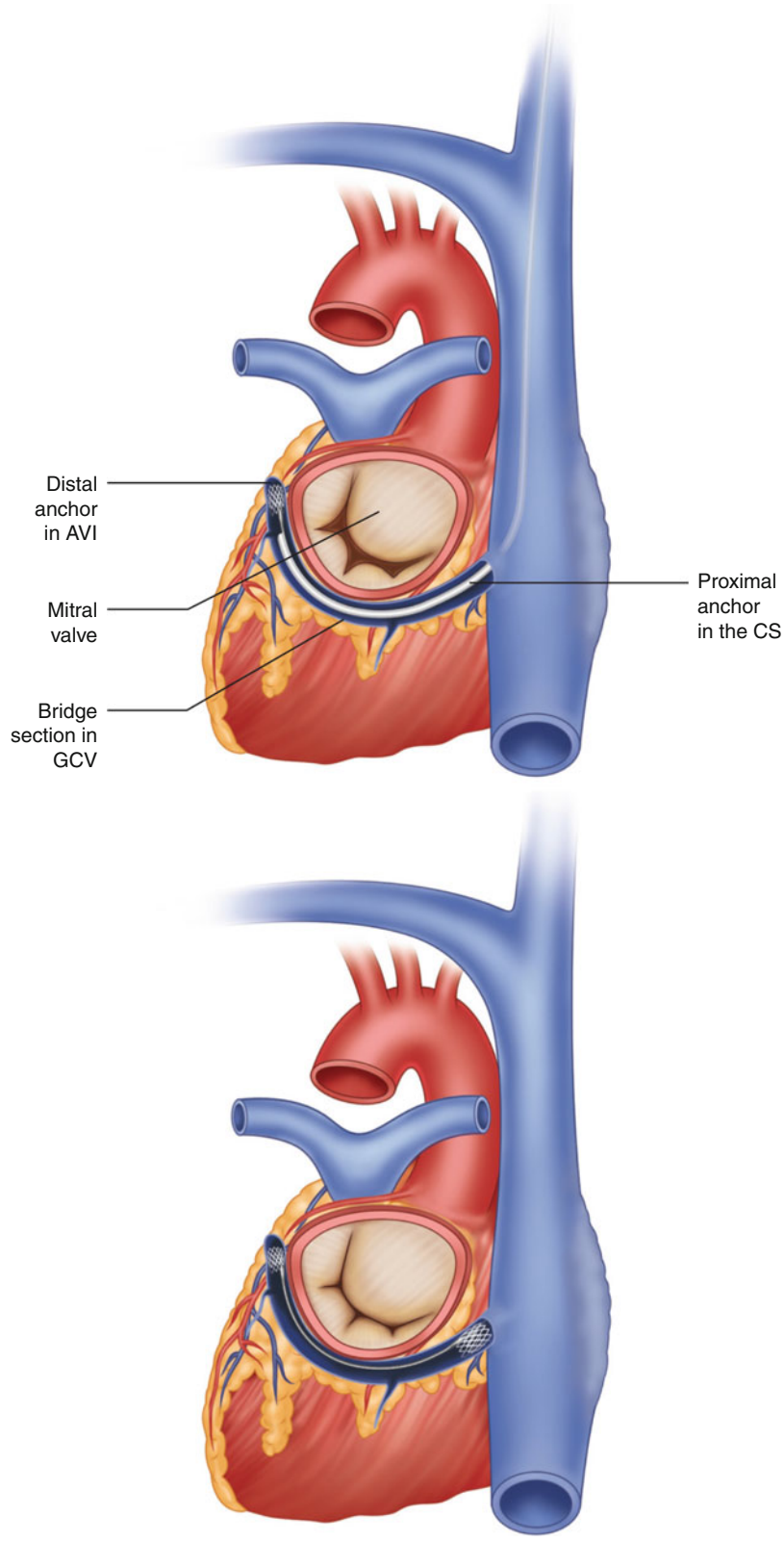

Fig. 8.8 (**a**, **b**) Edwards Monarch Device System. Primary safety endpoints were met in 91 % at 30 days, 82 % at 1 year (cardiac tamponade, myocardial infarction, death) (Modified from *JACC: Cardiovascular Intervention* [14])

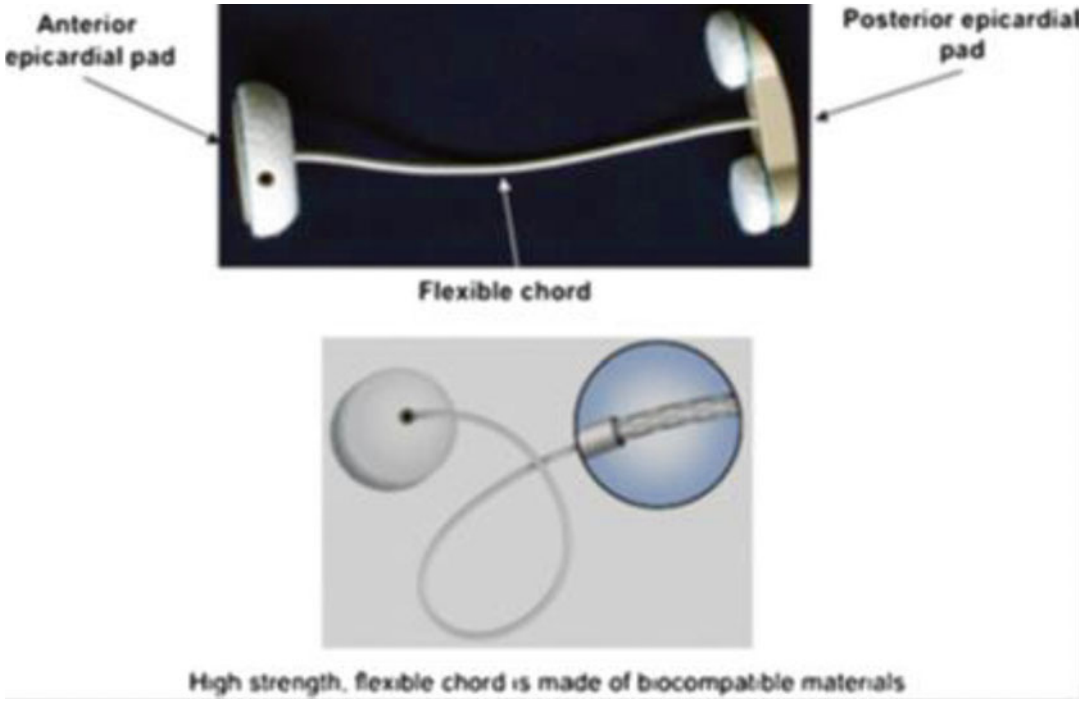

Fig. 8.9 The Coapsys device following deployment. A randomized study was completed in the US, called the RESTOR-MV trial and showed significant benefits in the treatment of functional MR by the Coapsys device [16]

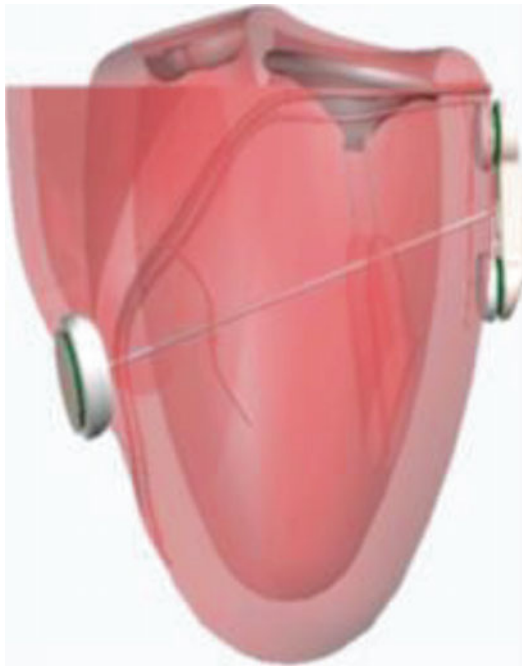

Fig. 8.10 The Coapsys device following deployment. A randomized study was completed in the US, called the RESTOR-MV trial and showed significant benefits in the treatment of functional MR by the Coapsys device

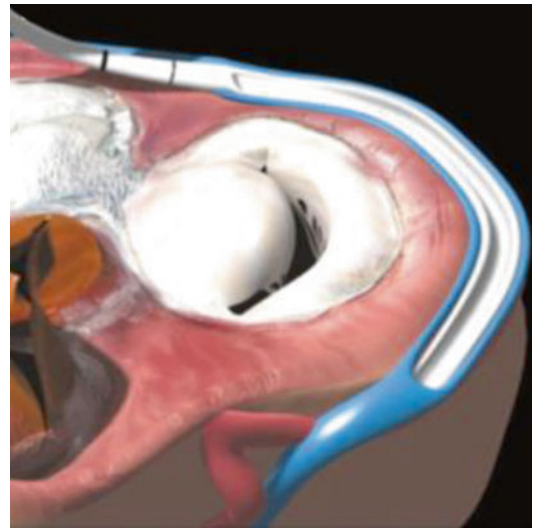

Fig. 8.11 The sheath in the coronary sinus while a tensioning rod within the coronary sinus sheath. The Viacor device as it tensions up the coronary sinus as an attempt to correct MR

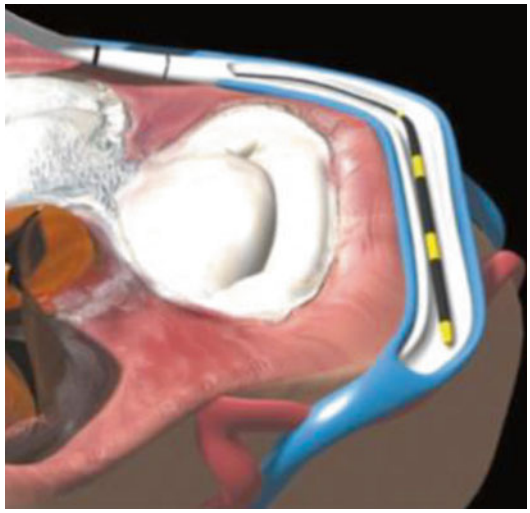

Fig. 8.12 The sheath in the coronary sinus while a tensioning rod within the coronary sinus sheath. The Viacor device as it tensions up the coronary sinus as an attempt to correct MR

- The variable relationship and size of the coronary sinus to the muscular portion of the mitral valve annulus.
- Purely annular tightening is not effective in functional or ischemic mitral regurgitation, because the annulus is often normal in size and the mechanism of mitral regurgitation is multi-factorial with displacement of papillary muscles, remodeling of the infero-basal region of the left ventricle, dilated ventricles, change in the plane of coaptation of the mitral leaflets to the ventricle, etc.
- The variable relationship of the circumflex coronary artery to the coronary sinus, whereby in a significant number of patients, tensioning the sinus can kink the underlying artery.

Although a phase II trial (PTOLEMY) was presented, revealing a 90 % procedural success rate, the company has discontinued further development and manufacturing of the device.

Carillon Device (CDI)

Cardiac Dimensions Inc. was set up by Clif Alferness, one of the original founders of Acorn Cardiovascular Inc. and the preliminary experimental work was performed by my colleague John Power, at his laboratory in Melbourne, Australia. Purported advantages include its adjustability, compatibility, and simplicity. Additionally, it is a retrievable system. Unlike its earlier version described in the prior edition, the limitations of this device being difficult to anchor it to the coronary sinus and other inherent problems with this approach have been corrected (Fig. 8.13).

In 2012, a 12- and 24-month follow-up study was published, the TITAN clinical trial, exhibited promising features with its cohorts when compared to the control group. The 30-day major adverse event rate was 1.9 %. Significant reduction in FMR based on the regurgitant volume, along with reductions in the LV diastolic and systolic volumes. NYHA classification and the 6-min walking distance were vastly improved. Adverse events included contrast related nephropathy, anchor wire fracture, coronary artery compromise. System recapture was identified in 17 of the 36 patients [19].

MitraClip

Ottavio Alfieri, an innovative surgeon from Milan suggested the concept of the edge-to-edge mitral valve repair in severely degenerative and myxomatous valves. He utilized the concept of double orifice mitral valves seen in congenital abnormalities and used sutures to approximate the corresponding portions of anterior and posterior leaflets [17]. However, this is most effective in the presence of an annuloplasty ring. The long-term results of this approach were not very satisfactory in the surgical population. This did not stop the development of this approach by the endovascular route by companies such as E-valve and Edwards. The maximum stress and strain is on the leaflets where they are approximated and this dooms this approach to early failure. Amazingly, despite evidence to the contrary, this device was tested in human patients, partly because it was a minimally invasive procedure and has had poor results.

The MitraClip (Figs. 8.14 and 8.15), which is a device developed by E-valve, acquired by Abbott cardiovascular for over $300 million. This uses the principles of the Alfieri repair, in the form of a device delivered through a femoral venous approach. However, the EVEREST I and

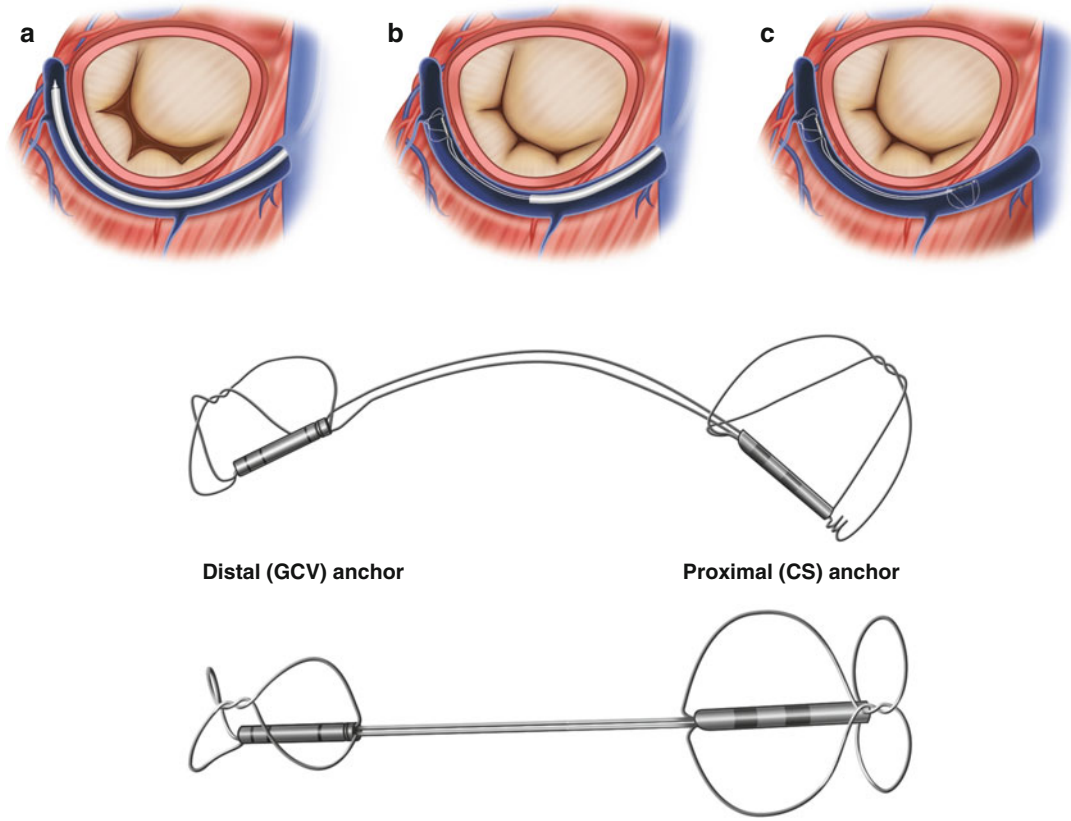

Fig. 8.13 The Carillion system with the nitinol bridge, proximal and distal anchors. (**a**) Delivery system in the CS; (**b**) Deployment of the Carillon system into the CS around the mitral valve annulus; (**c**) Carilon system deployed in position into the CS. *CS* coronary sinus, *GCV* great cardiac vein (Modified from Lago et al. [20])

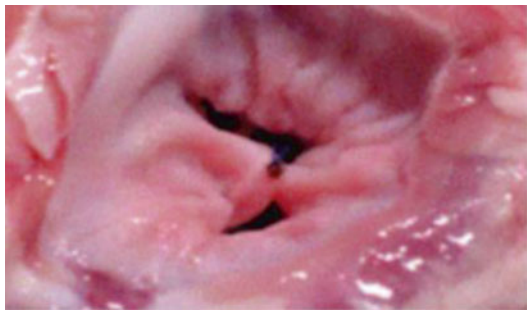

Fig. 8.14 Edge-to-edge or Alfieri repair: photograph of a clip approximating anterior and posterior mitral leaflets

II randomized trials, which compared this approach to open surgery showed a significantly lower level of efficacy with this approach. The long-term outcome with this device shows patients who undergo MitraClip implantation have a much higher rate of re-intervention in the form of mitral valve replacement. This device works best in patients with large and redundant leaflets, with some degree of annular dilatation. The COAPT trial is a study looking at this approach in patients with functional MR, with the control group being patients undergoing medical therapy.

Bace Device

Functional mitral regurgitation (FMR) is a common feature of ischemic cardiomyopathy that leads to abnormal ventricular mechanics. Mitral repair with restrictive annuloplasty or a formal replacement are reasonable therapeutic modalities for treatment of FMR. However, this tends to be involved with patients with severe MR. There is question regarding risks versus benefits involving

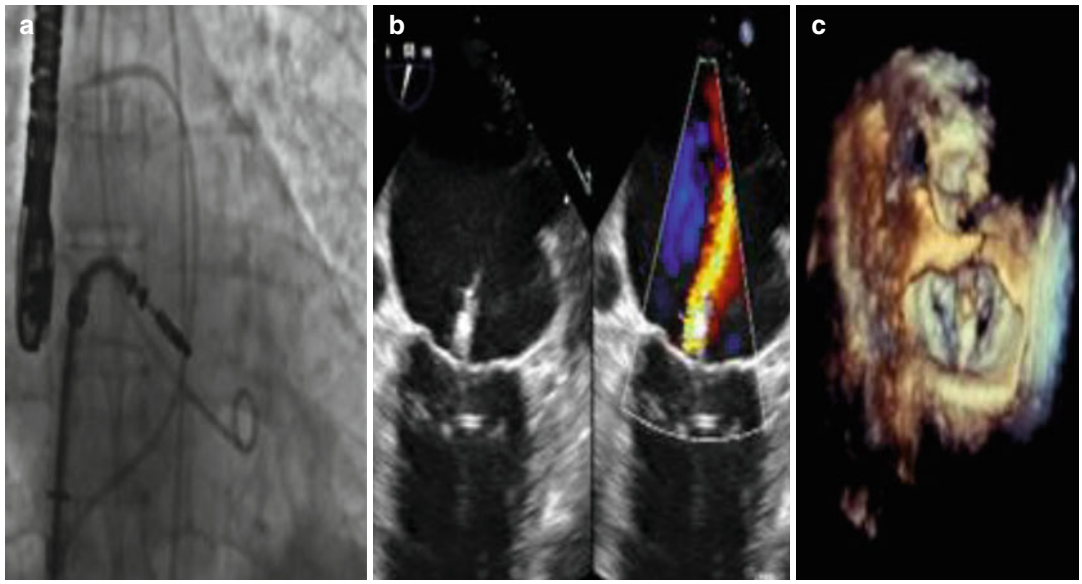

Fig. 8.15 (**a**–**c**) MitraClip placement under angiography with follow up 2-D and 3-D echocardiograms (Modified from [23])

a group of individuals with moderate MR and chronic ischemic heart disease, hence reluctance to refer for open operative correction. However, when understanding the pathophysiology behind FMR, the focus has turned to addressing the root cause – the diseased ventricle.

The BACE (Basal Annuloplasty of the Cardia Externally) device was developed by Mardil Inc. with further development by Phoenix Cardiac Devices (Fig. 8.16). An adjustable silicone belt-like structure with inflatable cuffs has been measured and created to be placed as an extracardiac device around the atrioventricular groove to support the mitral annulus and subannular musculature (Fig. 8.17). Under transesophageal echocardiogram, the device can be inflated gradually while assessing the mitral valve regurgitation along with quantifying the PISA, jet velocity, and vena contracta (Fig. 8.18). A revascularization procedure was then performed on a beating heart in most patients, but several were completed in an off-pump technique. Subcutaneous ports were placed in the required location with tunneling of the tube system.

Patients were followed for 1-, 3-, 6-, and 12-month intervals. Publication of the results involving mainly the 6-month follow-up was encouraging. MR Grading improved from 3 to 1. Patient's NYHA classification preoperatively was 3.14, declining significantly following device placement. Interestingly, three patients who had moderate to severe tricuspid regurgitation also showed significant improvement.

The BACE device is safe, citing no intraoperative complications. Morbidity and mortality recorded were not related to the device itself. No perioperative myocardial infarction was identified. One patient was coagulopathic and returned to surgery for inspection, whereas another patient identified as a single death was from a fatal arrhythmia after placement of an intra-aortic balloon pump to the lower extremity causing profound ischemia resulting in reperfusion injury upon removal.

Limitations to the study of the BACE device can be interpreted as a small sample size, an inadequate comparison to traditional open operative correction of mitral valve dysfunction, and the potential confounding variability of applying a revascularization procedure. These shortcomings notwithstanding, the findings in this study provide encouragement in terms of safety, which allows us to pursue a larger study to define efficacy and long-term effectiveness of this approach [18].

Overall, the main advantages to the BACE Device are:

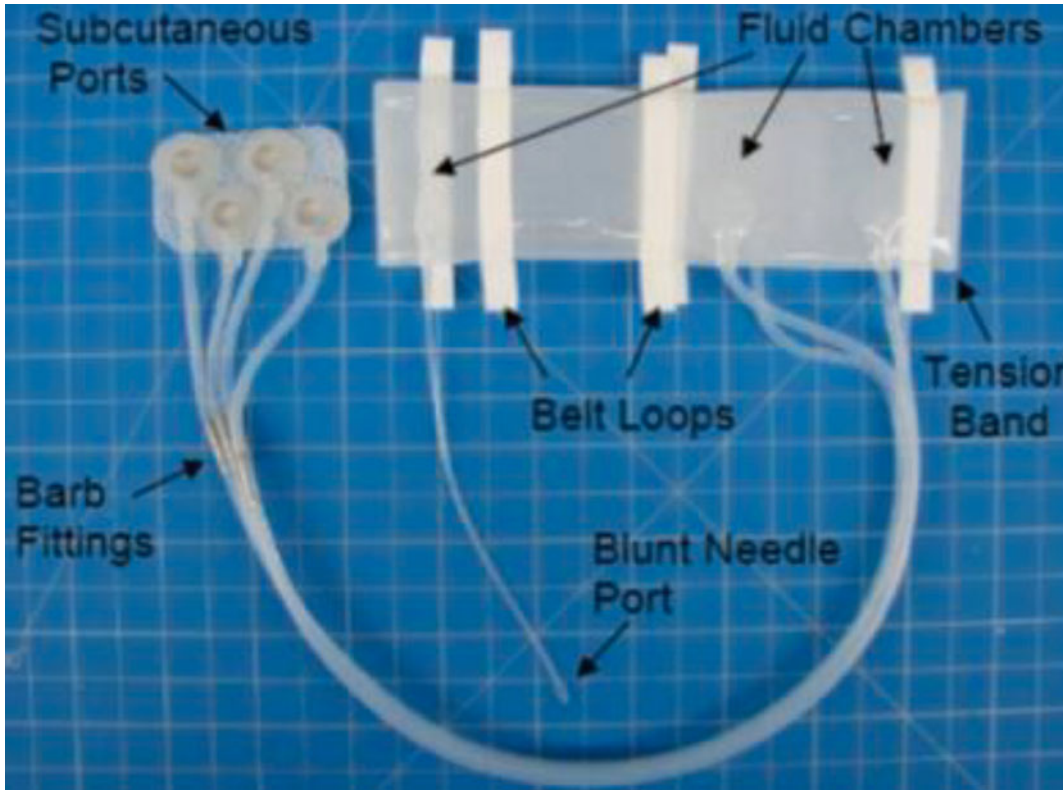

Fig. 8.16 The BACE device

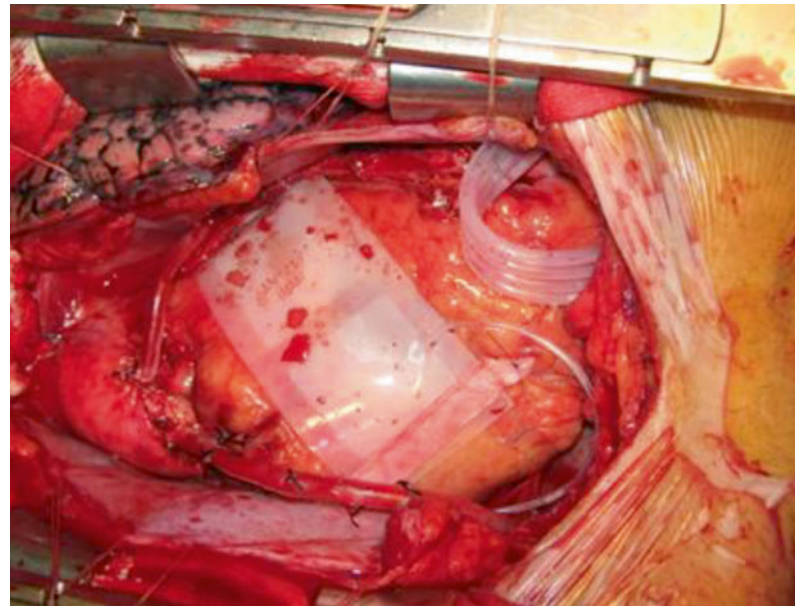

Fig. 8.17 Intraoperative photograph following the placement of the BACE Device, with tubing connection leading to the subcutaneously placed portacath (not seen)

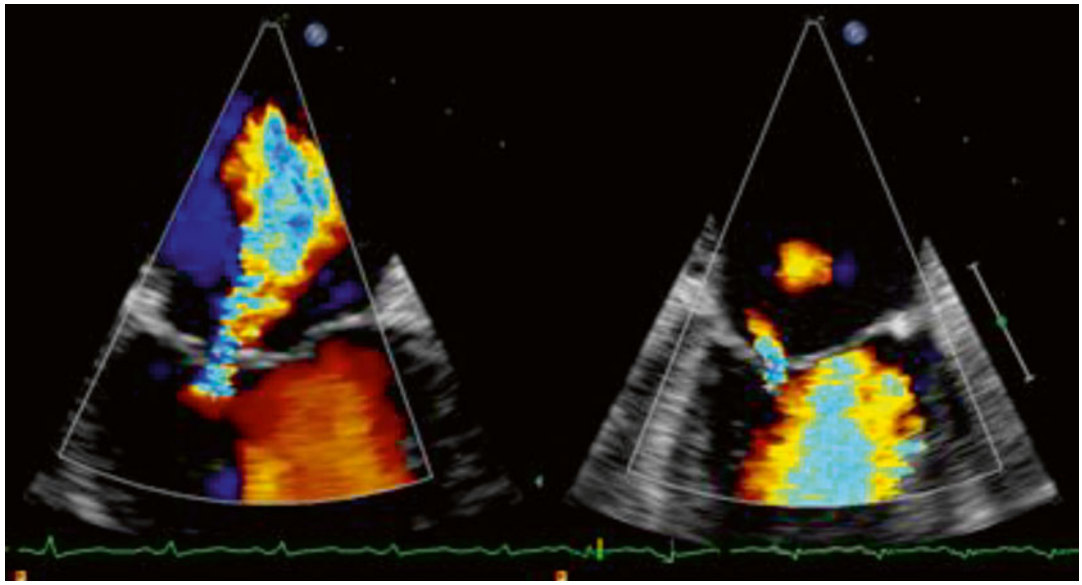

Fig. 8.18 Transesophageal Echocardiogram with PISA measurement, pre- and post-implant

1. It's noninvasiveness, avoiding intracavitary approaches;
2. Real time dynamic assessment of the mitral and tricuspid valves;
3. Aiding the subannular ventricular myocardium;
4. Potentially placed off pump or on a beating heart, avoiding the sequelae to cardiopulmonary bypass.

Summary

Ventricular remodeling is an elaborate, well-versed phenomenon of advanced cardiomyopathy. The therapies for impeding this detrimental process stem from various dietary and pharmacological treatment options with surgical adjuncts such as revascularization and/or valvular repair/replacement. However, reversing ventricular remodeling has been sensationalized for several decades. Since the advent (and eventual fall) of the Acorn *CorCap* in the late 1990s, cardiac support devices have gained notoriety with increased awareness through advancements in technology and surgical approaches. Just in the last few years, outcome based studies involving 1- to 5-year follow-up data have been published in regards to passive ventricular containment, restraint, or constraint devices (including the CorCap). Strengths highlighted within this innovation include improvements in NYHA classification, MR grading, and quality-of-life assessments while enhancing left ventricular indices (i.e. end diastolic dimensions, volume). Additionally, implantation can be achieved without violating the intracardiac chambers while refraining from utilizing cardiopulmonary bypass circuits; other approaches are via percutaneous deployment. Inherently, study and clinical weaknesses encompass low sample size, ambiguous endpoints, and the inability to lower repeat hospitalizations, morbidity plus mortality. Albeit, results from newer clinical trials of these shape changing devices are encouraging, including their safety profile. Further investigations will be required to determine efficacy and long-term effectiveness, such as the BACE Device. Ventricular dilatation with or without MR will demand careful planning before executing a reparative procedure. Annular support with favorable deformation of the adjacent myocardium externally may be an exciting way forward in performing mitral valve repair without entering the heart. Cellular therapy perhaps may aid in the future of reversing shape remodeling with cardiac support devices.

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Mitral Valve Repair

9

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Introduction

Congestive heart failure (CHF) has become an international heath care problem and it is one of the world's leading causes of hospitalization and mortality. In the United States alone, 4.9 million people (2.3 % of total population) are suffering from heart failure with 550,000 new cases diagnosed each year. Hospital discharge for CHF increased from 377,000 in 1979 to 970,000 in 2002, an increase of 157 %. Estimated health expenditures amount to $ 25.3 billion in 2005 [1]. In spite of these, only 2,100 of the 53,000 patients who die annually are offered transplantation, which many consider to be the standard treatment for selected patients with severe CHF and end-stage heart disease. Transplantation is severely limited by the paucity of donor availability and enormous cost. The inapplicability in the older patient or those with comorbid medical conditions as well as relatively fixed donor pool suggest that transplantation will likely never have a major epidemiological impact [2]. Treatment with mechanical circulatory support devices dances on the horns of the same dilemma. Consequently, despite improvements with medical management, 1 year, 3 year and 5-year survival after hospitalization from CHF have been reported at approximately 80–60 %, 50 % and 40–20 % respectively, which is worse than that of most cancers [3–7].

In an effort to solve these problems, many alternative surgical and interventional strategies to treat heart failure patients have emerged and evolved over time. Some of them have been evaluated as the first-line approach to heart failure including techniques to restore myocardial perfusion and ventricular synchronization, remodeling ventricular geometry and to eliminate mitral valve regurgitation (MR) in the setting of Ischemic and dilated cardiomyopathy (DCM).

Bolling et al. have been using mitral valve repair techniques from 1993 onwards, to help this patient population based on the assumption that the mitral valve is the geometric functional component of the left ventricle (LV) and that secondary or functional MR occurs in a mitral valve apparatus that is essentially normal and functional. The distorted geometry of the left ventricle is reflected in abnormal coaptation of the mitral valve leaflets leading to mitral regurgitation.

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_9

Secondary or functional MR can be thought of as geometric MR and mitral valve repair of this geometric MR as geometric mitral valve repair in this chapter. Dr Bolling's avid promotion of mitral valve competence in the setting of functional mitral regurgitation has transformed the management of heart failure. In days of cardiological yore, there was a common misconception that addressing mitral regurgitation in failing ventricles got rid of the "pop-off" valve that allowed these patients to survive.

Other methods of mitral valve reconstruction, such as chordal sparing mitral valve replacement, catheter based techniques such as the Mitraclip, etc. are also discussed as possible means of alleviating FMR.

Mitral Valve Structure and Function

In order to address the issues of heart failure and MR, one needs to understand the complex anatomy and functional relationship of the LV and mitral valve. Mitral valve competence depends on the coordinated function and geometry of the components of the mitral valve apparatus: mitral annulus, mitral leaflets, chordae tendinae, papillary muscles, and importantly LV wall [8–10]. The most "efficient" function of LV depends on all the components of the LV and mitral valve apparatus. There is substantial clinical and basic science evidence implicating the importance of preserving mitral valve continuity and geometry in order to preserve the function of the LV [11–13].

The mitral valve is the "inlet" to the LV and can be thought of a "set of French doors". The anterior (septal/aortic) and posterior (mural) leaflets are "nominally" separated near the annulus by the posteromedial and anterolateral commissures. However, it should be noted that leaflet part of mitral valve is entirely continuous within the annulus much like the curtain of a waterfall. The anterior leaflet is semicircular and spans the distance between the two commissures. At the portion of the annulus which serves as "hinge point" of both leaflets, the anterior leaflet is attached to the anterolateral wall of LV in the central region of fibrous skeleton of the heart between right and left fibrous trigone where it is in direct continuity with the left and part of the noncoronary aortic valve leaflets. The posterior leaflet is rectangular in shape, and is divided into three portions by natural clefts in the leaflet. Figure 9.1 shows the relationship of the mitral valve and its components to chords and papillary muscles.

The mitral annulus represents the junction that joins the left atrium and ventricle and consists of fibrous and muscular tissues. The average human mitral annular cross-sectional area is 5–11 cm^2. During systole, the annulus assumes an elliptical shape and is able to contract and decrease in diameter, whereas, in diastole, it assumes a more circular shape. Annular flexibility allows for increased leaflet coaptation during systole and increased annular orifice area during diastole. The anterior aspect of the annulus, which is composed of the fibrous skeleton of the heart and consists of rigid but elastic fibrous tissues, has limited flexibility, whereas the posterior aspect of the annulus, which is in continuity with the fibrous skeleton and consists of a mixture of muscular and gradually tapering fibrous tissues, contributes most of the annular flexibility.

The chordae tendinae are comprised of fibrous connective tissue chords and attach the leaflets to either the papillary muscles or the LV wall directly. The chordae are divided into three groups. The primary chordae attach directly to the free edge of the leaflet, and ensure that the leaflets coapt without prolapse or flail. The secondary chordae, which are more prominent on the anterior leaflet, attach to the leaflet along the line of coaptation, and are important in maintenance of ventricular function [14]. Tertiary chordae are only present on the posterior leaflet, and attach directly to the ventricular wall or to the trabeculae carnae. In addition, there are commissural chordae, which arise directly from either of the papillary muscles and attach to both leaflets.

The anterolateral and posteromedial papillary muscles project into ventricular cavity directly from the apical and mid portion of the ventricular wall, and give rise to chordae tendinae that attach to both leaflets. The anterolateral papillary muscle receives a dual blood supply from the left anterior descending and from either a

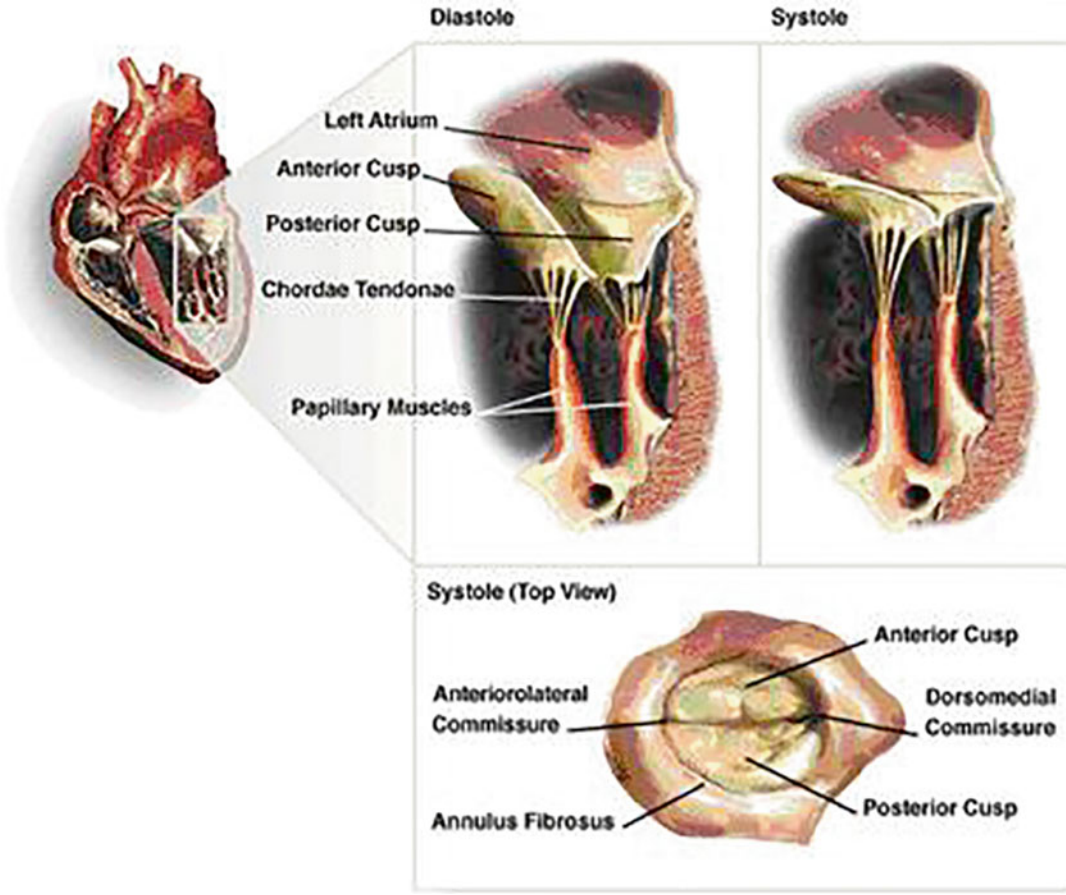

Fig. 9.1 Anatomy – anterior and posterior leaflets of the mitral valve

diagonal or marginal branch of the circumflex artery. In contrast, the posteromedial papillary muscle has a single blood supply, either from the right coronary or the circumflex artery. Therefore, the posteromedial aspect of the LV wall and the papillary muscle is more susceptible to ischemia and infarction and together play a very important role in valvular incompetence and leaflet malcoaptation in the instance of ischemic MR with a variable degree of posterior myocardial infarction.

The most important determinant of mitral valve competency centers on the zone of coaptation. Mitral valve leaflets accommodate high systolic LV pressure and establish competence through the distribution of force that can be likened to the stresses in a Roman arch in order to lessen the stress to the other parts of the ventricle and mitral valve apparatus. To maintain mitral valve competency in a systolic phase, the adequate zone of coaptation needs to be established in a coordinated fashion. To achieve adequate coaptation, both anterior and posterior leaflets should:

1. Be close enough to each other
2. Have enough tissue to cover the length of the zone of coaptation
3. Be guided at the line of coaptation by the leaflet chords at appropriate angle

Pathophysiology of MR

Acute MR vs Chronic MR

In MR, the regurgitant volume that is ejected into the left atrium is dependent upon regurgitant orifice size, ventricular to atrial pressure gradient,

atrial compliance and heart rate. The degree of increase in left atrial pressure, which is associated with congestive symptoms. is significantly affected by the regurgitant volume and the compliance of the left atrium.

The compliance of the left atrium is very different in acute and chronic MR, so it is important to fully recognize and differentiate the chronicity of MR in each patient being evaluated with heart failure.

Acute MR

Causes of acute MR include chordal rupture, endocarditis, blunt chest trauma, or myocardial infarction. The left atrium is of normal size with low compliance. A relatively small amount of acute MR can lead to an acute increase in left atrial pressure and lead to significant pulmonary edema that requires acute treatment. In this setting, symptoms and signs, along with the hemodynamic state dictate the proper timing of surgery. These are patients who benefit from mechanical support of the circulation perioperatively, either with intra-aortic balloon pump (IABP) counterpulsation or extra-corporeal membrane oxygenation (ECMO).

Chronic MR

In chronic MR, there is a gradual increase in regurgitant flow into the left atrium that leads to atrial enlargement and a significant increase in left atrial and pulmonary venous compliance. Therefore, signs and symptoms of pulmonary congestion may not become apparent until much later in the process of the disease in spite of the significant degree of MR and the significant volume overload and pathologic changes in the LV. In this setting, less symptomatic patients are difficult to triage in terms of proper timing of the intervention [15]. In this review, we treat geometric MR, which is chronic MR due to a distortion of the ventricular geometry. This is considered and treated as a different disease entity from acute MR.

Valvular MR vs Geometric MR

To understand the mechanism and the rational treatment of chronic MR, it is very useful to classify MR into primary/anatomic/valvular MR and secondary/functional/geometric MR.

In valvular MR, regurgitation is caused by structural valvular disease. The etiology of structural mitral valve diseases include degenerative (FED or Fibro-Elastic Degeneration, myxomatous disease, Barlow syndrome and fibroelastosis such as Marfan syndrome and connective tissue diseases), rheumatic, endocarditis, trauma, tumor, inflammatory and congenital. In this setting, problems with the components of the mitral valve apparatus cause MR.

Mitral valve repair of this valvular MR is systematically guided by three functional anatomic categories of mitral valve pathology proposed by Dr. Carpentier in 1983 [16];

- Annular dilatation
- Leaflet prolapse with elongated or ruptured chordae
- Leaflet restriction

The treatment of valvular MR aims to establish a zone of coaptation according to the functional anatomy. Mitral valve repair techniques in this setting include annuloplasty, variable degrees of leaflet resection, advancement or "sliding" plasty, chordal transplantation, and PTFE neochordal implantation.

In contrast, secondary or functional MR is defined as MR that is not caused by a structural defect of the components of the mitral valve apparatus but rather is caused by a distorted functional position of the components of the mitral valve apparatus related to LV dilatation. Therefore, functional MR is not a valvular disease but a geometric ventricular disease. Often in this setting, the dilatation of the ventricle may be secondary to an ischemic etiology with inferobasal akinesis or dyskinesis contributing to the MR. Figure 9.2 shows how inferobasal scarring and dyskinesis can contribute to mitral regurgitation. Figure 9.3 shows the stresses placed on the mitral valve leaflets through the connection of the chordae to the

ventricular muscle, suggesting that functional MR is a disease of the ventricle. Figure 9.4 shows that scarring of the muscle around insertion of the posteromedial papillary muscle.

DCM is defined by clinical evidence of chronic and progressive heart failure associated with echocardiographic findings of poor cardiac contractility (reduced LV systolic function reflected in reduced LV ejection fraction) and ventricular dilatation.

According to the primary etiology, DCM is usually classified into ischemic DCM and non-ischemic DCM because ischemic DCM is most prevalent.

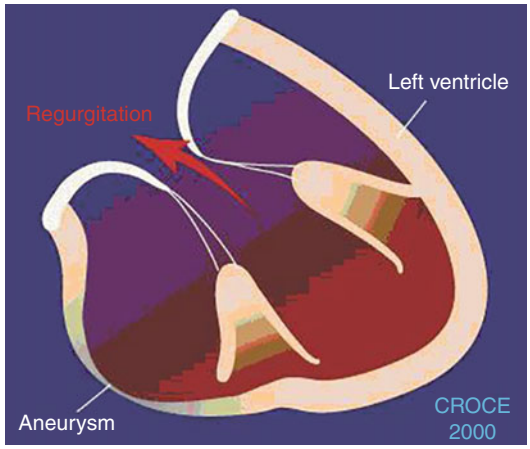

Fig. 9.2 Mechanism of MR with inferobasal scarring of the LV

Non-ischemic DCM can further be classified into idiopathic DCM (ventricular etiology) and valvular DCM (valvular etiology). Figure 9.5 shows the displaced papillary muscles causing central mitral regurgitation. It should be noted that there is a segment of this patient population that have concurrent ischemic heart disease and MR from degenerative mitral valve disease at the same time, commonly seen in elderly patients. This group is distinct from patients with geometric MR with ischemic DCM.

In geometric MR the components of the mitral valve apparatus itself are normal, two of the three functional anatomic categories proposed by Dr. Carpentier hold true;

- Annular dilatation, which may be mild or moderate
- Leaflet restriction: papillary muscle – LV wall displacement

Figure 9.3 shows the components of geometric MR. The treatment aim of geometric MR is to re-establish the zone of coaptation to eliminate regurgitation. To achieve this goal, a flexible complete ring annuloplasty technique was initially used [17]. As surgeons became more comfortable with this technique, more and more aggressive undersizing and overcorrecting ring annuloplasty was used based on the assumption that the most significant determinant of leaflet

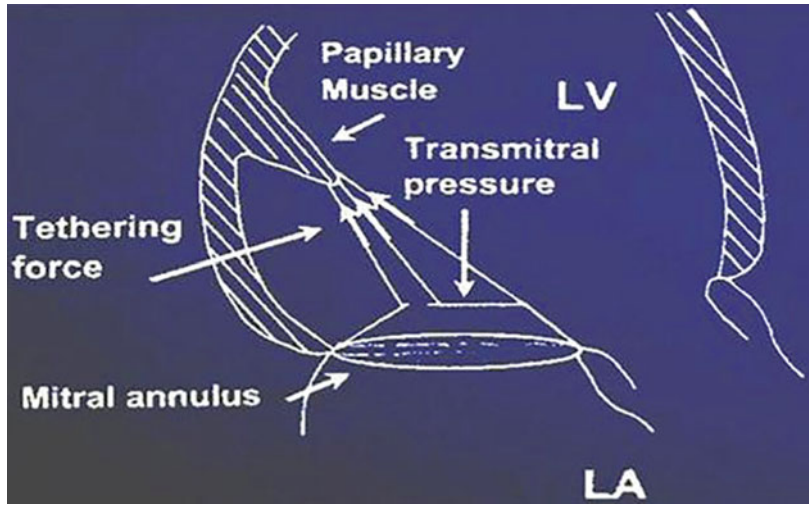

Fig. 9.3 Stresses on mitral valve leaflets and chordae attached to the papillary muscle

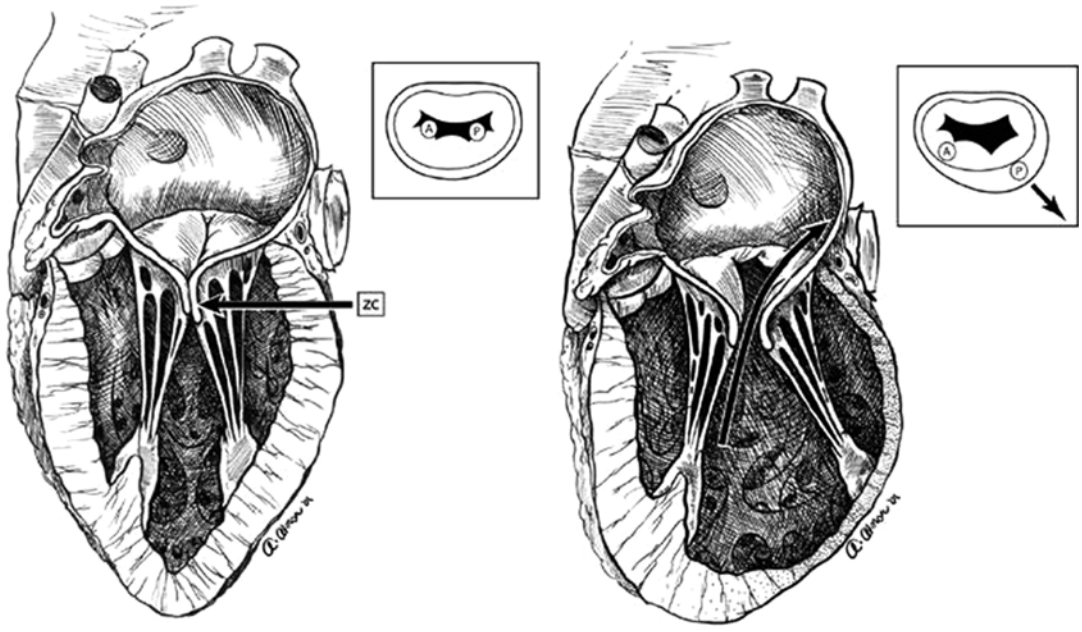

Fig. 9.4 Perturbation of coaptation of the mitral valve leaflets, due to scarring of left ventricle affecting the postero-basal papillary muscle, causing eccentric MR

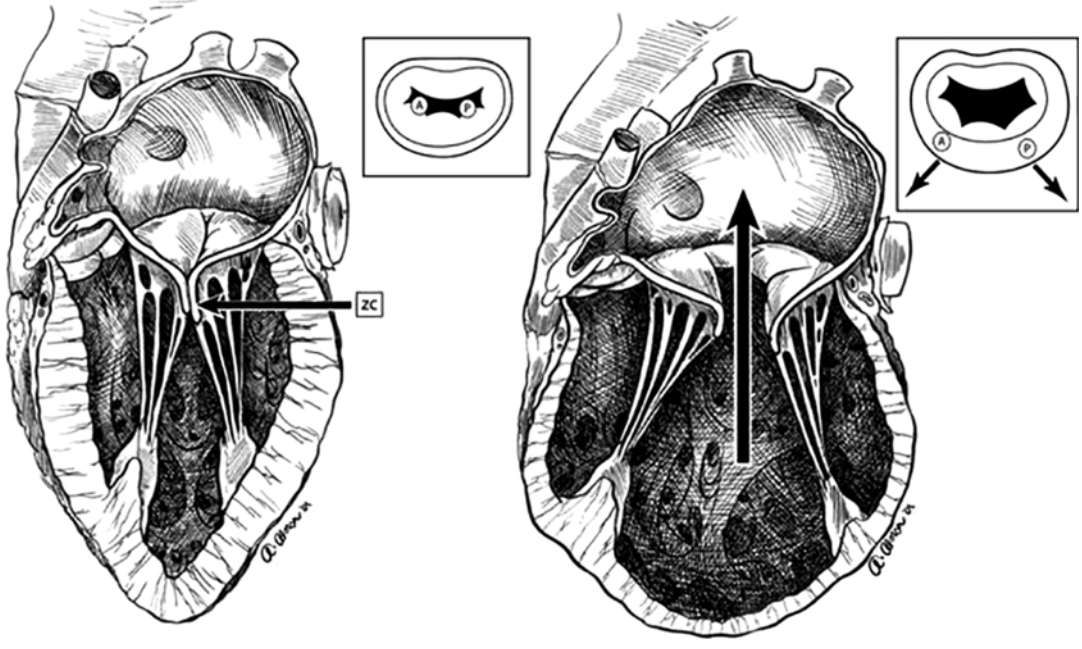

Fig. 9.5 Loss of coaptation of the mitral valve leaflets, due to displacement of both papillary muscles in dilated cardiomyopathy, causing central MR

coaptation in geometric MR is the diameter of the mitral valve annulus and that undersizing/over-correcting the annulus would also help to compensate the widened angle and the septolateral distance of the papillary muscles resulted from LV dilatation. These clinical observations

and acceptable surgical results were correlated with several key echo parameters as well as improvement of symptom and Quality of Life [18–20].

The natural history of chronic degenerative or rheumatic valvular MR can be protracted and long. The progression of the disease may be slow and span several decades. The onset of symptoms are often masked and may present late in the progress of the disease even with elevated left atrial and LV end-diastolic pressures because of a large compliant left atrium and the slow, gradual progression of this process. The presence of MR contributes to this increased back pressure and a decreased forward flow as well. Decreased forward flow is also well compensated with increased total stroke volume that is a combination of regurgitant volume plus effective forward stroke volume and increased heart rate. This leads to increased workload from volume overload to the LV. Short-term or medium-term neurohormonal compensatory mechanism also play a role in maintaining the same effective forward stroke volume in the setting of chronic MR. The normal LV can accommodate a fairly large amount of regurgitant volume and be well compensated before the LV starts to dilate. This is reflected in hyperdynamic wall motion and increased LV ejection fraction. However, once increased volume overload reaches beyond the compensatory adaptation of the LV, the LV is forced to dilate through homeostatic compensation mechanisms according to the Frank-Starling curve. This is reflected in an increased LV end–diastolic and end-systolic volume or dimension producing chronic LV dilatation and increased LV wall tension and stress. The LV reacts by trying to match the increased wall tension/stretch/stress by proportionally increasing LV mass via LV hypertrophy. As LV dilatation progresses, the LV wall tension/stretch/stress increases and coronary flow reserve decreases in addition to increased LV work load by volume overload [20–23]. Increased LV wall stress is the most potent stimulus for progressive heart failure through the mechanism of LV remodeling at a genetic, molecular and neurohormonal level. This chronic energy imbalance of increased workload plus increased wall tension/stretch/stress and decreased coronary flow reserve accelerates the damage to the LV muscle through the loss of LV contractile functional reserve. The poor survival of patients with chronic degenerative MR has been well established. Even though total resistance to the LV is decreased by MR, the total workload to produce the same forward flow is proportionally increased to volume overload with MR. The development of clinical symptoms usually reflects significant LV dysfunction and is a hallmark of reduced life expectancy. In the current setting of low operative mortality and high feasibility of repair, the timing of mitral valve repair can be offered at earlier stages of the disease in hopes of changing the natural history of the disease and before the development of left ventricular dysfunction [15]. A regurgitant volume of ≥60 ml/beat and effective regurgitant orifice area of ≥40 mm^2 are currently recommended as an index of quantitative assessment for the timing of mitral valve repair in asymptomatic patients with degenerative valvular MR [24, 25].

Geometric MR with DCM further contributes to LV dilatation and remodeling through chronic phenotypical changes triggered by increased volume work-load, increased LV wall tension/stretch/stress and decreased coronary flow reserve in addition to originally dysfunctional LV. This LV dilatation and spherical change further increases the magnitude of MR. Therefore, geometric MR sets up a vicious cycle and has been associated with worsened survival even with mild MR and few overt symptoms of heart failure [26–28].

Geometric MR in the setting of Ischemic MR is slightly different. In this instance the remodeling of the LV is predominantly in the region of the inferobasal wall. This area is akinetic, dyskinetic or just lagging the normal systolic function of the left ventricle. As the mitral leaflets try to coapt in systole, the lagging inferobasal wall has an effect on the posterior leaflet of the mitral valve. The downward pull or restriction of the posteromedial posterior leaflet in the P2–P3 area prevents good apposition of the two leaflets. The leads to eccentric mitral regurgitation.

Compared to valvular MR, the natural disease progression of geometric MR is rapid and prognosis remains poor. Geometric MR is a prevalent

complication of end-stage cardiomyopathy and may affect up to 60 % of all heart failure patients as a pre-terminal or terminal event [28–30]. Ischemic MR, that is, geometric MR in ischemic DCM doubles the mortality after myocardial infarction with a graded decrease in survival related to the severity of MR. Figure 9.4 reiterates the ischemic mechanism overlaid on the geometric components. It is reported that in ischemic DCM, the 5-year survival is 60 % without MR, 45–50 % with mild MR and 30–35 % with more than moderate MR [31, 32]. Decreased LV function reflected by a decreased ejection fraction further predicts a worse prognosis [33, 34]. The prognosis of ischemic DCM with MR is generally even worse than idiopathic DCM with MR [28].

However, the appropriate timing of intervention for chronic, geometric MR is still very controversial because of the higher operative risk and poorly defined late outcome measures.

With normal ventricular geometry, the redundant mitral leaflets are responsible for a zone of coaptation that is more than twice the area of the mitral valve orifice [10]. As the failing ventricle dilates, the multifactorial mechanisms of the progressive expansion of the mitral annulus and the dislocation of papillary muscles and LV wall leads to incomplete leaflet coaptation and a regurgitant jet of functional mitral insufficiency.

As more leaflet tissue is utilized for coverage of the enlarging orifice, a critical reduction in leaflet tissue available for coaptation is reached so that leaflet coaptation becomes ineffective and that a central regurgitant jet type of geometric MR develops [8, 35, 36]. In studies of patients with DCM, those with MR have significantly greater mitral leaflet orifice surface area and significantly larger dimensions of the mitral valve annulus than those without MR. However, these changes are minor compared to patients with fibro-elastic degeneration or myxomatous disease. Indeed, in many patients the annulus maybe normal in size. Chordal length and papillary muscle length are not significantly different in patients with cardiomyopathy, with or without MR [8]. It is also reported that pharmacologic reduction in the dynamic MR through the medical treatment of heart failure was through a reduction in the regurgitant orifice area which was related to the decreased mitral annular distention [36].

Therefore, the most significant determinant of leaflet coaptation in geometric MR is the diameter of the mitral valve annulus. This forms the basis of the approach to downsizing, and overcorrecting a complete MV ring annuloplasty. The spatial mis-alignment of the subvalvular mitral valve apparatus, that is papillary muscle – LV wall dislocation, also contributes to inability of leaflet coaptation [9, 37, 38]. As the ventricle dilates, the distance and the angle of the papillary muscles tends to become obtuse rather than acute, forcing the mitral valve leaflet coaptation zone apart. In addition, there is a large apical force that pulls the papillary muscle and chordal apparatus in an inferior and lateral direction and there is a weak closing force of the poorly functioning LV. All of these elements result in the loss of the zone of coaptation and subsequent regurgitation. This is illustrated in Fig. 9.5. The downsized and overcorrected complete ring annuloplasty also has some effect on the of the angle and the distance of de-arranged subvalvular mitral valve apparatus by indirectly providing more leaflet tissue for zone of coaptation and by directly influencing the reduced septal-lateral diameter at the level of papillary muscle through the continuum of papillary muscle-LV wall complex.

Although significant undersizing of a complete ring annuloplasty is performed to increase coaptation, no systolic anterior motion (SAM) of the anterior leaflet, or mitral stenosis was noted in the Bolling series. SAM is not usually seen in the setting of a large aorto-mitral angle and increased LV size, both conditions that are seen in DCM.

In contrast to primary or anatomic MR, geometric MR is also reported to have dilatation along the anterior aspect of the annulus [39]. This could possibly explain why the partial ring annuloplasty, rather than a complete ring annnuloplasty appears unlikely to produce a sustained long term result [40].

With ischemic DCM, geometric MR is furthermore compounded by the dynamic and

regional changes of LV muscle function and geometry. Ischemic papillary muscle dysfunction which is traditionally defined as the cause of geometric MR is a misnomer. It is not an isolated disorder of the contractive function of the papillary muscle, which is often preserved. There is often disturbance in the coordinated geometry of mitral valve complex including the annulus, chordae tendinae, papillary muscles and the LV wall. It is reported that MR cannot be reproduced through direct damage causing fibrosis of papillary muscle and it may actually decrease with papillary muscle ischemia [41, 42]. This is why "papillary muscle – LV wall dislocation "rather than" ischemic papillary muscle dysfunction" has been more recently used to describe this condition [43].

Geometric Mitral Valve Repair (University of Michigan Experience)

In 1993, Dr. Bolling and his group began to use mitral valve repair techniques very cautiously to selected DCM patients with severe MR who were suffering from progressive severe heart failure and were not eligible for transplantation, on the assumption that mitral valve is the geometric functional component of the LV and that geometric MR, in which mitral valve apparatus itself is originally normal, is the functional and geometric problem of the LV [17].

In 1995, a small initial series of patients at the University of Michigan was reported describing the early outcome (1993–1994) of mitral valve reconstruction in 16 consecutive patients with DCM and severe MR, refractory to maximum medical therapy. In that study, 16 patients (11 men and 5 women) ranged in age 44–78 years (64 ± 8 years) underwent mitral valve reconstruction with a simple, undersized, flexible, complete ring annuloplasty. The ejection fraction was 9–25 % (16 ± 5 %). Two patients were listed for transplantation. No postoperative patients required support with an intra-aortic balloon pump. There were no operative or hospital deaths and mean hospital stay was 10 days. There were three intermediate term deaths at 2, 6 and 7 months after procedure, and the 1-year actuarial survival rate was 75 %. At a mean follow-up of 8 months, all remaining patients were in NYHA class 1 or 2, with a mean post-operative ejection fraction of 25 ± 10 % [17].

Historically, while significance of MR in CHF was recognized and attempts were made to treat this surgically with mitral valve replacement, early surgical correction was associated with poor outcomes and surgical teaching evolved to enforce this idea [44–47]. Consequently, these patients were not considered operative candidates due to the prohibitively high morbidity and mortality in this patient population [48–52]. The prevailing surgical thought was that MR provided a "pop-off" effect for these impaired ventricles to function and that by removing the MR and the "pop-off" effect the LV was compromised which led to the high operative mortality. However, the poor outcomes of mitral valve replacement in that era were probably from the adverse consequences of the excision and the disruption of the annular-chordal-papillary muscle continuity, which has significant importance on LV systolic function [11, 53–56]. It has been demonstrated in a number of studies that preservation of the annulus-papillary muscle continuity is of paramount importance to preserve LV function, and this is even more critical in patients with severely compromised LV function [12, 57–62]. Preservation of the mitral valve apparatus and LV in mitral valve repair has been demonstrated to enhance and maintain LV function and geometry with an associated decrease in wall stress [63]. This procedure in degenerative valvular MR has been shown to be safe, with a significant decrease in operative morbidity and mortality, and good long-term outcomes [64–69]. There is no "pop-off" effect seen because the total workload to produce the same forward flow without MR is proportionally decreased compared to the setting of volume overload with MR, even though the total resistance to the LV is decreased by MR [70, 71].

Feasibility of a surgical treatment of geometric MR with DCM had been established through the use of the simple, undersized, flexible complete ring annuloplasty. Pre- and post echocardiography data showed some changes in parameters related to hemodynamic and geometric improvement. The basal angulation of the

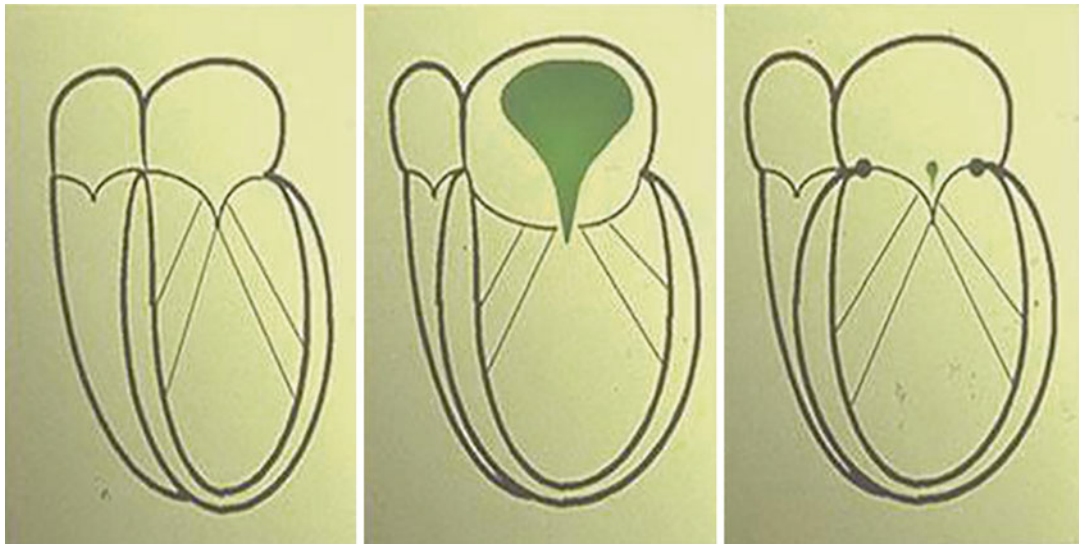

Fig. 9.6 Correction of coaptation by use of an undersized annuloplasty ring

heart was changed by undersizing, overcorrecting the annulus and the elliptical shape of the heart became re-established such that not only was MR acutely obliterated, but the cardiac geometry was also influenced, allowing the subsequent reverse remodeling [17–20]. Figure 9.6 shows schematically how this concept might work.

At the University of Michigan (1993–2003), 215 patients with end-stage cardiomyopathy and refractory MR underwent mitral valve repair with a simple, undersized, complete ring annuloplasty. The range in age was 30–87 years (64 ± 12 years). Ejection fraction was 6–30 % (20.8 ± 6 %). Preoperative NYHA class was 3.1 ± 0.9. A large number of patients (64/215, 30 %) had had a previous open-heart procedure. Thirty-day mortality was 4.7 % (10/215) for all mitral repairs. Postoperative low cardiac output syndrome was 2.3 % (5/215). Complication rates were low with CVA/TIA 2 % (4/215), prolonged ventilation 6 % (14/215), total infection 5 % (11/215), renal failure requiring dialysis 1 % (2/215) and reoperation for bleeding 0.5 % (1/215). Average ICU stay was 2.67 days and average hospital stay was 7.8 days. One and 2 year actuarial survival rates were 80 % and 70 %, respectively.

These techniques and principles have been adopted throughout the surgical community as the contribution of the mitral annulus, chordal structures and LV geometry to LV function were further understood [14, 72–77].

Numerous studies, from the other major surgical institutions, of mitral reconstruction in ischemia and idiopathic DCM, have also noted acceptable low operative mortality and been successful in relieving MR in CHF patients.

Chen from Brigham and Women's Hospital published in 1998 a report of 81 patients undergoing mitral valve surgery for mitral valve regurgitation in dilated cardiomyopathy with 11 % total perioperative mortality. In this series LVEF improved from 24 % to 32 % and there was an improvement in NYHA class from 3.2 to 1.6. Estimated survival in this study was 73 %, 58 %, and 38 % at 1, 3, and 5 years respectively [78].

Bishay and colleagues in Cleveland Clinic Foundation reported in 2000 on 44 patients with isolated mitral valve surgery with LV mean ejection fraction (LVEF) below 35 % with a 2.3 % mortality. In this series LVEF improved from 28 % to 36 % and NYHA functional class decreased from 2.8 to 1.2. Survival was 89 %, 86 %, and 67 % at 1, 2, and 5 years respectively. Furthermore they noted a decrease in the left ventricular chamber sphericity [79].

Bitran in Israel reported in 2001 a decrease in heart failure symptoms and a decrease in

New York Heart Association (NYHA) functional class without any operative mortality in 21 patients with LV mean ejection fraction (LVEF) below 25 % [80].

Rothenburger from Germany in 2002, described 31 patients with isolated mitral valve surgery with LV mean ejection fraction (LVEF) below 30 % with 6.5 % mortality. In this series LVEF improved from 23 % to 36 % and NYHA functional class decreased from 3.3 to 2.1. Survival was 91 %, 84 %, and 77 % at 1, 2, and 5 years respectively. Freedom from readmission for heart failure was 85 %, 79 % and 68 % at 1, 2, and 5 years respectively [81].

More recently Calafiore and associates in Italy published in 2004 a series of mitral repairs in 91 DCM patients (64 ischemic and 27 idiopathic). In this study, mitral valve annuloplasty was performed in 64 patients and 27 underwent a mitral valve replacement. The 30-day mortality rate was 4.4 %. LVEF improved from 27 % to 32 % and NYHA functional class improved from 3.5 to 2.1 in the 69 survivors. Interestingly, the probability of being alive at 5 years was 78 % and was higher in mitral valve repair group (81 %) than in mitral valve replacement group (67 %). The probability of being alive at 5 years with an improvement of at least one NYHA class was 66 % and was higher in the mitral valve repair group (77 %) than in mitral valve replacement group (52 %). Published series have come from numerous other units and countries and now constitute hundreds of cases performed with less than 5 % mortality [82].

The ACORN passive ventricular restraint device has also been studied in this group of patients. In the most recent ACORN series, a prospective, randomized and controlled, multi-institutional, multi-surgeon experience in 193 patients with MR and a mean EF of 23.9 %, LVEDD 69.7 mm, in which most of them underwent undersizing Geometric mitral valve repair, showed that mitral valve surgery in DCM patients with MR could be performed with a 1.6 % 30 day mortality. One-year and 2-year survival was 86.5 % and 85 % respectively. This Acorn trial is also a unique opportunity to assess the long-term efficacy of mitral valve surgery in patients with heart failure. In this report, surgery patients had a significant increase in 6 min walk times immediately after surgery and were associated with significant improvements in two different quality of life measures. Surgery patients were also associated with a remarkable reversal of LV remodeling, as manifested by a decrease in LVEDV and LVESV, an improvement in LVEF and sphericity index, and a reduction in LV mass. MR was effectively reduced and maintained for at least 18 months of follow-up [83]. However, the Acorn CSD has not been approved by the FDA and this is a trial of historic interest.

The latest set of data in mitral valve reconstruction in patients with heart failure have emerged from the NIH sponsored multi-center studies looking at these vexing issues.

One of these was a study involving 301 patients with moderate ischemic mitral regurgitation that were randomized to CABG alone or CABG plus mitral-valve repair (combined procedure). The primary end point was the left ventricular end-systolic volume index (LVESVI), a measure of left ventricular remodeling, at 1 year.

At 1 year, the mean LVESVI among surviving patients was 46.1 ± 22.4 ml per square meter of body-surface area in the CABG-alone group and 49.6 ± 31.5 ml per square meter in the combined-procedure group (mean change from baseline, −9.4 and −9.3 ml per square meter, respectively). The rate of death was 6.7 % in the combined-procedure group and 7.3 % in the CABG-alone group (hazard ratio with mitral-valve repair, 0.90; 95 % confidence interval, 0.38–2.12; $P = 0.81$). The rank-based assessment of LVESVI at 1 year (incorporating deaths) showed no significant between-group difference (z score, 0.50; $P = 0.61$). The addition of mitral-valve repair was associated with a longer bypass time ($P < 0.001$), a longer hospital stay after surgery ($P = 0.002$), and more neurologic events ($P = 0.03$). Moderate or severe mitral regurgitation was less common in the combined-procedure group than in the CABG-alone group (11.2 % vs. 31.0 %, $P < 0.001$). There were no significant between-group differences in major adverse cardiac or cerebrovascular events, deaths, readmissions, functional status, or

Fig. 9.7 Duran ring which is flexible, and can be partial or complete

quality of life at 1 year (ClinicalTrials.gov number, NCT00806988) [84].

An insightful editorial by Sundt into the findings of this article reported that "Entry into this study required multivessel coronary artery disease and a moderate degree of mitral regurgitation without structural valvular abnormalities; a previous myocardial infarction was not a requirement, and indeed only about 65 % of patients had such a history. The inclusion of patients with mitral regurgitation secondary to reversible ischemia may well explain why so many had an improvement in their mitral regurgitation with bypass alone. This may also explain in part why recurrent mitral regurgitation after repair was present in only about 10 % of patients, not the 30 % reported by others. It is possible that the authors set themselves up to show no significant difference between treatment groups" [85].

Many lessons have been learned in these geometric MR patients and further understanding and advances continue to be published in clinical and basic studies. The anterior trigone to trigone distance may enlarge variably in this type of CHF patient and it is not a good or useful guide for ring sizing. Anatomic and laboratory studies have confirmed this dilation of the anterior trigone to trigone distance from ischemia and dilated cardiomyopathy [39, 86, 87].

It has recently been reported that partial ring annuloplasty, not complete ring annnuloplasty is more likely to fail requiring repeat intervention [86]. Furthermore, undersizing or downsizing has been shown to be not only helpful in abolishing MR, but also in remodeling the base of the heart from the "bending" of the mitral annulus. This geometric re-arranging may have helped reestablish an ellipsoid shape to the base of the LV cavity. However, there is also emerging evidence that despite good early results, undersized annuloplasty does not serve all patients well in the short or intermediate term.

Based on the continually evolving understanding of this complex disease process and clinical experience, geometric mitral valve repair by using the simple, undersized, overcorrected, complete ring annuloplasty is safe and effective for improving both symptoms and heart function, in the short term. The durability of this procedure is open to question. It should be underscored that symptom reduction, reduced hospitalization and improvement in QOL should be the treatment targets for these patients in heart failure.

Figures 9.7, 9.8, 9.9, and 9.10 show some of the different types of rings commonly used to repair MR.

Unresolved Issues, Future Perspective

Despite these new insights, residual or recurrent MR and more importantly, limited LV reverse geometric remodeling have also been noted and potentially limit long term improvement [88–90]. LV remodeling is characterized by progressive LV dilatation with a change in the heart from an

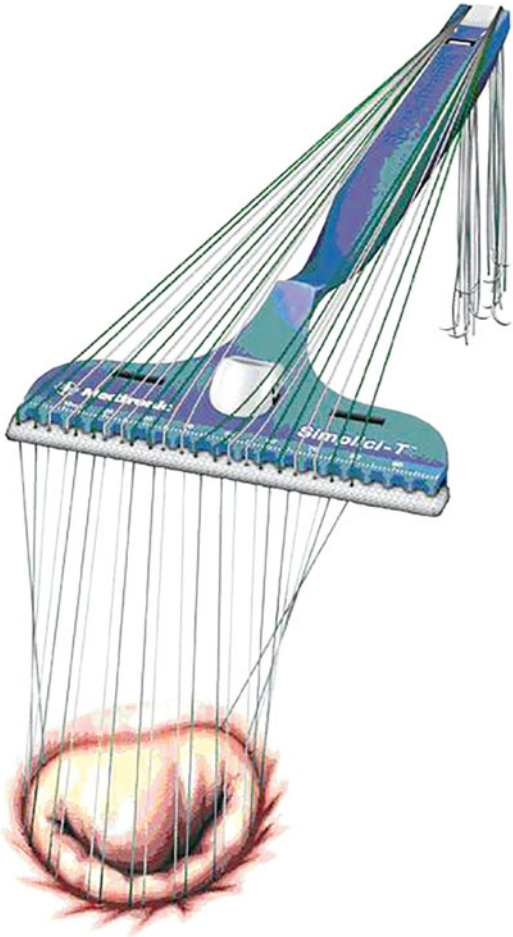

Fig. 9.8 The flexible simplicit band

Fig. 9.9 Semi-rigid band – CG band

ellipse to a more spherical shape and is one of the strongest predictors of mortality in heart failure patients. Despite optimal surgical and/or medical therapy, heart failure is often progressive without

Fig. 9.10 Rigid saddle-shaped ring

reversal of LV remodeling. Surgical CHF treatment must, therefore, be aimed not only at MR, but more importantly, also at LV reverse remodeling [91, 92].

In a recent retrospective analysis from the University of Michigan, the effect of MV repair was compared with medical therapy in heart failure patients with severe MR. Wu et al. examined 293 patients treated medically and 126 treated with MV repair, all with severe CHF, and found that MV repair did not predict a mortality benefit [93]. In this non-randomized, but propensity-matched series, the results showed, qualitative improvement, but that there appeared to be little mortality benefit of MV repair of functional MR in advanced heart failure and severe LV dysfunction over the 10 year period of the review. Indeed, the only predictor of mortality in this study, as in every CHF trial, medical or surgical, was reverse remodeling, which did not correlate well with the abolishment of MR. CHF associated MR from LV geometric distortion does not preclude successful mitral valve repair. However, it may be inferred that reducing MR in these patients may not be "enough", as MR is a late marker for CHF [94, 95]. Interestingly, with further analysis of the same data set, there is favorable trend upon mortality, during the last 5 years of the study, when MVR surgery evolved to include earlier surgical referral for CHF patients, and the use of rigid smaller, remodeling rings. Similarly, the recently presented ACORN trial results also showed quality of life benefit, but did not have a mortality benefit.

In this setting, when recurrent MR might prove to be the final pathway by which a patient decompensates, it might be worthwhile considering alternatives such as mitral valve replacement with complete preservation of chordal supports.

Others have found a group of patients with bad ventricles, especially with very tethered posterior leaflets or very large ventricles to have suboptimal long-term results with tight mitral annuloplasty alone. In these patients, either as a first procedure or at redo surgery, the preference is to reconstruct the mitral valve with a chord preserving prosthetic mitral valve replacement.

Young patients tend to get mechanical mitral valve prosthesis as shown in Fig. 9.11**.**

Older patients (over the age of 60–65 years of age) usually get a porcine bioprosthetic valve with chordal preservation. This is shown in the adjoining Fig. 9.12**.**

A review from the University of Michigan, evaluated the outcome in 289 patients with EF ≤ 30 %, who received an undersized complete mitral ring as their geometric mitral valve repair procedure. Of these, 170 patients had a flexible ring. In follow-up, 16 "flexible" patients (9.5 %) required a repeat procedure for significant recurrent geometric MR and CHF, (ten replacements, three re-repairs, three transplants). In contrast, 119 patients with an EF ≤ 30 % received an undersized non-flexible complete ring. Only one "non-flexible" patient required a repeat mitral valve procedure for recurrent mitral regurgitation secondary to ongoing ventricular remodeling and two patients required a heart transplant (2.5 %). A significant difference in reoperation rates, for recurrent MR, between the groups was noted at $p = 0.012$. There were no differences between groups, in terms of age, ring size, preop EF, LV size, MR grade or NYHA class [40]. From this study, it is concluded that the use of a non-flexible ring appeared to be associated with an increased incidence of recurrent MR and deserves further investigation through a randomized trial.

Recent developments in MV repair have included newer rings aimed at 3D modulation of LV geometry through an annular approach [96]. The GeoForm ring (Edwards Lifesciences, Irving CA) is a unique non-deformable titanium

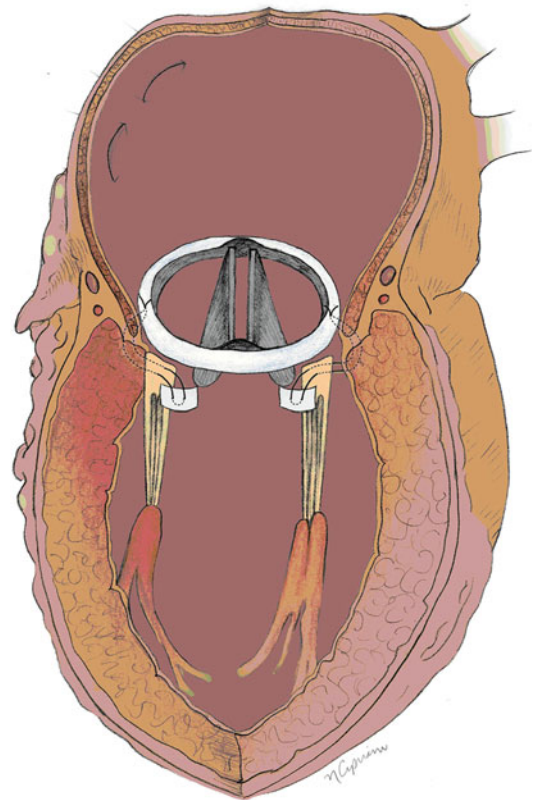

Fig. 9.11 Mechanical mitral valve with preserved chords

3D device aimed not only at abolishing MR, but also at acutely initiating reverse LV geometric remodeling and was developed by Drs Bolling and Alfieri. Figure 9.13 shows this ring. The AP or septal lateral diameter is 40 % reduced compared with standard ring dimensions. This AP reduction has been shown in mathematical computational modeling and in animal studies to dramatically abolish MR. This reduction in AP diameter was more effective than a reduction at P1 or P3 areas of the mitral annulus, even for "asymmetric" MR. While the GeoForm is reduced in AP diameter, the effective orifice area (EOA) of the ring is correspondingly bigger than a same size standard ring, due to the complex 3D orientation of the orifice and mitral stenosis has not been seen.

The 3D nature of the Geoform is directed to altering the geometry of LV. Based on the double toroid or saddle shape of the normal mitral valve during systole, the mid posterior ring is elevated

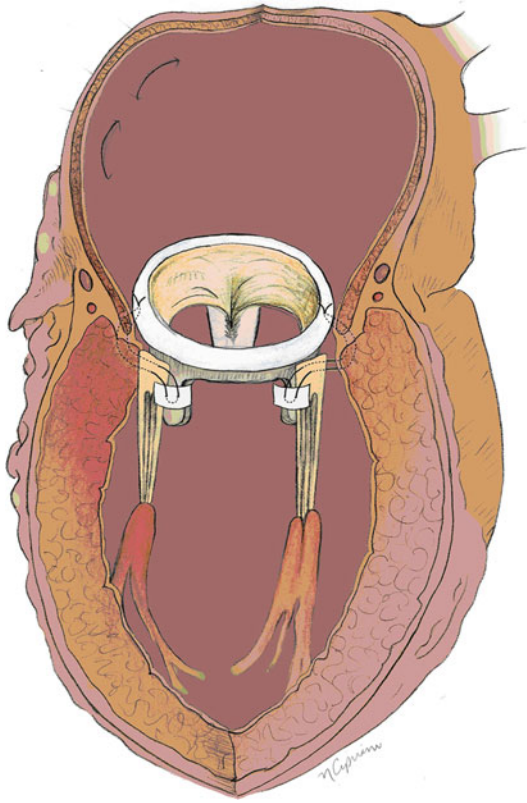

Fig. 9.12 Bioprosthetic mitral valve with preserved chords

Fig. 9.13 Geoform shaped ring

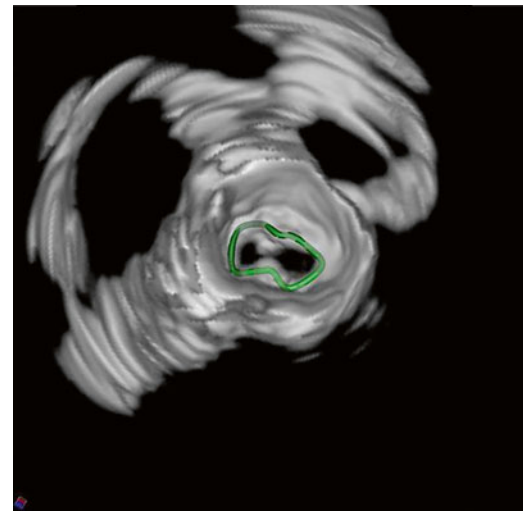

Fig. 9.14 Three dimensional echocardiographic appearance of the geoform ring

6 mm superior and drawn 5 mm anteriorly. Figure 9.13 shows the shape of the ring. From the surgeons viewpoint, this shape in essence, "moves" the LV and mitral annulus upward and forward as a whole to the normal position, directly reversing the trend of the CHF ventricle to "fall" down and outwards. Although coronary alteration is a theoretical concern of this shape, there has been no circumflex bending or resultant ischemia in any implant, animal or human. Additionally, chordal tensioning studies, both by computer modeling and in pulse duplicators, actually demonstrated less chordal tension after Geoform implant, which corrects LV geometry, than in the original state of a large myopathic, round heart. There has not been any chordal rupture following Geoform implant. The three-dimensional echocardiographic picture in Fig. 9.14 shows the ring maintaining the saddle shape of the annulus. Figure 9.15 shows the graphical improvement in LV size with this approach.

Between January and November 2004, in this initial feasibility series, ten consecutive, non-randomized patients at the University of Michigan Medical Center, with ischemia and/or dilated cardiomyopathy and refractory moderately-severe or severe mitral regurgitation, were studied prospectively. Patient ages ranged from 53 to 79 years (mean 73 ± 6). Five patients had nonischemic dilated cardiomyopathy, while five had ischemic disease. No patient was felt to have an acute myopathy. Pre-operatively, six patients had NYHA Class IV congestive heart failure and four had Class II–III. The mean duration of documented cardiomyopathy or symptomatic congestive heart failure was

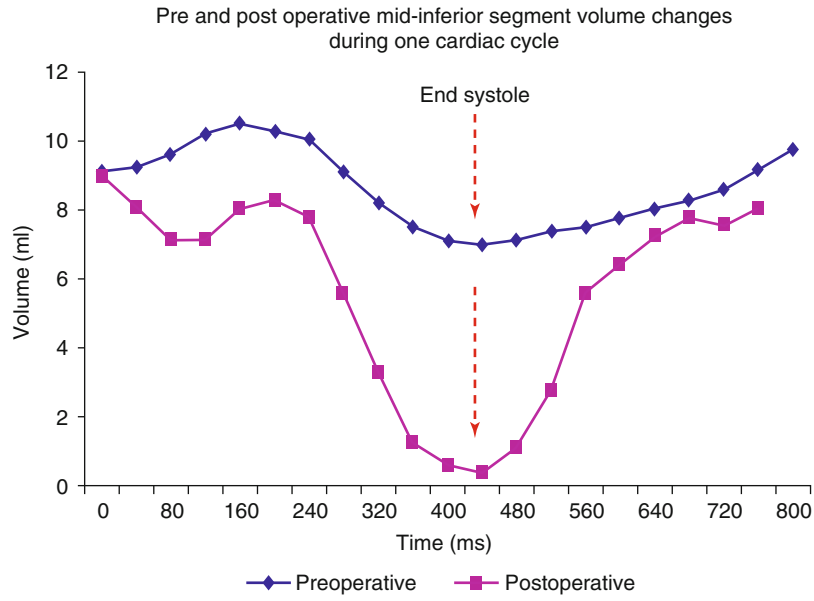

Fig. 9.15 Graph showing reduced left ventricular size with shaped ring

4 ± 6 years. Mean pre-operative ejection was 27 ± 11 (6–41) %.

At the time of surgery, patients underwent mitral reconstruction with a Geoform remodeling annuloplasty ring. Coronary artery bypass grafts (mean – 2.9) were placed in the five patients with coronary artery disease. Additional procedures included tricuspid annuloplasty in seven patients, ASD/PFO closure in four and modified Maze procedure in four patients, where indicated. There were no operative deaths.

There were no in-hospital deaths and the mean duration of hospitalization following surgery was 5.2 days (range 4–23) days. Follow-up was available for all patients. At a mean follow-up of 5 months, all surviving patients are in NYHA class I or II. The NYHA failure class significantly fell for every patient individually from a mean of 3.2 ± 0.4 to 1.4 ± 0.4 for the entire group.

Follow-up echocardiography at 1 week, 3 and 6 months was obtained in all patients. The mean transmitral gradient on follow-up at 1 week was 3 ± 1 (range 1–5) mmHg. All patients had a marked reduction in sphericity, regurgitant volume, regurgitant fraction and significantly improved LV EF, end-diastolic and end systolic volumes. There have been two late deaths, following Geoform mitral valve reconstruction. One late death occurred as a consequence of recurrent ARDS (ECMO supported patient, EF = 6 %) and CHF at 5 months and the other was from acute sudden death at 11 months, while watching television. No patient needed pacemaker or AICD implantation.

Interestingly, these GeoForm patients not only demonstrated immediate clinical improvement, but also showed acute favorable changes in LV geometry as shown by echo at 5 days post-op; decreased LV volumes, sphericity and tenting height with an increase in EF, as opposed to the expected drop in EF when MR is corrected. These types of changes are not dependent on volume loading and are not usually seen acutely with echos following the use of standard rings. These beneficial changes demonstrate potential acute reverse remodeling due to the 3D-shaped GeoForm ring in addition to the slow and chronic reverse remodeling. This favorable trend also appeared to be sustained in these high-risk geometric MR patients in short-term early observation.

The GeoForm ring appears to not only improve MR, but far more importantly for long term patient outcome, also reverses the LV remodeling acutely and chronically associated with CHF. Larger series with longer follow-up will be needed to confirm this novel approach.

As with all rigid structures trying to constrain a dynamic mitral annulus, there maybe excessive tension on the implanting sutures. Despite all the theoretical benefits of septal-lateral cinching of the mitral annulus in animal models, it must be remembered that addressing the annulus alone in patients where the abnormality is in the underlying ventricle may be a solution that does not address the root cause.

This approach has heralded the development of multiple shaped mitral rings by other investigators and companies. Once again, the role of the pioneer may be pathbreaking but laden with a variety of regulatory problems: Despite very encouraging results with the Geoform ring, this annuloplasty device is not being manufactured by Edwards any more.

Patient Selection for Geometric Mitral Valve Repair

Based on the clinical experience, the relative contraindications to mitral valve operations include right ventricular failure, severely enlarged left ventricular diameter and volumes, elevated pulmonary artery pressures, and extremely high norepinephrine levels, TNF, and BNP. All of these are markers of long-term CHF. These were all absolute contraindications early on in our series but we have since relaxed these considerably over time as our experience has grown and newer surgical techniques and patient management strategies have evolved.

Exact patient selection criteria remain to be elucidated, but these criteria may be considered when evaluating high-risk patients for MV repair. It is important to follow these patients closely after their procedures as the role of careful medical management of their heart failure should be emphasized.

It is important to decide which patients would benefit from mitral valve repair and which patients are likely to fail with a mitral ring approach. A recent presentation by Dr Alfieri's group suggested that the causes of positive outcomes in mitral repair in dilated cardiomyopathy were presence of reverse remodeling (>15 % reduction in left ventricular end-systolic volume), resolution of inferior wall ischemia, successful ablation of atrial fibrillation. Conversely, patients without these features tended to have a poor outcome with mitral valve repair.

Another important recent publication from the NIH clinical trials consortium looking at ischemic regurgitation showed superior outcomes with chordal preserving mitral valve replacement, compared to mitral valve repair [97]. While there was no significant difference in mortality, the patients with mitral valve replacement had greater freedom from recurrent MR.

Other Innovative Options to Approach Geometric MR

There are many other innovative surgical and interventional options to approach geometric MR that have been emerging and evolving, including; scar resection with papillary muscle reimplantation, [98] intraventricular papillary muscle imbrication [99], external infarct LV wall plication [100], chordal cutting [101], papillary muscle sling [102], papillary muscle relocation [103], BACE, Myocor, Myosplint, Coapsys: external bands buttressing device [104], localized epicardial balloon patch [105], percutaneous annular reduction by coronary sinus compression, [106] and percutaneous intraluminal edge to edge repair by using clip [107]. Most of these are still in experimental phase. Some are in preliminary clinical trial or small clinical series. The effectiveness, safety and durability of these techniques remain to be studied.

Summary

Considering the increasing incidence and growing population of patients with congestive heart failure, there remains a need for effective medical treatment options, and also effective non-transplant, non-mechanical circulatory support device surgical treatment options. In an effort to solve these problems, many alternative surgical and interventional strategies to treat heart failure have been emerging and evolving. Geometric MV repair is one of these important treatment options and the growing experience with this technique has evolved to the point that the current

excellent results are being tested by a prospective randomized clinical trial [94]. The procedure is safe with operative mortality rates reported from most of the major institutions in the world under 5 %. The most recent ACORN study which included multi-institution and multi-surgeon results reported an operative mortality rate of mitral valve surgery including valve replacement with DCM patients of only 1.6 % [83]. This study also showed that mitral valve surgery was associated with an immediate improvement of QOL and a chronic reversal of LV remodeling. In addition to the benefits of eradicating MR, potential benefits of this conventional surgical therapy should be extended the other patient subgroups not previously considered for surgical intervention. Findings of a future prospective randomized control studies could make new therapeutic options available to millions of patients who suffer from congestive heart failure. It must be remembered that functional and ischemic mitral regurgitation are due to dysfunction of the ventricle and not the annulus. Hence the most effective solutions will incorporate ventricular components while maintaining valvular integrity.

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Aortic Valve Surgery in Patients with Congestive Heart Failure

10

Juan A. Crestanello

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AS	Aortic stenosis
AR	Aortic regurgitation
AVA	Aortic valve area
AVR	Aortic valve replacement
CABG	Coronary arteries bypass graft surgery
CAD	Coronary artery disease
CHF	Congestive heart failure
DST	Dobutamine stress test
ESC	European Society of Cardiology
LV	Left ventricle
LVEDD	Left ventricle end diastolic diameter
LVEF	Left ventricular ejection fraction
LVESD	Left ventricle end systolic diameter
NYHA	New York Heart Association
SV	Stroke volume

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Introduction

Congestive heart failure (CHF) is a common manifestation of aortic stenosis and aortic regurgitation [1, 2]. CHF in the setting of aortic valve disease carries a dismal prognosis. Patients with aortic stenosis (AS) and CHF have an expected survival of less than 2 years when treated medically [3]. More contemporary data demonstrated that 1-year mortality is 50 % and at 10 years 98 % of patients are death [4, 10] (Table 10.1). Patients with heart failure symptoms secondary to aortic regurgitation (AR) also have a dismal prognosis. The expected 3-year survival is only 50 % [11].

Aortic valve surgery is a well-established and reproducible procedure that is associated with low peri-procedure morbidity and mortality, symptomatic improvement, and improvement in long-term survival [1, 12]. In spite of its safety and benefits, a large proportion of patients with CHF secondary to aortic valve disorders don't have surgery. Reasons for no intervention include too advanced cardiac disease, advanced age, presence of comorbidities, and short life expectancy [2, 13]. The notion that surgery is associated with prohibitively high operative risk and no significant clinical improvement in patients with advanced heart failure secondary to aortic valve disease dissuade many practitioners to recommend aortic valve replacement (AVR). In this

J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_10

Table 10.1 Medical management of severe aortic stenosis: outcomes in patients with congestive heart failure

Baseline									Long term survival				Follow up
Author	Year	Ref	Subgroups	N	LVEF	Mean gradient	AVA	NYHA class III–IV	1 year	3 year	5 year	10 year	NYHA class III–IV
					(%)	(mmHg)	(cm^2)	(%)	(%)	(%)	(%)	(%)	(%)
Monin	2003	[4]	Contractile reserve	28	**31(23–35)**	27(22–35)	0.7(0.6–0.9)	85	70[a]	n/a	20[a]		82
			No Contractile reserve	13	**30(27–35)**	30(23–34)	0.8(0.7–0.9)	83	35[a]	n/a	12[a]		93
Varadarajan	2006	[5]	All	453	52±21	40±16	0.71±0.17	n/a	62		32	18	
			CHF	189					50		20		
			Systolic PAP ≥ 60	83					38		<20		
			LVEF ≤40 %	159					40		20		
			3–4+ mitral regurgitation	118					50		25		
Brown	2008	[6]		90	60±12	n/a	0.9±0.3	n/a	50		15	2	
Clavel	2008	[7]		57	**29±8**	21±8	0.92±0.2	47	70[a]	50[a]			
Pai	2008	[8]	Low LVEF (<35 %)	136	**24±0.8**	33±14	0.67±0.18	n/a	47	n/a	23	n/a	n/a
			Low gradient (<30 mmHg)	121	**39±19**	24±6	0.76±0.15	n/a	60	40(2 years)	22	n/a	
Tribouilloy	2009	[9]		26	**27±6**	24±6	0.74±0.18	81	35[a]		13±7	n/a	n/a
Kapadia	2015	[10]		179	51±14	43±15	0.6±0.2	93	49	11	6.4	n/a	40

[a]Data not provided. Estimated from Kaplan Meier survival curve

chapter we review the indications for surgical management and the outcomes of patients with advance heart failure symptoms (NYHA class III–IV) and left ventricular dysfunction (LVEF ≤35 %) secondary to aortic valve stenosis and regurgitation. Notwithstanding their high operative risk, most of these patients benefit form AVR. AVR improve their symptoms, cardiac function, and long-term survival compared to medical management.

Aortic Stenosis and Congestive Heart Failure

Aortic stenosis is a disease of the elderly [14, 15]. It is estimated that 2.8 % of the population older than 70 years have aortic stenosis [14, 15]. Of them, 40–60 % have class III–IV symptoms and only one third of patients with LVEF ≤35 % have AVR [2, 8, 16].

Aortic stenosis leads to left ventricular outflow obstruction and chronic pressure overload of the left ventricle. The LV hypertrophies in order to decrease wall stress. The magnitude and adequacy of that hypertrophy and the associated changes in systolic ventricular function determine the clinical presentation, hemodynamic characteristics, response to treatment, and prognosis [17–20] (Fig. 10.1). Aortic stenosis can lead to heart failure symptom by several mechanisms: (1) **Diastolic dysfunction**: it is the result of LV hypertrophy, increased wall thickness and decreased LV volume to mass ratio. LV end diastolic pressure (LVEDP) is increases from diminished compliance and not from systolic failure [21–24]. (2) **Systolic dysfunction secondary to afterload mismatch**: if the hypertrophic process is inadequate to compensate for the increased afterload, wall stress increases and the ejection fraction falls. This condition is called "afterload mismatch" and limits fiber shortening [18–21]. There are two subgroups in this category: (a) patients that preserve their stroke volume and therefore their transaortic gradients are elevated and (b) patients on whom the stroke volume diminishes and therefore the transaortic gradient is low. This last group is difficult to differentiate from the next one. (3) **Systolic dysfunction secondary to intrinsic myocardial dysfunction**: Persistently elevated wall stress, inadequate blood supply, and superimposed ischemia or infarction, myocardial fibrosis, and abnormalities of calcium handling further depress myocardial contractility. As before, these patients have diminished stroke volume and low transvalvular gradients but the benefits of surgery are less well established [20, 21]. If myocardial dysfunction is secondary to afterload mismatch, AVR is associated with good outcomes. If intrinsic myocardial dysfunction predominates, the response to AVR is less favorable with higher operative mortality and less LVEF improvement after AVR [18, 20, 25, 26]. Nevertheless their less favorable outcome with AVR, these patients have a significantly better prognosis with surgery that with medical management.

CHF Secondary to Aortic Stenosis with Normal Left Ventricular Function and Normal Stroke Volume

If the LV hypertrophy is adequate, the wall stress normalizes and the left ventricular function is maintained (Fig. 10.1) [18, 19, 21]. These patients have normal left ventricular function as evidenced by a normal stroke volume and ejection fraction. The transvalvular gradient is elevated. LVEDP is elevated secondary to decreased compliance from diastolic dysfunction and increased afterload.

They respond very well to aortic valve replacement. The surgical risk is low [1, 12]. Risk adjusted operative mortality is 2.3 % and has steadily declined over the last 10 years [1]. The operative mortality increases with the severity of the symptoms and lower LVEF [1, 12]. Patients with congestive heart failure symptoms have an operative mortality of 4.4 % vs. 1.6 % on those without [1]. Operative mortality in patients with a LVEF ≥30 % is 2.4 % vs. 5.2 % if LVEF <30 % [1].

AVR effectively relieves symptoms and improves quality of life [27]. Long-term survival is similar to that expected for an age and sex matched population for patients with normal

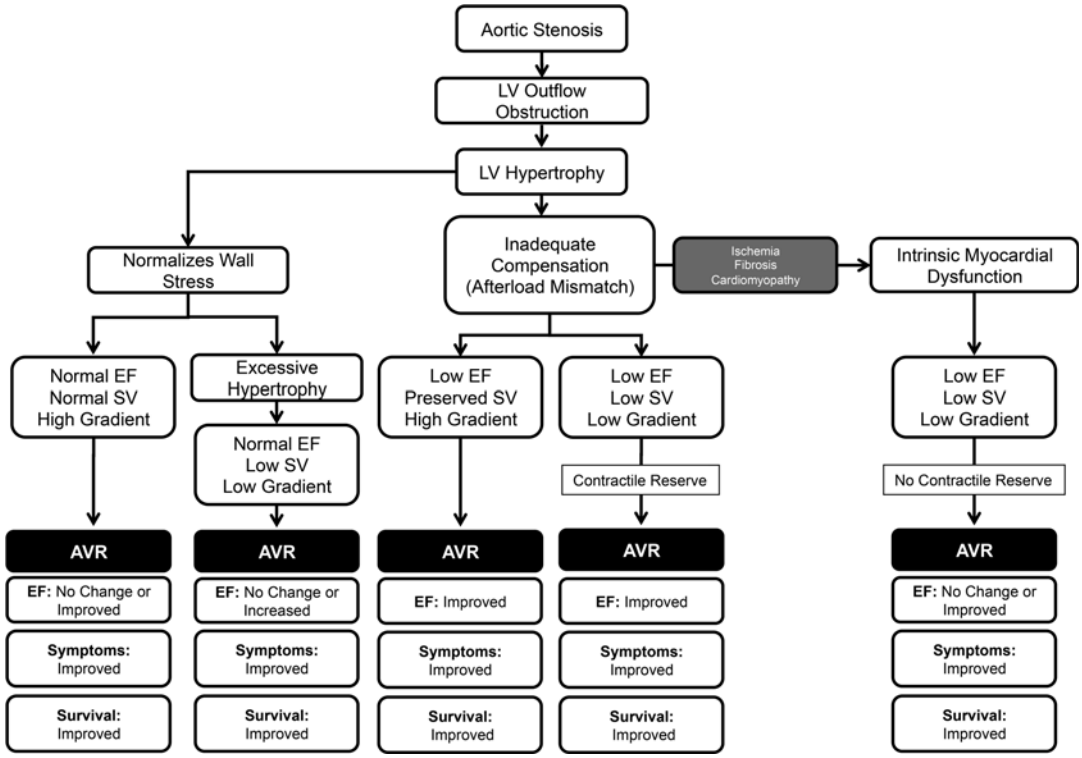

Fig. 10.1 Mechanisms responsible for heart failure in aortic stenosis and response to aortic valve replacement

LVEF, but there is an excess mortality for patients with NYHA class III–IV symptoms [27–29]. Contemporary series have demonstrated that AVR can be performed with no operative mortality and 1 and 3-year survival of 97 and 94 % respectively [30]. Mihaljevic demonstrated in 3,049 patients operated for aortic stenosis that 5-year survival for patients with no LV dysfunction was 80 %. However, for those in NYHA class III–IV, 5-year survival was 65–70 %[28]. The New York State database demonstrated that 30-month survival for patients with EF >40 % was 87.5 % and with CHF was 83.4 % [31].

AVR decreases ventricular afterload and is associated with improved LVEF, regression of LV hypertrophy, and LV mass [25, 32, 33]. Sharma described that LVEF improved by 6.8 EF points after AVR. The improvement was evident at 6 months and was maintained for up to 10 years after surgery (EF 56 ± 4 % preoperatively, 63 ± 3 % at 0–6 months, 63 ± 5 % at 7–24 months, and 63 ± 4 at 25–120 months) [34]. Some studies showed no change in LVEF after AVR in patients with normal LVEF. LV mass regression was more marked in the first 6 months after surgery and maintained for up to 10 years (181 ± 26 g/m^2 preoperative vs. 124 ± 27 g/m^2 at 6 months, 117 ± 15 g/m^2 at 24 months, and 113 ± 14 g/m^2 at 120 months after AVR) [34].

CHF Secondary to Aortic Stenosis with Normal Left Ventricular Function and Low Transvalvular Gradient (AVA ≤0.8 cm^2, EF ≥50 %, Mean Aortic Valve Gradient <40 mmHg) (Table 10.2)

These patients have more hypertrophy than the necessary to compensate for the increased afterload and wall stress (Fig. 10.1) [21]. This group represents 9–35 % of patients with severe AS and normal LVEF [8, 35–38]. They are commonly overlooked in clinical practice. Since they have preserved LVEF

Table 10.2 Severe aortic stenosis with normal left ventricular function and low transvalvular gradient: AVR vs. medical management

Preoperative									Surgery		Long term survival				Postoperative	
Author	Year	Ref	Subgroups	N	LVEF	Mean gradient	AVA	NYHA class III–IV	CABG	30 day mortality	1 year	3 year	5 year	10 year	NYHA class III–IV	LVEF
					(%)	(mmHg)	(cm^2)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Aortic valve replacement																
Hachicha	2007	[38]		80	62 ± 8	32 ± 17	0.76 ± 0.23	n/a	n/a	n/a	>95[a]	93 ± 3	>80[a]		n/a	n/a
Pai	2008	[8]		18	66 ± 7	26 ± 5	0.77 ± 0.14	n/a	66	n/a	92	88 (2 years)	88	n/a	n/a	n/a
Tarantini	2011	[36]		72	61(56–67)	33(27–39)	0.9(0.8–0.99)	35	52	2.7	90[a]		78[a]	15	18	n/a
Herrmann	2011	[37]		11	61 ± 5	33 ± 7	0.8 ± 0.2	100	n/a	18	n/a	n/a	n/a		100	Improved by 3 %
Medical management																
Hachicha	2007	[38]		91	62 ± 8	32 ± 17	0.76 ± 0.23		–	–	81[a]	58 ± 8	<40[a]			
Pai	2008	[8]		14	66 ± 7	26 ± 5	0.77 ± 0.14		–	–	82		10			
Tarantini	2011	[36]		29	60 (50–66)	33 (27–37)	0.90 (0.75–1.00)	90	–	–	80[a]		35[a]			

[a]Data not provided. Estimated from Kaplan Meier survival curve

and low transvalvular gradient, the small AVA is often attributed to calculation error [35]. The severity of their stenosis is erroneously underestimated [35]. Therefore, they are 40–50 % less likely to be referred to surgery [35, 38].

These patients are often elderly females, have severe left ventricular hypertrophy, thicker ventricles, smaller left ventricular cavities with a restrictive filling pattern (diastolic dysfunction) and intrinsic myocardial dysfunction secondary to myocardial fibrosis [8, 35, 37, 39, 40]. The low transvalvular gradient results from decreased flow across the aortic valve secondary to low stroke volume or prolonged systolic ejection period [36]. These patients are in more advanced stages of their disease and have worse prognosis than patients with normal EF and high gradient aortic stenosis [38, 39].

Symptomatically the majority of these patients are in NYHA functional class III–IV [36, 37].

Several studies have demonstrated that these patients have better survival when treated with AVR compared to medical management (Table 10.2). The operative mortality is between 2.7 % and 18 %. These patients are predisposed to low cardiac output postoperatively given their severe left ventricular hypertrophy and diastolic dysfunction, and decreased systemic arterial compliance [39]. Aggressive volume resuscitation and beta blockade is often necessary.

Pai studied 52 patients with severe aortic stenosis, EF ≥55 % and a mean transvalvular gradient <30 mmHg [8]. By propensity score matching 18 patients who had AVR were compared with 14 patients without AVR. One and 5-year survival were 92 % and 88 % in the AVR group compared with 82 % and 10 % in the non-AVR group. Series from Tarantini and Hachicha also confirmed those findings (Table 10.2) [36, 38]. LVEF an NYHA functional class improved after surgery [36].

CHF Secondary to Aortic Stenosis with Low Left Ventricular Ejection Fraction

Poor preoperative left ventricular function is the major predictor of outcomes in patients with aortic stenosis [25, 28, 29, 31].

The incidence of left ventricular dysfunction in patients with severe aortic stenosis is difficult to precise. It varies with the definition used and the population investigated. 5.4 % of patients in the Society of Thoracic Surgeons database who had isolated AVR between 1997 and 2006 had LVEF <30 % [1]. The Euro Heart Survey of Valvular Heart Disease showed that 2.9 % of the patients who underwent AVR had LVEF <30 % and 16.4 % had LVEF between 30 % and 50 % [2]. In AVR series, the incidence ranges from 12 % to 21 % depending on the LVEF threshold used [18, 41]. In a study from an echocardiography database, 26 % of patients with severe aortic stenosis had LVEF ≤35 % and 23 % had a mean transvalvular gradient ≤30 mmHg [8]. Only one third of them had AVR [8].

CHF Secondary to Aortic Stenosis with Low Left Ventricular Ejection Fraction and High Transvalvular Gradients (Table 10.3)

These patients with CHF secondary to severe AS and depressed LVEF but able to generate transaortic gradients ≥40 mmHg, benefit significantly from AVR [8, 25, 41–45] (Fig. 10.1, Table 10.3). They represent 20 % of the patients with severe AS and low LVEF [41].

Thirty-day mortality ranged from 9 % to 19.5 %. Predictors of operative mortality were preoperative myocardial infarction, coronary artery disease, and cardiomegaly.

Symptomatic improvement occurred in the majority of patients after AVR. Most patients were in functional class I or II at late follow-up. LVEF improved early after AVR and continued to improve at late follow-up [34, 44]. The improvement in LVEF was usually more pronounced than in patients with preserved LVEF and severe AS [34]. Improvement in LVEF was associated with greater AS severity as determined by smaller aortic valve area and higher mean gradients, better preoperative ejection fraction, less remodeled ventricles, and the absence of coronary artery disease or previous myocardial infarction [25, 42, 46].

Aggregated long-term survival ranged from 77 % to >90 % at 1 year and from 58 % to 71 % at 5 years. In the absence of coronary artery disease

Table 10.3 AVR for severe aortic stenosis with left ventricular dysfunction and high transvalvular gradient

Preoperative									Surgery		Long term survival				Postoperative	
Author	Year	Ref	Subgroups	N	LVEF	Mean gradient	AVA	NYHA class III–IV	CABG	30 day mortality	1 year	3 year	5 year	10 year	NYHA class III–IV	LVEF
					(%)	(mmHg)	(cm^2)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Connolly	1997	[25]		154	27 ± 6	44 ± 18	0.6 ± 0.2	88	51	9	82[a]	60[a]	58		7	39 ± 14
Powell	2000	[43]		55	22 ± 6	41 ± 14	0.5 ± 0.2	84	55	18	77 % and 33 % without and with preop MI				Increased by 22 points in 95 %	n/a
Vaquette	2005	[44]		155	25 ± 5	43 ± 13	0.6 ± 0.15	89	13	12	>90[a]		71		3	47
Matsumura	2008	[46]		90	37 ± 10	42 ± 17	0.7 ± 0.2	n/a	0	n/a	n/a	n/a	n/a	n/a	n/a	57 ± 11
Pai	2008	[8]	Low LVEF (<35 %)	58	26 ± 7	40 ± 16	0.64 ± 0.17	n/a	59	9	80	n/a	58	n/a	n/a	n/a
Flores Marin	2009	[42]		82	33 ± 6	42 ± 18	0.58 ± 0.2	84	29	19.5	80[a]		70		5	n/a
Halkos	2009	[45]	LVEF<40	119	<40	n/a	n/a	42	45	10.9	82[a]		62		n/a	n/a
			LVEF 25–40	83	n/a	n/a		n/a		14.5						
			LVEF<25	36	n/a	n/a		n/a		2.7						

[a]Data not provided. Estimated from Kaplan Meier survival curve

survival of patients with severe aortic and reduced left ventricular function with elevated gradients was similar to the expected survival of the overall population [25]. Independent predictors of long-term survival by multivariate analysis are listed in Table 10.4.

Table 10.4 Risk factors associated with early mortality, long-term survival and improvement in LVEF after aortic valve replacement for low left ventricular ejection fraction low gradient aortic stenosis

Independent risk factors associated with 30 day mortality after AVR for low LVEF-low gradient aortic stenosis					
Author	**Ref**	**Factor**	**HR or RR**	**95 CI**	**Association**
Coronary artery disease					
Powell	[43]	Previous myocardial infarction	14.9	2.4–92.1	Positive
Levy	[47]	Multivessel coronary artery disease	2.2	1.02–5.02	Positive
Connolly	[25]		4.6	1.4–15	Positive
Flores Marin	[42]		2.09	1.261–51	Positive
Tribouilloy	[9]	Concomitant CABG	9.7	1.9–49.9	Positive
Rothenburger	[48]		4.12	0.94–18.7	Positive
Myocardial dysfunction					
Tribouilloy	[9]	Mean aortic valve gradient ≤20 mmHg	10	1.2–84.9	Positive
Monin	[4]		4.7	1.1–21	Positive
Levy	[47]	Preoperative mean aortic valve gradient	0.89	0.83–0.96	Positive
Levy	[47]	Absence of contractile reserve	4.4	1.1–17.5	Positive
Monin	[4, 49]		10.9	2.6–43.4	Positive
Rothenburger	[48]	LVESD>54 mm	0.24	0.05–1.05	Positive
Vaquette	[44]	Cardiothoracic ratio ≥0.6	12.2	5.4–27.4	Positive
Flores Marin	[42]	Preoperative mitral regurgitation	2.37	1.44–80	Positive
Rothenburger	[48]	NYHA class III or IV	0.14	0.02–1.12	Positive
Comorbidities and other factors					
Halkos	[45]	Age	1.05	1.01–1.08	Positive
Flores Marin	[42]	Female gender	2.6	2.2–89	Positive
Rothenburger	[48]	Creatinine ≥1.4	11	2.34–56.82	Positive
Halkos	[45]	Emergent status	5.9	1.21–28.08	Positive
Halkos	[45]	Cardiopulmonary bypass time	1.03	1.01–1.03	Positive
Connolly	[26]	Small prosthesis	n/a		
Independent risk factors associated with long term survival after AVR for low LVEF-low gradient aortic stenosis					
Author	**Ref**	**Factor**	**HR or RR**	**95 CI**	**Association**
Aortic valve replacement					
Monin	[4]	AVR	0.3	0.17–0.53	Positive
Pai	[8]		0.5	0.3–0.87	Positive
Tribouilloy	[9]		0.16	0.12–3.16	Positive
Pereira	[54]		0.19	0.09–0.39	Positive
Coronary artery disease					
Levy	[47]	Multivessel coronary artery disease	1.85	1.05–2.72	Negative
Tribouilloy	[9]		1.3	1.08–2.07	Negative
Connolly	[25]		n/a		Negative
Pai	[8]	Concomitant CABG	n/a		Negative

Table 10.4 (continued)

Myocardial dysfunction					
Monin	[4, 49]	Contractile reserve	0.4	0.23–0.69	Positive
Levy	[47]	Preoperative mean aortic valve gradient >20 mmHg	0.95	0.91–0.99	Positive
Tribouilloy	[9]	Preoperative mean aortic valve gradient ≤20 mmHg	11.25	1.83–14.7	Negative
Connolly 97	[25]	Preoperative low cardiac output	n/a		Negative
Flores Marin	[42]	Postoperative low cardiac output	4.4	1.20–15.5	Negative
Tarantini	[83]	LVESVI ≤ 90 ml/m^2	n/a		Positive
Vaquette	[44]	Postoperative early increase in EF ≤ 10 units	0.96	0.94–0.97	Negative
Halkos	[45]	Low preoperative LVEF	0.98	0.97–1.0	Negative
Levy	[47]	Preoperative atrial fibrillation	1.75	1.07–2.85	Negative
Comorbidities					
Pereira	[54]	Age	1.05	1.02–1.07	Negative
Halkos	[45]		1.05	1.03–1.09	Negative
Vaquette	[44]		2.6	2.1–4.1	Negative
Pereira	[54]	Creatinine>1.5	1.5	(1.2–1.9)	Negative
Pai	[8]	Renal failure	n/a		Negative
Halkos	[45]	Peripheral vascular disease	1.86	1.13–3.06	Negative
Halkos	[45]	Previous stroke	1.94	1.16–3.85	Negative
Halkos	[45]	Renal failure requiring dialysis	2.95	1.13–7.75	Negative
Levy	[47]	Euroscore >10	1.13	1.04–1.25	Negative
Independent risk factors associated with LVEF improvement after AVR for low LVEF-low gradient aortic stenosis					
Author	**Ref**	**Factor**	**HR or RR**	**95 CI**	**Association**
Coronary artery disease					
Quere	[53]	Multivessel coronary artery disease	–0.2		Negative
Connoly	[25]	Less coronary artery disease	n/a		Positive
Myocardial dysfunction					
Quere	[53]	Mean aortic valve gradient ≤30 mmHg	–0.5		Negative
Vaquette	[44]	High mean aortic valve gradient	1.05	1.0–1.1	Positive
Matsumura	[46]	Preoperative LVEF	n/a		Positive
Matsumura	[46]	End systolic volume index <48 ml/m^2	n/a		Positive
Matsumura	[46]	End diastolic sphericity <0.57	n/a		Positive
Vaquette	[44]	Cardiothoracic ratio <0.6	5.95	3.0–11.6	Negative
Other					
Connolly	[26]	Female gender	n/a		Positive
Connolly	[26]	Small preoperative aortic valve area	n/a		Positive
Pereira	[54]	Preoperative syncope	n/a		Positive
Pereira	[54]	Systemic Hypertension	n/a		Negative

CHF Secondary to Aortic Stenosis with Low Left Ventricular Ejection Fraction and Low Transvalvular Gradients (Table 10.5)

These are the most challenging patients with CHF and AS. They have more advanced myocardial dysfunction secondary to (a) afterload mismatch and therefore reversible or (b) to the combination of afterload mismatch and intrinsic myocardial dysfunction that will not reverse with AVR [20, 50]. While most patients will benefit form AVR, the ones that would benefit the most are those with reversible myocardial dysfunction. The determination of contractile reserve (defined as an increase in the stroke volume ≥20 % by the infusion of low dose of dobutamine) is useful to determine the presence of reversible or irreversible myocardial dysfunction [4, 21, 49, 51, 52] (Fig. 10.2). It is believed that the myocardial dysfunction in patients with AS, low LVEF, and low transvalvular gradient (mean aortic valve gradient <40 mmHg) who have contractile reserve is primarily due to afterload mismatch and therefore reversible, while patients without contractile reserve are believe to have intrinsic myocardial dysfunction [4, 21, 49, 51, 52]. The determination of irreversible myocardial dysfunction by the absence of contractile reserve is not perfect since a large number of patients without contractile reserve will benefit from AVR [4, 9, 53].

The dobutamine challenge also helps to differentiate patients with low cardiac output and true severe aortic stenosis from those with low cardiac output and mild aortic stenosis or pseudo aortic stenosis by examining the changes in aortic valve area, stroke volume, and mean aortic valve gradient (Fig. 10.2). Patients with true severe aortic stenosis respond to the dobutamine induced increase in stroke volume with an increase in the mean gradient while the calculated aortic valve area remains low. Patients with pseudo aortic stenosis increase their aortic valve area. They do not benefit from AVR [4, 49, 51, 52].

The presence of contractile reserve has prognostic implications for patients treated either with AVR or with medical management. It predicts the operative risk as well as the long-term survival of patients with low EF low gradient aortic stenosis. Early mortality in patients with contractile reserve ranges from 5 % to 7 % while in those without ranges from 26 % to 33 % [4, 9, 52].

Long-term survival and functional status after AVR is also influenced by contractile reserve. Monin in a multicenter study demonstrated that patients with contractile reserve had improved 1-year (90 vs. 60 %) and a 5-year (74 vs. 37 %) survival after AVR compared to those without contractile reserve. In the same study, NYHA functional class improvement occurred in 84 % of patients with contractile reserve vs. in 45 % of patients without [4]. In a subsequent sub study, Quere analyzed the outcomes of patients who survived AVR and showed that contractile reserve did not influence long-term survival suggesting that the contractile reserve is only a primary determinant of surgical risk [53].

In spite of the high operative mortality and limited long-term survival associated with AVR in patients without contractile reserve, AVR significantly improve their prognosis compared to medical management. Monin demonstrated that 1 and 5-year survival with or without contractile reserve was better for patients treated with AVR than for patients who received medical therapy (Tables 10.1 and 10.5) [4].

Tribouilloy demonstrated on 81 patients with low-flow/low-gradient AS without contractile reserve that AVR was associated with lower 1-year (75 vs. 35 %) and 5-year (54 vs. 13 %) mortality than medical therapy. In addition only 9 % of the AVR patients had heart failure symptoms at follow-up compared with 81 % of the medically managed patients [9].

Clavel (2003) demonstrated in the same group of patients that AVR was only associated with improved overall survival compared with medical management in the subset of patients with more severe stenosis (AVA <1.0 cm^2). This lack of improvement was likely due to the high operative mortality (18 %) [7]. Once operative mortality was excluded, patients who survived AVR had excellent late survival compared with patients treated medically (70 vs. 50 %) (Table 10.5) [7].

Early postoperative improvement in ejection fraction is associated with improved long-term survival and functional status [53, 55]. Connolly

Table 10.5 AVR for severe aortic stenosis with left ventricular dysfunction and low transvalvular gradient

Preoperative									Surgery		Long term survival				Postoperative	
Author	Year	Ref	Subgroups	N	LVEF	Mean gradient	AVA	NYHA class III–IV	CABG	30 day mortality	1 year	3 year	5 year	10 year	NYHA class III–IV	LVEF
					(%)	(mmHg)	(cm^2)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Brogan	1993	[17]		18	n/a	≤30	≤0.4 cm^2/m^2	100		33.0	n/a	n/a	n/a	n/a	11	n/a
Connolly	2000	[26]		52	26±8	23±3	0.7±0.2	85	62	21.0	65[a]	62	38[a]		23	32±14
Pereira	2002	[54]		68	22±6	25±4	0.6±0.1	65	60	8.0	82±6		78±7 (4 years)		18	30±12
Rothenburger	2003	[48]		35	25±4	26±6	0.6±0.18	90	(14 pts)	17.1	72	68 (2 years)	64		24	40±5
Monin	2003	[4]	All	95	30 (24–35)	29(23–34)	0.7(0.6–0.8)	80	30	14.0		79			30	n/a
		[4]	Contractile Reserve	64	31(23–35)	7(22–35)	0.7(0.6–0.9)	85	30	5	90		74	n/a	16	n/a
		[4]	No Contractile Reserve	31	30(27–37)	30(23–34)	0.8(0.7–0.9)	83	6	32	65		37	n/a	55	n/a
Tarantini	2003	[83]		52	28±7	29±6	0.57±0.2	n/a	31	8.0	95[a]		89[a]		Improvement in 85 %	43±10
Chukwuemeka	2006	[18]		60	26±4	27±19	0.76±0.37	93	25	3.3	93		77	48		
Quere	2006	[53]	All	66	29±6	31±6	0.68±0.16	89							9	47±11
		[53]	Contractile reserve	46	28±6	31±7	0.65±0.16	89		6			90±5			47±11
		[53]	No contractile reserve	20	31±6	32±6	0.74±0.13	90		33			92±7			48±11
Kulik	2006	[41]		79	<40 % in 72 %	29±7	0.8±0.2	53	62	7.5	97±2		83±5	72±8	16	
Clavel	2008	[7]		44	29±11	26±8	0.9±0.2	52	68	18.0	75[a]	70[a]				Improvement >10 %
Levy	2008	[47]		217	28±6	25±5	0.7±0.2	83	34	16.0	80[a]		49±4		16	41±13
Pai	2008	[8]	Low gradient (<30 mmHg)	47	45±20	25±4	0.76±0.15	n/a	n/a	n/a	89	82 (2 years)	80			
Tribouilloy	2009	[9]		55	27±7	29±7	0.74±0.15	29	27	22.0	75[a]		54±7		9	46±10

[a]Data not provided. Estimated from Kaplan Meier survival curve

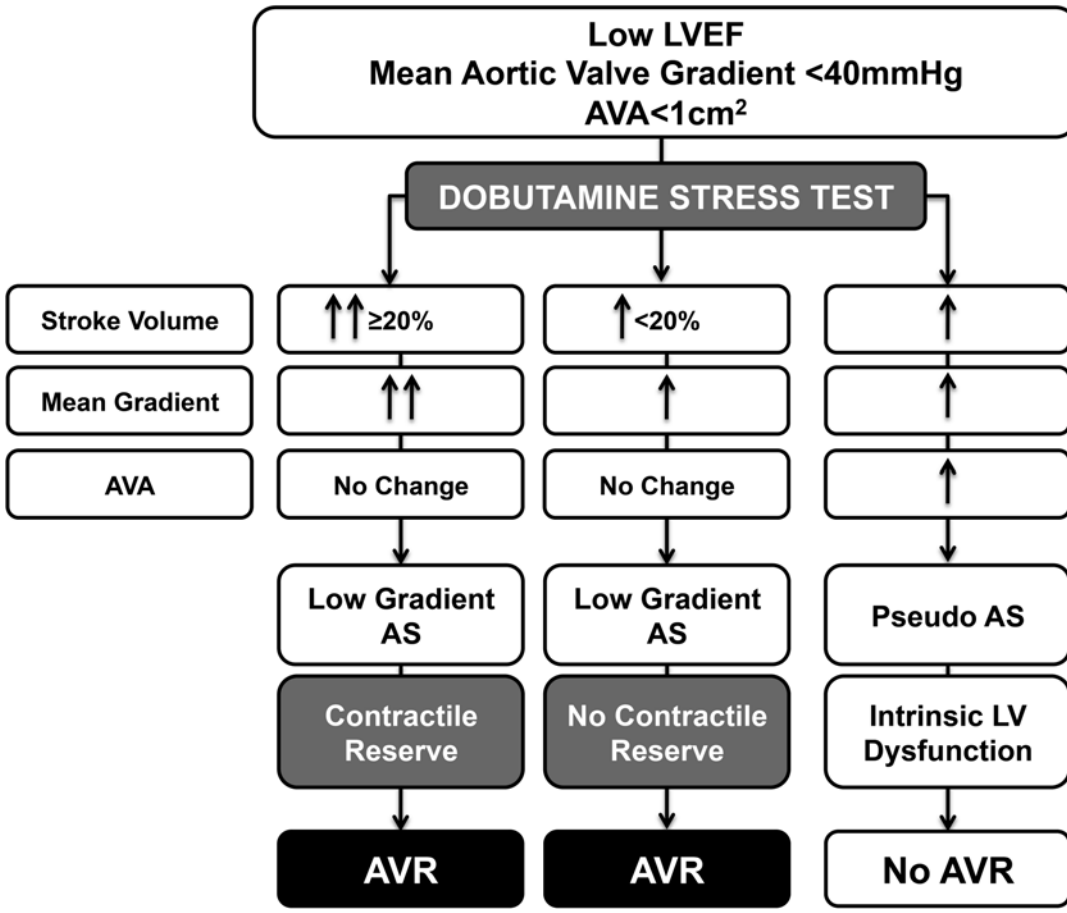

Fig. 10.2 Dobutamine stress test for the determination of contractile reserve and aortic stenosis severity

demonstrated that LVEF improved in 74 % of the survivors. The mean improvement was an increase of 10 ± 14 EF units. Positive change in LVEF was associated with female sex and smaller preoperative aortic valve area [26]. Those who did not improve probably had intrinsic myocardial dysfunction from previous myocardial infarction or myocardial fibrosis (see above).

Quarre demonstrated that LVEF improvement can be observed in patients without contractile reserve after AVR [53]. 83 % of patients with and 65 % of the patients without contractile reserve obtained ≥10 % improvement in LVEF after AVR. The magnitude of the improvement was similar regardless the presence of contractile reserve. Contractile reserve was not a predictor of improvement in LVEF after AVR. Therefore absence of contractile reserve does not always predict irreversible myocardial dysfunction. Higher preoperative mean aortic valve gradient and absence of multivessel coronary artery disease were associated with improvement in LVEF after AVR [53].

Predictors of Outcomes

Since contractile reserve alone does not accurately predict long-term outcomes in severe aortic stenosis with low LVEF and low transvalvular gradients, other factors should be considered to risk stratify patients before AVR [53]. Several studies have identified independent predictors of early mortality, long-term survival and improvement in LVEF and functional class (Table 10.4).

Predictors of 30-day mortality include coronary artery disease (CAD) (as defined by previous MI, multivessel CAD, and concomitant CABG), which likely indicates the presence of intrinsic and probably irreversible myocardial dysfunction secondary to fibrosis or myocardial infarction [9, 25, 42, 43, 47, 48]. In addition, concomitant CABG increases the operative time and complexity of the surgery. Surrogates for more advanced left ventricular dysfunction are low mean transaortic gradients, absence of contractile reserve, and dilated left ventricle [4, 9, 42, 44, 47–49]. The increased mortality with small prosthesis size may be the result of high residual aortic valve gradient and incomplete relieve of the LV outflow obstruction [26]. Patients with LV dysfunction tolerate poorly residual aortic gradient and patient prosthesis mismatch since they are highly sensitive to increased afterload [26, 41, 56, 57]. Patient prosthesis mismatch results in decreased survival, lower freedom from heart failure, and incomplete left ventricular mass regression [41, 57]. Patient prosthesis mismatch should be avoided by implanting prosthesis with superior hemodynamic performance and considering the prosthetic effective orifice area indexed to body surface area at the time of AVR. Some have advocated the use of stentless valves [58]. Percutaneous aortic valves may have an advantage in this group since they have better hemodynamic performance with larger postoperative aortic valve area and lower transvalvular gradient than surgically placed valves [41, 59].

Other factors associated with early mortality are common predictors of increased surgical risk (age, presence of comorbidities, advanced functional status, emergency surgery, and female gender) (Table 10.4).

Aortic valve replacement is the main factor associated with long-term survival, LVEF improvement, and improved functional status in patients with low LVEF and low gradient aortic stenosis [4, 8, 9, 54]. This reinforces the notion that even risky, AVR provides a significant survival advantage to these patient compared to medical management alone.

Other factor negatively associated with long-term survival was presence of coronary artery disease [8, 9, 25, 47]. As in early mortality, CAD indicates intrinsic myocardial dysfunction. Factors associated with ventricular dysfunction (contractile reserve, low preoperative mean gradient, pre and postoperative low cardiac output, remodeled ventricles, and atrial fibrillation) also negatively affected long-term survival [4, 9, 25, 36, 42, 44, 45, 47, 49]. Early improvement in LVEF [44] predicted long-term survival indicating that most of myocardial dysfunction was reversible secondary to afterload mismatch. Advance age, comorbidities, and elevated EuroSCORE also predicted decreased survival [8, 44, 45, 47, 54].

Improvement in LVEF was associated with similar factor as those that predict early and late survival [25, 43, 44, 46, 53, 54]. Coronary artery disease, myocardial dysfunction, less ventricular remodeling. In addition the presence of systemic hypertension was negatively associated with improvement in LVEF. It was presumed that systemic hypertension was associated with myocardial fibrosis.

The only independent factor associated with improved functional status at late follow-up was the early improvement in LVEF >10 ejection fraction units [44].

Many of the variables associated with adverse outcomes are similar to those associated with adverse outcomes in the general population of aortic stenosis patients. Hannan identified age >60 years, LVEF <50 %, CHF, myocardial infarction less than 24 h before surgery, lower body surface area, previous cardiac operation, and several comorbidities as independent predictors of 30 day mortality [31]. Factors associated with increased long-term mortality were concomitant CABG, age >60, small body surface area, emergency status, and comorbidities [31]. Mihaljevic identified the following risk factors as associated with early death: older age, LV dilatation, and smaller prosthetic size. Risk factors for late death were older age, greater degree of aortic stenosis, greater LV mass index, smaller prosthetic size, LV dysfunction, and advanced symptoms. Risk factors associated with advanced symptoms include calcific aortic stenosis and severe LV dysfunction [28].

Emerging Therapies for Aortic Stenosis: Role of TAVR and Percutaneous Valvuloplasty

Transcatheter Aortic Valve Replacement (TAVR)

Transcatheter aortic valve replacement (TAVR): has become an alternative to surgical AVR for high surgical risk or inoperable patients with aortic stenosis [10, 59]. AVR for patients with severe aortic stenosis with low ejection fraction and low gradient is associated with significant operative mortality and morbidity (Table 10.5). It is expected that TAVR would decrease operative mortality due to the less invasive nature of the procedure and the avoidance of cardiopulmonary bypass. Clavel compared TAVR to AVR in this group of patients [60]. Mean LVEF was 34 ± 10 %. Aortic valve area was 0.72 ± 0.17 cm^2 in AVR and 0.64 ± 0.18 cm^2 in the TAVR group. Mean aortic valve gradient was 36 ± 14 mmHg. Operative mortality was higher in the TAVR group (19 vs. 12 %) partially related to the high-risk profile in this group. TAVR was also associated with a better improvement in aortic valve area and transvalvular gradient compared to AVR and with a lower incidence of patient prosthesis mismatch. As a consequence, TAVR patients had a faster and more complete recovery of their LVEF. At 1 year follow-up 58 % of the TAVR patients had normalized their LVEF compared with 28 % of the AVR patients. Unbenhaum reported transapical aortic vale replacement in 21 patients with advanced heart failure and severe ventricular dysfunction (LVEF 20 ± 5 %) secondary to aortic stenosis (AVA 0.8 ± 0.3 cm^2, mean gradient 33 ± 13 mmHg) [61]. Operative mortality was 4.8 %. One and 2-year survival was 76 and 62 %. There was early improvement of LVEF to 38 ± 11 %. This study demonstrates the feasibility of treating patients with low gradient low EF aortic stenosis with a percutaneous transapical approach. TAVR may be an alternative to AVR in these high-risk patients as long as 30-day mortality is lower than AVR.

Percutaneous Aortic Valvuloplasty

Percutaneous aortic valvuloplasty is an alternative for patients with severe acquired aortic stenosis and LV dysfunction who are not candidates for surgery. Percutaneous aortic valvuloplasty was associated with temporary reduction of transvalvular gradients (from 55 to 29 mmHg), increase in the aortic valve area (mean increase 0.3 cm^2), improvement in left ventricular performance, and symptomatic improvement [62]. However, it had several disadvantages: (1) it was associated with a 25 % risk of complications, (2) the improvement was short lived with recurrence of the symptoms within a few months and (3) there was no survival benefit [63–66]. With the advent of transcatheter aortic valve replacement, aortic valvuloplasty has reemerged as a procedure for the treatment of aortic stenosis [67]. It is usually utilized in patients with congestive heart failure or cardiogenic shock to stabilize them and bridge them to TAVR or to a high-risk aortic valve replacement [66, 67].

Aortic Regurgitation and CHF

Aortic insufficiency leads to both pressure and volume overload on the left ventricle [18, 21, 68]. Volume overload (increased preload) results from the diastolic regurgitant volume. Increased afterload is the result of the increased aortic stroke volume (regurgitant volume plus forward stroke volume) that leads to systolic arterial hypertension. The increase in wall stress leads to compensatory LV dilatation and eccentric hypertrophy. These changes decrease wall stress and preserve ejection fraction. Progressive LV dilatation overcomes those compensatory mechanisms leading to myocardial dysfunction and decreased EF. At this point, LV function will improve after AVR. Persistent regurgitation and further increase in wall stress lead to further systolic dysfunction secondary to ischemia and myocardial fibrosis [68, 69]. At this stage, when the ventricle is severely dilated, intrinsic myocardial dysfunction becomes the predominant mechanism responsible for LV dysfunction and AVR is less likely to improve LV function. However, even without LVEF improvement, AVR will improve loading conditions and facilitate CHF management [21].

Congestive heart failure secondary to severe aortic regurgitation (AR) has several

commonalities with the one secondary to severe aortic stenosis. It is common, its medical management results in poor outcomes, and it is undertreated.

In the Euro Heart Survey, AR was the third most common valve pathology after aortic stenosis and mitral regurgitation. Only one third of those patients were treated surgically. That proportion is even lower in patients with left ventricular dysfunction: only 22 % of patients with LVEF between 30 % and 50 % and 3 % of patients with LVEF <30 % had AVR [2, 11, 70].

In the STS database, 47 % of isolated AVR patients had some degree of AR. Fifty-two percent were in NYHA class III–IV. However, only 5 % had LVEF <30 % [1].

Twenty percent of patients with severe AR from and echocardiography database have LVEF ≤35 % [11]. In other series, they represent 11 % of patients who received AVR [18].

The natural history of asymptomatic severe AR with normal LVEF and normal ventricular dimensions is benign [21, 68, 72, 73]. However, once congestive heart failure, ventricular dilatation, or LV dysfunction develops, the prognosis of medically treated patients is poor. Survival ranges from 20 % to 50 % at 5 years and the majority of patients are in NYHA class III–IV [11, 68, 74, 75]. Thus, surgery is recommended when (a) patients become symptomatic (ACC-AHA guidelines class I and ESC guidelines class IB), (b) the LVEF is ≤50 % independently of symptoms (ACC-AHA guidelines class I and ESC class IB) or (c) the LV dilates (LVEDD >75 mm or LVESD >55 mm,ACC-AHA guidelines class IIa) [21, 75]. The ESC guidelines recommends surgery with lesser degree of LV dilatation (LVEDD >70 mm or LVESD >50 mm, class IIaC) [75].

The surgical outcomes of patients with advanced CHF (NYHA class III–IV) and severe LV dysfunction (LVEF ≤35 %) secondary to chronic AR has only been studied in a few series (Table 10.6).

The operative mortality in this group was high (Table 10.6). Operative mortality was four time higher in low ejection fraction patients than in patients with normal EF (14 vs. 3.7 %) [78]. Concomitant procedures and advanced NYHA class increased operative mortality [78]. Klodas demonstrated that patients in NYHA class III–IV had a six time higher operative mortality (7.8 vs. 1.2 %) [77].

Aortic valve replacement improves long-term survival compared to medical management. One-year survival ranged from 80 % to 99 %. Five-year survival ranged from 60 % to 80 %. The only study that compared medical management with AVR showed that AVR improved 1-year survival from 65 % to 88 % and 5-year survival from 37 % to 70 % (Table 10.6) [11]. After adjusting for baseline variables AVR was associated with a significantly lower hazard of mortality (HR 0.59, 95 % CI 0.42–0.98, $P<0.04$) [11].

Other independent predictors of long-term survival were preoperative LVEF, NYHA class, and age [78]. Five year survival for patients with LVEF <35 % was 60 % compared with 85 % for patients with normal EF. This survival, although better than with medical management, was 65 % lower than the expected survival of an age and sex matched population [78]. This suggests that AVR does not completely reverse the myocardial dysfunction induced by long-standing AR.

Other factor associated with poor long-term survival was dilated left ventricle as identified by indexed LV dimensions. Patients with LVESDi ≥20 mm/m^2 and LVEDDi ≥30 mm/m^2 had worse long-term survival independently of their preoperative LVEF and NYHA functional class [79]. Previous studies have shown that extreme LV dilatation (LVEDD≥80 mm) did not prevent improvement in LV function after AVR [80].

Even patient with extremely reduced LVEF (LVEF <20 %) achieved a survival advantage with AVR compared to medical management [11]. Severe pulmonary hypertension (systolic pulmonary pressure >60 mmHg) and functional mitral regurgitation adversely affect long-term survival [75, 81]. AVR and mitral valve repair were also associated with a better survival than medical management [75, 81].

AVR result in symptomatic improvement. The majority of patients remain free of CHF symptoms after AVR [48, 78].

Similarly to aortic stenosis the impairment in LVEF in AR is related to a combination of (a)

Table 10.6 AVR for severe aortic regurgitation with left ventricular dysfunction

Preoperative									Surgery		Long term survival				Postoperative	
Author	Year	Ref	Subgroups	N	LVEF	LVEDD	LVESD	NYHA class III–IV	CABG	30 day mortality	1 year	3 year	5 year	10 year	NYHA class III–IV	LVEF
					(%)	(cm)	(cm)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Klodas	1997	[77]		128	49 ± 14	n/a	n/a	100	32	7.8			72 ± 4	45 ± 4		
Chaliki	2002	[78]	Low LVEF	43	**28 ± 5**	7.4 ± 0.8	4.1 ± 0.7	58		14	80[a]		60[a]	41 ± 9	25 ± 9	34 ± 14
			Moderate LVEF	134	43 ± 5	7.0 ± 0.8	6.5 ± 0.9	49		6.7	90[a]		78[a]	56 ± 5	17 ± 4	47 ± 12
			Normal LVEF	273	59 ± 6	5.3 ± 0.7	4.2 ± 0.8	29		3.5	95[a]		85[a]	70 ± 3	9 ± 2	56 ± 10
Rothenburger	2003	[48]		20	**24 ± 6**	6.7 ± 0.8	5.6 ± 0.3	90	70	0	94	86 (2 years)	74		45	40 ± 5
Chukwuemeka	2006	[18]		132	**28 ± 6**	6.6 ± 0.9	5.2 ± 0.8	72	18	1.4	99		81	61		
Kamath	2009	[11]		53	**27 ± 6**	7.0 ± 1.0	5.7 ± 1.2	62	32	4	88		70			
Kandhar	2009	[75]		32	53 ± 16	6.3 ± 1.0	4.3 ± 1.3	87	n/a	n/a	90		62			
Sionis	2010	[74]		26	**36 ± 4**	6.9 ± 9	5	100		0	92				12	45

[a]Data not provided. Estimated from Kaplan Meier survival curve

afterload mismatch and (b) intrinsic myocardial dysfunction. LVEF improvement after AVR will depend of the relative contribution of each mechanism. AVR resulted in LVEF improvement in the majority of patients with severe LV dysfunction [78, 79]. The improvement is more pronounced in patients with lower preoperative EF [78, 79]. The time course of LVEF improvement show a modest initial decrement in EF followed by a gradual improvement over the course of the next 6 months [69, 79]. Late improvement in LVEF was associated with the presence of early LV reverse remodeling defined as a 10 % reduction in LVEDD [69]. LVEF decreased significantly late after AVR in patients with no early LV reverse remodeling. Preoperative LV stroke volume >97 ml was the best independent predictor of early reverse remodeling [69].

Heart transplantation and mechanical circulatory support should be considered as an alternative treatment in this group of patients [82]. However, in spite of the high operative mortality most patients with congestive heart failure secondary to severe AR with severely reduced LVEF greatly benefit from AVR [78]. Most patients achieved lasting symptomatic improvement and improvement in their ejection fraction. Long-term survival is better than the one after heart transplantation without the side effects and complications of immunosuppression and rejection.

Conclusions

Patients with aortic valve disorders and associated left ventricular dysfunction usually present with congestive heart failure. Their prognosis with medical management is extremely poor. Aortic valve replacement, although risky is associated with improved long-term survival, improved ventricular function, and functional class compared to medical management. The decision to perform aortic valve surgery in these patients is challenging. Associated comorbidities, frailty and other factors may limit their life expectancy in addition to the cardiac disease [2, 84]. These factors should be carefully considered to risk stratify and guide the decision to perform surgery. The use of risk calculators (EuroSCORE and STS risk calculator) is a helpful tool to guide therapy [85, 86]. However, they may over or underestimate the risk [87]. Surgery should be considered on those patients whose life expectancy is not limited by their comorbidities or frailty. Transcatheter aortic valve implantation may benefit these patients if their use results in lower procedural mortality than surgery.

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Left Ventricular Assist Devices for Long-Term Circulatory Support

11

Abbasali S. Badami and Shahab A. Akhter

Introduction

Left ventricular assist devices (LVADs) have become an increasingly utilized therapy for advanced heart failure (HF) due to recent innovations in technology, which have led to significantly improved outcomes. With a rapidly aging population in the United States and industrialized world, it is expected that the prevalence and incidence of HF will continue to increase. It is estimated that there are currently between 110,000 and 280,000 adults in the United States alone with NYHA Class IIIB and Class IV HF that could potentially be candidates for LVAD therapy [1]. Currently, <5000 LVAD implants are being performed annually in the US so it appears that this therapy is significantly underutilized.

The indications for LVAD support have evolved over time with increasing experience and improved durability of implantable devices. The most common indication for long-term mechanical circulatory support (MCS) is bridge to transplantation (BTT). Commonly, these patients deteriorate or develop cardiogenic shock while on the heart transplant waiting list. Historically, 20–30 % of patients who underwent LVAD implant for BTT did not survive to transplant. Over the past decade, this mortality has been reduced significantly with the use of the new generation of continuous-flow devices [2]. There is an estimated 10–15 % mortality in patients on the waiting list for transplant who are not supported by an LVAD [3]. It is unclear how many of these deaths could be prevented by MCS, but it is likely a significant number. The recent changes in UNOS guidelines for organ sharing to prioritize use of donors for primarily status 1A patients has had a substantial impact on the use of LVADs as BTT [4]. Patients who are status 1B are now much less likely to be transplanted and status two patients rarely receive a suitable donor organ. These changes have shifted the number of patients undergoing transplant who are supported with an LVAD to approximately 40–50 % [5].

There are few alternative strategies for patients with end-stage HF. Several studies have shown that outcomes with VADs are significantly better than with intravenous inotropes [6]. A cohort of patients followed as a contemporary control group that declined LVAD implant in the INTREPID trial had a 20 % survival at 1 year [7]. Given that there are many variables which determine length of time on the waiting list prior

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_11

to transplant such as blood type, body size, and sensitization, use of intravenous inotropes as a bridging strategy is unpredictable and can lead to poor outcomes. The success in terms of improved survival, reduced adverse events, and greatly enhanced device durability reported with the new generation of continuous-flow LVADs compared with the poor survival reported with the use of outpatient continuous inotrope therapy has nearly eliminated use of intravenous inotropes as an alternative to LVADS.

Current Devices for Long-Term Mechanical Circulatory Support

Pulsatile Devices

Implantable pulsatile VADs were developed in the 1970s and 1980s and the technology was designed to essentially replace ventricular function by having a stroke volume, heart rate, and cardiac output that was similar to the native heart. The design of these devices necessitated larger size both for LVADs and total artificial heart (TAH) and this required a more extensive operation for implantation. Given the significant number of mobile parts, long-term durability was also limited by mechanical wear over time. Despite these limitations, many patients have been supported for extended periods of time and these devices remain in use today for selected patients. The HeartMate XVE LVAD (Thoratec Corp., Pleasanton CA) was the first implantable device approved for both BTT and DT and has been used worldwide (Fig. 11.1) [8]. The landmark REMATCH trial showed a significant survival and quality of life benefit with the HeartMate XVE versus optimal medical therapy [9]. The XVE is an electrically powered pusher-plate device that is implanted in the left upper quadrant of the abdomen and pumps blood from the left ventricle to the ascending aorta. The pump housing is made of a titanium alloy and a flexible polyurethane diaphragm separates the internal blood and motor chambers. Porcine valves in the inlet and outflow conduits direct blood flow through the pump and prevent regurgitant flow. The XVE LVAD has a stroke volume of 83 mL and pumps at a rate of 50–120 times per minute. A constant rate can be set in fixed mode, or the auto mode can be selected so the device pumps with each full stroke volume and can allow for changes in physiological demand. Portable batteries can power the device and the patient also wears a microprocessor system controller during ambulatory operation. A unique feature of the HeartMate XVE is its textured blood-contacting surfaces which create a non-thrombogenic cellular lining [10]. The titanium surfaces are textured by the sintering of titanium microspheres, and the diaphragm is textured by the extrusion of polyurethane fibrils. This nonthrombogenic surface eliminates the need for anti-coagulation with warfarin and only aspirin is recommended. The size and limited long-term durability of this device (18 months) have led to minimal use as there

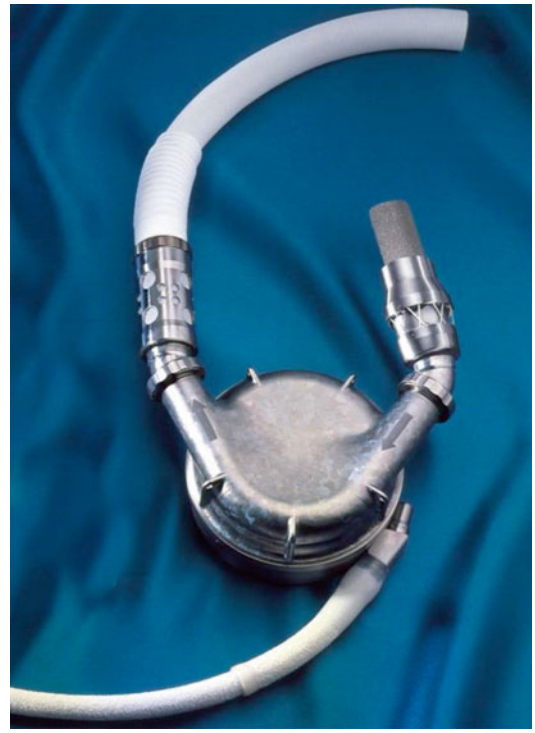

Fig. 11.1 HeartMate XVE left ventricular assist device (Permission from Thoratec Corporation)

has been a transition in the field to the use of continuous-flow pumps.

The Thoratec VAD (Thoratec Corp) is a pneumatically powered device that is available in paracorporeal (PVAD) and intracorporeal (IVAD) versions (Figs. 11.2 and 11.3). Both devices can be utilized for uni- or bi-ventricular support. There is a hospital-based external pneumatic drive console and a portable pneumatic driver allows ambulatory outpatient support. These devices are implanted as BTT or for bridge to recovery (BTR) and received FDA approval for the BTT indication in 1995. The Thoratec device is the primary VAD used for biventricular support and does not have the size limitation associated with the Syncardia TAH. In addition, this system allows for explant in the case of myocardial recovery. The Thoratec VAD has a 65 mL stroke volume with a polyurethane blood pumping chamber and two mechanical valves. It produces a clinical beat range of 40–110 beats per minute and a flow rate of 1.3–7.2 L/min. The PVAD is positioned paracorporeally on the anterior abdominal wall and can be used in patients with a BSA of >0.75 m^2. For an LVAD, the left ventricular apex is most commonly used for inflow and outflow is to the ascending aorta. For an RVAD configuration, drainage is typically from the right atrium and outflow is to the main pulmonary artery. For the IVAD, the device has a titanium housing and can be implanted either in a preperitoneal pocket or intraperitoneal location.

Fig. 11.2 Thoratec paracorporeal ventricular assist device (PVAD) (Permission from Thoratec Corporation)

Fig. 11.3 Thoratec intracorporeal ventricular assist device (IVAD) (Permission from Thoratec Corporation)

The SynCardia Cardio West (SynCardia Systems, Inc., Tucson, AZ) total artificial heart (TAH) (Fig. 11.4) was under development since the 1960s and the first successful implant of a TAH was performed in 1985 as BTT [11]. The SynCardia TAH is a biventricular, pneumatic pulsatile pump that replaces the native ventricles and all valves. The complete displacement of the ventricles produces a stroke volume of 70 mL per beat with a cardiac output of 7–8 L/min. The ventricles are placed in orthotopic position after suturing polyurethane inflow connectors to the right and left atrial cuffs of the patient. Dacron outflow conduits are snapped onto the mounts of the TAH ventricles after completion of the anastomoses to the great vessels. The percutaneous driveline connects to the external console that contains the pneumatic drivers. A portable driver now potentially allows patients to be discharged from the hospital. Due to the size of the device and because it is fully implanted within the pericardial cavity, careful patient selection is necessary to avoid size mis-

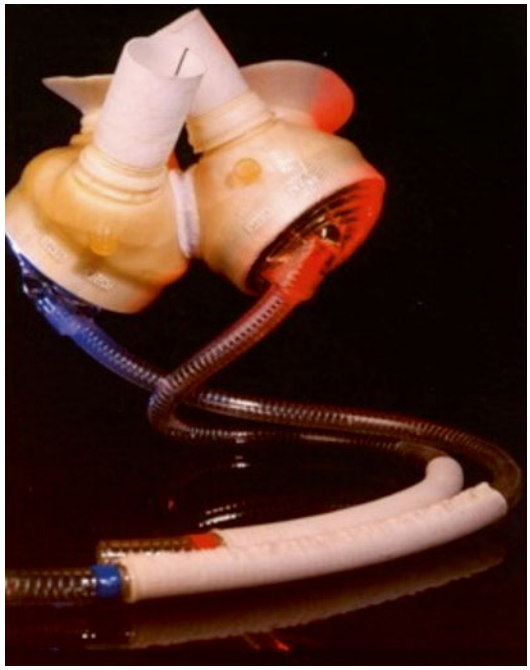

Fig. 11.4 Syncardia Cardio West total artificial heart (TAH) (Permission from Syncardia)

Fig. 11.5 HeartMate II left ventricular assist device (Permission from Thoratec Corporation)

match and potential compression of the inferior vena cava or left superior pulmonary vein. Selection criteria include: left ventricular end-diastolic diameter >70 mm, cardiothoracic ratio >0.5, computed tomography scan volume >1500 mL, and antero-posterior chest diameter (from sternum to spine) >10 cm.

Continuous-Flow Left Ventricular Assist Devices

There has been a major shift to the use of continuous-flow LVADs since 2008 when the HeartMate II device was approved for the BTT indication by the United States FDA. Axial and centrifugal flow LVADs are much smaller, lighter, and more durable than the previous generation of volume displacement, pulsatile pumps (Fig. 11.5). The HeartMate II (Thoratec Corp) is an implantable axial flow LVAD that is indicated for long-term support as BTT or DT in patients with end-stage HF. This has been the most widely used implantable LVAD in recent years. The pump is typically placed in a pre-peritoneal pocket created inferior to the diaphragm, with the inflow cannula inserted at the left ventricular apex and the outflow graft anastomosed to the ascending aorta. A percutaneous driveline from the pump exits the right or the left upper quadrant of the abdomen. Other components include a microprocessor-based system controller, which is worn or carried by the patient, and controls and monitors the function of the pump. The HeartMate II can provide up to 10 L/min of flow with an operating speed range of 6000–15,000 rpm although speeds are rarely set above 10,000 rpm. Power is provided by both AC and DC power sources with portable batteries for ambulatory operation. The system monitor displays the pump speed, flow, pulsatility index (PI), and power. The monitor can be queried for device parameter history and changes in pump speed are made from this component. The HeartMate II axial flow rotary pump contains a magnet that is rotated by the electromotive force generated by the motor. Rotation of the rotor provides the force to propel

blood from the left ventricle through the pump and into the ascending aorta. Pump flow depends on the rotational speed of the rotor and the pressure difference between the inlet and outlet of the pump. The device is very sensitive to afterload and hypertension must be managed appropriately. The internal pump surfaces including the rotor, inlet and outlet stators, have a smooth polished titanium surface. The inflow and outflow conduits have a textured titanium microsphere surface similar to the HeartMate XVE. These surfaces are designed to minimize thrombus development and anticoagulation is recommended for all patients with aspirin and warfarin. The BTT clinical trial for this device demonstrated a 68 % survival rate at 1 year in the initial study cohort and this has continued to improve in subsequent studies [3]. Recent institutional series have reported 1 year survival of >80 % [12]. The HeartMate II DT trial was a 2:1 randomized comparison with the HeartMate XVE LVAD in 200 patients [13]. There were 134 in the HeartMate II group and 66 in the XVE group. The actuarial survival rates of 68 % at 1 year and 58 % at 2 years were a significant improvement over the HeartMate XVE at 55 % and 24 % respectively.

The HeartWare Ventricular Assist Device (HVAD) (HeartWare, Inc., Framingham, MA) is a centrifugal flow pump that is implanted in the pericardial space at the apex of the left ventricle (Fig. 11.6). The HVAD was designed for use as a long-term implantable device. A short integrated inflow cannula and the small size of the pump allow for the intra-pericardial placement without the need for developing a pump pocket. The HeartWare system consists of the HVAD pump, controller with rechargeable batteries, and the system monitor. The HVAD pump incorporates an integrated inflow cannula, a 10 mm gel-impregnated polyester outflow graft with strain relief, a percutaneous driveline, and an apical sewing ring. The strain relief prevents kinking of the outflow graft. The HVAD has a displaced volume of 50 mL and weighs 140 g. The pump can generate a flow of 10 L/min and has a pump speed operating range of 1800–4000 rpm. The impeller has integrated rotor magnets and uses a passive, noncontacting suspension system for rotation of the impeller [14]. A hermetically sealed electric motor within the pump housing generates electromagnetic fields to move the impeller with dual motor stators to create laminar flow. The frictionless movement of the impeller eliminates heat generation and wear of the components which greatly increases durability. The short integrated inflow cannula is inserted into the left ventricle, and the outflow graft connects the HVAD pump to the ascending aorta via an end-to-side anastomosis. A sewing ring secures the pump to the left ventricle. The HVAD has also been used in isolated cases as an implantable bi-VAD with separate pumps being implanted for right and left ventricular support [15]. The HVAD has been approved by the U.S. Food and Drug administration for BTT in 2013 [16] and is currently undergoing clinical trials for DT. Initial clinical experience and reports have indicated that long-term support with this device has been safe and effective with a 1 year survival rate of 86 % in a BTT population [17]. The BTT clinical trial data that was recently published demonstrated overall non-inferiority versus contemporaneously implanted, commercially available VADs at 180 days [18]. Kaplan-Meier survival at 1 year was 86 % compared to 85 % in the control group.

Fig. 11.6 Heartware HVAD (Permission from Heartware Corporation)

Timing of MCS for End-Stage Heart Failure

Continued improvement in LVAD technology and clinical outcomes has made this option available to more patients with advanced heart failure. The current generation of continuous-flow devices has significantly decreased the incidence of perioperative and long-term complications including bleeding, adverse neurological events, infection, right heart failure, arrhythmias, and rate of hospital re-admission relative to the previous generation of pulsatile, volume displacement pumps [19]. In addition, the durability of these continuous-flow devices is far superior to the pulsatile devices with patients having been supported for up to 7 years without any device-related issues. The timing of LVAD implantation is critical to both short and long-term outcomes. The majority of patients being referred for MCS continue to be hospitalized for decompensated heart failure and are being supported with inotropes and/or an intra-aortic balloon pump (IABP). Postoperative survival and rate of discharge to home is far superior for patients who are not in critical cardiogenic shock at the time of implant [20]. For patients who are transplant candidates the timing of LVAD implant should be based on the balance of the clinical status and factors that may prolong the time on the waiting list. These include an elevated panel reactive antibody level, greater weight, and O blood type. Another important factor in the timing of LVAD implant is the inability to tolerate short-term inotropic support, typically as a result of stimulating ventricular arrhythmias. Long-term inotropic support is associated with a 1-year survival of <10 % [21] and patients who are inotrope-dependent should be considered for earlier LVAD implant if the waiting time for transplant is prolonged. In addition, patients who need a combined heart-kidney or other abdominal organ transplant will also have longer wait times due to the limitation of typically needing a local donor. Patients with these characteristics that prolong wait list time should be considered for earlier referral for MCS before they decompensate and become critically ill. As recently reported, each of the following clinical factors has a significant negative impact on 1-year survival and should be taken into consideration for patients who are being evaluated for transplant or are already listed with regard to referral for MCS: worsening renal function with creatinine >1.8 mg/dL, inability to tolerate ACE inhibitors, ARBs, or beta-blockers, diuretic dose >.5 mg/kg/day, recurrent admission for heart failure, no clinical improvement with CRT, inability to walk one block without dyspnea, and dyspnea at rest [22]. Another indication for earlier consideration of MCS is irreversible elevated pulmonary vascular resistance which is a contraindication to heart transplant, generally >4 Woods units. Pulmonary hypertension has been shown to have a favorable response to unloading with an LVAD allowing subsequent transplantation without the high risk of right ventricular failure [23].

Recent data for HeartMate II patients shows the relationship between clinical status at the time of implant and short and long-term outcomes [24]. Patients were stratified into three groups based on INTERMACS score: Group 1 (INTERMACS 1), Group 2 (INTERMACS 2 and 3), and Group 3 (INTERMACS 4–7). Boyle et al. Survival to discharge was 67.9 % for Group 1 (n = 28), 93.5 % for Group 2 (n = 49), and 95.8 % for Group 3 (n = 24). Length of stay also correlated with INTERMACS score: Group 1: 45.1 days, Group 2: 40.1 days, and Group 3: 18.3 days. One-year survival was greatest for patients in Group 3 at 95.8 % versus 73 % for Groups 1 and 2. Longer-term survival at 18 months was also significantly improved for Group 3 (95.8 %) versus Group 1 (50.2 %) and Group 2 (72.7 %). In addition, a recent study of 468 patients who underwent HeartMate II LVAD implant at 36 centers as bridge to transplant showed equivalent 30-day and 1-year survival compared to conventional cardiac transplantation (97 % and 87 % respectively) [25]. Furthermore, post-transplant survival was not found to be influenced by duration of LVAD support. The authors conclude that the improved durability and reduced short and long-term morbidity associated with the HeartMate II LVAD has reduced the need for urgent cardiac transplantation, which may have adversely influ-

enced post-transplant survival in the pulsatile LVAD era. There is a recent trend to consider implant of most LVADs on an elective, scheduled basis. Patients are typically evaluated and accepted for LVAD therapy as BTT or DT. Most of these patients can tolerate 2–3 days off inotropic drugs and be discharged from the hospital and return home and come into the hospital the day of the surgery. This reduces the risk of nosocomial infection and other comorbidities. Some patients are clearly dependent on more aggressive medical therapy and cannot be discharged pre-LVAD. This trend is increasing as a recent poll indicated that 85 % of programs reported using this strategy with increasing practice due to good associated results.

LVAD Versus Bi-VAD or TAH

The incidence of right heart failure requiring an RVAD at the time of LVAD implant has decreased with the transition to continuous-flow devices. The reasons for this are unclear but may be related to less volume loading of the right heart by this new generation of pumps. Only 4 % of patients in the HeartMate II Bridge to transplant trial required RVAD support, however, 13 % required extended inotropic support [3]. Patients who require RVAD support at the time of LVAD implant have significantly worse survival than those with adequate right heart function [26]. In addition, planned biventricular support has much better outcomes than LVAD implant followed by RVAD implant [27]. Therefore, it is imperative to be able to identify patients who are at high risk for right ventricular failure and plan for bi-VAD or TAH support. The University of Michigan group has recently developed a right ventricular failure risk score (RVFRS) as a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates [28]. Right ventricular failure was defined as the need for RVAD implant, inotropic support for >14 days, or hospital discharge on an inotrope. Of 197 LVAD implants, 68 (35 %) were complicated by post-operative RV failure. These LVAD implants were primarily pulsatile devices with only 15 % being continuous-flow pumps. A vasopressor requirement (4 points), aspartate aminotransferase ≥80 IU/I (2 points), bilirubin ≥2.0 mg/dL (2.5 points), and creatinine ≥2.3 mg/dL (3 points) were independent predictors of RV failure. The odds ratio for RV failure for patients with an RVFRS ≤3.0, 4.0–5.0, and ≥5.5 were 0.49 (95 % CI 0.37–0.64), 2.8 (1.4–5.9) and 7.6 (3.4–17.1), respectively, and 180-day survival was 90±3 %, 80±8 %, and 66±9 % for each group (Fig. 11.7). Fitzpatrick and colleagues identified risk factors for requiring an RVAD at the time of LVAD implant based on 266 patients who underwent LVAD placement at the University of Pennsylvania between 1995 and 2007 [29]. Of these patients, 99 (37 %) required RVAD support. The most significant predictors for RVAD support at the time of LVAD implant were cardiac index ≤2.2 L/min/m^2, RV stroke work index ≤0.25 mmHg • L/m^2, severe preoperative RV dysfunction, creatinine ≥1.9 mg/dL, previous cardiac surgery, and systolic blood pressure ≤96 mmHg. Each of these criteria that are met is assigned a score of 1 or 0 if they are or are not met, and a risk score was derived from the following equation: $18"(\text{CI})+18"(\text{RVSWI})+17(\text{creatinine})+16"(\text{previous cardiac surgery})+16"(\text{RV dysfunction})+13"(\text{SBP})$. The maximum possible score is 98 and a score of ≥50 was predictive of the need for bi-VAD support with a sensitivity and specificity of 83 % and 80 %, respectively. In our experience at the University of Chicago Medical Center with >120 continuous-flow LVAD implants, the ratio of mean pulmonary artery pressure to right atrial pressure has been very predictive of the degree of RV dysfunction and potential need for an RVAD. When this ratio is ≥2, none of the patients required RVAD support, however, this ratio was <2 for the patients who did require an RVAD at the time of HeartMate II LVAD implant (n=5). It is our observation that higher pulmonary artery pressures are associated with better RV function.

The typical hemodynamic scenario during weaning from cardiopulmonary bypass with severe RV dysfunction is poor LVAD flow, elevated right atrial pressure, and low pulmonary artery and systemic blood pressures. TEE shows

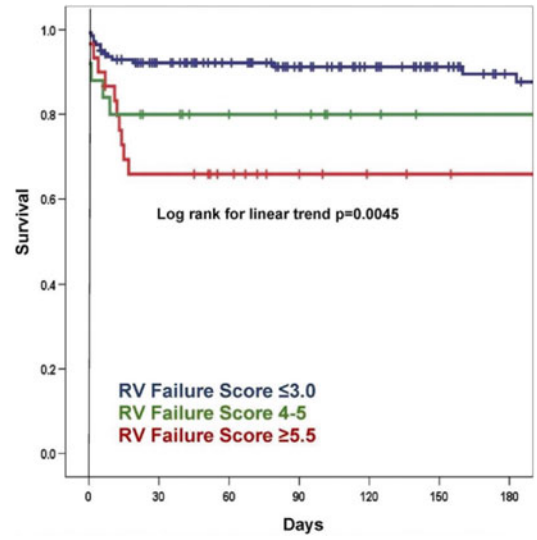

Fig. 11.7 Kaplan-Meier survival curve for each RV failure risk score strata. The 180-day post-left ventricular assist device survival curves for each score strata are displayed. *RV* right ventricular (Permission from Matthews et al. [28])

poor RV function and dilation with bowing of the interventricular septum to the left. Inotropic support should be initiated prior to weaning from bypass and inhaled NO can be utilized as an adjunctive therapy in the setting of RV dysfunction. If two high dose inotropes are required to achieve adequate hemodynamics, consideration should be given to short-term RVAD support. At our center, we have primarily used the Levitronix CentriMag device as an RVAD due to its ease of use and cost-effectiveness. Weaning of the RVAD can be done at the bedside and is usually able to be removed within 3–5 days of implant using low-moderate dose inotropic support.

For transplant candidates with severe biventricular dysfunction and very high risk scores for RV failure following LVAD implant, the Thoratec PVAD/IVAD, SynCardia total artificial heart, and ABIOMED AB 5000 are the current options for long-term biventricular support as a bridge to transplant. These devices are currently FDA approved for discharge to home.

Destination Therapy

It is estimated that 250,000 patients in the United States are in the terminal phase of systolic heart failure and are suffering from severe symptoms that are refractory to maximal medical therapy [1]. Heart transplantation remains the best long-term solution for this population, but is available to only a very small fraction of these patients due to the extremely limited number of donor organs available and many are not suitable candidates for transplant due to other co-morbidities. Long-term mechanical circulatory support with a pulsatile LVAD was shown to be superior at 1 and 2-years versus optimal medical therapy in the landmark REMATCH trial which was published in 2001 for patients ineligible for cardiac transplant [10]. This was the first trial to evaluate an LVAD as destination therapy (DT) and also demonstrated a marked improvement in functional capacity and quality of life. The enthusiasm for DT was tempered by the 2-year survival rate of only 23 % versus 8 % with medical therapy and a high post-operative mortality. The recent results of the HeartMate II destination therapy trial show significantly better survival rates, device durability, and lower incidence of device-related complications [13]. One and 2-year survival was 68 % and 58 % respectively, which is far superior compared to the pulsatile device utilized in the REMATCH trial.

Candidate selection and timing of LVAD implant are critical for achieving excellent outcomes in the destination therapy patient population. The most common indication for DT LVAD implant versus listing for heart transplantation is

age. Other co-morbidities that may be a contraindication to listing for transplant include significant end-organ dysfunction, treated malignancy within the past 5 years, severe pulmonary hypertension (PVR >5 Woods units), peripheral vascular disease, obesity (BMI >35), substance abuse, and psychosocial factors. Patients with any of these issues who are refractory to optimal medical therapy should be considered for an LVAD as destination therapy. Renal failure and pulmonary dysfunction may be relative contraindications for DT, however, the experience with continuous-flow devices and chronic dialysis is very limited and long-term results have not been published to date. Lietz and co-authors developed a risk score for in-hospital mortality following pulsatile LVAD implantation for DT by studying 309 patients who were underwent implant in the post-REMATCH period between 2002 and 2005 at 66 hospitals [30]. Overall survival on LVAD support was 86.1 %, 56.0 %, and 30.9 % at 30 days, 1 year, and 2 years. The following predictors of 90-day in-hospital mortality after LVAD implantation were identified by multivariable analysis: platelet count ≤148,000, serum albumin ≤3.3 g/dL, international normalized ratio >1.1, vasodilator therapy at time of implantation, mean pulmonary artery pressure ≤25.3 mmHg, aspartate aminotransferase >45 U/dL, hematocrit ≤34 %, blood urea nitrogen >51 U/dL, and lack of intravenous inotropic support. The risk factors and scoring are likely to be somewhat different in the current era of continuous-flow LVADs but are very useful to estimate the risk of operative mortality.

Complications of Mechanical Circulatory Support

Continued advances in VAD technology and increasing clinical experience with VADs have resulted in improved patient outcomes, particularly in the current era of continuous flow devices. VAD support is still associated with serious complications and adverse events, while reduced in frequency, can still limit treatment efficacy, benefit, and safety. A study was recently published which reported outcomes for patients who underwent HeartMate II LVAD implant post-FDA approval using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) [31]. This was a prospective evaluation of the first 169 consecutive HeartMate II patients enrolled in INTERMACS who were listed for transplant or likely to be listed. They were enrolled from April through August 2008 in the initial period following FDA approval of this device for BTT. Kaplan-Meier survival was 90 % at 6 months and 85 % at 1 year. The duration of follow-up was 306 ± 173 days. The most frequent complication was bleeding which occurred in 44.4 % of patients. This included early postoperative bleeding and mucosal/GI bleeding that occurred later. Infection was present in 46.2 % of patients with 17.8 % being driveline infections and 1.8 % pump pocket infections. These data indicate that the majority of infection complications were not LVAD-related. There was an overall 6.5 % incidence of stroke with 1.2 % being hemorrhagic and 4.7 % embolic in nature. Renal dysfunction occurred in 10.1 % of patients and 6.5 % developed hepatic failure. Respiratory failure, defined as prolonged mechanical ventilation, had an incidence of 20.1 %. Right heart failure, defined as prolonged need for inotropic support or RVAD implant, occurred in 14.8 %, however, only 4 % required an RVAD. There was a low incidence of hemolysis at 3 %. The overall rate of device replacement was 1.2 % (Table 11.1).

In the long-term, driveline infection, GI/mucosal bleeding, and right heart failure are significant issues that have significant impact on long-term survival and quality of life. Our group has recently reported a modified driveline externalization technique for the HeartMate II which has decreased the infection rate to <5 % [32]. Although right heart failure in the acute implant period has been significantly decreased in the continuous flow LVAD era, the incidence of late right heart failure has been reported to be up to 50 % at 1 year [33]. Strategies for optimization of device function and medical therapy to prevent this complication are currently being investigated.

A recent report in the New England Journal suggested an increased risk of pump thrombosis

Table 11.1 Adverse events for the HM II and COMPs reported to INTERMACS

	HM II (n = 169) cumulative: 142.0 pt-yrs, mean duration: 306 ± 173 days				COMP (n = 169) cumulative: 96.2 pt-yrs, mean duration: 207 ± 188 days						
Event	n	% pts	Events (n)	Events/pt-yr	n	% pts	Events (n)	Events/pt-yr	RR	95% CI	p value
Bleeding	75	44.4	204	1.44	65	38.5	172	1.79	0.80	0.58–1.12	0.1931
Infection[a]	78	46.2	142	1.00	72	42.6	204	2.12	0.47	0.34–0.66	<0.0001[b]
Driveline	30	17.8	45	0.32	27	16.0	44	0.46	0.69	0.42–1.13	0.1419
Pump pocket	3	1.8	4	0.03	12	7.1	16	0.17	0.17	0.06–0.52	0.0006[b]
Pump interior	1	0.6	2	0.01	0	0.0	0	0.00	—	—	0.2466
Blood	32	18.9	47	0.33	36	21.3	71	0.74	0.45	0.29–0.70	0.0004[b]
Line sepsis	3	1.8	3	0.02	9	5.3	10	0.10	0.20	0.05–0.76	0.0096[b]
Other infection[a]	49	29.0	86	0.61	50	29.6	119	1.24	0.49	0.34–0.72	0.0002[b]
Stroke	11	6.5	11	0.08	9	5.3	11	0.11	0.68	0.28–1.63	0.3821
Hemorrhagic	2	1.2	2	0.01	2	1.2	2	0.02	0.68	0.09–4.89	0.6986
Embolic	8	4.7	8	0.06	6	3.6	7	0.07	0.77	0.27–2.21	0.6323
Unknown	1	0.6	1	0.01	2	1.2	2	0.02	0.34	0.03–3.79	0.3584
Other neurological dysfunction	7	4.1	7	0.05	13	7.7	16	0.17	0.30	0.12–0.75	0.0071[b]
Myocardial infarction	3	1.8	3	0.02	1	0.6	1	0.01	2.03	0.21–19.8	0.5342
Pericardial drainage	17	10.1	20	0.14	20	11.8	22	0.23	0.62	0.32–1.19	0.1477
Psychiatric episode	14	8.3	17	0.12	17	10.1	23	0.24	0.50	0.25–0.99	0.0435[b]
Renal dysfunction	17	10.1	19	0.13	21	12.4	28	0.29	0.46	0.24–0.87	0.0156[b]
Hepatic dysfunction	11	6.5	12	0.08	9	5.3	11	0.11	0.74	0.31–1.74	0.4899
Respiratory failure	34	20.1	41	0.29	43	25.4	53	0.55	0.52	0.32–0.85	0.0084[b]
Right heart failure[c]	25	14.8	26	0.18	20	11.8	22	0.23	0.80	0.43–1.49	0.4859
Hemolysis	5	3.0	5	0.04	2	1.2	2	0.02	1.69	0.32–8.91	0.5300
Hypertension	3	1.8	4	0.03	26	15.4	35	0.36	0.08	0.03–0.23	<0.0001[b]
Cardiac arrhythmia	46	27.2	69	0.49	47	27.8	85	0.88	0.55	0.37–0.83	0.0041[b]
Arterial non-CNS thromboembolism	1	0.6	1	0.01	2	1.2	3	0.03	0.23	0.02–2.20	0.1637

Venous thromboembolism	11	6.5	13	0.09	13	7.7	15	0.16	0.59	0.27–1.29	0.1820
Wound dehiscence	3	1.8	3	0.02	3	1.8	3	0.03	0.68	0.13–3.43	0.6368
Device replacement	2	1.2	2	0.01	13	7.7	13	0.14	0.10	0.02–0.47	0.0005

[a]Other Infections Include pneumonia, urinary tract, mediastinum, peripheral wound, and unknown
[b]Statistically significant
[c]Including 5 (3.0%) HM II patients and 21 (12%) COMP patients requiring RVAD support
CI confidence Interval, *CNS* central nervous system, *pt* patient, *RR* relative risk ratio of adverse event rates between HM II versus the COMP.

with Heartmate II devices in three high-volume centers [34]. While this was not the experience in all centers around the world, it raised important points about potential complications.

INTERMACS analyzed the overall multicenter experience regarding HeartMate II pump exchanges for thrombus in the commercial era (http://www.uab.edu/medicine/intermacs/research/statistical-summaries). This analysis shows that there has been a decrease in freedom from device removal for definite and probable pump thrombosis at 6 months from 98 % to 95 % over the last several years. While that was a small but significant change, the analysis also showed no impact on the overall survival rate between the two periods. As the HeartMate II will be used as the study device in the upcoming REVIVE-IT study, FDA, NHLBI, the REVIVE-IT leadership and the independent REVIVE-IT DSMB also reviewed the INTERMACS analysis with respect to pump thrombus and its impact for use in a patient population with less advanced heart failure. All parties supported continuation of the REVIVE-IT study with the HeartMate II. Survival rates continue to be improved in the commercial era compared to the original HeartMate II clinical trial, along with notable improvements in other key adverse events (e.g. hemorrhagic stroke, bleeding, infection).

Conclusions

As a result of the current limitations of medical therapy for advanced heart failure, the significant donor organ shortage for cardiac transplantation and an increasing incidence of heart failure, VAD therapy will continue to be an increasingly utilized option for this patient population. VAD technology has transitioned from pulsatile, volume displacement pumps to continuous flow devices with no negative effects on end-organ perfusion. Clinical outcomes continue to improve and quality of life is significantly enhanced with a decreasing incidence of adverse events. Future devices will be smaller and potentially allow for less invasive approaches for implantation. The development of transcutaneous energy transfer systems that provide long battery life and are relatively cost-effective is also on the horizon for future LVAD technology. Continued innovation in the development of implantable devices will allow for more patients to benefit from this currently underutilized therapy.

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The Economics of Ventricular Assist Devices

12

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Introduction

"Disruptive technology," a phrase coined by economist Clayton M. Christensen approximately 10 years ago, describes a new technology that unexpectedly displaces an established technology. Whereas sustained technology applies incremental improvements to an established approach, disruptive technology, often lacking in refinement, has the ability to transform common practice. Such has been the case with ventricular assist devices (VADs), which have rapidly transformed the management of end stage heart failure from sole pharmacologic therapy to enhancement with mechanical circulatory support.

As with most forms of disruptive technology, however, VADs are not without a significant burden on healthcare costs in a patient population already consuming healthcare resources at the extreme. Today, nearly five million Americans are diagnosed with heart failure, with an incidence approaching 10 per 1,000 of the population after the age of 65 [1]. The 5 year mortality rate remains at 50 % despite improvements in medical and surgical therapies, with the number of deaths and hospitalizations continuing to rise. In 2001, the estimated cost of heart failure in the US was $21 billion. Heart failure represents a significant public health burden, but also represents an area of intense healthcare resource consumption in an era where there is growing attention, and greater constraints, on healthcare spending. With increasing interests and necessity in comparative effectiveness research, novel therapeutics must be studied not only from the perspective of safety and efficacy but also with respect to their relative cost effectiveness. In this chapter, we briefly discuss the history and landmark trials of ventricular assist devices and focus on the innovations and futures challenges of these devices from a medical economics perspective.

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VADs in Historical Context

In 1964, the National Institutes of Health established the Artificial Heart Program [2]. There was significant early enthusiasm for the development of a total artificial heart. However, in the 1970s, failures in this arena combined with challenges in transplantation secondary to the lack of modern immunosuppression, led to the

J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_12

development of the National Heart, Lung, and Blood Institute clinical ventricular assist device program in 1975. This program initially focused on mechanical circulatory support for patients who had recently undergone cardiac surgery [3], but ultimately expanded to focus on support for patients requiring mechanical assistance as a bridge to transplantation (BTT).

Throughout the 1970s and 1980s several VADs were developed, characterized by their large size and use of pulsatile flow and positive displacement. These devices, now commonly referred to as "first generation" VADs, underwent significant evolution, and three devices ultimately received Food and Drug Administration (FDA) approval for use in BTT support – the Thoratec paracorporeal VAD (PVAD)/implantable VAD (IVAD), the Heartmate IP/VE/XVE, and the Novacor LVAS, which is no longer marketed in the United States [4–8].

Much of the early focus on mechanical circulatory support involved use of VADs for temporary support after cardiac surgery or as BTT in critically ill patients on the wait list. Given the early success of VADs, attention turned to investigating an indication for use in destination therapy (DT) among end-stage heart failure patients who were not eligible for transplantation. The results of the landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) were published in 2001 [9]. The HeartMate XVE was introduced in 2001 with structural modifications, and received FDA approval for a BTT indication in 2001 and for destination therapy in 2003 based on the results of REMATCH.

Despite the significant impact on survival observed in early VAD trials, major opportunity remained for device improvement and innovation. In the REMATCH trial, patients in the device group were more than twice as likely to have a serious adverse event compared to the medical management group. In 1994, the NHLBI issued proposals for "Innovative Ventricular Assist Systems," which sought to improve the durability of ventricular assist systems to at least 5 years and increase reliability to at least 90 %. As an outgrowth of this request for proposals, rotary axial flow devices were developed. These smaller, "second generation" devices differed from their pulsatile counterparts in that they employed rotary axial flow and thus provided continuous flow [10]. The HeartMate II, a continuous flow device first used clinically in 2001, was approved for BTT in 2008 and DT in January 2010 [11].

Since 2008, continued innovation has occurred through the development of third generation, or centrifugal, devices. Through the use of a bearingless design, these devices may have improved durability. Moreover, the smaller size of these devices has important implications for improved quality of life after implantation. The potential for such a device may be reflected by the recent early conclusion of enrollment in the ADVANCE trial, which tests HeartWare's (Framingham, Massachusetts) miniaturized, third-generation VAD in a BTT population. At the 2010 meeting of the American Heart Association, HeartWare reported that 92 % of enrolled patients had achieved the primary endpoint at 180 days [12].

This past year, the NIH issued a request for proposals for the Randomized Evaluation of VAD InterVEntion before Inotropic Therapy (REVIVE-IT) trial [13]. The goal of this study is to explore the potential benefit of mechanical circulatory support in less severe but functionally-impaired heart failure patients, not eligible for transplantation. Largely as a result of an improved durability and safety profile, the REVIVE-IT trial represents a potential paradigm shift in viewing VADs as salvage therapy for the most critically ill heart failure patients, to support for less critically ill patients with impaired functional capacity. The REVIVE-IT trial has yet to begin enrollment, however, the results of this trial have the potential to further expand the role of VADs. The evolution and innovation of VADs over the course of 40 years has not only led to improvements in safety profiles and durability but also expanded the potential clinical indications for mechanical circulatory support.

Early Economic Outcomes with Ventricular Assist Devices

The early focus on mechanical circulatory support was on the safety and efficacy of such devices in the management of end-stage heart failure. As VAD trials completed enrollment and

FDA approval was granted, attention gradually turned toward the challenging issues of insurance coverage and the cost of such devices. Not only were VADs resource intensive due to the cost of the device itself, but they were an added cost in the management of end-stage heart failure patients – an already resource intensive group. Economic evaluation of device therapy includes the costs of operative implantation, post-operative recovery and hospitalization, and management of complications which occur at relatively high rates when compared to most other surgical interventions. Clearly VADs prolonged survival of end-stage heart failure patients, but were these devices cost effective?

Pre-REMATCH In one of the first analyses focused on costs, Moskowitz and colleagues reported on resource utilization among 12 VAD recipients in 1994 and 1995 [14]. The outcomes of this population included two deaths, eight transplants, and two patients on continued support. The average number of LVAD supported days was 177, with a range of 13–481 days, and an initial-implant related hospitalization cost of $141,287 ± 18,513. When hospital costs were broken down, the three most resource-intensive categories were: the device itself (48 % of total cost), professional payments (17 %), and intensive care unit length of stay (10 %). The authors further calculated outpatient costs and the costs of readmission bringing the total cost of LVAD therapy during the first year after implant to $222,460 whereas the cost of cardiac transplantation was estimated to be $176,605.

REMATCH In a follow-up analysis involving the majority of patients enrolled in the REMATCH trial, Oz and colleagues reported a mean and median total hospital cost of $210,187 ± 193,295 and $137,717, respectively, with a wide range of $72,583 to $1,123,565 depending on number of days spent in the intensive care unit [15]. This study was the first to cast light on the potential factors responsible for the high cost of LVADs. Sepsis, pump housing infection, and perioperative bleeding were all significant predictors of the cost of the index hospitalization. When these three factors were all present, the cost of hospitalization was projected at $869,199 and when these factors were all absent the cost was estimated at $119,874. In addition to device-related complications, the study also examined annual readmission costs. Notably, there were approximately 4.5 readmissions per patient, with the annual cost for the entire costing cohort estimated at $309,273. In the 27 patients who survived greater than 1 year, the annual cost decreased to $196,116. This analysis of the REMATCH device cohort demonstrated that improvements in the cost-effectiveness of VADs would require not only device innovation to reduce the frequency of post-operative complications, but also improvements in patient selection given the significant difference in cost between patients who survived greater than 1 year and those that did not.

Despite the significant cost associated with LVAD therapy, it is essential when considering the cost effectiveness of LVADs, to understand the cost of alternative treatments – heart transplantation in the BTT population, and optimal medical management (OMM) in the DT population. DiGiorgi and colleagues examined the costs of patients bridged with the HeartMate XVE versus those receiving a heart transplant [16]. Their results demonstrated that overall, total actual hospital costs of LVADs exceed that of transplantation, with total hospital costs post-LVAD estimated at $197,957 and total hospital costs for transplanted patients estimated at $151,646. The overall net revenue for transplantation was $29,916 whereas for LVADs, net revenue was – $53,201. Importantly, there were a significantly greater number of readmissions among the LVAD group, with readmission costs in the device group estimated at $16,596 and only $6,356 in the transplantation group. In addition to the difference in number of readmissions, the authors also highlight the importance of length of stay which was 36.8 days in the sicker device group and 18.2 days in the healthier transplant group.

Russo and colleagues examined the costs of medical management in the final 2 years of life among the optimal medical management cohort in the REMATCH trial [17]. The mean total cost per patient in the final 2 years of life was $156,168, with more than half of the total cost

incurred during the final 6 months of life. Approximately 75 % of the inpatient costs in the last 6 months were related to hospitalizations for heart failure exacerbations. Notably, during the final 6 months of life, patients spent approximately 1 out of every 4 days of life as hospital inpatients. The results of the analyses by DiGiorgi and Russo demonstrate that although the costs of VADs is great, the costs of alternative strategies for end-stage heart disease, such as transplantation and intensive medical management, are not without a significant cost burden. Thus, early data demonstrated that there existed an opportunity for mechanical circulatory support to compete with the currently available alternatives from a cost-effectiveness standpoint, but improvements would first be necessary in terms of device innovation, clinician experience, and patient selection.

Innovation, Experience, and Improved Cost Effectiveness

Kenneth Arrow, who received the 1972 Nobel Prize in economics, described in his classic text, "The Economic Implications of Learning By Doing," the process whereby workers improve productivity by repetition of a given action which results in increased productivity through practice and innovation [18]. Unlike pharmaceuticals, a "learning by doing" approach is particularly critical in the innovative process of medical devices and surgical procedures, whereby learning and ultimately innovation occur gradually through use and experience with a device or technique [19]. While innovation clearly occurs in the laboratory, there is a feedback pathway where research and development lead to clinical trials which in turn lead to clinic practice, and then ultimately to experience that informs and feeds back to the research and development process [20].

Such an innovative process can be seen in the development of LVADs. Experience with the first generation HeartMate device in the REMATCH trial led to several mechanical device innovations. For example, locking screw ring connectors were added to prevent detachment of the blood transport conduits, and outflow graft bend relief was added to prevent kinking and valve flow incompetence [21]. In addition to changes in the mechanical design of the device, experience in REMATCH gained from clinical practice or "learning by doing" led to refinements in patient selection and management.

As discussed previously in this chapter, early economic evaluation of LVADs highlighted the significant impact of device-related complications, such as sepsis, on total hospital costs. As such, institutions have developed specific guidelines on surgical infection prophylaxis for LVAD recipients. In addition, early economic analysis demonstrated the significant difference in cost of total hospitalization between LVAD recipients who survived the first year of implantation versus those who did not. Work by Leitz and colleagues demonstrated that use of a pre-operative risk score could be used to stratify LVAD recipients into low, medium, high, and very high risk which correlated with 1-year survival rates of 81 %, 62 %, 28 %, and 11 %, respectively [22]. As experience with VADs has grown, several subsequent risk models have been developed to more precisely predict peri-operative morbidity and mortality and aid in patient selection.

Early experience with LVADs clearly led to refinements in device technology and patient selection, which ultimately led to improvements in clinical outcomes. However, have refinements in devices themselves and the selection of device recipients ultimately led to improvements in the cost-effectiveness of VADs?

Initial economic evaluation of VADs focused largely on reporting of costs rather than cost-effective analysis. However, even a cursory examination of the reported hospital costs from the REMATCH trial, driven largely by the costs of the index hospitalization, hospital readmissions, and the need for device replacement, demonstrated that VADs would far exceed the generally accepted incremental cost effectiveness ratio (ICER) threshold of $50,000–$100,000 per quality adjusted life year (QALY). In fact, economic modeling by Clegg and colleagues demonstrated that LVADs offered an additional 0.6 QALYs per patient over the 5-year duration of their model at

an additional cost of £102,000 or an ICER of £170,616, approximately $341,232 using a currency conversion adjusted for the time of publication [23]. One-way sensitivity analysis showed that the results were not sensitive to variations in cost, discount rate, or utility. Similarly, in 2002 the Technology Evaluation Center of Blue Cross and Blue Shield performed an independent cost-effectiveness analysis of LVADs using parameter estimates from published sources at the time. The results demonstrated that use of LVADs led to an increase in cost of $802,700 per one QALY gained, compared with optimal medical management. The calculated ICER was stable despite sensitivity analysis on the utility of New York Heart Association Category III/IV, cost of outpatient care, cost discount rate, cost of rehospitalization, and probability of rehospitalization for LVAD. Russo and colleagues calculated the ICER of patients enrolled in REMATCH to be $602,361/QALY [24].

Early American and European estimates of the cost-effectiveness of VADs were bleak. Not only were calculated ICERs far outside the range of medical therapies that would be considered cost-effective, sensitivity analyses demonstrated that acceptable ICER thresholds could be achieved only at the extremes of clinical variables that composed the economic models.

Measuring Device Technologies

With growing constraints in healthcare funding, there is increasing demand for objective clinical and economic evidence to demonstrate that a particular intervention will be safe and effective while providing improved quality of life at an acceptable cost. However, given the rate of technological change, evidence to support the use of new technologies frequently lags behind their application. The need to evaluate device-based therapies has increased exponentially, particularly in cardiovascular disease.

Historically, tools to evaluate clinical therapies were developed for the evaluation of drug-based therapies. However, devices and drugs are inherently different – drugs are "discrete technologies." That is, drugs are singular and driven by a fixed active agent. Research and development occurs at the benchtop, and they do not undergo significant evolution after introduction to the market. Application in clinical practice signals the end of the development process. Although doses and delivery mechanisms may change, the active chemical agent remains fixed. Therefore, the life-cycle of a drug is linear, and advances in therapy are discrete and discontinuous.

Devices, in contrast, are "complex technologies," consisting of a number of modular components where changes in any component may impact outcomes. Application does not signal the end of the development process. Significant research and development continues to occur in the clinical setting. Outcomes are operator dependent, and operators learn by doing and, in addition, incremental advances may occur continuously. Clinical experience with devices can feed back to the research and development stages resulting in design refinements and further innovation. This may be ongoing even in a randomized clinical trial setting.

As a result, traditional methods of evaluation suffer from inherent limitations. Specifically, while innovation is dynamic and medical technologies change over time, evidence is static with findings from a fixed time period. Therefore, while clinical decision makers demand information from today, and policy makers require data for the future, frequently evidence from clinical trials is limited to the past.

The dynamic nature of surgically implantable devices and their application complicates the ability of policy makers to obtain rigorous and timely evidence to guide decisions on the adoption and use of a new technology. Quantifying uncertainties regarding emerging technologies is challenging. In order to overcome these challenges, economic modeling needs to incorporate the dynamics of technological change and learning into analysis as it may alter conclusions. This includes use of advance analytical techniques to account for potential changes in the technology, operator experience, patient management, and target populations over the study period. These include patient risk stratification, volume-outcome

analysis, learning analysis, assessment of temporal trends, and incorporation of data collected beyond the close of the study period. Sensitivity analyses and Markov modeling offer analytical means to control for uncertainty and changes over time. In addition, post-marketing surveillance, including capturing outcomes in everyday practice and revisiting payment decisions, is also crucial to assessing and reassessing the clinical and cost effectiveness of rapidly evolving technologies.

VADs as an Evolving Technology

One might have expected innovations in VADs to occur in a protracted manner; however, as discussed previously, innovation and improvements in clinical outcomes with VADs occurred relatively quickly through experience. In fact, such improvements in clinical outcomes could already be observed during the REMACH trial. Park and colleagues demonstrated that there was a 15 % improvement in overall survival among patients randomized during the second half of the trial when compared to those randomized during the first half [25]. In addition, there were significantly fewer adverse events when the two trial time periods were compared with improvements in sepsis, pump housing inflow and outflow graft infections, bleeding, and renal failure in patients enrolled in the second half of the trial.

Such observed improvements in clinical outcomes during the REMATCH trial appear to have translated into significant improvements in cost-effectiveness during the course of the trial. While the mean ICER of device therapy was $602,361/QALY over the entire study period, there was a significant decrease in the ICER from the first to the second half of the trial with estimated ICERs of $898,666/QALY and $505,286/QALY, respectively [24].

REMATCH

During the REMATCH trial, several changes to the device technology were implemented, including modification of the driveline, introduction of a locking screw ring to prevent detachment of the blood-transport conduits to and from the pump/inflow valve reinforcement, and bend relief of outflow graft [26]. Meanwhile, clinicians improved their management of LVAD patients by modifying the operative procedure [27], developing clinical protocol to prevent and manage driveline infections with antimicrobial agents [28–30], and changing anticoagulation regimens, which reduced the adverse event profile associated with the therapy [31, 32]. As previously noted, even within the study period, measurable improvements in outcomes were evident, including decreased costs, improved survival, and decreased ICER [25].

Post-REMATCH

Approval of the HeartMate XVE by the FDA, Medicare, and a number of private insurers, allowed for expanding experience. In the 2 years following Medicare approval for reimbursement, an analysis of a post-marketing registry showed that the overall survival rate of LVAD patients remained similar to that seen in the trial [22]. However, over time, the length of stay for the implant hospitalization, the most costly part of the care process, fell by 25 % from an average of 44 days in the pivotal FDA trial (with a mean cost of $210,187) to 33 days within 3 years of dissemination [33]. This is important, because the cost of index hospitalization accounted for the majority of the mean total costs in the VAD group. Furthermore, the implementation of new protocols has reduced the incidence of adverse events, specifically in driveline infections and thrombosis [28–32]. The modeled ICER of the Heartmate XVE during the post-REMATCH time period was less than half of the overall REMATCH ICER. This ICER reflects improvements in device reliability and a reduction in the cost of the index hospitalization in the VAD group, and an increase in survival and costs in the OMM arm to account for the application of biventricular pacing and implantable cardiac defibrillators [24].

Second Generation Devices

Despite early evidence demonstrating the potential importance of patient selection and risk stratification using variables such as end-organ dysfunction and right ventricular failure, malnutrition, or infection; the acuity of patients implanted during the early post-REMATCH period did not differ significantly from the original REMATCH study population [22]. In the current era, with growing evidence of the importance of risk stratification in patient selection, there has been a gradual shift away from viewing LVADs as a salvage therapy for patients who are sliding on inotropes or progressing to multisystem organ failure. Instead, LVADs now form an important potential component of heart failure management in the functionally impaired as well as the less severe heart failure population. A multivariable regression analysis of the larger population captured by the registry (n = 262) showed that baseline risk factors, such as poor nutrition, hematological abnormalities, and markers of end-organ dysfunction, distinguish patient risk groups. Stratification of destination therapy candidates into low, medium, high, and very high risk on the basis of a risk score corresponded with dramatically different 1-year survival rates (81 %, 62 %, 28 %, and 11 %, respectively) [34].

Consistent with these observations, recent studies have demonstrated that less acutely ill but functionally impaired heart failure patients receiving continuous flow LVADs as BTT or DT experienced shorter lengths of stay and greater short- and long-term survival compared to non LVAD patients [35]. Furthermore, significant improvements in device durability have been demonstrated in recent years [10, 11]. The device used during REMATCH, the Heartmate VE, was known to have limited durability even prior to its clinical application. Engineers projected that the lifetime of the device was between 18 and 24 months. With mean cost of hospitalizations related to device replacement exceeding $180,000, 5 % of total costs were related to hospital readmissions in which a device replacement occurred. Currently, a number of second generation devices have completed various trial phases. The devices, which are smaller, axial flow pumps with blood-immersed or pivotal bearings, possess a life expectancy of up to 15 years. More recently, third generation devices have entered clinical trials. These devices, which are further miniaturized and eliminate the mechanical bearing, may potentially have a nearly unlimited life.

Collectively these important advances have led to further improvements in the ICER related to long-term use of LVADs. For the second generation era, assuming improvements in survival during index hospitalization and further improvements in reliability with no further changes in OMM, the ICER improved, approaching the important $100,000 threshold [24].

Similarly, Slaughter and colleagues recently compared costs and clinical outcomes data from patients enrolled in the HeartMate II DT trial who received a continuous flow LVAD with patients from the LVAD arm of the REMATCH trial [36]. The results demonstrated that inflation-adjusted costs were significantly lower in the continuous flow group, estimated at $193,812, as compared to the pulsatile flow group, estimated at $384,260. In addition, the authors report a significant decrease in mean length of stay from 44.7 to 27.2 days and a reduction in in-hospital mortality from 31 % to 8 % among continuous flow patients. Moreover, Rogers and colleagues recently demonstrated that the ICER of continuous flow devices was $198,184 per QALY which equates to a 75 % reduction in ICER compared to the $802,700 per QALY for pulsatile flow devices.

Despite improvements in clinical outcomes and cost effectiveness, however, current research demonstrates that there is room for continued improvement in reducing the economic burden of complications. Iribarne and colleagues studied the effect of post-operative complications on total hospital costs of LVAD recipients over a 7-year time period [37]. The results demonstrated that the most common complications included renal failure requiring dialysis, pneumonia, and unplanned return to the operating room, resulting in an average median increase in hospital costs of $123,966. Importantly, infections were among the most costly complications, with sternal

wound infection, LVAD pocket infection, and sepsis resulting in an average median increase in hospital costs of $250,227 and an average median increase in length of stay of 43.1 days.

Over a relatively short time, LVADs demonstrated significant improvements in clinical outcomes which have been largely the result of improvements in patient selection and device innovation resulting from clinical experience. Although initial estimates demonstrated that VADs were clearly far outside the range of what is generally considered cost-effective, improvements in outcomes correlate with reductions in cost, which has gradually led to more reasonable ICERs. Room for continued improvement does remain however. Inasmuch as VADs demonstrate the rapidity in which a given technology can improve, these devices also highlight the challenges of assessing a dynamic technology, where device innovation often outpaces clinical trials and a "learning by doing" approach affords future innovation. Such challenges not only face clinicians and clinical trialists in their assessment and implementation of medical devices, but also policy makers who must often make policy decisions on rapidly evolving technology.

Health Policy and Coverage Decisions

Different healthcare systems approach the evaluation and application of new technologies in different ways. European nations tend to put a greater emphasis on planning laws and payment policies to help shape diffusion than the US does. Planning laws target the dissemination of expensive, high technology device therapies, such as nuclear medicine imaging and open-heart surgery units, and reimbursement systems affect demand for all types of technology. Recently, the United Kingdom's National Health Systems have strengthened their analytical enterprise by creating the National Institute for Health and Clinical Evidence (NICE) to advise National Health Service (NHS) clinicians and administrators about the clinical and cost effectiveness of interventions by issuing clinical guidelines for specific medical conditions or individual technology appraisals [38]. About 140 of such appraisals were published by May 2008, of which 19 focused on medical devices. If technologies are found to be cost-effective, purchasers within the NHS are obligated to fund them. NICE elected not to support LVADs for destination therapy patients based on findings from their own cost-effectiveness analysis [23].

By contrast, Medicare, lacking cost-effectiveness as a criterion for coverage decisions, approved the LVAD for coverage. In addition, Blue Cross and Blue Shield Association (BC/BS), a private US insurer, approved reimbursement for VAD implantation. BC/BS has a well-established coverage decision-making process, and its Technology Evaluation Center (TEC) assesses about 15–20 technologies annually to provide guidance to health plans [39]. TEC not only calculated an exceedingly high ICER ($802,700/QALY) but found that "within the range of values used in this analysis, the ICER was fairly stable amid changes in these variables".

These observations highlight that while rigorous evidence is needed to guide clinical application and adoption decisions related to the introduction of new technologies, coverage decisions should not be binary "go/no go" decisions. Health care systems may need some flexibility to allow for short-term inefficiencies to garner long-term value. Among the criteria affecting coverage, cost effectiveness analyses can provide important guidance, but these ratios should not entirely drive the decision making process. Other considerations, such as equity concerns, if a clinical condition is life threatening or if the device is an emerging technology with serious prospects of improvement within a realistic period of time, should play a role as well. Approval of LVADs by the FDA, Medicare, and a number of private insurers, despite a widely recognized unfavorable ICER, allowed for expanding experience and improved clinical and economic outcomes.

BTT and DT

Most current VAD studies define patients as bridge-to-transplantation or destination therapy, with eligibility for transplantation being the distinction between the two. These are, however,

artificial labels devised for regulatory purposes and not exclusive categories of patients. The clinical characteristics that make a patient ineligible for transplant are dynamic. Similarly, with the adoption of alternate list criteria, even the clinical contraindications to transplantation are not fixed. For these reasons it is often difficult to clinically differentiate between DT and BTT patients.

Discussion to this point has focused on implantable VADs as DT, however, it should be pointed out that VADs in the BTT setting have been shown to be cost-effective [40] and comparable to other end-stage heart failure therapies such as biventricular pacers and ICDs. Future studies should avoid this classification system, and focus on all implantable VAD patients. Twenty-five percent of DT patients are ultimately transplanted [41] and therefore achieve prolonged survival after transplant, and a small number of patients are recovered with subsequent explanation. It is likely that if cost-effectiveness studies looked at all VAD patients (BTT, DT and recovery) results would be more generalizable and thus offer more clinically relevant data to guide the application of these devices.

Future Directions

VADs represent a rapidly evolving, "disruptive" technology that have and continue to have a significant impact on the management of patients with end stage heart failure awaiting transplantation as well as those with severe heart failure who are ineligible for transplantation. As with most forms of disruptive technology, VADs were introduced in a somewhat unrefined form, but quickly evolved through a "learning by doing" approach where clinicians directly involved with such devices in clinical trials helped inform the mechanics of future innovation and the medicine of optimal patient selection. Improvements in survival and morbidity over the past decade have translated into observed improvements in length of hospitalization, complications, total hospital costs, and ultimately cost-effectiveness. However, inasmuch as LVADs have evolved, they still represent a technology that is resource intensive in a heart failure population consuming healthcare resources at the extreme. Economic modeling suggests that LVADs have the potential to represent a cost-effective therapy, perhaps even in a functionally impaired, but less severe heart failure population. Continued assessment, however, is necessary. Assessing rapidly evolving technology is challenging as technological advancement often outpaces the clinical trials that establish a technology's safety and efficacy. Policy makers must understand the implications of such rapid technologic evolution when making coverage decisions, and more importantly understand that only through use of devices can innovation and improved clinical practice be realized. Investigators, likewise, must continue to refine patient selection to improve survival and reduce post-operative complications which continue to serve as significant predictors of total hospital costs. Just as LVADs continue to evolve with greater refinement, so too must our methods of economic evaluation evolve to encompass the dynamics and uncertainties of this rapidly evolving technology.

Acknowledgements The authors would like to thank Aurelie Merlo and Rachel Easterwood for their invaluable assistance in preparing this chapter.

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Atrial Fibrillation and Heart Failure: Medical Management and Catheter Ablation

13

Andrew J. Sauer and Bradley P. Knight

Introduction

Atrial fibrillation (AF) and heart failure (HF) are two important coexisting epidemics that are expected to rise in prevalence as the growing population ages. Epidemiologic studies have demonstrated that the presence of both conditions as comorbidities leads to worse outcomes than those of either AF or HF alone. The existing literature has yet to demonstrate a clear superiority of either rate or rhythm control pharmacologic strategies for the treatment of atrial fibrillation in all HF patients. Regardless, some degree of rate control (using beta-blockade and occasionally digoxin) is warranted in almost all patients with HF albeit the definition of optimal rate control has not been well-defined for this population. There is emerging evidence for the role of invasive therapeutic approaches such as pulmonary vein isolation as a method for improving reverse remodeling and left ventricular systolic function. While we are learning to tailor rhythm versus rate control therapies in this complex and heterogeneous population, anticoagulation remains a mainstay of therapy for stroke prevention in this high-risk population. Nevertheless, the purpose of this chapter is to first summarize the literature as it applies to AF in HF with a specific focus on the evidence for rhythm versus rate control strategies, including both pharmacologic and catheter-based interventions. Following the literature review we will discuss practical approaches to the medical and catheter-based management of these patients.

The Atrial Fibrillation and Heart Failure Relationship

Atrial fibrillation and HF have been described as the twin cardiovascular epidemics of the twenty-first century as they are growing and associated with significant morbidity and mortality among the aging population. Lifetime risk projections from the Framingham Heart Study demonstrate a one in four probability of developing AF and a one in five probability of developing HF after the age of 40 years [1, 2]. However, the prevalence of both conditions effectively doubles with each decade of life leading to a disproportionate burden of these comorbidities among elderly patients. Observational studies have demonstrated that while AF and HF often coexist in the same patient population, the causative relationship

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_13

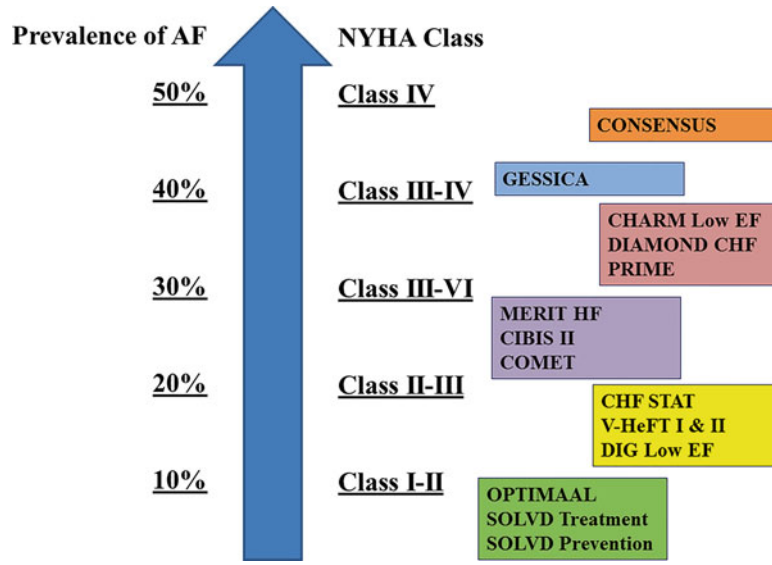

Fig. 13.1 Association of increasing prevalence of atrial fibrillation with increasing severity of symptoms of heart failure

possibly existing between the two comorbidities is at least reciprocal. In Framingham studies 31 % of patients had AF diagnosed prior to HF while 21 % received dual diagnoses in an the initial observation [3]. Meanwhile, these data also demonstrate that 41 % of patients with HF experience AF while 42 % of patients with AF carry a concurrent diagnosis of HF.

The prevalence of AF in patients with HF is known to be associated with the severity of HF as defined by New York Heart Association (NYHA) class in a variety of clinical trials (Fig. 13.1). For instance, in patients with asymptomatic left ventricular systolic dysfunction the prevalence of AF is as low as 5 % but rises to nearly 50 % in patients with advanced symptomatic systolic HF. Atrial fibrillation is also observed with increasing frequency based on the severity of echocardiographic diastolic dysfunction, ranging from 1 % prevalence with normal diastolic function to 21 % prevalence with restrictive diastolic filling pattern [4].

Mechanisms of Pathophysiology

There is a developing appreciation for the complex reciprocal pathophysiologic relationship between the development of AF and HF [5]. Both of these comorbidities share a common set of well-defined risk factors such as age, hypertension, diabetes, valvular disease and coronary disease, which partially explains these tandem epidemics. However, the interplay between these conditions likely involves a positive feedback loop whereby HF leads to a volume and pressure overload state promoting interstitial fibrosis leading to altered atrial refractory properties and heterogeneity of repolarization. This substrate eventually gives way to AF, which then causes a loss of atrial-ventricular synchrony, rapid ventricular response and irregularity of heart rhythm which further promotes atrial and ventricular remodeling thus continuing the cycle of AF and HF.

Influence of Atrial Fibrillation on Cardiac Performance

The onset of AF is known to impair cardiac performance particularly in patients with underlying HF [6]. A rapid ventricular rate can lead to inadequate stroke volume via suboptimal diastolic filling as well as the development of rate-related cardiomyopathy over time. Bradycardia may lead to syncope or other manifestations of inadequate cardiac output in the setting of low stroke volume. The irregular rhythm inherent to AF impairs both diastolic filling of the ventricles and leads to reduced stroke volume. Cardiac

output may be further impaired by the loss of atrial systole and for some patients the transition from sinus rhythm to AF and sudden loss of atrial "kick" can exacerbate HF leading to acute symptoms prompting hospitalization. Atrial fibrillation activates the neurohormonal axis leading to further maladaptive atrial and ventricular remodeling as well as a pro-inflammatory state as evidenced by increased circulating levels of cytokines IL-6 and TNF-alpha [7]. Patients with HF who have persistent AF have demonstrated diminished exercise capacity (as measured by peak oxygen consumption during cardiopulmonary exercise testing) as well as decreased stroke volume index (as measured by oxygen pulse) when compared to patients with HF who are in sinus rhythm [8]. Nevertheless, one of the challenges of determining the hemodynamic and functional impact of AF on HF is distinguishing between true cause and effect versus the identification of AF as a surrogate marker of HF disease severity.

Influence of Atrial Fibrillation on Heart Failure Mortality

The role of AF as an independent contributor toward mortality in patients with HF is not well established. However, observational data from the Framingham heart study suggest that patients with AF and HF are 1.5–3 times more likely to die than patients in sinus rhythm [9]. On the other hand, subsequent cohort studies involving optimally medically managed HF patients found no independent association between AF and mortality after controlling for NYHA class, coronary artery disease, diuretic use, hemoglobin level and serum creatinine [10]. Clinical trials involving subset analyses of patients with AF and symptomatic HF have also presented conflicting data. Both SOLVD [11] (Studies Of Left Ventricular Dysfunction prevention and treatment) and CHARM [12] (Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity program) involved large samples of symptomatic HF patients (6,517 and 7,599, respectively) and demonstrated an independent association with all-cause mortality in patients with AF. However, these findings conflicted with the much smaller Veterans Affairs Vasodilator-Heart Failure Trials (V-HeFT-I, II) that evaluated a total of 1,427 patients with mild to moderate symptoms of HF in which 14 % had AF, yet there was no independent association with increased mortality or hospitalization [13].

Clinical Trial Evidence for Pharmacologic Restoration of Sinus Rhythm

In the setting of observational data as well as trial data suggesting the possible contribution of AF to increased mortality in patients with underlying HF, many have hypothesized that restoration of sinus rhythm may be a superior approach to rate control in patients with HF. To date, no large clinical trial has been able to demonstrate clear survival advantage of antiarrhythmic drug (AAD) therapy as a rhythm control strategy. However, the evidence-based medicine paradigm for following the intention-to-treat principle in clinical trials can make the interpretation of each trial more complicated than the summary headline; careful review of each relevant trial as well as a recent meta-analysis tells a more complete story of the net benefits of restoration of sinus rhythm in heart failure (Table 13.1) [14].

A clear observational trend has been the association of successful restoration of sinus rhythm with improved survival and reduced secondary endpoints such as hospitalization. What remains unclear is whether achieving sinus restoration resembles a marker of improved prognosis independent of AADs or if therapeutic intervention with AADs confers a survival benefit that is counter-balanced by known drug toxicity and proarrhythmia. Regardless, approved AADs (particularly amiodarone and dofetilide) used for the restoration and maintenance of sinus rhythm appear to be safe in patients with HF when administered appropriately in accordance with published guidelines. Dronedarone should clearly be avoided in patients with recently decompensated or advanced HF (NYHA class III–VI). The

Table 13.1 Summary of rate versus rhythm control studies in heart failure patients

Study	Sample size	Age (years)	Study population/intervention	Outcome variables	Outcome
AFFIRM	4,060	70	10 % with LVEF <40 %; 9 % with CHF	Mortality	No difference
			46 % paroxysmal, 54 % persistent	Hospitalization	No difference
			Dofetilide not used at all		
AF-CHF	1,376	67	100 % with LVEF ≤35 %, NYHA III–IV	Cardiac mortality	No difference
			32 % paroxysmal, 68 % persistent	CHF, stroke, or death	No difference
			Predominantly amiodarone		
RACE	522	69	9 % with dilated cardiomyopathy	Cardiac mortality	No difference
			50 % NYHA I, 47 % NYHA II	Heart failure	No difference
			100 % paroxysmal AF, median of 33 days		
HOT CAFE	205	61	NYHA class I–II, unknown LVEF	All cause mortality	No difference
			Chronic persistent AF, 84 % 1–24 months	Stroke, embolic event	No difference
			Mostly disopyramide, sotalol, propafenone	Bleeding	No difference
Okcun	154	60	Non-ischemic CM, mean LVEF 32 %	All cause mortality	Sinus superior
			Persistent AF, mean 12 months	CHF, embolic event	Sinus superior
			Amiodarone only	LVEF improvement	Sinus superior
CAFÉ-II	61	72	NYHA class II–III, LVEF 30–40 %	Quality of life	Sinus superior
			Persistent AF, median 14 months	Exercise capacity	Sinus superior
			Amiodarone load + DCCV + amiodarone	LVEF, NT-proBNP	Sinus superior
Kanorskii	223	56	NYHA class II–III, reduced LVEF	All cause mortality	Sinus superior
			Persistent atrial fibrillation	Cardiac mortality	Sinus superior
			Undefined rhythm control strategy	Stroke	Sinus superior

PALLAS trial suggests that it should be avoided altogether in patients with any heart failure [15]. No other AADs have been sufficiently studied to comment on safety or efficacy in HF. The following section summarizes select relevant trials of AADs involving patients with HF and/or reduced left ventricular systolic function. A general review of rate versus rhythm control trials involving patients without HF is described elsewhere [16].

The AFFIRM Trial

The frequently cited Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial sought to address the larger question of rate versus rhythm control involving a heterogeneous population of 4,060 patients with both persistent and paroxysmal AF as well as largely preserved ejection fraction; only 9 % of patients with a

history of HF [17]. The most commonly used rhythm control agents included amiodarone and sotalol and it is noteworthy that the period of enrollment preceded the modern utilization of rhythm control agents dofetilide and dronedarone. There was no statistically significant difference in the primary endpoint of death between the rate and rhythm control groups, by intention-to-treat analysis.

On-treatment analysis of AFFIRM, however, was notable for lower death rates in those patients who achieved restoration of sinus rhythm [18]. However, when adjusted for sinus rhythm, AAD therapy was associated with increased mortality, leading the authors to suggest the benefits of AADs may be negated by drug toxicity. Further analyses demonstrated that patients over age 65 years and without a history of HF fared better with a rate control strategy [19]. Additional subset analyses of all the AFFIRM patients with abnormal left ventricular systolic function was notable for similar findings of no difference in mortality [20]. However, only 155 patients out of the original 4,060 had a left ventricular ejection fraction (LVEF) <30 %. Less than half of those 155 patients had AF at the time of enrollment, further suggesting the limited application of AFFIRM when trying to determine the superiority of a rate or rhythm control strategy in patients with severe systolic dysfunction. Similar findings were noted in a small subset analysis of 261 HF patients in the Rate Control versus Electrical Cardioversion (RACE) trial, which randomized patients to rate control versus serial cardioversion with institution of AADs [21].

The DIAMOND CHF Trial

The Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) CHF study evaluated 1,518 patients with symptomatic HF and LVEF <35 % randomizing them to placebo or dose-adjusted dofetilide [22]. The study did not base enrollment on the presence or absence of AF since the hypothesis was that dofetilide would reduce mortality and/or morbidity by decreasing the occurrence of AF or flutter. Patients had a mean age of 70 years, many had chronic kidney disease, and most had NYHA Class II–III symptoms of HF. Approximately 26 % were noted to have AF at the time of enrollment. Notably only 10 % of patients were taking a beta-blocker at enrollment. Nearly half of all the patients enrolled in the study died, but there was no survival difference between the dofetilide and the placebo groups, arguing for the overall safety of this medication in severe systolic HF.

Subset analyses of DIAMOND-CHF demonstrated that the proportion of patients maintaining sinus rhythm following cardioversion of AF or flutter was 79 % among patients on dofetilide, compared to 42 % for those treated with placebo [23]. Furthermore, patients who achieved restoration of sinus rhythm had significantly improved overall survival as well as reduced rates of hospitalization. Findings in DIAMOND-CHF resembled those from the Veterans Affairs Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) in which HF patients with a low LVEF given amiodarone (versus placebo) had an increased likelihood of restored sinus rhythm, maintained sinus rhythm, and improved survival when sinus rhythm was restored.

The AF-CHF Trial

The Atrial Fibrillation and Congestive Heart Failure Trial (AF-CHF) is the first large randomized trial that directly compared the rate and rhythm control strategies in 1,376 patients with HF symptoms and an ejection fraction <35 % [24]. The patients were elderly (most over 80 years of age), and a majority had NYHA class II symptoms and persistent AF. Nearly half presented with greater than 6 months of persistent AF. The patients were randomized to rate control or rhythm control strategies involving electrical cardioversion plus AAD with nearly all patients receiving amiodarone (<2 % received sotalol and <1 % received dofetilide). While rhythm control therapy was more successful in restoring and maintaining sinus rhythm, rates of overall

mortality, stroke, and worsening HF did not significantly differ between the two groups. Reasonable conclusions from this trial may be that elderly patients with low LVEF, mild symptoms of HF, and persistent AF experience no difference in survival benefit when treated with standard rate control strategies (beta-blockers and digoxin) versus when treated with electrical cardioversion and amiodarone therapy. A major limitation of studies such as the AF-CHF trial, however, are the possibility that they are unable to detect subtle, yet meaningful, improvements in quality of life and functional capacity that might be associated with restoration of sinus rhythm in individual patients with heart failure.

The Role of Dronedarone in Heart Failure

Dronedarone is a benzofuran-derivative class III antiarrhythmic agent thought to have pharmacologic properties similar to amiodarone, although it offers a shorter half-life without the iodine toxicity profile associated with amiodarone. Enthusiasm for dronedarone has been driven by its ability to improve survival and/or reduce hospitalizations and to restore sinus rhythm in more patients when compared to placebo after being studied in a population very similar to that in AFFIRM [25]. However, when evaluated in patients with recent decompensated HF, particularly NYHA class III–IV, dronedarone doubled the all-cause mortality (related to progressive HF and arrhythmias) leading to early termination of the study [26]. The most recent PALLAS trial (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy) enrolled 3,236 patients with at least 6 months of permanent atrial fibrillation, of whom over 50 % presented with symptoms of heart failure and approximately 20 % had an LVEF <40 % [15]. The study was stopped prematurely for safety reasons due to increased rates of cardiovascular death, stroke, and hospitalizations for heart failure.

Observational and Clinical Trial Evidence for Catheter-Based Interventions

Few trials have been directed specifically toward studying invasive methods for treating AF in HF. Early evidence has been observational, suggesting the possible role for pulmonary vein isolation (PVI) as a catheter-based therapy for AF in patients with a reduced LVEF. Catheter ablation for AF is based on contemporary understanding that most of the ectopic foci that trigger AF, and the substrate for maintenance of AF, originate from the pulmonary veins and surrounding atrial antral tissue [27]. The technique begins with left atrial transseptal catheterization, often using the assistance of intra-cardiac echocardiography, followed by placement of both ablation and mapping catheters into the left atrium allowing for contiguous point-by-point delivery of a radiofrequency current around ipsilateral pairs of pulmonary veins, thereby achieving electrical isolation from the left atrium (Fig. 13.2). For patients with HF and AF, especially for patients with HF and persistent AF, additional focal or linear left atrial ablation, beyond PVI, that targets potential drivers of the AF, such as sites associated with complex fractionated electrograms, is often required to prevent recurrent AF.

Technical challenges of PVI for patients with impaired LV systolic function include elevated left atrial filling pressures leading to hypertrophied and dilated atrial tissues as well as dilated pulmonary vein ostia leading to a potentially greater tissue depth and area requiring ablation to achieve effective isolation. For patients with significantly symptomatic paroxysmal AF who have failed pharmacologic restoration of sinus rhythm and have nearly normal left atrial size and normal or mildly reduced LVEF, the most recent societal guidelines give a Class I recommendation (Level of Evidence: A) for catheter ablation to be performed in experienced centers [28]. There remains a need for more studies regarding the role for catheter-based interventions in the treatment of AF in HF.

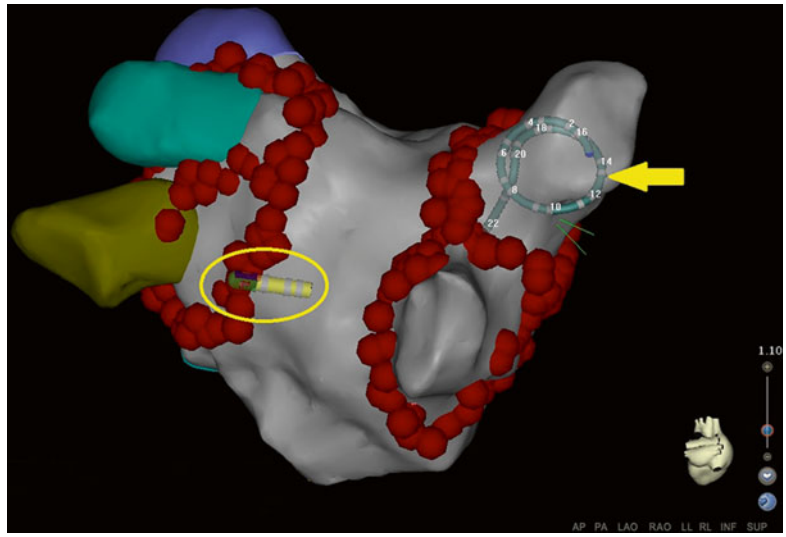

Fig. 13.2 Pulmonary vein isolation represented on electroanatomical mapping system. The electroanatomical mapping system is a software program that constructs a spatial representation of each contiguous radiofrequency ablation point (represented by the *red dots*). The *yellow arrow* indicates the mapping "lasso" catheter used to demonstrate the intracardiac electrogram which is important for confirming electrical isolation of the pulmonary veins. Note the numbering of each electrode on the mapping catheter beginning distally and ending proximally. The *yellow circle* is highlighting the ablation catheter used to perform each sequential radiofrequency ablation during the pulmonary vein isolation

Initial evidence for the potential role for PVI in patients with AF and HF came from retrospective and prospective cohort studies. In one such single center retrospective study, 377 consecutive unselected patients referred for PVI for symptomatic AF refractory to AAD were included in the analysis [29]. Ninety-four patients, mostly men with a mean age of 57 years, had an average LVEF of 36 % with symptoms of HF prior to PVI (64 % had NYHA Class III symptoms). The proportions of paroxysmal and permanent AF were similar. Compared to patients with preserved LV function, patients with HF and impaired LV function had a higher rate of recurrence of AF (27 % vs 13 %) but 78 patients (73 %) had sinus rhythm at the mean follow-up period of 14 months. Twenty-one of the original 94 patients required repeat PVI, but 96 % of the repeated procedures led to complete freedom from AF/flutter. The LVEF did improve by 5 % without meeting statistical significance. A subsequent case-control study involving 58 consecutive cases of HF and a low LVEF undergoing catheter ablation for AF, matched with 58 controls without HF, demonstrated similar findings, including improved LVEF, symptoms, exercise capacity, and quality of life among HF patients [30].

The PABA-CHF Trial

The Pulmonary-Vein Isolation for Atrial Fibrillation in Patients with Heart Failure study (PABA-CHF) remains the only prospective, multicenter, randomized clinical trial of its kind—recruiting a total of 91 patients with symptomatic AF resistant to AADs, HF (NYHA Class II–III), and an LVEF of 40 % or less [31]. The patients were assigned to PVI or atrioventricular-node ablation with biventricular pacing (since biventricular pacing had been deemed superior to right ventricular pacing in ventricular pacemaker-dependent patients). Patients were predominantly men with a mean age of 61 years. Approximately

Table 13.2 Characteristics and outcomes of patients with heart failure or left ventricular systolic dysfunction undergoing catheter-directed pulmonary vein isolation for atrial fibrillation

Characteristics	Observed outcomes	Factors associated with favorable outcomes
Heterogeneous population	Complication rate 6–7 % overall[a]	Non-ischemic etiology of HF
Male sex = 77–95 %	No mortality difference	Symptomatic atrial fibrillation
Mean age = 49–62 years	Increased freedom from AF	Paroxysmal atrial fibrillation
LVEF = 35–43 %	Mean 11 % improvement in LVEF	Maintained sinus during follow-up
LVEDD = 5.6–6.2 cm	Improved exercise capacity[b]	Younger age
Ischemic and non-ischemic	Improved quality of life[b]	Poor rate control

[a]Complications include stroke, pericardial tamponade, pulmonary edema, pulmonary vein stenosis, bleeding
[b]Methods for assessing exercise capacity and quality of life were inconsistent between studies

70 % had coronary artery disease and there was an even split between paroxysmal or persistent AF with the mean duration of AF approaching 4 years in both groups. The average ejection fraction was approximately 28 % for both groups and the left atrial diameter was nearly 5 cm. Patients had similar normal baseline heart rates and normal QRS duration without any patients with left bundle-branch block. Endpoints included echocardiogram-determined LVEF, the 6-min walk test, the Minnesota Living with Heart Failure (MLWHF) score as well as rates of symptomatic and asymptomatic episodes of AF. At 6 months, patients that underwent PVI demonstrated an improved MLWHF score, a longer 6-min walk distance (340 m versus 297 m), and a higher ejection fraction (35 % versus 28 %). Also, 71 % of patients who underwent PVI were free from AF at 6 months without any AADs while 88 % were free from AF regardless of the use of AADs.

Conflicting Evidence for Pulmonary Vein Isolation

Few studies have conflicted with the PABA-CHF study, but one single-center trial recruited AF patients from HF clinics in Scotland and randomized them to PVI or rate control therapy [32]. Overall, patients enrolled were very similar to patients in PABA-CHF, although all patients had persistent AF rather than paroxysmal AF. The study was powered to detect a mean difference in change in ejection fraction of 6.8 % (using an unusual combination of radionuclide ventriculography and cardiac magnetic resonance imaging) assuming an 80 % success rate of PVI restoring sinus rhythm after 6 months. The study ultimately failed to meet its target assumptions and there was no difference between the two groups. Other important findings included a restoration of sinus rhythm in only 50 % of patients at 6 months in the PVI group. Findings from this trial are difficult to interpret given the many limitations of the study design. However, one could hypothesize that patients with severe HF and persistent AF may not be as amenable to restoration of sinus using catheter ablation. A recently published meta-analysis evaluating all nine applicable cohort studies, case-control studies, and clinical trials demonstrated that, in general, catheter ablation for AF in symptomatic patients with low LVEF appears to result in improved cardiac performance (Table 13.2) [33]. No study has been able to demonstrate an overall survival benefit or reduction in clinical events such as HF hospitalizations.

A Practical Approach to Management of Atrial Fibrillation in Heart Failure

After reviewing the evidence for strategies for restoring sinus rhythm, one is left with a paucity of data to guide therapy of AF in HF. Indeed, the only clearly established and agreed upon therapy that uniquely pertains to AF in HF is anticoagulation for stroke prevention. However, some themes

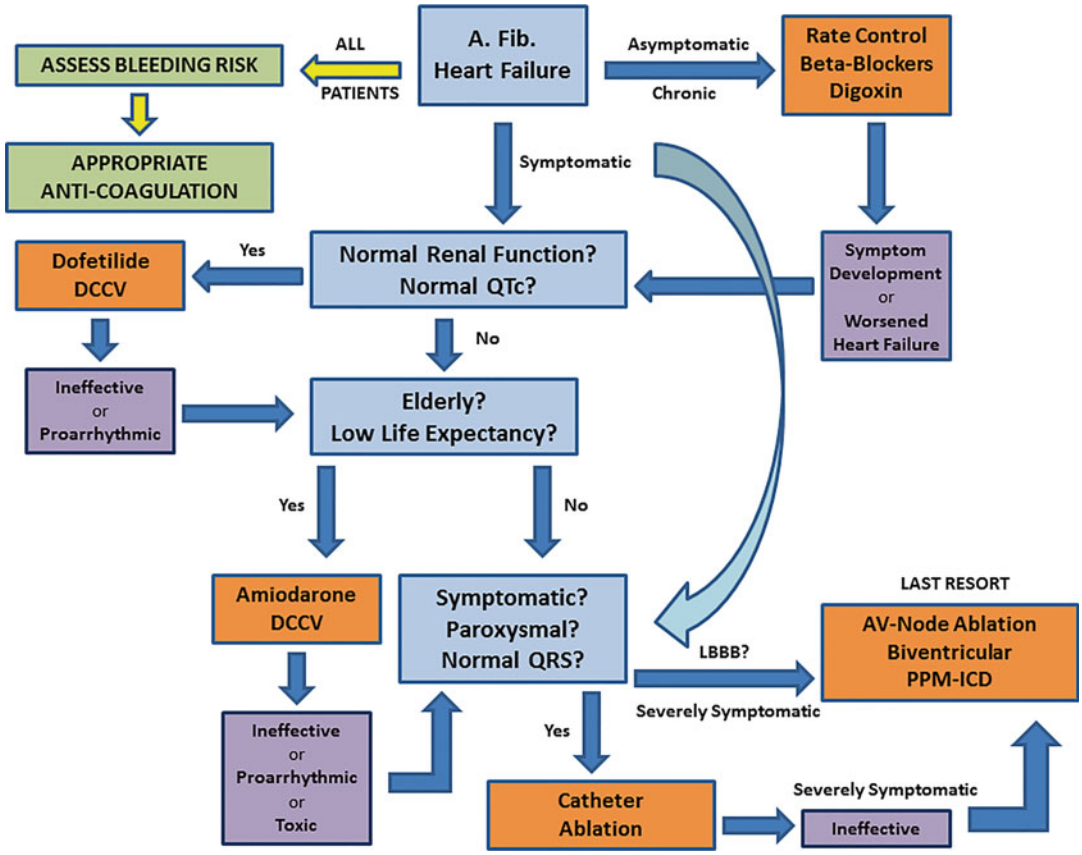

Fig. 13.3 A practical approach to patient individualized treatment of atrial fibrillation in heart failure

can be gathered from the existing studies summarized previously that can help provide suggestions for therapy (Fig. 13.3). First, since no study has ever established clear mortality benefit of rhythm control when compared to optimal rate control, patients with persistent AF who are tolerating a rate control strategy without significant symptoms or further decompensation of HF should continue a rate control strategy. This approach probably pertains more to patients who are older and have more established AF since the old adage "AF begets AF" holds true in patients with structurally abnormal hearts. However, we can also conclude from the evidence that amiodarone and dofetilide (if initiated and monitored appropriately) have an established safety profile even among older patients with persistent AF and more advanced HF. Rhythm control strategies may be uniquely suited for patients with new onset AF, symptomatic paroxysmal AF, or HF symptoms that can be temporally associated with paroxysms of AF. Moreover, patients with AF less amenable to rate control may also have a more notable improvement with a strategy to restore sinus rhythm.

Rate Control Strategies

For patients who are deemed most appropriate for a rate control strategy, there are limited data to guide the choice of rate control agent. Given the known beneficial effects of beta-blockade in patients with chronic HF, these agents (particularly bisoprolol, carvedilol, and metoprolol) should be the first-line treatment particularly in the setting of reduced left ventricular systolic function when long-term rate control is needed.

There have been a few small studies demonstrating the improved rate control and improved HF symptoms when patients have digoxin added to standard beta-blockade therapy, particularly when added to carvedilol [34]. Generally non-dihydropyridine calcium-channel blockers should be avoided in HF. However, there are very limited data demonstrating a possible role for intravenous diltiazem when acute rate control is needed for the treatment of patients with AF, rapid ventricular response, and moderate to severe decompensated HF [35].

Optimal long-term ventricular response rate for patients with persistent AF and heart remains unclear. The RACE II trial attempted to address this question although the vast majority of patients had no HF symptoms and only 15 % of patients had an LVEF <40 % [36]. Moreover, only 75 % of patients in the strict rate control cohort achieved the target heart rate of less than 80 bpm which may have biased the results of the study toward non-inferiority of lenient control. In addition, only 22 % of the lenient control cohort had a heart rate over 100 bpm at rest.

Conclusions

Heart failure and AF often coexist. Atrial fibrillation is associated with increased mortality and hospitalizations among patients with HF, particularly within the elderly population. All patients with AF and HF should be anticoagulated unless a significant contraindication is present. Rhythm control strategies have not been demonstrated to provide superior mortality benefit, although an individualized approach to treatment remains an appropriate strategy for improving patient symptoms and possibly reducing hospitalizations. Dofetilide and amiodarone are the only agents sufficiently studied to be deemed safe for patients with AF and symptoms of HF. Catheter-directed pulmonary vein isolation may have an emerging role for treating patients with symptomatic AF in the setting of chronic HF. Beta-blockers plus digoxin achieve the best rate control in HF patients who are deemed inappropriate for restoration of sinus rhythm or while awaiting cardioversion. AV-nodal ablation and biventricular pacemaker placement should be reserved for patients with refractory symptoms and inadequate rate control despite all other attempts at rate or rhythm control.

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Surgical Therapy for Atrial Fibrillation

14

Gil Bolotin and J.G. Maessen

Background

The first modern successful surgical approach to atrial fibrillation was presented in 1980 by Boineau et al. [1, 2]. They described left atrial isolation, which was capable of confining atrial fibrillation to the left atrium while leaving the remainder of the heart in normal sinus rhythm. However, since the left atrium continued to fibrillate, the risk of thromboembolism remained unchanged. The corridor procedure, described by Guiraudon in 1985, isolated a band of atrial septum, including the SA node and the AV node [3]. Again, the disadvantage was that both atria continued to fibrillate postoperatively. The results were therefore disappointing, in terms of both the hemodynamics as well as the risk for thromboembolism. After talented and thorough basic research on animal models, Cox and coworkers presented the Maze procedure aimed to direct the propagation of the sinus impulse throughout both atria, thereby restoring normal cardiac hemodynamics and reducing the risk for thromboembolism.

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The Maze Procedure

The Maze-I procedure was presented in 1991 [4]. However, due to some late chronotropic complications and intra-atrial conduction delays that resulted in decreased left atrial contraction, a modification named Maze-II was presented [5]. A third version of the procedure (Maze III) was presented in 1995 in order to simplify the procedure [7]. In the Cox-Maze III operation, incisions and cryolesions are strategically made to interrupt the multiple reentrant circuits of AF. Right and left atrial incisions interrupt the most common reentrant circuits and direct the sinus impulse from the sinoatrial node to the atrioventricular node along a specified route.

Maze III Surgical Technique

The right atrial appendix is excised, leaving at least 2 cm of visible atrial tissue between the incision and the anterior SVC. A second perpendicular incision is made from the middle of the first incision 2 cm down toward the free wall of the right atrium. A posterior longitudinal right atriotomy is then placed from the SVC toward the IVC. From the latter incision, another perpendicular incision is made 1 cm above the IVC cannula, and up to the tricuspid annulus. An adjuvant cryolesion is added at the level of the annulus to be certain that no fibers capable of

J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_14

conduction will be left. The last incision on the right side is directed anterolaterally from the excised appendix, and up to the tricuspid annulus. This is accompanied by an adjuvant cryoablation at the annular level. The left atrial and septal incisions include a standard left atrial incision in the inter-atrial groove and another incision of the atrial septum through the fossa ovalis. The first incision in the inter-atrial groove is then enlarged under vision to encircle and isolate the pulmonary veins from the left atrium. The last part of the circle is completed with cryoablation. The left atrial appendix is amputated from the inside. The last incision is from the pulmonary circle toward the mitral annulus. To complete that part of the procedure, cryoablation is performed at the mitral annulus level and around the coronary sinus. All incisions made are closed using a continuous suturing technique. In 2000 Cox presented a minimally invasive modification for the procedure, in which cryolesions replace most of the incisions and the left atrial appendange does not need to be removed. The orifice of the appendage was cryoablated circumferentially and then closed from inside the left atrium [7].

Maze III Results

The Cox-Maze III operation is the gold standard for surgical treatment of AF. Cox and colleagues have reported excellent results of patients undergoing Cox-Maze procedures of all types [8]. Out of 346 patients, operative mortality was 2 %. AF was cured in 99 %, and only 2 % required long-term postoperative anti-arrhythmic medication. Successful ablation of AF was unaffected by the presence of mitral valve disease, left atrial size, and type of AF (paroxysmal versus persistent). Temporary postoperative AF was common, occurring in 37 % of patients. The authors' explanation was that because of the immediate postoperative period and until the atria heal from surgery, local refractory periods may be much shorter and thus the macro-reentrant circuits can be much smaller [9]. Fifteen percent of patients required new pacemakers after surgery. Right atrial transport function was demonstrated in 98 % and left atrial transport function in 93 %.

The results of the Maze III as reported by other centers were less favorable. At the Cleveland Clinic and Mayo Clinic, late freedom from AF is reported to be around 90 % [10]. In a wide review of all the published data done by Khargi and coworkers in 2005, the results of 1,553 patients that underwent Maze III (out of 16 publications) is summarized [11]. The mean postoperative SR rates were 84.9 %. Personal experiences of the editor of this book and Dr Melo from Carnaxide, Portugal, with the cut-and-sew maze procedure have been even less favorable. Major limitations of many of the follow-up studies of these surgical series are that they often relied on postal or telephonic follow-up. Atrial transport function was frequently measured with erroneous measures such as trans-mitral Doppler velocities (such as e/a ratios). Despite the supposed excellent results of the Maze procedure from the early 1990s onwards, less than 4,000 cut-and-sew maze procedures have been performed worldwide. This may also be in part due to longer operative times and increased morbidity and mortality of this procedure.

Less-Invasive Surgical Procedures

Partial Mazes

Many groups have reported procedures [12, 13] that include some of the incisions and cryoablation lesions of the Cox-Maze III operation, but not all; these are categorized as partial-Maze procedures. They tend to focus on the left atrium, including isolation of the pulmonary veins and excision or exclusion of the left atrial appendage. They generally ignore the coronary sinus, which supposedly increases the risk of atrial flutter [14].

Alternative Energy Sources to the Classical Cut-and-Sew Technique

In the last few years, several alternative energy sources have been introduced for ablating the

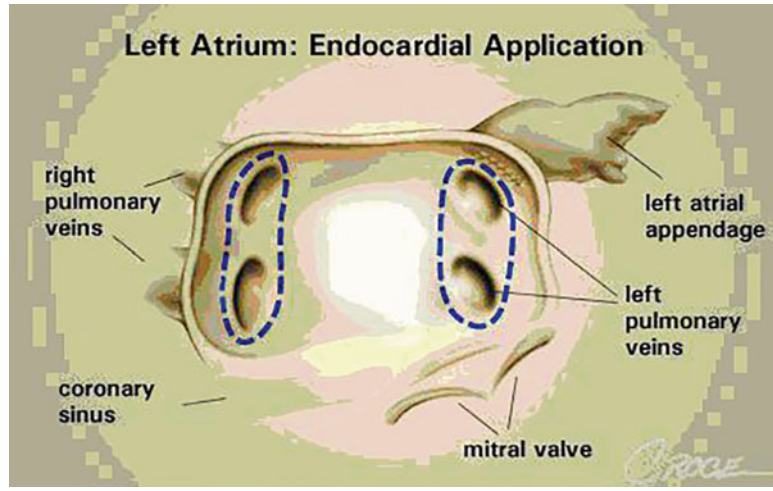

Fig. 14.1 Early endocardial lesion set – proposed by Melo, based on bilateral isolation of pulmonary veins with LAA closure

heart tissue during atrial fibrillation surgical procedures [14]. The main advantages are less time and less risk as compared to the classic Maze III. The main problem with all of the energy sources is whether or not a transmural lesion is achieved (Fig. 14.1).

Radiofrequency

Unipolar, unipolar with irrigated cooling, and bipolar systems with irrigated cooling are available in the market. The unipolar probes are used mainly endocardially, though there have been reports of unipolar epicardial applications also. Bipolar radiogrequency ablation is usually for epicardial ablation. Most bipolar systems have a flaw in that high impedance is often equated with a transmural lesion. Probably, the bipolar systems have some advantage in creating trans-mural lesions because of capture of the tissue between the electrodes. However, bunching of the tissue and incomplete coverage may be an issue. Furthermore, connecting lesions to remote areas of the left and right atrium are impossible to achieve. Although lesions sets created with radiofrequency energy vary, results are similar: AF is ablated in 70–80 % of patients [15–17]. Perioperative AF after radiofrequency ablation is common, occurring in approximately two-thirds of patients [18] (Figs. 14.2, 14.3, and 14.4).

Fig. 14.2 Cobra-adhere – Unipolar Radio-frequency ablation device. This device delivers unipolar radio-frequency to the atrial along with some weak suction to promote contact of the electrodes with the tissue

Microwave

The microwave probes are used mainly epicardially. The long Flex 10 probe was designed to be used for minimally invasive approaches and robotic-assisted ablation [19, 20]. This energy source has largely been abandoned.

Cryo-ablation

Sueda and colleagues reported successful ablation using cryothermy ablation [12]. Gaita and coworkers have reported limited left atrial cryo-ablation combined with isolation of the pulmonary veins cures AF in approximately 70 % of patients [21] (Figs. 14.5, 14.6, and 14.7).

Fig. 14.3 Shows Medtronic Cardioblate, a bipolar Irrigated Radio-frequency Ablation Device, that has been used widely in Europe

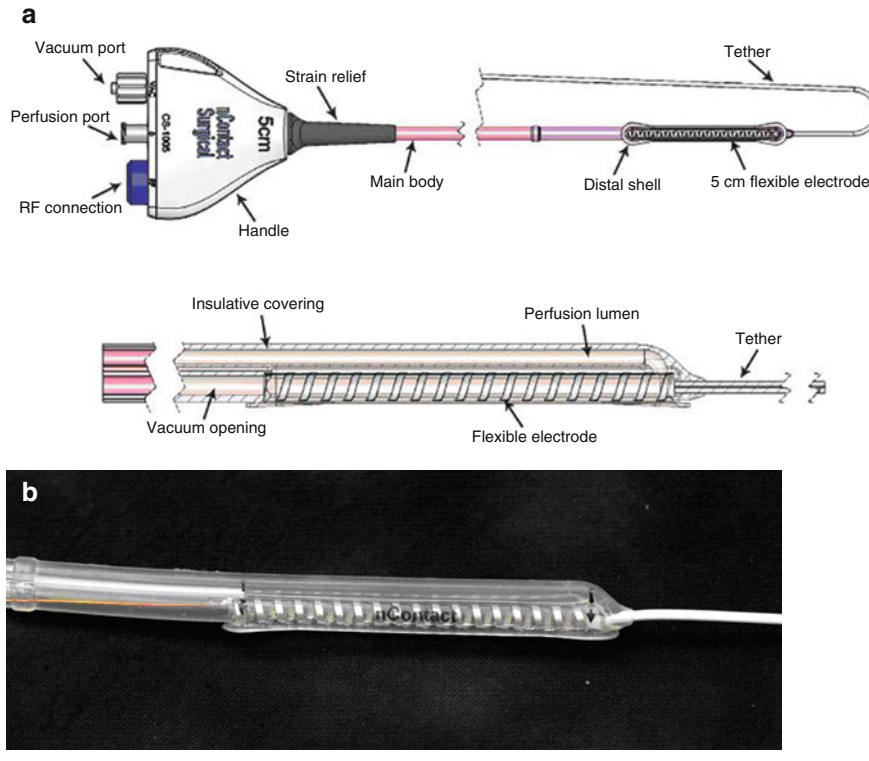

Fig. 14.4 (**a**, **b**) Shows the new nContact probe, that utilizes irrigated unipolar radio-frequency and suction based tissue adhesion during lesion creation

The Issue of Transmurality in Surgical Ablation for Atrial Fibrillation

The only goal of producing lesions with any ablation tool is the substitution of conducting tissue by non-conducting, scar tissue. The golden standard has been supposedly set by the "cut and sew" technique in the original Cox-Maze procedure. This is a "gold standard" that few discerning surgeons and even fewer in the cardiological community accept. In percutaneous ablation approaches, cardiologists have translated this goal in achieving conduction block as evidenced

by electrophysiological measurements. The percutaneous approach allows checking for conduction block during the intervention. In line with the Maze procedure, surgeons redefined this goal into the production of histologically transmural lesions. In contrast to their Cardiology colleagues, they can check the histological quality of their lesions only by indirect means. Despite excellent clinical results obtained by surgeons in treating atrial fibrillation, recent studies have shown that the establishment of histologically transmural lesions is not as obvious as generally assumed. The question is whether this is important for our routine ablation procedures, and if so, how should we deal with it, based on the current evidence available [22–25].

Tissue characteristics considerably influence the continuity of lesions and lesion depth in the first place. The thickness of the atrial wall may vary tenfold within one ablation line. Similarly, the amount of fat tissue present in the different areas around the pulmonary veins shows a high intra and inter-individual variability. Furthermore,

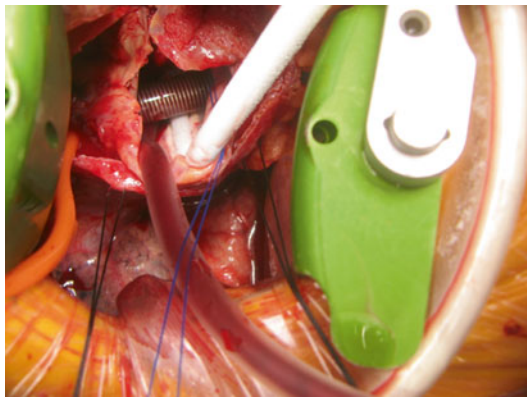

Fig. 14.5 This operative photograph of a mini-thoracotomy Maze procedure. It shows the flexible SurgiFrost, with the malleable cryo-probe inside the right atrium, adherent to the inner wall with cryotherapy while going around the venous cannula

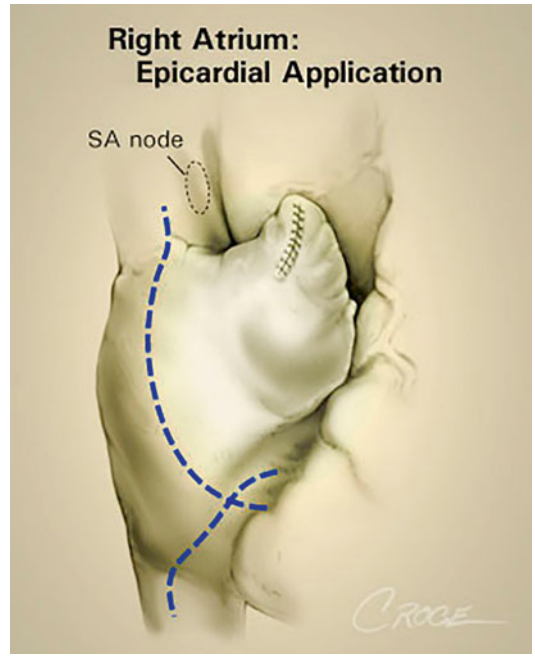

Fig. 14.7 Shows the proposed lesion sets on the right and left atria, that have the best likelihood of replicating the Cox-maze 3 lines of block with a variety of energy sources

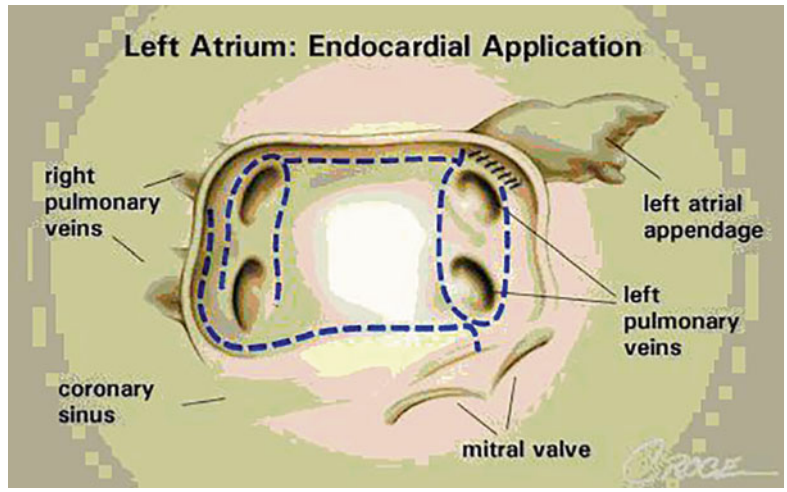

Fig. 14.6 Shows the proposed lesion sets on the right and left atria, that have the best likelihood of replicating the Cox-maze 3 lines of block with a variety of energy sources

trabeculated areas creating bridges from isolated regions to normal conducting tissue may be responsible for persistent conduction. In the elderly and in patients with manifest hypertrophy of the atrial tissue, the presence of scattered fibrosis may offer another hurdle for ablation techniques to make smooth, consistent lesions. The temperature of the tissue and its surroundings is also likely to affect the lesion depth but poorly studied in the clinical setting. Beating heart versus the arrested heart, hypothermic perfusion versus normothermic perfusion, epicardial versus endocardial, all these approaches offer different environmental conditions for the ablation tools. An experimental study suggested that with radiofrequency ablation the endocardial approach is more effective than the epicardial approach. It is very likely that these unpredictable and mostly uncontrollable conditions determine the quality of a lesion set rather than the energy source used for the ablation or the design of the tool [26].

Most information on the quality of ablation lesions has been offered by studies on isolating pulmonary veins. The human anatomy allows ablation of the pulmonary veins, one by one, two by two, and sometimes, all four or five together in one encircling. The existence of an entrance and exit block between the pulmonary vein area and the atrial tissue, proving electrophysiological isolation, can thus be easily determined by monitoring the EKG during pacing from within and outside the isolated area. From such studies, the need for transmurality and the equivalence between transmurality and electrophysiological isolation, has been questioned. First, it was shown that transmurality may not be obtained until several weeks after ablation whereas electrical isolation is achieved immediately during the procedure suggesting that lesions may develop in time. Secondly, an autopsy study revealed that certain patients in sinus rhythm with proven conduction block during surgery, appear to have incomplete continuity of their lesion set and partially, incomplete transmural lesions at autopsy [26]. This observation was confirmed in a study in which 58 ablation lesions from seven patients who died between 2 and 22 days postoperatively, were studied [27]. These seven patients had a concomitant anti- arrhythmic procedure using saline irrigated cooled tip radiofrequency ablation (SICTRA) to treat permanent AF. Histological examination showed transmurality in 96–100 % of the SICTRA lesions at the pulmonary vein orifices and the posterior left atrial wall, but only in 14 % of the left atrial isthmus lesions, resulting in an overall transmurality rate of 76 % of the induced SICTRA lesions. Finally, it was demonstrated that in a large group of patients with clinically successful treatment and proven electrophysiological block initially during the intervention, conduction block was lost several months after the ablation procedure without recurrence of atrial fibrillation [28]. What all these means clinically is open to question. The left atrial isthmus lesion along with the coronary sinus lesion were insisted as being essential by Cox, based on anecdotal experience with a few patients and this may in itself be fallacious.

From these observations one can only conclude that our current understanding of the success of our ablation procedures is at least incomplete. In an effort to address this problem, a recent experimental study showed that the effect of isolating the pulmonary veins is not an all-or-none phenomenon. Complete isolation of the pulmonary veins revealed a 100 % success rate. However, if deliberately a gap was left in the encircling of the veins, still a very significant reduction of the susceptibility of the atrial tissue for atrial fibrillation was observed [20]. However, these were animal studies not conducted in a chronic AF model. These findings may offer an explanation for the discrepancy between the claims and reality of relatively high success rate of today's pulmonary veins ablation procedures despite the conflicting data about continuity and transmurality of the lesions produced by these techniques. Apparently, these procedures not only affect the pulmonary veins but other structures involved in the initiation or maintenance of atrial fibrillation as well [29–33].

Transmurality has become an important issue, partly because several companies claim that their tools create transmural lesions suggesting that others don't. Comparative, clinical studies are in progress but do not yet allow final conclusions on superior efficacy of certain tools. The current

clinical impact of the transmurality issue is difficult to assess. A systematic review offered some important hints in this respect. The results of the classic "cut and sew" Cox-maze III procedures were compared to results of procedures using alternative sources of energy to obtain a bi-atrial lesion pattern. Patients in the first group had a 85.3 % post-operative SR conversion rate versus 79.7 % in the ablation group. If this difference of 5.6 % can be completely attributed to problems in achieving transmurality, the impact is distinct but small [11]. This may also be partly due to inadequate appreciation of the limitations of each of the alternative energy sources by the surgeons.

Based on the currently available evidence, one might conclude that histological transmurality is not a prerequisite for clinical success. Measuring the occurrence of a conduction block during ablation is an informative but not conclusive tool to determine successful treatment. Sophisticated mapping techniques might appear necessary to guide ablation strategies and control its efficacy in the future. More comparative clinical as well as experimental studies are needed to test the effectiveness of various ablation tools in this respect. The ultimate target for more successful ablation procedures has yet to be defined.

Results

In general the results of all ablation-based surgical procedures range around 70 % sinus rhythm at 6 months post-operatively. Neither energy source nor surgical technique (excluding the classic Maze III procedure) has been found to be superior. The reason for this is probably multifactorial, including lack of transmural lesions in many cases, different lines of ablation, and different patient selection as compared to that in Cox's reports [12, 15]. As mentioned before, this may be partly because of misleading advertising by the various vendors: surgeons using the techniques are not as familiar with the limitations of their energy sources as cutting-and-sewing! Another reason for the lack of a clear difference between the various procedures was suggested by Thomas and coworkers, who reported that pulmonary vein isolation is indeed an advantage; however, freedom from AF was demonstrated in a significant number of cases without completely successful pulmonary vein isolation [20].

The results of the less-invasive approach for surgical treatment of AF are good enough to perform ablation for both paroxysmal and chronic atrial fibrillation in most of the patients undergoing cardiac operations for other indications. However, it is clear that more pre-clinical and clinical work should be done before surgical treatment will be indicated on a wide scale for patients with isolated AF.

Event Monitoring

The subcutaneous event loop recorder is trying to keep electro-physiologists and surgeons honest. The Reveal XT (Fig. 14.8) is a flash drive shaped device that is typically implanted in a subcutaneous pocket in the left anterior chest wall. This provides data remotely for 3 years about the rhythm of the patient, using a software algorithm that utilizes R wave detection (Table 14.1).

Table 14.1 gives an overview of consensus from the HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation [34].

Fig. 14.8 Shows the Reveal XT loop recorder device

Table 14.1 Areas of consensus: definitions, indications, technique, and laboratory management AF Definition

1. Paroxysmal AF is defined as recurrent AF (≥2 episodes) that terminates spontaneously within 7 days
2. Persistent AF is defined as AF which is sustained beyond 7 days, or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion
3. Longstanding persistent AF is defined as continuous AF of greater than 1-year duration
4. The term permanent AF is not appropriate in the context of patients undergoing catheter ablation of AF as it refers to a group of patients where a decision has been made not to pursue restoration of sinus rhythm by any means, including catheter or surgical ablation
Indications for catheter AF ablation
1. Symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication
2. In rare clinical situations, it may be appropriate to perform AF ablation as first line therapy
3. Selected symptomatic patients with heart failure and/or reduced ejection fraction
4. The presence of a LA thrombus is a contraindication to catheter ablation of AF
Indications for surgical AF ablation
1. Symptomatic AF patients undergoing other cardiac surgery
2. Selected asymptomatic AF patients undergoing cardiac surgery in whom the ablation can be performed with minimal risk
3. Stand-alone AF surgery should be considered for symptomatic AF patients who prefer a surgical approach, have failed one or more attempts at catheter ablation, or are not candidates for catheter ablation
Pre-procedure management
1. Patients with persistent AF who are in AF at the time of ablation should have a TEE performed to screen for thrombus
Technique and lab management
1. Ablation strategies which target the PVs and/or PV antrum are the cornerstone for most AF ablation procedures
2. If the PVs are targeted, complete electrical isolation should be the goal
3. For surgical PV isolation, entrance and/or exit block should be demonstrated
4. Careful identification of the PV ostia is mandatory to avoid ablation within the PVs
5. If a focal trigger is identified outside a PV at the time of an AF ablation procedure, it should be targeted if possible
6. If additional linear lesions are applied, line completeness should be demonstrated by mapping or pacing maneuvers
7. Ablation of the cavotricuspid isthmus is recommended only in patients with a history of typical atrial flutter or inducible cavotricuspid isthmus dependent atrial flutter
8. If patients with longstanding persistent AF are approached, ostial PV isolation alone may not be sufficient
9. Heparin should be administered during AF ablation procedures to achieve and maintain an ACT of 300–400 s

Key-Points to Remember

Surgical ablation for atrial fibrillation is a growing area of development and use. While the Cox-maze cut-and-sew experience is considered the "gold standard", it must be realized that those experiments that formed the foundations of this arena were performed in animals with an acute model of AF. The best therapy may yet be guided by detailed mapping of the atria. Surgically, the most important aspect seems to be obliteration of atrial appendages to reduce the thromboembolic risk. Atrial transport function may never recover after long-standing AF or an extensive ablative maze procedure.

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15 Other Techniques in Special Circumstances: Pulmonary Thromboendarterectomy in Right Heart Failure

Travis L. Pollema and Michael M. Madani

Introduction

Pulmonary thromboendarterectomy (PTE) is the definitive treatment for chronic pulmonary hypertension as the result of thromboembolic disease and is now widely recognized as the treatment of choice for patients suffering from right heart failure as the result of chronic thromboembolic pulmonary hypertension (CTEPH). Although the procedure is curative and in experienced hands carries a low morbidity and mortality, it is only rarely performed. The main problem is the fact that CTEPH remains significantly underrecognized. It is not uncommon for the patients suffering from this disease to be misdiagnosed and mistreated for a variety of other conditions. Furthermore, of those who are truly diagnosed, the majority will be at later stages of the disease. However, once correctly diagnosed and referred, pulmonary thromboendarterectomy can be highly effective and promises to provide a lifetime cure for such patients.

Unlike other forms of heart failure, patients with CTEPH often have full recovery of their right heart function and size, as long as the pulmonary hypertension has resolved. This is an interesting and unexplained phenomenon that is a unique feature of the right heart failure associated with CTEPH. In most other causes of heart failure especially left ventricular failure, even when the obstruction has been removed, the ventricle does not fully recover and certainly does not normalize in size. In contrast, in the setting of CTEPH, the right ventricle does so. The improvement in right heart failure and its associated tricuspid regurgitation is proportional to the degree of resolution achieved in the patient's pulmonary hypertension. Therefore one can expect full recovery of the right heart and normal tricuspid function in patients who have had successful outcomes with normal post-operative pulmonary pressures.

Pulmonary hypertension and subsequent right heart failure secondary to chronic thromboembolic disease is a relatively uncommon condition occurring in 1–5 % of adult patients who survive an acute pulmonary embolic event [1, 2]. More recent studies however suggest a higher incidence in patients with an acute episode of pulmonary embolism; 3.1 % at 1 year and 3.8 % at 2 years [2, 3]. It is extremely hard to accurately determine the true incidence of chronic thromboembolic pulmonary hypertension for obvious reasons, but one can come up with educated estimates of this disease. The estimated incidence of acute pulmonary embolism is approximately 630,000 per year in the United States, based on clinical data [4, 5], and is related to approximately

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_15

235,000 deaths per year, based on autopsy data [6]. Calculations extrapolated from mortality rates and the random incidence of major thrombotic occlusion of pulmonary vessels at autopsy support an estimate that more than 100,000 people in the United States currently suffer from pulmonary hypertension that could be relieved by operation [7]. Given an incidence of about 4 % after an episode of acute PE, one can estimate that there are about 25,000 new patients annually in the US alone suffering from this disease, yet the number of pulmonary endarterectomies performed remains low at about 250–300 cases annually in the US, the majority of which are performed at the authors' institution, University of California San Diego.

Once chronic pulmonary hypertension develops, the prognosis is poor, and this prognosis is even worse in patients without an intracardiac shunt. As a rule patients with pulmonary hypertension caused by pulmonary emboli fall into a higher risk category than those with Eisenmenger's syndrome and encounter a higher mortality rate. In fact, survival of patients with chronic thromboembolic pulmonary hypertension is inversely related to the magnitude of pulmonary artery systolic pressure and pulmonary vascular resistance [8]. When the mean pulmonary artery pressure in patients with thromboembolic disease exceeds 50 mmHg, the 5-year mortality approaches 90 % [9].

Regardless of the exact incidence or the circumstances, it is clear that acute embolism and its chronic relation, fixed chronic thromboembolic occlusive disease, are both much more common than generally appreciated and are seriously underdiagnosed. Houk and colleagues [10] in 1963 reviewed the literature of 240 reported cases of chronic thromboembolic obstruction of major pulmonary arteries but found that only 6 cases had been diagnosed correctly before death. Calculations extrapolated from mortality rates and the random incidence of major thrombotic occlusion found at autopsy would support a postulate that more than 100,000 people in the United States currently have pulmonary hypertension that could be relieved by operation. Therefore, despite an improved understanding of pathogenesis, diagnosis, and management, pulmonary emboli and the long-term sequelae of thromboembolic pulmonary hypertension, remain frequent and often fatal disorders.

Clinical Presentation

There are no signs or symptoms specific for chronic thromboembolism. The most common symptom associated with thromboembolic pulmonary hypertension, as with all other causes of pulmonary hypertension and right heart failure is exertional dyspnea. This dyspnea is out of proportion to any abnormalities found on clinical examination. Like complaints of easy fatigability, dyspnea that initially occurs only with exertion is often attributed to anxiety or being "out of shape". Syncope, or presyncope (lightheadedness during exertion) is another common symptom in pulmonary hypertension. Generally, it occurs in patients with more advanced disease and higher pulmonary arterial pressures.

Non-specific chest pains or tightness occur in approximately 50 % of patients with more severe pulmonary hypertension. Hemoptysis can occur in all forms of pulmonary hypertension and probably results from abnormally dilated vessels distended by increased intravascular pressures. Peripheral edema, early satiety, and epigastric or right upper quadrant fullness or discomfort will develop as the right heart failure progresses. Some patients with chronic pulmonary thromboembolic disease present after a small acute pulmonary embolus that may produce acute symptoms of right heart failure. A careful history brings out symptoms of dyspnea on minimal exertion, easy fatigability, diminishing activities, and episodes or angina-like pain or lightheadedness. Further examination reveals the signs of pulmonary hypertension and right heart failure.

The physical signs of pulmonary hypertension are the same no matter what the underlying pathophysiology. Initially the jugular venous pulse is characterized by a large A-wave. As the right heart fails, the V-wave becomes predominant. The right ventricle is usually palpable near

the lower left sternal border, and pulmonary valve closure may be audible in the second intercostal space. Occasional patients with advanced disease are hypoxic and slightly cyanotic. Clubbing is an uncommon finding.

The second heart sound is often narrowly split and varies normally with respiration; P2 is accentuated. A sharp systolic ejection click may be heard over the pulmonary artery. As the right heart fails, a right atrial gallop usually is present, and tricuspid insufficiency develops. Because of the large pressure gradient across the tricuspid valve in pulmonary hypertension, the murmur is high pitched and may not exhibit respiratory variation. These findings are quite different from those usually observed in tricuspid valvular disease. A murmur of pulmonic regurgitation may also be detected.

Diagnosis

To ensure diagnosis in patients with right heart failure secondary to chronic pulmonary thromboembolism, a standardized evaluation is recommended for all patients who present with unexplained pulmonary hypertension. This workup includes a chest radiograph, which may show either apparent vessel cutoffs of the lobar or segmental pulmonary arteries or regions of oligemia suggesting vascular occlusion. Central pulmonary arteries are generally enlarged, and the right ventricle may also be enlarged without any enlargement of the left atrium or ventricle. However, one should keep in mind that despite these classic findings, a large number of patients might present with a relatively normal chest radiograph, even in the setting of high degrees of pulmonary hypertension or right heart failure. The electrocardiogram demonstrates findings of right ventricular hypertrophy (right axis deviation, dominant R-wave in V1). Pulmonary function tests are necessary to exclude obstructive or restrictive intrinsic pulmonary parenchymal disease as the cause or the hypertension.

The most useful screening studies are two-dimensional surface echocardiography with Doppler imaging and ventilation-perfusion (V/Q) scanning. The standard echo helps to define the presence and severity of right heart failure, tricuspid regurgitation, and severity of pulmonary hypertension. In addition it is also helpful to rule out other causes, such as Eisenmenger's Syndrome. The echocardiogram rapidly demonstrates right sided chamber enlargement and right ventricular hypertrophy (Fig. 15.1). The main pulmonary artery is usually enlarged; the intraventricular septum may appear flattened and often exhibits paradoxical motion, with encroachment of the right ventricular septum in the left ventricle. Varying degrees of tricuspid regurgitation are usually present. Continuous wave Doppler scanning of the tricuspid regurgitation jet is helpful in the estimation of the pulmonary artery systolic pressure. In addition, because exercise characteristically increases the pulmonary hypertension, echocardiography with exercise should always be applied whenever the disease is suspected but when the resting echocardiogram demonstrates only subtle abnormalities.

The ventilation-perfusion lung scan is the fundamental test for establishing the diagnosis of unresolved pulmonary thromboembolism. An entirely normal lung scan excludes the diagnosis of both acute or chronic, unresolved thromboembolism. The usual lung scan pattern in most patients with primary pulmonary hypertension either is relatively normal or shows a diffuse nonuniform perfusion. When subsegmental or larger perfusion defects are noted on the scan, even when matched with ventilatory defects, pulmonary angiography is appropriate to confirm or rule out thromboembolic disease. It is important to note that any patient with unexplained dyspnea should be worked up for pulmonary hypertension, and any patient with a diagnosis of pulmonary hypertension should undergo a V/Q scan.

Currently, pulmonary angiography still remains the gold standard for diagnosis of CTEPH, however with the advent of high resolution scans, and magnetic resonance imaging, more and more centers rely on the diagnostic power and the non-invasive nature of these tests to confirm the diagnosis. Organized thromboembolic lesions do not have the appearance of the intravascular filling defects seen with acute

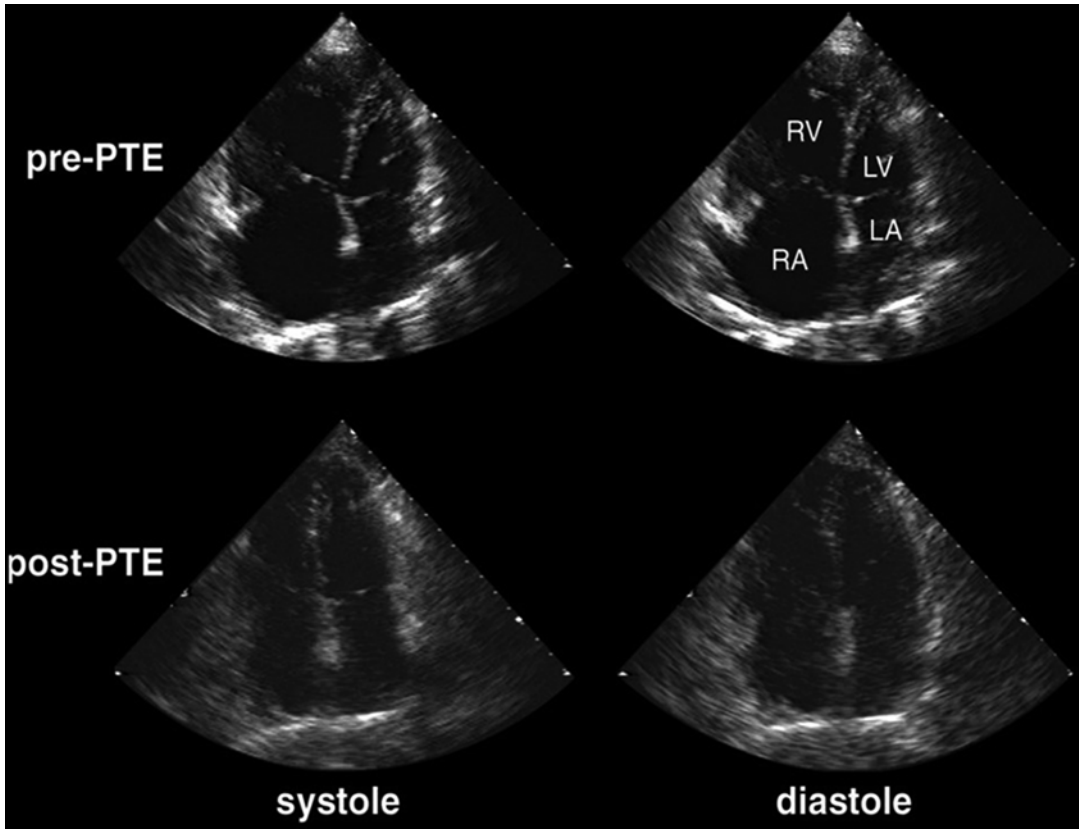

Fig. 15.1 Echocardiographic appearances of the heart before (pre-PTE; *top*) and after (post-PTE; *bottom*) operation. Note the shift of the intraventricular septum toward the left in systole before the operation (*top left*), together with the relatively small left atrial and left ventricular chambers. After the operation, the septum is restored to its normal geometry, and the massive enlargement of the right atrium and right ventricle has resolved

pulmonary emboli, and experience is essential for the proper interpretation of pulmonary angiograms in patients with unresolved, chronic embolic disease. Organized thrombi appear as unusual filling defects, webs, or bands, or completely thrombosed vessels that may resemble congenital absence of the vessel [11] (Fig. 15.2). In addition to pulmonary angiography, patients over 45 undergo coronary arteriography and other cardiac investigation as necessary. If significant disease is found, additional cardiac surgery is performed at the time of pulmonary thromboendarterectomy.

In recent years higher resolution helical computed tomography (CT) scans of the chest have been used more frequently in diagnosis of pulmonary thromboembolic disease. Presence of large clots in lobar or segmental vessels generally confirms the diagnosis. CT features of chronic thromboembolic pulmonary hypertension include evidence of organized thrombus lining the pulmonary vessels in an eccentric fashion, enlargement of the right ventricle and the central arteries, variation in size of segmental arteries, and parenchymal changes characteristic of pulmonary infarction. In addition, in rare situations where there are concerns of external compression, or occlusion of main pulmonary arteries are present, CT scans can be helpful in differentiating thromboembolic disease from other causes such as mediastinal fibrosis, lymph nodes, or tumors. In the current era of multi-detector CT scans, the resolution of the pulmonary arteries is much better and it is possible that this diagnostic modality may eventually replace pulmonary angiography as the gold standard in diagnosing CTEPH and in

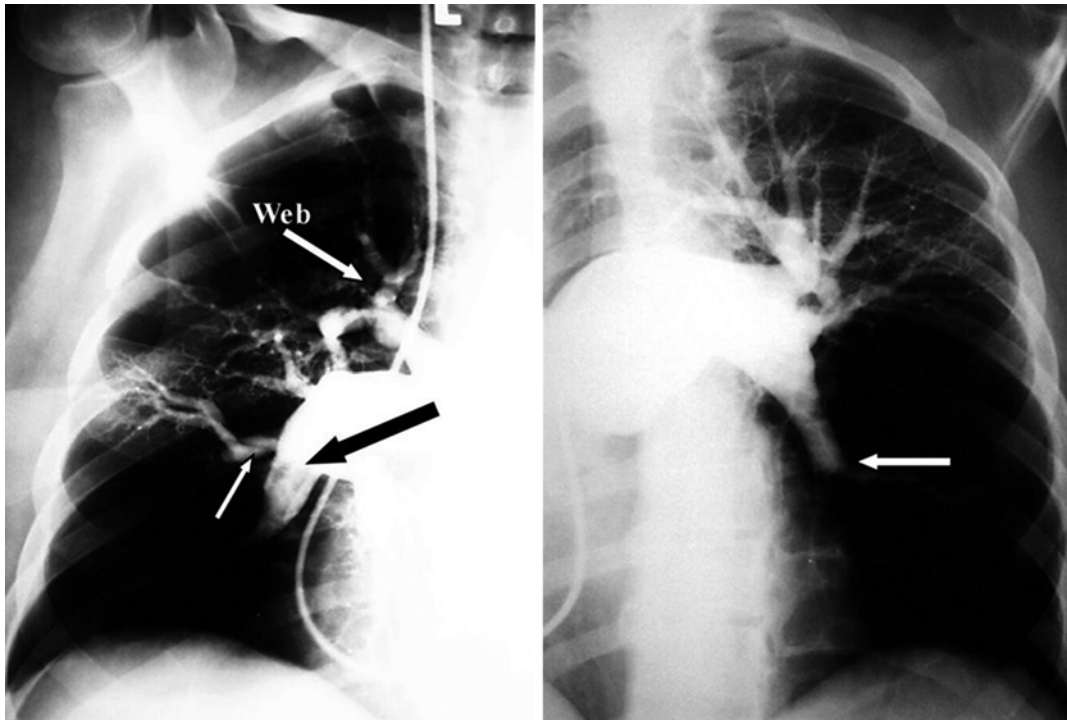

Fig. 15.2 Pulmonary angiogram in a patient with chronic thromboembolic pulmonary hypertension. Please note the extensive areas of hypoperfusion as a result of complete occlusion, as well as luminal irregularities, webs, bands, and pouches, shown by *arrows*

planning the surgical treatment once the diagnosis is made. In addition, the volumetric assessment of the right ventricle can be more accurately performed with multi-detector CT. It is important to remember, however, that the diagnosis of CTEPH by CT scans is difficult and requires experienced radiologists with expertise in this area and currently remains an adjunct to pre-operative planning.

Medical Treatment

There is no curative role for medical management of these patients and at best it is palliative. There are a number of new pulmonary vasodilators that are now available for the treatment of the pulmonary hypertension and right heart failure in these patients; but considering the fact that the primary pathology is the physical obstruction of pulmonary vasculature, there is no surprise that their effects are only transient at best. Right ventricular failure may show some improvement with combination of diuretics and vasodilators, but because the failure is due to a mechanical obstruction it will not resolve until the obstruction is removed. Similarly, the prognosis is unaffected by medical therapy [12, 13], which should be regarded as only supportive. Because of the bronchial circulation, pulmonary embolization seldom results in tissue necrosis. Surgical endarterectomy therefore will allow distal pulmonary tissue to be used once more in gas exchange.

Currently there is only one FDA approved drug for the treatment of CTEPH in patients deemed to have inoperable disease and also patients who continue to have residual pulmonary hypertension following pulmonary thromboendarterectomy. Riociguat is a new drug in the class of soluble guanylate cyclase stimulators that has been shown to increase 6 min walk distance and decrease PVR in patients with CTEPH [20]. The observed improvements in exercise capacity and PVR of the patients in this study

continue to remain significantly inferior to surgery and their durability is not proven. Pulmonary thromboendarterectomy remains the gold standard treatment and determination of inoperable disease should be made by an experienced center. Initiation of medical treatment in a patient with potentially operable disease may prevent someone from a curative procedure [21], or result in delay of referral.

Chronic anticoagulation represents the mainstay of the medical regimen. Anticoagulation is primarily used to prevent future embolic episodes, but it also serves to limit the development of thrombus in regions of low flow within the pulmonary vasculature. Inferior vena caval filters are used routinely to prevent recurrent embolization.

Operative Procedure

Pulmonary thromboendarterectomy is a technically demanding operation that is performed only in select centers around the world. Proper patient selection, meticulous surgical technique, and vigilant postoperative management have contributed to the success of this operation. A true endarterectomy (not an embolectomy) of all affected parts of the lung is essential to clear all affected areas of the pulmonary vasculature. It is clear that pulmonary endarterectomy relieves pulmonary hypertension by improving lung ventilation-perfusion match, improving right ventricular function and tricuspid regurgitation, limiting retrograde extension of clot obstruction, and preventing arteriopathic changes in the remaining patent small pulmonary vessels [14, 15]. Furthermore with resolving pulmonary hypertension, the right ventricle will regress to a normal size and improve its overall function.

The description of a surgical procedure for removal of thromboembolic material dates back to 1908, when Trendelenburg [16] first illustrated an approach in a dying patient. However it was not until the introduction and development of cardiopulmonary bypass when more procedures with better outcomes were performed. By the mid 1980s there were a total of 85 reported cases that were managed surgically but still carried a high mortality rate of about 22 % [17]. Although there have been other reports of surgical treatment of CTEPH, most of the surgical experience in pulmonary endarterectomy has been reported from the UCSD Medical Center [7, 11], and it is this experience that forms the basis of this chapter.

With our growing experience now accounting for over 3300 of these procedures, we know that there are certain principles of this procedure that have to be adhered to. Although an endarterectomy is possible even if one deviates from these principles, a successful and complete endarterectomy is not, and such outcomes are questionable. What follows is a description of the techniques of this procedure highlighting the fundamental points.

Technical Principles of the Procedure

There are several guiding principles for this operation. First and foremost the approach must be bilateral; because, for pulmonary hypertension to be a major factor, both pulmonary arteries must be substantially involved. Furthermore, it is extremely unlikely to have unilateral disease as the result of thromboembolism. In fact we believe that a small subgroup of our patients who truly do have unilateral disease, perhaps suffer from an underlying pulmonary vascular pathology with subsequent thrombosis, rather than true thromboembolism. The only reasonable approach to both pulmonary arteries is through a median sternotomy incision. Historically, there have been many reports of unilateral operation, and occasionally this is still performed with various results in inexperienced centers, through a thoracotomy. However, the unilateral approach ignores the disease on the contralateral side, subjects the patient to hemodynamic jeopardy during the clamping of the pulmonary artery, and does not allow good visibility because of the continued presence of bronchial blood flow. In addition, collateral channels develop in chronic thrombotic hypertension not only through the bronchial arteries but also from diaphragmatic, intercostal, and pleural

vessels. The dissection of the lung in the pleural space via a thoracotomy incision can therefore be extremely bloody. The median sternotomy incision, apart from providing bilateral access, avoids entry into the pleural cavities, and allows the ready institution of cardiopulmonary bypass.

Cardiopulmonary bypass is an essential part of this operation and integral to ensure cardiovascular stability during the procedure. In addition cardiopulmonary bypass allows cooling the patient in preparation of circulatory arrest. Given the extent and the location of thromboembolic material, which have now transformed into a scar like fibrotic tissue adherent to the pulmonary vasculature, superior visibility is required. This is only achievable in a bloodless field so the surgeon can define an adequate endarterectomy plane and then can follow the pulmonary endarterectomy specimen deep into the subsegmental vessels. Because of the copious bronchial blood flow usually present in these patients, periods of circulatory arrest are necessary to ensure perfect visibility. Again, there continue to be sporadic reports of performing this operation without circulatory arrest with various outcomes. However, it should be emphasized that although endarterectomy is clearly possible without circulatory arrest, a complete endarterectomy is not. Surgeons claiming success with a complete endarterectomy without circulatory arrest are likely to leave behind distal disease in the subsegmental branches without ever recognizing it. We always initiate the procedure without circulatory arrest, and depending on the collateral flow through the bronchial arteries and other channels, a variable amount of dissection is possible before the circulation has to be stopped, but never a complete dissection. The circulatory arrest periods are typically limited to 20 min, with restoration of flow between each arrest. With experience, a complete endarterectomy usually can be performed within a single period of circulatory arrest on each side.

The next principle of this operation relies mainly on the experience of the operator in recognizing the true endarterectomy plane of the media, and following the specimen to its feathered tail end in each branch. It is essential to appreciate that the removal of visible thrombus is largely incidental to this operation. Indeed, in most patients, no free thrombus is present; and on initial direct examination, the pulmonary vascular bed may appear normal. The early literature on this procedure indicates that thrombectomy was often performed without endarterectomy, and in these cases the pulmonary artery pressures did not improve, often with the resultant death of the patient.

Surgical Technique

The surgical approach for this procedure is through a median sternotomy to gain access to both sides. Typically the right heart is severely enlarged, with a tense right atrium and a variable degree of tricuspid regurgitation. There is usually significant right ventricular hypertrophy and associated right heart failure, and with critical degrees of obstruction, the patient's condition may become unstable with the manipulation of the heart. Care must be taken to avoid any unnecessary manipulation of the heart while the patient is safely placed on cardiopulmonary bypass.

Anticoagulation is achieved with the use of heparin sodium (400 units/kg, intravenously) administered to prolong the activated clotting time beyond 400 s. Full cardiopulmonary bypass is instituted with high ascending aortic cannulation and bi-caval cannulation. The heart is emptied on bypass, and a temporary pulmonary artery vent is placed in the midline of the main pulmonary artery about 1 cm distal to the pulmonary valve. The insertion site can then be used for the beginning of the left pulmonary arteriotomy. The patient is then actively cooled to a core temperature of about 18–20 °C.

Initially, it is most convenient for the primary surgeon to stand on the patient's left side, and perform the endarterectomy on the right side. The superior vena cava is also fully mobilized. The approach to the right pulmonary artery is made medial, not lateral, to the superior vena cava. Once the superior vena cava is fully mobilized, and the core temperature has reached 20 °C, an aortic cross clamp is applied and

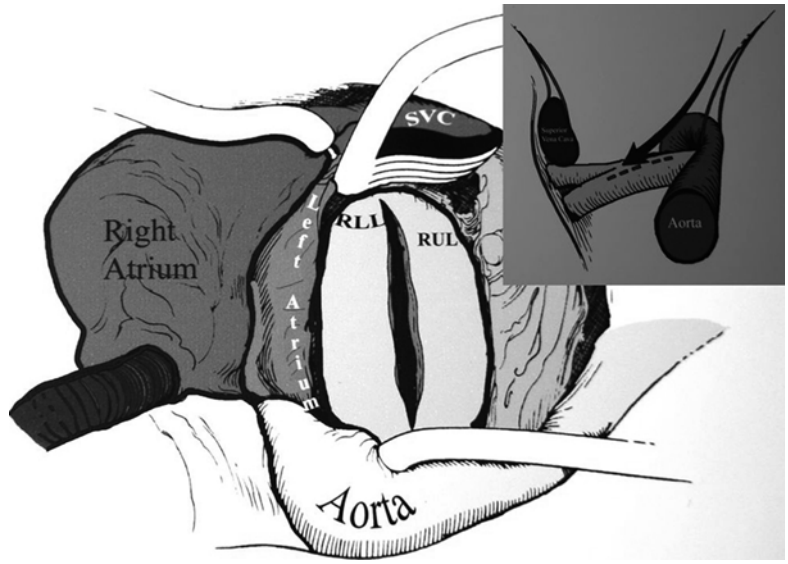

Fig. 15.3 Exposure of the right pulmonary artery, as viewed by the surgeon standing on the left side. The incision is placed between the superior vena cava (SVC) and the Aorta, as shown in the insert. It is imperative that the incision towards the right lower lobe artery is made in the middle of the vessel. During the dissection the edges of this incision is left intact for easier and more hemostatic closure

myocardial protection is provided through a single dose of antegrade cold blood cardioplegia (1 L). The entire procedure is now performed with a single aortic cross-clamp period with no further administration of cardioplegic solution. Additional myocardial protection is provided by using a cooling jacket surrounding the heart throughout the remainder of the procedure. Both tourniquets are now secured around the superior and inferior vena cavae to ensure complete drainage and to avoid any air entry in the venous cannulae during circulatory arrest.

A modified cerebellar retractor is then used to expose the pulmonary artery between the aorta and the superior vena cavae. An incision is made in the right pulmonary artery from beneath the ascending aorta out under the superior vena cava and entering the lower lobe branch of the pulmonary artery just after the take-off of the middle lobe artery (Fig. 15.3). It is important that the incision stays in the center of the vessel and continues in the middle of the descending pulmonary artery into the lower, rather than the middle lobe artery. The incision is carried past the take-off of the middle lobe artery.

Any loose thrombus, if present, is now removed. This is necessary to obtain good visualization. It is most important to recognize, however, that first, an embolectomy without subsequent endarterectomy is quite ineffective and, second, that in most patients with chronic thromboembolic hypertension, direct examination of the pulmonary vascular bed at operation generally shows no obvious embolic material. Therefore, to the inexperienced or cursory glance, the pulmonary vascular bed may well appear normal even in patients with severe chronic embolic pulmonary hypertension.

If the bronchial circulation is not excessive, the endarterectomy plane can be found during this early dissection. However, although a small amount of dissection can be performed before the initiation of circulatory arrest, it is unwise to proceed unless perfect visibility is obtained because the development of a correct plane is essential.

The correct plane appears pearly white, which is smooth and silky in appearance and lies between the intima and media. A microtome knife is used to develop the endarterectomy plane posteriorly, because any inadvertent egress in this site could be repaired readily, or simply left alone. Dissection in the correct plane is critical because if the plane is too deep the pulmonary artery may perforate, with fatal results, and if the dissection plane is not deep enough, inadequate amounts of the chronically thromboembolic material will be removed. When the proper plane is entered, the layer will strip easily, and the

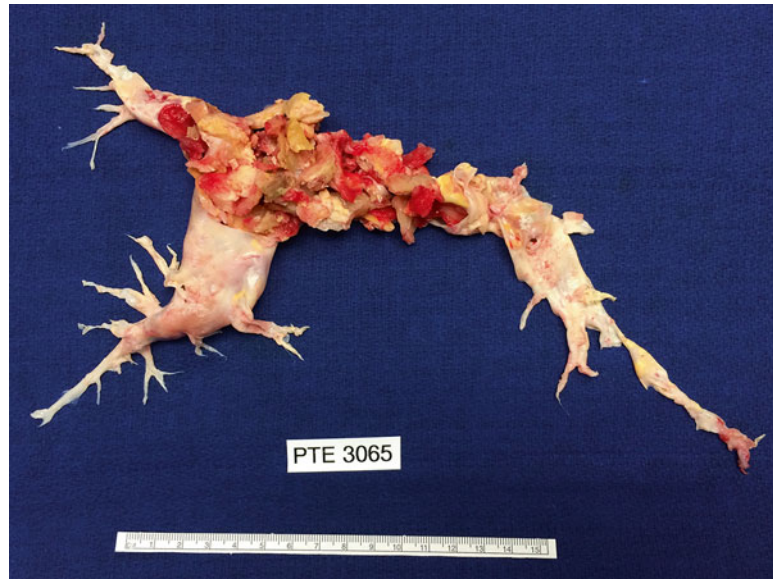

Fig. 15.4 Surgical specimen removed from right and left pulmonary arteries. Fresh thrombus in major arteries indicates level I disease. Note that removal of only the fresh material leaves a large amount of disease behind. The ruler measures 15 cm

material left with the outer layers of the pulmonary artery will appear somewhat yellow, but there should be no residual yellow plaque.

If the dissection is too deep, a reddish or pinkish color indicates the adventitia has been reached. As a general rule while developing the plane of dissection a non-smooth light purplish or pinkish color is an indication that the plane of dissection is too deep and care must be taken to immediately get back into the more superficial correct plane before the vessel wall is injured. Once the correct plane is recognized the dissection is carried into each one of the lobar, segmental, and subsegmental branches until a feathered tail is obtained.

There are five categories of pulmonary occlusive disease related to thrombus that can be appreciated, and we use the UCSD classification system which describes the different levels of the thromboembolic specimen [22], and corresponds to the degree of difficulty of the endarterectomy. Level 0 is no evidence of chronic thromboembolic disease present, in other words there has been a misdiagnosis or perhaps one lung is completely unaffected by thromboembolic disease, both of which are rare. In this entity there is intrinsic small vessel disease, although secondary thrombus may occur as a result of stasis. Small-vessel disease may be unrelated to thromboembolic events ("primary" pulmonary hypertension) or occur in relation to thromboembolic hypertension as a result of a high flow or high pressure state in previously unaffected vessels similar to the generation of Eisenmenger's syndrome. We believe that there may also be sympathetic "cross-talk" from an affected contralateral side or stenotic areas in the same lung.

Level I disease (Fig. 15.4) refers to the situation in which thromboembolic material is present and readily visible on the opening of the main left and right pulmonary arteries. A subset of level I disease, level Ic, is complete occlusion of either the left or right pulmonary artery and nonperfusion of that lung. Complete occlusion may present an entirely different disease, especially when it is unilateral and on the left side. This group of patients, typically a young female with complete occlusion of the left pulmonary artery, may not reperfuse their affected lung despite a complete endarterectomy, indicating a different intrinsic pulmonary vascular disease, unrelated to thromboembolic disease. In level II (Fig. 15.5), the disease starts at the lobar or intermediate level arteries and the main pulmonary arteries are unaffected. Level III disease is limited to thromboembolic disease originating in the segmental vessels only (Fig. 15.6). Level IV is disease of the subsegmental vessels (Fig. 15.7), with no other

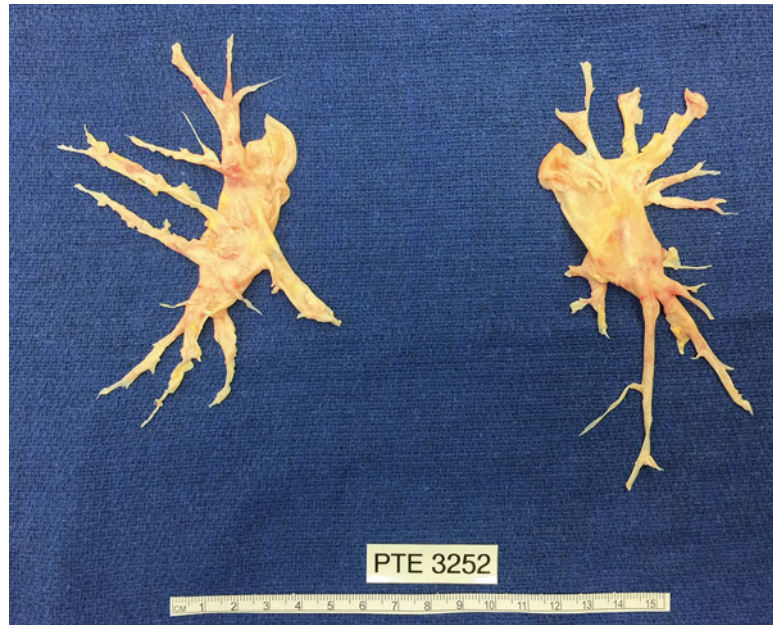

Fig. 15.5 Surgical specimen removed from right and left pulmonary arteries indicating evidence of level II disease. There is no fresh thromboembolic material in this specimen. Note the extent of dissection down to the tail end of each one of the branches. The ruler measures 15 cm

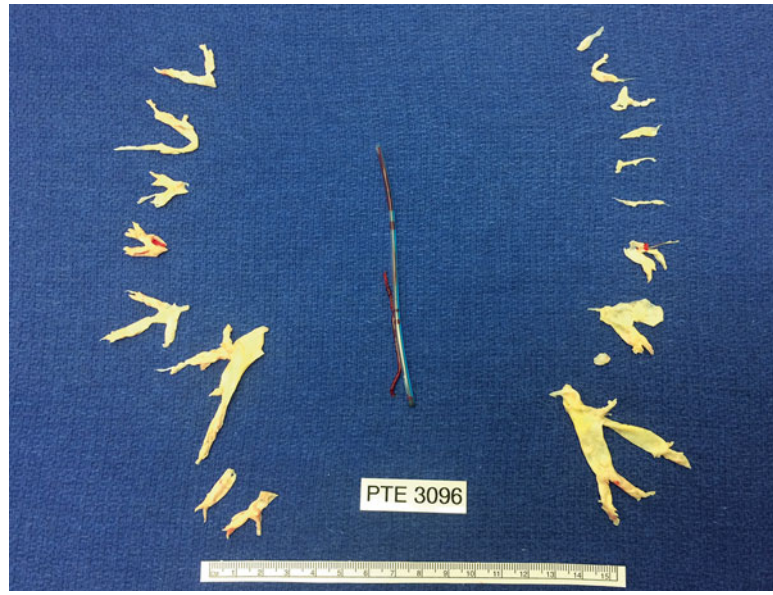

Fig. 15.6 Surgical specimen removed from right and left pulmonary arteries in a patient with level III disease. Note that in this patient the dissection plane has to be developed and raised at each segmental level. The center of the pictures shows a remnant of a chronic indwelling catheter. The ruler measures 15 cm

disease appreciated at more proximal levels. Level III and level IV disease present the most challenging surgical situation. The disease is very distal and confined to the segmental and subsegmental branches. These levels are most often associated with presumed repetitive thrombi from upper extremity sources, indwelling catheters (such as pacemaker wires) or ventriculoatrial shunts.

With the modified cerebellar retractor in place and the artery well exposed the dissection is then carried on. When blood obscures direct vision of the pulmonary vascular bed, circulatory arrest is then initiated, and the patient undergoes exsanguination. It is rare that one 20-min period for each side is exceeded.

The endarterectomy is then performed with an eversion technique. Because the vessel is everted

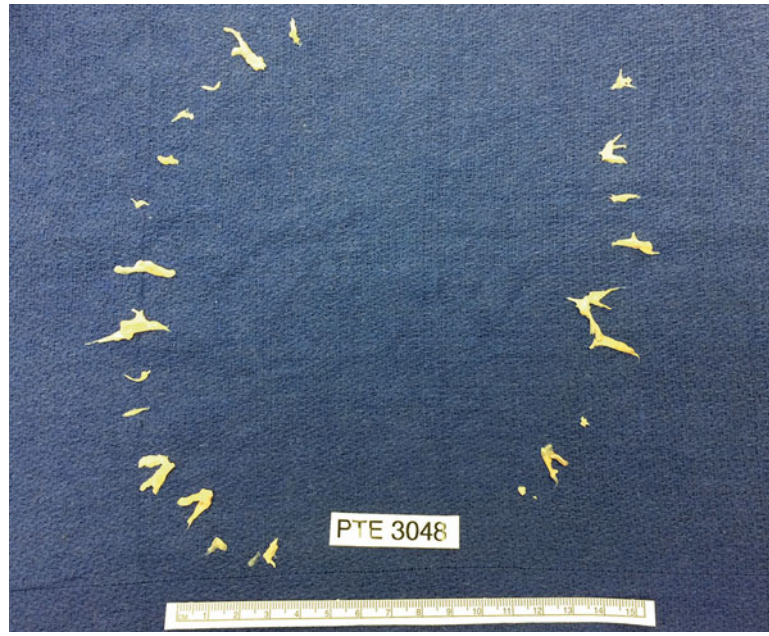

Fig. 15.7 Surgical specimen removed from right and left pulmonary arteries in a patient with level IV disease. The disease is entirely of the subsegmental level vessels. The ruler measures 15 cm

and subsegmental branches are being worked on, a perforation here will become completely inaccessible and invisible later. This is why the absolute visualization in a completely bloodless field provided by circulatory arrest is essential. It is important that each subsegmental branch is followed and freed individually until it ends in a "tail," beyond which there is no further obstruction. Residual material should never be cut free; the entire specimen should "tail off" and come free spontaneously.

Once the right-sided endarterectomy is completed, circulation is re-started, and the arteriotomy is repaired with a continuous 6-0 polypropylene suture. The hemostatic nature of this closure is aided by the nature of the initial dissection, with the full thickness of the pulmonary artery being preserved immediately adjacent to the incision.

After the completion of the repair of the right arteriotomy, the surgeon moves to the patient's right side.

The left-sided dissection is virtually analogous in all respects to that accomplished on the right. The duration of circulatory arrest intervals during the performance of the left-sided dissection is subject to the same restriction as the right.

After the completion of the endarterectomy, cardiopulmonary bypass is reinstituted and warming is commenced. The rewarming period generally takes approximately 90–120 min but varies according to the body mass of the patient.

Based on the results of the pre-operative echo and the intra-operative TEE, we would then decide if a right atrial exploration is necessary. In general if either one of the two test is positive for a bubble test we would explore the right atrium. The right atrium is then opened through a small atriotomy located over the site of fossa ovalis. Any intra-atrial communication is then closed. Although tricuspid valve regurgitation is invariable in these patients and is often severe, tricuspid valve repair is not performed. Right ventricular remodeling occurs within a few days, with the return of tricuspid competence.

If other cardiac procedures are required, such as coronary artery or mitral or aortic valve surgery, these are conveniently performed during the systemic rewarming period [14].

When the patient has fully rewarmed, cardiopulmonary bypass is discontinued. Dopamine is routinely administered at low doses, and other inotropic agents and vasodilators are titrated as necessary to sustain acceptable hemodynamics. With a successful endarterectomy, the cardiac output is generally high, with a low systemic vascular resistance. Temporary atrial and ventricular epicardial pacing wires are placed.

Despite the duration of extracorporeal circulation, hemostasis is readily achieved, and the administration of platelets or coagulation factors is rarely necessary. Wound closure is routine. Given the degree of pre-operative volume overload, the relief of pulmonary obstruction, in addition to the previous systemic hypothermia, a vigorous diuresis is usual for the following few hours.

Results

In our most recent series involving about 2700 patients, the trend shows improving mortality rates [18]. There were no mortalities in the last 260 patients. Currently our overall mortality rate is about 1 % for patients who undergo isolated pulmonary endarterectomy. A similar number of men and women were referred for operation. With the exception of closure of patent foramen ovale, in 10 % of cases, at least one additional cardiac procedure was performed at the time of operation. Most commonly, the adjunct procedures were coronary revascularization, aortic valve replacement, or mitral valve repair/replacement. There was no significant difference between patients undergoing pulmonary endarterectomy alone or combined with other cardiac operations with respect to cardiopulmonary bypass time, crossclamp time, or circulatory arrest time. In general total cardiopulmonary bypass time correlates with body mass and cooling-rewarming intervals.

With this operation, a reduction in pulmonary artery pressures and pulmonary vascular resistance to normal levels and corresponding improvement in pulmonary blood flow and cardiac output are generally immediate and sustained. Improvement in the right ventricular function correlates with the decrease in the pulmonary pressures and the pulmonary vascular resistance. Generally the improvement is evident on the post-operative echocardiogram performed before discharge. This is in contrast to other conditions causing ventricular failure, and especially in disparity to the left ventricular failure caused as a result of outflow obstruction. In those patients, even when the insulting lesion or obstruction has been resolved, the ventricular dysfunction will not normalize. A good example is left ventricular failure as the result of aortic valve stenosis. After a vavular replacement, neither the LV dysfunction nor its hypertrophy will improve much. It is true that the failure will not progress, the patients will be much improved, and there maybe some subtle enhancement in the LV function, but very rarely the function and size will normalize.

Before the operation, more than 85 % of the patients were in New York Heart Association (NYHA) functional class III or IV; at the time of discharge, 80.2 % were re-classified as NYHA functional class I or II. Echocardiographic studies on this patient cohort and other previous studies from our institution [19] demonstrated that, with the elimination of chronic pressure overload, right ventricular geometry rapidly reverted to normal. Tricuspid valve function (as measured by tricuspid regurgitant velocity) returned to normal within a few days as a result of restoration of tricuspid annular geometry after the remodeling of the right ventricle. Tricuspid valve annuloplasty was not performed, even when severe tricuspid regurgitation was documented preoperatively.

Reperfusion edema is the single most frequent complication after pulmonary endarterectomy, occurring in up to 11 % of patients. In most patients with reperfusion injury, the problem resolved with avoidance of hypercarbia, and a short period of ventilatory support and aggressive diuresis. A minority of patients with severe lung reperfusion injury required long periods of ventilatory support, and extreme cases (approximately 1 %) required veno-venous extracorporeal support for blood carbon dioxide removal and oxygenation. Neurologic complications from circulatory arrest largely have been eliminated by shorter circulatory arrest periods and the use of a direct cooling jacket placed around the head. Rates of perioperative confusion and stroke for pulmonary endarterectomy were similar to those seen with conventional open heart surgery.

Conclusion

It is increasingly apparent that pulmonary hypertension caused by chronic pulmonary embolism is a condition which is under-recognized, and carries a poor prognosis. Because of the obstructive nature of this disease, medical therapy remains ineffective in prolonging life and at best only transiently improves the symptoms. The only therapeutic alternative to pulmonary thromboendarterectomy is lung transplantation. The advantages of thromboendarterectomy include a lower operative mortality and excellent long-term results without the risks associated with chronic immunosuppression and chronic allograft rejection.

Technical advances of the procedure over the last four decades, and in particular in the last 15 years have significantly improved outcomes. Newly designed instruments allow better visualization and more complete endarterectomy in the distal segmental and subsegmental branches. Attention to the surgical principles of this procedure is of paramount importance. The procedure is performed through a median sternotomy for bilateral exposure and exploration. It should be performed with the use of circulatory arrest for excellent exposure of the distal branches. The correct plane is recognized, developed, and should then be followed all the way to the distal feathered tails in each branch. With careful and meticulous intra-operative techniques as well as vigilant post-operative care, the mortality for thromboendarterectomy at our institution is now in the range of 1 %, with sustained benefit. These results are clearly superior to those for transplantation both in the short and long term.

Although PTE is technically demanding for the surgeon, and requires careful dissection of the pulmonary artery planes and the use of circulatory arrest; excellent short- and long-term results can be achieved. It is the successive improvements in operative technique that allow pulmonary endarterectomy to be offered to patients with an acceptable mortality rate and excellent anticipation of clinical improvement. With this growing experience, we are now offering this procedure to all patients including some very high risk candidates, as long as there is evidence of thromboembolic disease, regardless of the degree of pulmonary hypertension or right ventricular failure.

The primary problem remains that this is an under-recognized condition, and unfortunately there are still a large number of patients with CTEPH who carry other diagnoses and are mistreated as such. Increased understanding of both the prevalence of this condition and the opportunity and availability of a surgical cure should benefit more patients. Surgical removal of the thromboembolic material by means of a complete endarterectomy provides these patients an opportunity for relief from this debilitating and ultimately fatal disease.

Editor's Note

While the bulk of the experience has been at UCSD, other selected centers worldwide have adopted this technique with reasonable results. An alternative to circulatory arrest is antegrade cerebral perfusion at low temperatures with low flow cardiopulmonary bypass, with acceptable visualization. One presumes that with increased use of multi-detector CT scanning, we will see more of these patients being referred for further management and surgery.

Key Points to Remember

Chronic thrombo-embolic pulmonary hypertension is a potentially treatable condition. The prognosis is best before the mean PA pressure crosses 50 mmHg and is good in patients with proximal thrombo-emboli.

Diagnosis of this condition requires a high index of suspicion and this is a large underdiagnosed clinical entity.

Treatment is almost always surgical. This entails complete dissection and removal of thrombo-emboli from both sides. Visualization of the plane between the lining of pulmonary arterial branches

and thrombo-emboli is best under conditions of circulatory arrest. However, in selected patients and instances, antegrade cerebral perfusion with low flow cardiopulmonary bypass may be provide adequate visualization. The hallmark of success is the fall in pulmonary artery pressures immediately and gradual resolution of tricuspid regurgitation.

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Right Heart Failure in Pediatric and Congenital Cardiac Surgery

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Introduction

The Morphologic Right Ventricle in Subpulmonary or Systemic Position

There cannot be too much argument about the notion, that the right heart, in a way or another, is involved in the majority of structural congenital heart defects. For a long time, however, the right ventricle as a subpulmonary ventricle has been regarded merely as an appendix to the systemic, mostly left ventricle, which from an embryological view actually is completely true [82]. This belief, that the pulmonary circulation, also known as lesser circulation is of lesser importance and of an undemanding nature, was further supported by the fact that patients can attain a near normal lifestyle during childhood after a Fontan operation: An operation where the circulation is completely devoid of an immediate subpulmonary ventricle.

With time the function of the right ventricle in particular, and the subpulmonary ventricle in a broader sense emerged as issues of serious concern when patients thought to be healed by corrective surgery early in live reached maturity: a plethora of negative events occurred. It was discovered almost simultaneously that the dysfunctional right ventricle, whether it represents a systemic pump or is chronically volume overloaded in the subpulmonary position post surgery deserves more attention than previously thought. The numerous detrimental issues arising in the ageing and continuously growing post-Fontan population further substantiated the newly awakened interest in the physiologic and pathophysiologic parameters of the lesser circulation. These causes and sequelae clinicians have been unaware of before.

It was the group at the Royal Brompton and National Heart and Lung Hospital London, England, led by Andrew Redington who first questioned the benign nature of the large right ventricle following TOF repair [10, 31]. At the opposite side of the globe, encouraged by the success of the arterial switch operation as a therapy for transposition of the great arteries, the surgical group from Royal Children's Hospital

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_16

Melbourne, Australia, under the leadership of Roger Mee [58] had begun earlier to revert patients with failing systemic right ventricles years after atrial switch surgery. This resulted in anatomically corrected normal, concordant ventriculo-arterial connection.

A complete and comprehensive discussion of the issue of a failing (or lacking) right ventricle comprises many different aspects and a structured, logical inventory is rather complex. We will distinguish between two settings with two subsettings each. The first setting is the inadequacy of the cavopulmonary pathway which we consider as the clinical syndrome of right heart failure, it may occur with or without subpulmonary ventricle, in a bi- or univentricular subsetting. The second setting is the failure of the morphological right ventricle in the systemic circulation, also with a bi-or univentricular subsetting.

The Clinical Syndrome of Right Heart Failure: Inadequacy of the Cavo-pulmonary Pathway with or without Subpulmonary Ventricle

For many readers the term cavo-pulmonary pathway is clearly associated with the Fontan type of circulation. In the following, however, we consider its inadequacy as a clinical entity characterized by insufficient return of the systemic venous blood into the pulmonary circulation, independent from the presence or absence of a subpulmonary ventricle, almost always a right ventricle.

The classical clinical signs of peripheral venous congestion with interstitial and intracavitary water retention are the hallmarks of this syndrome. If communications at atrial and/or ventricular level are present peripheral desaturation (cyanosis) can also be observed. Currently the full-blown chronic clinical syndrome is rarely seen in the pediatric age group due to rigorous medical and surgical follow-up of patients with operated or non-operated congenital heart disease. There is, however, also an incidence of acute early postoperative failure.

The issues arising from inadaequate systemic venous to pulmonary pathway, encountered as sequelae of congenital heart disease, can be categorized as being either acute or chronic.

Acute issues:

- acute postoperative right ventricular failure
- acute dysfunction of a systemic-pulmonary shunt
- neonates with congenital heart disease:
  - partially or completely ductal dependent pulmonary circulation
  - rare conditions with non ductal dependent pulmonary circulation

Chronic issues:

- a failing Fontan circulation
- preoperative decisions regarding incorporation of "small" right ventricles into the pulmonary circulation
- late sequelae of the right ventricle after previous surgery

The issue of Eisenmenger syndrome was intently omitted being considered a more or less historical and fortunately vanishing entity.

Acute Issues

Acute Postoperative Right Ventricular Failure

The right ventricle may fail acutely in the early postoperative hours or days due to many potentially reversible intraoperative issues such as inadequate myocardial protection, large incisions on the free wall or extensive septal reconstructions and last but not least pulmonary hypertensive crises.

Pulmonary hypertensive crises, once dreaded complications of corrective surgery of left to right shunt lesions performed beyond infancy, are currently less frequently encountered and generally have a limited clinical impact. This positive trend is due to the fact that now a days timing of the operations is well before the development of increased pulmonary resistance.

There is also the current awareness of the caring personnel and the preventive measures available in standardized postoperative care. Despite these measures, however, dramatic forms of acute pulmonary hypertensive crisis may be encountered, especially after repair of an obstructed total anomalous pulmonary connection (in simple and complex heterotaxy forms either) and in infants with trisomy 21 whose pulmonary vascular tone is particularly unstable and unpredictable, especially when repair is performed late in infancy. The condition is reversible and the success of recovery is highly dependent upon a prompt management, which should include establishing immediate extacorporeal life support after 10 min of CPR in patients not responding to pharmacologic support [25].

The preferred support modality for any acute severe cardiac or pulmonary dysfunction is a veno-arterial extracorporeal membrane oxygenation (ECMO) setup. This is functionally a standard cardiopulmonary bypass circuit with extracorporal circulation as employed in any open heart surgery these days. The use of the PediMag (modified CentriMag) circuit marketed by Thoratec Corp (Pleasanton, CA) has made setting up and maintenance of ECMO a routine. In the early postoperative patient the circuit is established between the right atrium and the ascending aorta, although cannulation of the neck vessels in the young, as well as the groin or iliac vessels in the occasional older patient could be considered. The latter especially, if ongoing sufficient mechanical chest compression outside the operating room, is prevailing. Lack of an adequate aortic cannulation site may prevent intrathoracal cannulation also.

In modern pediatric ECMO systems centrifugal pumps and heparin coated hollow fiber membrane oxygenators have replaced the roller pumps and silicone membrane oxygenators used earlier. Heparin coating of the entire circuit, requiring less anticoagulation have greatly improved the management of time and resources consuming bleeding complications encountered earlier. Full Heparinisation, however, has still to be considered when the ventricle(s) is (are) not ejecting. The support of the neonates with shunt dependent univentricular circulation posed some controversies in the past concerning shunt management. The previously recommended temporary shunt closure during support has been circumvented by doubling, or at least increasing the flow of the assist device. The temporary shunt closure entails the risk of thrombosis, so that shunt revision is eventually mandatory during ECMO weaning. The high flow rates compensate for the pulmonary run-off and offer a more physiologic environment for the pulmonary circulation. Should the pulmonary function be of no concern early postoperatively one can perform the assist without the inclusion of an oxygenator. This concept known as the NOMO VAD (no membrane oxygenator ventricular assist device as in contrast to ECMO: extracorporal membrane oxygenation) was popularized by Ross Ungerleider and his group [15], the authors recommending it to be routinely performed during the first 24–48 h postoperatively in patients undergoing stage I. reconstruction for hypoplastic left heart syndrome.

Results of ECMO support for reversible right heart dysfunction are encouraging. Outcome analysis of support instituted intraoperatively due to inability to wean from CPB after open heart surgery remain poorer than those instituted after a period of relative stability or acute postoperative failure. The database of the ELSO (Extracorporal Life Support Organization) for patients suffering from congenital heart disease has been reviewed many times since its establishment in 1986. The benchmark outcome data of 60 % successful weaning and 40 % successful hospital discharge [26] are only marginally improving over the time, these results being confirmed by numerous single institutional reviews, also. The different efforts to identify outcome predictors led to very conflicting results, so that it may be postulated that the lack of predictive factors makes every patient a potential candidate for ECLS (ECMO, NOMOVAD).

Acute Dysfunction of an Aorto Pulmonary Shunt

Acute shunt dysfunction in a palliated neonate and infant is almost always a fatal event. Besides tech-

nical issues which usually occur early postoperatively [64] dehydration and infection represent the main causes of shunt thrombosis. With rare exceptions the establishment of rapid circulatory support represent the only therapeutic modality in the event of an acute hypoxemic circulatory collapse. As highlighted earlier in neonates and infants outside the early preoperative phase the peripheral cannulation is performed via the rightsided neck vessels.

Neonatal CHD with Non-ductal Dependent Pulmonary Circulation

Due to the persistence of functional intrauterine shunts many congenital heart defects with potentially ductal dependent pulmonary circulation rarely manifest themselves as an acute insufficiency of the pulmonary circulation immediately after birth. Gradual ductal closure within the first days heralded by deepening cyanosis alerts the neonatologists. Reviewing the abundance of conditions with completely or partially ductal dependent pulmonary circulation is beyond the scope of this chapter, yet some conditions with borderline right ventricles present at birth will be dealt with in the following subchapter.

Nevertheless there are some rare conditions with severe cyanosis present right after birth where the physiologic closure of the ductus arteriosus is not involved in the newly developing pathomechanism.

Acute intrauterine tricuspidal insufficiency produced by papillary head avulsion due to acute and massive RV afterload increase secondary to premature closure of the ductus arteriosus [50] or a congenital large PA to LA fistula [60, 85] are some of the conditions which are relatively straightforward to treat but represent an extreme perinatal emergency. Success can be only expected after immediate postpartal diagnosis, or better: fetal diagnosis.

Acute/Chronic Issues

The Small Subpulmonary Ventricle and the One-and-a-Half-Ventricle Concept

The previous chapter has highlighted the benefits of incorporating a subpulmonary ventricle in the cavopulmonary pathway, also as a mechanical device. It is therefore mandatory to consider incorporating an even distinctly small pumping chamber between the systemic veins and the pulmonary artery in any setting of complex congenital heart disease. The commitment to a high risk septation to reach a complete biventricular repair in anatomically equivocal hearts may be more disadvantageous, as large intraventricular baffles and tunnels might not only lead to an inadequate RV volume but can also compromise ventricular outflow [21]. Yet there are some well-described anatomical entities where a borderline ventricle can handle the IVC return, with the SVC being directly connected to the pulmonary arteries.

This concept originated in the early 1990s [34, 80] and is routinely used in hypoplastic right hearts such as left dominant imbalanced AV-canals/AV-septal defects, Ebstein's anomaly and Pulmonary Atresia with Intact Ventricular Septum (PA/IVS).

Left Dominant AV-Canals/AV Septal Defects

This anatomic variant is significantly less frequently encountered in patients without heterotaxy than the right dominant form, yet the criteria of Cohen (1997) with its more recent modifications [46] are helpful to distinguish them preoperatively. A staged reconstruction with primary pulmonary artery banding followed by second stage intracardiac repair and a superior bidirectional cavo-pulmonary connection (BCPC) is the currently preferred strategy for these patients.

As a bail-out intraoperative maneuver in the presence of a preoperatively unprotected pulmonary arteries in a baby with reactively increased pulmonary vascular resistance the unloading of the hypoplastic right ventricle by an adjunctive bidirectional cavopulmonary connection is not a safe maneuver, as the elevated pulmonary resistances might prohibitively compromise the outflow from the SVC.

In cases where a previously unrecognized RV hypoplasia presents as an acute intraoperative problem after an already completed intracardiac biventricular repair, a temporary systemic-pulmonary shunt, with atrial septal patch fenestration (alternatively ventricular septal patch

fenestration) is sometimes the only alternative to a total takedown of the intracardiac repair. A BCPC with closure of the previously created left-right communication (s) can be performed after documented normalization of the pulmonary vascular resistance.

In the rare patient with low pulmonary resistances the BCPC is performed straightforwardly during the operation for AV canal repair.

Ebstein's Anomaly of the Tricuspid Valve

Besides the extreme neonatal form, which requires immediate, or even emergency attention, these patients will become symptomatic later in life. The leading clinical symptoms presenting are very useful for the selection of patients with inadequate RV. The presence of severe preoperative desaturation in the presence of an ASD may be also a sign of the incapacity of the right ventricle to handle the entire cardiac output and the plan for the one and a half ventricle repair has to be considered. The different aspects of the repair of an insufficient Ebstein valve [9, 14, 16, 41] are beyond the scope of the current chapter, yet the desire and efforts to obtain a competent tricuspid valve might end up in creating a functionally stenotic tricuspid orifice. Given the poor prognosis of a prosthetic valve in the tricuspid position in small children, a restrictive but competent tricuspid valve, especially in pediatric patients is a better alternative than a normal sized prosthesis. Under these circumstances the solution is also a BCPC. Malhootra et al. [53] in a recently published very elegant paper delineate an intraoperative decision algorithm, where the indication for the need of an unloading BCPC can be decided upon the intraoperative postrepair hemodynamics. Any postrepair RA:LA pressure ratio above 1.5 should prompt a one-and-a-half repair.

Pulmonary Atresia and Intact Ventricular Septum (PA/IVS)

The issues discussed for Ebstein's anomaly can generally be applied for PA/IVS as well, except that in these patients a neonatal stage I palliation is mandatory. Extremely underdeveloped right ventricles with lacking inlet or outlet components [18], will clearly speak against any attempt of recruiting the right ventricle. In patients where the neonatal size and morphology of the right ventricle is ambiguous opening the right ventricular outflow tract by a transanular patch completed by a systemic-pulmonary shunt could stimulate "catch-up growth" of the hypoplastic right ventricle.

The decision for the further reconstruction strategy to be pursued should be taken at the time of the second stage operation usually around 6 months of age. Despite some isolated reports upon growing right ventricles following opening the RVOT by inserting a transanular patch in the neonatal period [28, 73] the majority of the literature data do not support the idea of size gain in ventricles where the initial Z- value of the tricuspid valve was under −4 [39]. Patients for whom an eventual one-and-a-half ventricle reconstruction can be seriously contemplated are those with initial tricuspid annular Z values between −4 and −2. They represent a minority among the patients with PA/IVS, their proportion being about 5 % of all patients born with PA/IVS [2].

Chronic Issues

The Sequelae Right Ventricle, the RV after RVOT Surgery

The right ventricle tolerates the deleterious hemodynamic consequences of valve related volume overload for a relatively long time after corrective surgeries in infancy and early childhood. Occasionally dysfunctional valves may result from avoidable technical imperfections, but in their majority they represent a clear choice taken by the surgeon. The perfect case for this "lesser of two evils" compromise is the transannular patching (TAP) and/or pulmonary valvectomy during right ventricular outflow tract reconstruction in patients presenting with Tetralogy of Fallot (TOF). Classical repair in the 1960s and 1970s consisted of an extremely large incision extending into the body of the right ventricle far beyond the lower boundaries of the infundibulum. The length of the incision combined with the extent of the resection of the hypertrophied wall as well as a sometimes very generous (wide!) transannular patch size left the patients with a more or less free regurgitation from the pulmo-

nary arteries into an surgically impaired right ventricle.

Due to the compliant nature of the pulmonary arteries in childhood the volume overload initially is handled well by the hypertrophied and less compliant right ventricle. The progressive regression of the hypertrophy as well as ageing of the pulmonary arteries causes progressive ventricular dilatation in large number of patients. Gatzoulis in a series of benchmark studies demonstrated that an end diastolic RV volume of 180 ml/m^2 as well as a QRS length of >160 ms can be considered cut-off values, above which the incidence of malignant ventricular arrhythmias as well as the contractile dysfunction is significantly higher [32]. These data were further supported by the results of other investigators [45, 74].

Limiting the length or complete avoidance of the infundibulotomy, or even ventriculotomy, and performing only minimal or completely avoiding muscle resections are considered by many cornerstones of an efficient preemptive strategy [3, 45, 63]. Others recommend so called pulmonary valve sparing, but rather function preserving, reconstructive strategies [1, 76] and the implantation of an autologous pericardial monocusp valve during the initial surgery [38].

Whether these recent modifications will stand the trial of time regarding their efficiency to reduce the incidence and extent of the pathology related to the unguarded right ventricular outflow tract is not clear yet. There are clear indices that the magnitude of regurgitation, ventricular dilatation and dysfunction following TAP repair are more profound, but patients who have undergone transatrial repair are presenting with progressive dilatation, also [7, 24, 81, own not published experience]. Anatomically the pulmonary valve, devoid of a proper fibrous annulus is suspended inside a muscular collar represented by the infundibulum. As the infundibulum is characteristically involved in the obstruction seen in TOF, surgical manipulation will always alter its architecture. Even initially well-developed and unobstructive pulmonary valves will have an altered and weakened muscular support prone to dilatation and ultimately leading to valvular insufficiency.

Moreover there are claims that the infundibulum itself is having a sphincter like function, which is profoundly altered in TOF patients.

TOF patients are the most numerous but not the only category where a valveless communication is established between the right ventricle and the pulmonary arteries following corrective surgery. In a large, homogenous and carefully documented follow-up series [22] of the valveless REV procedure ("reconstruction a l'etage ventriculaire") applied for TGA/VSD/PS after an average of 12 years the need for secondary pulmonary valve implantation was strikingly lower 5/171 (2.7 %) as it would have been expected in a similar TOF population. RVOT-Reoperations in a European Multicenter Study, however, was as high as 40 % [40].

Addressing right ventricular systolic and diastolic function in patients following biventricular PA/IVS repair in adolescents Liang and coworkers [52] found surprisingly high incidence of a restrictive right ventricle (81 %) with low volume indexes and almost normal exercise capacity. Other reports on this patient group found a significantly higher proportion of dysfunctional tricuspid valves altering RV function than in the control group of TOF patients, which the authors ascribe to the dysplastic nature of the tricuspid valve in patients with PA/IVS [5]. Although consistent data on long term outcome of these patients are lacking, in the light of the above findings the incidence of reoperations on the RVOT will be eventually lower but this will be biased by a higher incidence of tricuspid valve interventions.

Pulmonary Valve Implantation

After repair of TOF and other similar conditions with eventual RV volume overload, the majority of the adolescents are completely asymptomatic. With changing echocardiographic and MR indexes, the indications for intervention are not clear-cut for the time being. Improvements of the RV systolic function and reversal of the RV dilatation have been documented by some reports, but these findings were not universally supported. From the multitude of studies whose methodologies and results significantly differ

from each other, it is hard to exactly formulate values on which a pulmonary valve implantation should be decided upon. Age ≥17.5 years [30], altered LV function [35] and end diastolic volume indexes above 170 ml/m^2 (Therrien 2005) are among the many other predictors found accountable for an unfavourable outcome following pulmonary valve implantation. During recent years the end diastolic RV volume indexes where an operation should be contemplated came down progressively from 200 to 150 ml/m^2 BSA [30] or even lower. Given the extreme reduced mortality and morbidity of this intervention this policy does not seem exaggerated. Simple infundibular valve implantation in form of a homograft or other biological valved conduits suffice for the moderately dilated ventricles. Larger ventricles, especially in patients operated upon in earlier eras by a wide and long transannular patch reaching deep into the ventricle, the thinned out non functional anterior wall after previous resection may have to be excised to improve the mechanical efficacy of the ventricle. This operation which factually is equivalent to a postinfarction left ventricular aneurysmectomy, is called RV remodeling and is gaining more and more acceptance in the recent years [20, 37]. The first midterm results of such an aggressive approach could not show a benefit over pulmonary valve replacement alone [36].

Conclusions: In a recent review on the topic Kantor and Redington [47] concluded, that: "some lesions (single-ventricle physiology, tetralogy of Fallot, and systemic RV amongst others) are never completely repaired, and others may have persistent abnormal hemodynamic loading abnormalities; patients with these remain at risk of postoperative heart failure. Treatment is multifaceted and relies on focused surgical reintervention, timely medical therapy, and, occasionally, innovative measures, such as resynchronization therapy". We can only humbly agree with them…

Our aggressive pulmonary valve replacement at RV-enddiastolic volumes between 120 and 130 ml cc/m^2 had led to 40 % cumulative valves implanted, in a group of 116 consecutive primary infant and neonatal TOF repair after 12 years (Unpublished data). At this time there was no difference between transatrial and transinfundibular repair. A final benefit of better preserved RV-function or the disadvantage of additional interventions may be recognized only after 20–30 years.

The failing Circulation Late after Fontan-Kreutzer Surgery

The Fontan-Kreutzer operation has in many ways changed not only the fate of children born with heart defects unsuitable for biventricular repair, but also the way clinicians perceive hemyodynamics, particularly the hemodynamics of the pulmonary circulation. The clinical experience has confirmed what earlier experimental studies have by then demonstrated, namely that the entire pulmonary blood flow can be propelled at the expense of only 6 mmHg pressure drop. Yet it lasted almost 20 years until the maturation of the strategy made it possible to reach the current operative mortality of around 5 % [49, 56, 75] with a relatively low postoperative attrition rate in the first 20 years of life. The stepwise improvement of patient selection, introduction of the staged reconstruction, as well as the many technical refinements helped to prevent many of the complications seen earlier, nevertheless skepticism concerning the long term fate of the Fontan operation, or rather the fear of imminent failure in the adulthood persists. This fear [43] is based on two assumptions: first the ageing process will stiffen the pulmonary vessels determining an increase in the pulmonary vascular resistance, and second the age determined reduction of the ventricular compliance will lead to the increase of the ventricular preload. This ventricular preload in a Fontan-Kreutzer Circulation had been relatively low before leading to chronic underfilling of the systemic ventricle and therefore finally adding to ventricular failure.

All of these factors, tolerated and also easily adjusted in a biventricular setting, will increase the impedance the systemic and pulmonary flow has to work against, and will ultimately cause a progressive hemodynamic alteration ending in circulatory failure.

In lack of concrete clinical experience it is hard to predict at which age the Fontan-Kreutzer circu-

lation will ultimately fail, educated pessimists anticipate it to happen in the fourth decade [72].

During the recent years many attempts have been made to develope a therapeutic modality for these patients. Optimization of the hydrodynamics [19, 62] by converting the less efficient atriopulmonary connections to a more efficient cavopulmonary pathway with eventual complete exclusion of the atria from the Fontan circuit [55] and aggressive management of atrial arrhytmias [17] represent all well justified and beneficial interventions, yet the ultimate therapeutic modality of a cardiac transplantation or some form of long term mechanical circulatory support should always be kept in mind as the Fontan population becomes older.

As long-term mechanical support for left ventricular failure has become an accepted and viable alternative for many patients suffering from acquired end stage heart disease the perspective of supporting these patients will become a definitive challenge for specialists treating these patients in the next few years.

The precise aims of the support need also to be defined: Should it be a temporary support or a rather a destination therapy? Should the device assist the ventricle or should it be limited to the cavopulmonary pathway? These are just few of the many questions the current clinical experience cannot answer yet, and which need to be cleared relatively soon [69].

Transplant policies across the world are more and more strictly regulated. It is not clear how patients with relatively well preserved ventricular function, but a prohibitively elevated CVP will fit into the urgency listings prior to development of a more or less irreversible kidney or liver damage. Although the liver and kidney function of supported patients recovers relatively promptly [67] under isolated cavopulmonary mechanical support, so that theoretically a temporary withdrawal can be contemplated if the systemic ventricle shows an acceptable function, the benefits of such a policy are more than questionable since the pulmonary vascular and diastolic properties of the ventricle are unlikely to reverse during the support phase. It is therefore more realistic to view the cavopulmonary support as a destination or "bridge to transplantation" rather than a "bridge to recovery" therapeutic modality. Certain design requirements have been postulated during the recent years, two of them being particularly important to consider:

- the need for an adequate inflow chamber
- the reduced passive internal flow resistance of the device in case of pump failure.

The currently available axial flow pumps are adequate for a cavopulmonary support, but adaptations are definitively required. As the cavopulmonary pathway has a low pressure and energy demand, the current axial pumps need to be modified in terms of pressure/suction relationship. From an engineering standpoint, at least in computer models, this is completely feasible [65, 78, 83]. Some of these devices have already been materialized beyond the stages of computer-assisted design, but there are not yet in the phase of animal studies or clinical trials.

The proposed anatomical approaches for the implantation are also different. While the group from the University of Colorado is working on a long-term support device, implanted surgically, others favor percutaneous devices.

Both approaches have their benefits and shortcomings.

The first approach needs an extended surgery to reconnect the two caval veins and redirect the blood into the pulmonary artery through an interposed segment containing the axial flow pump [84]. This variant is certainly more efficient since it creates effectively a biventricular circulation. The objections against this type of device include the need for an extensive surgery and the definitive/irreversible character, which does not allow explantation and reversal to a Fontan circulation without further major surgery. The other approaches favor percutaneously introduced expandable devices, which are meant to augment solely the IVC return. Such a system is rapidly deployable without any need to alter the existing pathways, and the model worked on by the group from Indiana University [69] is even claimed to be able to decompress the SVC, too, using a pump based on Kármán's principles [68]. Time

will tell which system will prevail, but in our opinion, the two modalities should be regarded rather as complementary: the role of the percutaneous systems being the "bridge to bridge", while the surgical systems will become the modality for longer term support. Whether the percutaneous "4-way" device, once available for neonatal or infant use will revolutionize surgery for leading to a neonatal Fontan-Kreutzer Procedure with temporal two ventricle dynamics has to be speculated. Also speculation is the potential to ameliorate the current longterm problem.

There are no published clinical or experimental attempts of using intracorporeal pneumatic devices, yet successful survival to transplant with an extracorporeal pneumatic pump is documented [67].

Ventricular dysfunction is the other failure modality of the Fontan patients. From a theoretical standpoint they can be regarded as suffering from biventricular failure, but the need for a biventricular support is questionable. Univentricular support devices have been successfully implanted as rescue "bridge to transplant" strategies for perioperative failure [29, 63, 71], but results of a systematic program to address a progressive ventricular decline in Fontan patients has not been reported, yet.

The Morphological Right Ventricle in the Systemic Circulation

Biventricular Setting: Congenitally Corrected Transposition of the Great Arteries (ccTGA)

Transposition complexes are defined as congenital heart defects with ventriculoarterial discordance with or without additional atrioventricular discordance. In a broader sense cases of univentricular hearts with right ventricular morphology can be included in this group as well.

Although the first arterial Switch operation was published 1975 [Jatene], functional repair of complete transposition remained to the late 1980s. Switching the circulation at the atrial level, the morphologically RV ended up supporting the systemic circulation. The subpulmonary left ventricle rapidly thins out and developes a crescent like shape in this configuration, while the right ventricle becomes circular in cross section and its wall thickness is adapting to the systemic requirements.

The introduction of the arterial switch operation not only changed the treatment strategy for transposition of the great arteries, but also highlighted some of the intimate details of the dynamics of the many adaptative mechanisms which take place not only at macroarchitctural but also at histological and cellular level when switching a ventricle form the systemic to the pulmonary circulation and vice versa [11, 23]. The bullet-like elliptical shape of the morphologically left ventricle makes it a more efficient high pressure pumping chamber as opposed to the L-shaped right ventricle. The relatively convergent alignment of the subvalvular elements of the mitral valve as opposed to the more divergent disposition of the tricuspid valve predestines the former to better handle not only pressure but also of volume loads without becoming insufficient [82].

Subtle subclinical changes [42] as well as reduced exercise capacity are documented in the majority of the patients with systemic right ventricles. In addition to the issues related to the systemic right ventricle and the systemic tricuspid valve these patients experience various problems later on due to obstructions in the atrial baffles and rhythm disturbances.

Patients after an atrial switch operation performed during infancy and early childhood are relatively free from ventricular dysfunction, and experience normal life during their first two decades. Longitudinal studies, however, demonstrate a progressive decline of the clinical state much later after the operation [70].

In contrast to the patients with an intact ventricular septum those who presented originally with a VSD as part of their anatomy have a significantly worse outcome in both the s/p atrial switch (d-TGA) and the operated upon congenitally corrected Transposition (ccTGA) patients. Both subgroups with VSD show a higher incidence of tricuspid insufficiency.

Whereas some ccTGA patients can present with dysplastic, Ebstein-like tricuspid valve from

birth, the mechanism implicated in tricuspid insufficiency in systemic right ventricles seen postoperatively is almost always secondary to leaflet distortion induced by the placement of the VSD patch. In addition septal dysfunction secondary to patch suture placement also may play a role [27]. In a recent report Szymanski et al. [77] studied the mechanism of tricuspid insufficiency in systemic right ventricles. They demonstrated in the majority of their patients the typical tenting, characteristic for functional mitral insufficiency seen in left ventricular dysfunction: downward tethering of the leaflets correlating well with the dilatation and systolic dysfunction of the systemic RV.

In a downward spiral, this secondary RV volume overload with the divergent arrangement of the tricuspid subvalvar apparatus present, further tethers the tricuspid leaflets impeding the valvular function and further worsening the ventricular dysfunction.

A secondary arterial switch as treatment option for these patients was inaugurated by the group of Roger Mee [58]. Their left ventricular retraining was achieved by placing a pulmonary artery band based on an earlier technique introduced by Yacoub [79]. The strategy of preliminary banding, although a relatively straightforward procedure seems to play an important role of the ultimate success of the operation. The group of Mee more and more moved to a stepwise tightening to avoid primary LV dysfunction, preferring 1.5 reoperations/patient, whereas Brawn's group in Birmingham prefers a one stage banding to the LV:RV target ratios ranging between 65 and 80 %. As technical variants to the progressive banding some groups use off-label adjustable gastric bands [6], but a bulky dedicated telemetry driven system (Flow-Watch) [12] is also available. Independent from the strategy used to prepare the LV, late dysfunction of the left ventricle seems to develop in some of the patients following this "anatomic repair" [4, 8] so that many groups are introducing novel policies. One of them consists of routine PAB in even asymptomatic neonates born with ccTGA [13, 59]. The advantage of such a routine banding is that the LV is switchable at any age, should the patient become symptomatic, and additionally the septal shift preserves the RV geometry and theoretically prevents a secondary subvalvular left ventricular obstruction. Recent animal studies [51, 61] suggested a more physiologic LV training by applying a chronic intermittent (12 h on/12 h off) banding, the function of the LV being superior to the continuous controls. Patients in the ccTGA group are often presenting with subvalvular or valvular stenoses in the left ventricular outflow tract, which can interfere with the arterial switch. In these patients a Rastelli type of reconstruction was added to an atrial switch. As the aortic root often is relatively remote to the VSD, the intraventricular Rastelli tunnel can be very voluminous. This is further aggravated by the fact that resection along the anterocephalad rim of the VSD, bearing the conduction tissue cannot be performed. The direct consequence of large intraventricular baffles is reduction of the right ventricular volume. These problems were addressed in two different ways.

The group from Stanford [54] liberally performs a BCPC to unload the right ventricle in this setting. Doing this, an inferior Hemi-Mustard procedure, completes the double switch procedure, which in their view promises less long term atrial rhythm disturbances and baffle obstructions. They deem this approach especially advantageous in hearts with atrio apical discordance where the pulmonary venous atrium is very diminuative, which further complicates atrial reconstruction.

Another method to circumvene this issue is the performance of a Nikaidoh type aortic translocation, which is also very advantageous in the prospect of later subaortic obstructions along the ventricular baffle [44].

From the accumulated experience of numerous groups pursuing a strategy to retrain the LV and obtain an anatomic correction for a dysfunctional systemic RV some fundamental principles can be derived.

– the indication for a switch-back strategy and retraining the LV should be put early, as soon as significant tricuspid dysfunction occurs.

- the need to achieve at least a two-thirds systemic pressure without significant LV dysfunction prior to the secondary arterial switch.
- the need for careful monitoring of the cardiac chamber shape and of the hemodynamic parameters to recognize the requirement for secondary band adjustments.
- the ability to retrain the left ventricle is progressively lost with increasing age, and the time required therefore maybe too long, so that currently patients beyond adolescent age are not candidates for an LV retraining strategy, anymore.
- even in patients where the ultimate goal of incorporating the LV in the systemic circulation cannot be obtained, the pulmonary artery banding is beneficial as it shifts the septum back towards the right ventricle and thereby may ameliorate the functional component of the tricuspid insufficiency;
- in patients where a switch back strategy is improbable, early aggressive treatment of the tricuspid valve insufficiency is recommended.

The Right Ventricular Dependent Univentricular Circulation

In univentricular hearts where a morphologically right ventricle acts as a systemic pump it was intuitively anticipated, that it would perform very poorly and the rate of midterm attrition due to ventricular failure would be significant. Yet the clinical experience with the repair of HLHS and other similar univentricular defects has not confirmed this presumption [33, 57] so far.

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Anesthetic Management and Hemodynamic Management

17

Richa Dhawan and Mark A. Chaney

Introduction

Medical management of patients with heart failure is certainly challenging. Perioperative anesthetic management of these oftentimes extremely sick individuals is even more challenging for a wide variety of reasons (essentially all anesthetic techniques compromise the cardiovascular system, patients are undergoing major invasive surgery, detrimental physiologic effects associated with cardiopulmonary bypass, etc.). In order to ensure acceptable postoperative outcome, a true team approach is required by the surgeon, anesthesiologist, perfusionist, and nursing staff. Adequate communication is required by all to identify and attain perioperative goals. The anesthesiologist's job is to choose and safely administer an appropriate anesthetic technique for each particular patient undergoing their specific surgery. Most times, no specific drug or technique is truly indicated. As we will see, identified goals (analgesia, amnesia, muscle relaxation) can be safely attained in many ways. One of the most challenging tasks confronting the anesthesiologist when managing these patients is that of maintaining perioperative hemodynamic stability. The key to successfully managing this problem is correctly identifying the cause of hemodynamic instability (preload, myocardial contractility, afterload) via a wide variety of monitoring techniques (electrocardiography, pulmonary artery catheter, transesophageal echocardiography, etc.). Once again, as we will see, identified goals (optimize preload, optimize myocardial contractility, optimize afterload) can be safely attained in many ways.

The successful perioperative anesthetic management of patients with heart failure is complex and challenging. Anesthesiologists managing these patients need to have extensive knowledge regarding cardiovascular physiology and pharmacology, physiologic effects of anesthetic drugs and techniques on the cardiovascular system, and rational assessment/pharmacologic treatment of hemodynamic instability. In the current era, all such anesthesiologists managing these extremely sick individuals should possess appropriate skills regarding use of transesophageal echocardiography. Identified perioperative goals may be attained safely in many ways. Thus, there is much "art" (which requires extensive clinical experience) to the successful perioperative anesthetic management of patients with heart failure.

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_17

Anesthetic Management

Preoperative Assessment

The goals of preoperative assessment include reducing surgical morbidity, increasing quality and decreasing cost of perioperative care, and allowing the patient to return to desirable functioning as quickly as possible. Traditionally, the anesthesiologist will meet with the patient to review medical and surgical history, order appropriate laboratory rests, obtain informed consent, educate the patient regarding all aspects of perioperative care, and answer questions the patient may have. A thorough history and physical exam are performed, and the airway is assessed for ease in intubation.

Table 17.1 lists items reviewed by the anesthesiologist during preoperative assessment. Numerous factors profoundly influence perioperative anesthetic management. For instance, the presence of renal failure and/or hepatic failure dictates which specific anesthetic medications may or may not be administered. Specifically regarding patients with heart failure, knowledge of current cardiac medications (beta-adrenergic blockers, diuretics, digitalis, etc.) is required prior to planning technique of anesthesia. Additionally, certain preoperative tests (echocardiography, cardiac catheterization, etc.) give the anesthesiologists valuable information regarding left ventricular function and valvular function; again, knowledge required to adequately plan anesthetic technique.

Patients with heart failure undergo a wide variety of surgical procedures. Thus, it is important for all perioperative caregivers (surgeon, anesthesiologist, perfusionist, and nursing staff) to "be on the same page" regarding the planned surgical procedure (coronary artery bypass grafting, valve repair or replacement, ventricular reconstruction, etc.). Additionally, it should be determined whether or not cardiopulmonary bypass will be utilized. Numerous surgical procedures are now being attempted without assist of cardiopulmonary bypass (off-pump). If cardiopulmonary bypass is to be utilized, it should be clear to all what specific technique will be used (normothermic, hypothermic, beating heart, arrested heart, etc.). The planned surgical procedure and use/non-use/technique of cardiopulmonary bypass (decisions arrived at oftentimes only after intraoperative transesophageal echocardiographic evaluation) profoundly influence technique of anesthesia.

Goals of Anesthetic Management

The major goals of anesthesia include analgesia (pain relief), amnesia (lack of recall), hemodynamic stability, and perhaps muscle relaxation (paralysis). Table 17.2 presents the variety of most common ways the anesthesiologist may safely attain these goals (methods of attaining hemodynamic stability will be addressed later). Most commonly, a combination of intravenous opioid (analgesia), intravenous benzodiazepine (amnesia), and inhalational anesthetic (analgesia and amnesia) is used for induction and maintenance of anesthesia. In the current era of "fast-tracking", specific drugs and amounts are

Table 17.1 Preoperative assessment

Age/gender/race/height/weight
Proposed surgery
Past medical history
Past surgical history
Allergies
Current medications
Vital signs
Physical exam
Laboratory tests
Additional tests

Table 17.2 Agents commonly used during anesthesia

Intravenous opioids
Morphine, fentanyl, sufentanil
Intravenous benzodiazepines
Diazepam, midazolam
Inhaled anesthetics
Isoflurane, desflurane, sevoflurane
Intravenous alpha-2 receptor agonists
Dexmedetomidine
Intravenous muscle relaxants
Pancuronium, vecuronium, rocuronium

chosen for specific anesthetic goals in each individual patient in order to allow the patient to awaken from anesthesia in the immediate postoperative period. Thus, short-acting drugs (fentanyl, midazolam) and/or inhalational anesthetics are favored.

Monitored Anesthesia Care

The term monitored anesthesia care (MAC) generally implies intravenous sedation without laryngeal intubation. Most commonly, a combination of intravenous opioid and benzodiazepine is administered to a spontaneously breathing patient and titrated to facilitate surgery while keeping the patient comfortable. Because amounts of opioid and benzodiazepine must be carefully kept to an appropriate minimum (both drug classes promote respiratory depression), only certain minimally invasive surgeries may be performed in patients with heart failure under monitored anesthesia care. Procedures that may be amenable to MAC include pacemaker insertion/replacement, transcatheter aortic valve implantation, transesophageal echocardiography, and cardioversion.

Regional Anesthesia

The term regional anesthesia generally implies the use of a wide variety of peripheral nerve blocks (parasternal block, intercostal nerve block, etc.), intrathecal techniques, and/or epidural techniques [1]. While general anesthesia may be supplemented with regional anesthetic techniques, the traditional use of the term regional anesthesia usually implies the use of regional anesthetic techniques and intravenous sedation in a spontaneously breathing patient. Thus, amounts of intravenous opioid and benzodiazepine must be carefully kept to an appropriate minimum, limiting the scope of surgeries that may be performed in patients with heart failure under regional anesthesia.

Use of regional anesthetic techniques in patients undergoing cardiac surgery, while seemingly increasing in popularity, remains extremely controversial, prompting numerous Editorials by recognized experts in the field of cardiac anesthesia. One of the main reasons such controversy exists (and likely will continue for some time) is that the numerous clinical investigations regarding this topic are suboptimally designed and utilize a wide array of disparate techniques preventing clinically useful conclusions all can agree on [2–5].

General Anesthesia

The term general anesthesia usually implies the use of moderate to large doses of intravenous agents and/or inhalational agents (with or without intravenous muscle relaxants) along with endotracheal intubation and mechanical ventilation. The vast majority of cardiac surgeries performed in patients (with or without heart failure) are performed under general endotracheal anesthesia. The total control over the respiratory system via mechanical ventilation allows the anesthesiologist to administer large amounts of intravenous anesthetics and/or inhalational anesthetics to the patient, permitting invasive cardiac surgery to occur. General anesthesia is sometimes supplemented with regional anesthetic techniques.

Premedication

The goals of premedication include decreased patient anxiety, production of amnesia, and minimization of pain associated with vascular cannulation in the preanesthetic period without producing ventilation or cardiac depression. These goals are most commonly met by administering small and appropriate amounts of intravenous opioids for analgesia and intravenous benzodiapines for amnesia. Additionally, most anesthesiologists have patients take their routine cardiovascular medications (beta-adrenergic blockers, etc.) the morning of surgery (with small sips of water) in hopes of promoting perioperative hemodynamic stability.

Monitoring

Numerous physiologic parameters are monitored in patients undergoing cardiac surgery (Table 17.3). Arterial blood pressure may be monitored noninvasively or invasively. Cardiac rate and rhythm is assessed via electrocardiography. Cardiac function (preload, myocardial contractility, etc.) is most commonly monitored via the pulmonary artery catheter and/or transesophageal echocardiography, and will be discussed in greater detail later in this chapter. Pulmonary function is assessed in a wide variety of ways, including assessment of pulmonary compliance and interpretation of arterial blood gas tensions (oxygen, carbon dioxide). Urine output is closely monitored in all patients undergoing cardiac surgery, especially so in patients with preoperative renal dysfunction. Maintenance of normothermia in patients is extremely important (and sometimes difficult), especially in cardiac surgeries without assist of cardiopulmonary bypass. Numerous arterial blood samples are obtained perioperatively in order to monitor pulmonary function, a wide variety of serum electrolytes (potassium, magnesium, etc.), glucose levels, and hemoglobin levels. Frequent assessment of coagulation is important as well, because essentially all patients undergoing cardiac surgery will be subjected to at least some degree of anticoagulation (and possibly reversal of anticoagulation). Cerebral function monitoring is somewhat controversial. Neurologic insult (via microemboli and/or macroemboli) continues to haunt cardiac surgery. Although numerous investigators have valiantly tried, we are still without a monitor that reliably and effectively predicts intraoperative recall or the development of postoperative neurologic insult (stroke or diffuse neuropsychological dysfunction).

Table 17.3 Monitored physiologic parameters

Arterial blood pressure
Cardiac rate and rhythm
Cardiac function
Pulmonary function
Renal function
Body temperature
Blood gas analysis
Coagulation analysis
Cerebral function

Anesthesia and Transesophageal Echocardiography

Intraoperative transesophageal echocardiography (TEE) was introduced in 1980s, and there has been significant development in training and technology since that time. The most common applications intraoperatively include assessment of left and right ventricular function, valvular anatomy and function, intracardiac air, clot, or masses, detection of pericardial fluid, and evaluation of the aortic root and ascending aorta. Minhaj et al. found that the routine use of TEE during cardiac surgery revealed new findings in 30 % of patients and of these 20 % had a change in surgical plan [6]. Many cardiothoracic anesthesiologists undergo extensive training and/or certification in perioperative TEE. Newer three dimensional technology is available that allows very accurate reconstruction of anatomy and assessment of function. It is particularly useful in mitral valve repair because of the ability to accurately identify the lesion (P2, ruptured cordae, etc.) and target the surgical approach.

Induction of General Anesthesia

Prior to induction of general anesthesia in patients scheduled for cardiac surgery, a wide variety of items need to be prepared and checked out. The anesthesia machine needs to be checked out and airway materials (laryngoscope) prepared. Appropriate medications (anesthetic drugs, potent cardiovascular drugs) need to be prepared as well. Preoperatively, peripheral venous access is obtained and intravenous premedication administered. Most anesthesiologists insert invasive arterial catheters (usually radial artery) prior to induction of general anesthesia. Induction of anesthesia (depending on the choice and dose of drugs and the patients' cardiac reserve) can result

in significant hemodynamic changes. Safe induction of general anesthesia in patients with heart failure can be accomplished in a wide variety of ways. A variety of anesthetic drugs can be selected on the basis of both their anesthetic properties and their hemodynamic effects. However, one must realize that essentially all intravenous and inhalational anesthetics can initiate profound (dose-related) cardiorespiratory depression. Additionally, the anesthesiologist should thoroughly understand the patient's underlying cardiac status (left ventricular function, extent of valvular disease, etc.) prior to induction of general anesthesia because specific choices of anesthetic drugs may be determined by specific physiologic goals in individual patients (for example; avoidance of arterial vasodilation in a patient with aortic stenosis). Most commonly, a combination of intravenous opioid (analgesia), intravenous benzodiazepine (amnesia), and inhalational anesthetic (analgesia and amnesia) is used. Following induction of general anesthesia, the trachea is intubated with a cuffed endotracheal tube (following administration of an intravenous muscle relaxant). The choice of a particular muscle relaxant is based upon pharmacokinetics (speed of onset, half-life, etc.) and autonomic and hemodynamic side effects. In most patients, tracheal intubation is accomplished via direct laryngoscopy. However, in patients with altered airway anatomy, tracheal intubation must be accomplished in another manner (awake fiberoptic, asleep fiberoptic, etc.). Once the airway is secured, mechanical ventilation is appropriately initiated.

Maintenance of General Anesthesia

Maintenance of general anesthesia involves continued administration of intravenous anesthetics and/or inhalational anesthetics to achieve the goals of analgesia and amnesia (and possibly muscle relaxation). While muscle relaxation during cardiac surgery is not required, it is often achieved for a wide variety of reasons (facilitate endotracheal intubation, limit oxygen consumption, prevent shivering, and prevent unexpected movement during critical periods of the operation). The drawback of continuous muscular paralysis is its interference with somatic signs (movement) of light anesthesia. If cardiopulmonary bypass is used, maintenance of general anesthesia is attained via continued administration of intravenous anesthetics and/or inhalational anesthetics.

Emergence from General Anesthesia

With the focus on reducing costs by shortening the length of stay in the intensive care unit, the anesthesiologist in encouraged to design an anesthetic plan that not only fulfills the requirements of general anesthesia (analgesia, amnesia, muscle relaxation, hemodynamic stability, etc.) during intense noxious stimulation intraoperatively, but also allows an appropriately rapid recovery of consciousness and spontaneous ventilation postoperatively. In the uncomplicated case, the goal is to allow tracheal extubation very soon after the patient's condition is stabilized in the intensive care unit, usually within two to fours hours postoperatively. Hence, there is continuing effort to develop rapid-onset, short-acting anesthetics, opioids, benzodiazepines, and muscle relaxants that allow efficient titration of dose (or infusion rate) according to the individual patient's needs both intraoperatively and postoperatively.

Hemodynamic Management

Potential therapeutic interventions in managing patients with hypotension and/or decreased cardiac output include manipulation of heart rate or rhythm, optimizing preload, optimizing myocardial contractility, and/or optimizing systemic vascular resistance [7, 8]. When managing patients with hypotension and/or decreased cardiac output, the initial important task for the clinician is to appropriately assess the hemodynamic instability to determine the etiologic roles that heart rate/rhythm, preload, myocardial contractility, and/or systemic vascular resistance contribute to the hemodynamic instability. Once the cause

(or causes) of hemodynamic instability are identified, the physiologic goal (or goals) are identified and appropriate specific therapy is initiated. Such decisions are clinically important. Appropriate clinical interventions can prove lifesaving. Conversely, inappropriate clinical interventions can prove deadly. For example, administering a vasoconstrictor to a patient who has hypotension/decreased cardiac output from left ventricular failure will most certainly precipitate clinical deterioration. This patient requires agents that increase myocardial contractility and/or initiate afterload reduction (not vasoconstrictors). This section will focus on how clinicians should appropriately assess hemodynamic instability, choose the physiologic goal (or goals), initiate appropriate specific therapy, and assess the outcome of the chosen therapy [9, 10].

Hemodynamic Instability Assessment

Numerous clinical variables must be contemplated during assessment of hemodynamic instability (Table 17.4). Determination of blood pressure and evaluation of heart rate and rhythm obviously play an important role in initial early assessment of hemodynamic instability. Level of hypotension (mild, moderate, severe) determines the time frame in which the clinician must operate. In certain patients, manipulation of heart rate and/or heart rhythm may restore hemodynamic stability. While the physical examination may be of great value in diagnosing gross or acute pathology (pneumothorax, hemothorax, acute valvular insufficiency), it is of limited value in diagnosing and managing ventricular failure. While level of mental status and amount of urine output may be beneficial in certain patients, classic clinical indicators of decreased cardiac output (oliguria, metabolic acidosis) may not always be reliable. Thus, in essentially all patients with clinically significant hemodynamic instability that requires more than routine therapy, more information will be required then is routinely obtained in order to appropriately assess the hemodynamic instability. Such information is most commonly obtained via assessment of central venous pressure, insertion of a pulmonary artery catheter, and/or some form of echocardiography. Each of these three methods has unique advantages and disadvantages.

Table 17.4 Hemodynamic instability assessment

Blood pressure/heart rate
Electrocardiogram
Mental status/urine output
Arterial/venous blood analysis
Central venous pressure
Pulmonary artery catheter
Echocardiography

The routine use of a pulmonary artery catheter in all patients with hemodynamic instability has progressively been replaced by a more selective approach. In general, a central venous pressure catheter alone may be used for monitoring in patients with preserved left ventricular function (ejection fraction greater than 40 %) and no severe valvular pathology. If the patient continues to clinically deteriorate (progressive hypotension, unexplained oliguria, and/or acidosis), then a pulmonary artery catheter may then be inserted to gather additional information, such as right ventricular pressure, pulmonary artery pressure, and pulmonary artery occlusive pressure. Derived variables, such as cardiac output/cardiac index, pulmonary vascular resistance, and systemic vascular resistance may also then be obtained. Special purpose pulmonary artery catheters for continuous cardiac output measurements, continuous mixed venous oximetry measurements, pacing ability, and/or right ventricular ejection fraction are also available.

The introduction of the flow-directed pulmonary artery catheter in the 1970s represented, at the time, a major advance in the monitoring of hemodynamically unstable patients. A very large amount of information (intracardiac pressures, derived hemodynamic and pulmonary parameters) can be gathered. However, one must keep in mind that clinical data obtained from a pulmonary artery catheter may be erroneous and/or misleading [11, 12]. Some recent clinical investigations have indicated that information obtained from pulmonary artery

catheters may in fact lead clinicians to initiate inappropriate therapy, which may increase morbidity and mortality. Such clinical investigations have stirred controversy regarding proper clinical utilization of (and interpretation of data from) the pulmonary artery catheter. Some Investigators/Editors have even suggested that use of the pulmonary artery catheter should be abandoned.

Probably the major reason for the "demise" of the pulmonary artery catheter has been the emergence of echocardiography (specifically transesophageal echocardiography) over the past two decades. It is now clear that information obtained from echocardiography is far superior (in quality and quantity) to that obtained from the pulmonary artery catheter. Furthermore, information from echocardiography has helped prove that much of the information obtained from the pulmonary artery catheter may be erroneous and/or misleading. Specifically, echocardiography provides definitive clinical data regarding preload, myocardial contractility, and systemic vascular resistance whereas the pulmonary artery catheter can only provide surrogates of these important variables. Furthermore, echocardiography can provide additional useful clinical data that the pulmonary artery catheter cannot, such as information regarding diastolic function, myocardial ischemia, valvular function, potential aneurysm/dissection, potential effusion/tamponade, and the presence/position of intracardiac catheters (Table 17.5). The American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography deemed that unexplained hemodynamic disturbances not responsive to conventional therapy is a Class I indication for use of transesophageal echocardiography ("frequently useful in improving clinical outcome") [13].

Physiologic Goals of Therapy

By utilizing a clinically appropriate physical examination, invasive monitoring (central venous pressure, pulmonary artery catheter), and/or echocardiography, one can determine the physiologic goal(s) of therapy. Once assured that heart rate and rhythm are optimized, the clinician must then choose the appropriate mixture of optimizing intravascular volume, optimizing myocardial contractility, and/or optimizing systemic vascular resistance (Table 17.6). The relative importance of each (preload, myocardial contractility, afterload) will vary in each individual patient and clinical scenario and is determined by the clinician during assessment of hemodynamic instability. Once specific physiologic goal(s) of therapy are determined, choice of specific therapy may then be contemplated.

Table 17.6 Physiologic goals of therapy

Intravascular volume?
Colloid/crystalloid
Myocardial contractility?
Inotropic agents
Systemic vascular resistance?
Vasopressor agents

Table 17.5 Comparison of pulmonary artery catheter data and echocardiography data

Determinant	PA CATH	ECHO
Preload	CVP, PAOP	Direct
Afterload	SVR	Wall stress
Systolic function	SV, CO	FAC, EF, SV, CO, ESPVR
Diastolic function	CVP, PAOP	Filling profiles
Ischemia	Insensitive	Sensitive
Valvular function	Indirect	Direct
Aneurysm/dissection	Not useful	Extremely useful
Effusion/tamponade	Indirect	Direct
Intracardiac catheters	Not useful	Extremely useful

Choice of Specific Therapy

Optimization of intravascular volume (preload) requires administration of intravenous crystalloid and/or colloid, enhancing myocardial contractility involves administration of intravenous inotropic agents, and increasing systemic vascular resistance (afterload) requires use of intravenous vasopressor agents. The most commonly utilized inotropic agents and vasopressor agents are listed in Table 17.7.

Dopamine is an endogenous catecholamine and is an immediate precursor of norepinephrine and epinephrine. Its actions are mediated via stimulation of alpha, beta, and dopaminergic receptors. In low doses (1–3 mcg/kg/min), dopamine predominantly stimulates dopaminergic receptors. Increasing the dose to 6–14 mcg/kg/min predominantly stimulates beta receptors and further increases in dosing (>14 mcg/kg/min) leads to exclusive stimulation of alpha receptors. Such dose-dependent effects of dopamine are not very specific and can be influenced by many factors. Dopamine is unique in comparison with other endogenous catecholomines owing to its effects on the kidneys. It may increase renal artery blood flow by causing direct vasodilation of the afferent arteries and indirect vasoconstriction of the efferent arteries. This results in an increase in glomerular filtration pressure and in glomerular filtration rate.

Table 17.7 Choice of specific therapy

Inotropic agents
Beta-receptor agonists
Dopamine
Dobutamine
Dopexamine
Epinephrine
Isoproterenol
Phosphodiesterase inhibitors
Amrinone
Milrinone
Enoximone
Miscellaneous
Digitalis preparations
Thyroid hormone
Calcium
Magnesium
Vasopressor agents
Alpha-receptor agonists
Norepinephrine
Phenylephrine
Arginine vasopressin
Methylene blue

Dobutamine is a synthetic catecholamine that generally produces dose-dependent increases in cardiac output and reductions in diastolic filling pressures. Its primary physiologic effects are mediated via stimulation of beta receptors (does possess minimal alpha receptor activity). Venous return, augmented by adrenergic reduction of venous capacitance, likely contributes to the increase in cardiac output. In addition to increasing contractility, dobutamine may have favorable metabolic effects on ischemic myocardium.

Dopexamine is a relatively newly developed synthetic catecholamine, structurally related to dopamine and dobutamine. The drug stimulates both dopaminrergic and beta receptors. An inhibitory action in the neuronal catecholamine uptake mechanism has also been demonstrated and may account for the positive inotropic action of this drug. Continuous infusion of dopexamine results in systemic and preferential renal vasodilation, causing afterload reduction, increases in cardiac output, and improved renal perfusion. Dopexamine reduces afterload through pronounced systemic arterial vasodilation, increased renal perfusion by selective renal vasodilation, and cardiac stimulation through direct and indirect positive inotropic mechanisms. The increase in cardiac output appears to occur predominantly as a result of an increase in heart rate, as stroke volume demonstrates only a minimal change. Dopexamine's physiologic effects are most pronounced when used as a continuous infusion of 1–4 mcg/kg/min.

Epinephrine stimulates both alpha and beta receptors in a dose-dependent fashion. The sympathoadrenal (endogenous) secretion of epinephrine is critical to support cardiac contractility, exert tonic control of vascular beds, and in the modulation of the body's "stress response". Epinephrine increases stroke volume and cardiac

output in a dose-dependent fashion (10–40 ng/kg/min). However, heart rate may also be increased to unacceptable levels.

Isoproterenol is a potent beta receptor agonist devoid of alpha receptor agonist activity. Isoproterenol dilates skeletal, renal, and mesenteric vascular beds and decreases diastolic blood pressure. The drug's potent chronotropic action, combined with the potential to decrease coronary perfusion pressure (via decreased diastolic blood pressure), may limit its usefulness in patients with coronary artery disease. Isoproterenol may be uniquely useful for stimulation of cardiac pacemaker cells in the management of acute bradyarrhythmias or heart block. It reduces refractoriness to conduction and increases automoaticity in myocardial tissues. The tachycardia seen with isoproterenol is a result of both direct effects of the drug on the heart and reflex effects caused by peripheral vasodilation. Additional application of isoprotereonol has included management of right ventricular dysfunction associated with pulmonary hypertension. However, although isoproterenol is an excellent pulmonary vasodilator, decreases in perfusion pressure (particularly diastolic arterial pressure) may lead to right ventricular ischemia.

Phosphodiesterase inhibitors are noncatecholamine and nonadrenergic agents [14]. Therefore, they do not rely upon beta receptor stimulation for their positive inotropic activity. As a result, the clinical effectiveness of the phosphodiesterase inhibitors is not altered by previous beta blockade nor is it reduced in patients who may experience beta receptor down-regulation. Although the precise mechanism of action of the phosphodiesterase inhibitors has yet to be elucidated, the proposed theory of action involves the inhibition of type III phosphodiesterase found predominantly in cardiac muscle. This inhibition results in a secondary increase in cyclic AMP, which leads to an increase in calcium channel entry into the cell, accounting for the positive inotropic action. These agents also produce systemic and pulmonary vasodilation. As a result of this combination of hemodynamic effects (positive inotropic support and vasodilation), the term "inodilator" has been coined to describe this class of drugs. Because these agents exert their hemodynamic effects by a nonadrenergic mechanism of action, when used in combination with traditional beta receptor agonists, phosphodiesterase inhibitors have been shown to result in an additive effect on myocardial performance. Phosphodiesterase inhibitors decrease pulmonary vascular resistance by both a direct action on the pulmonary vasculature (increasing cGMP) and an indirect effect (increasing cardiac output, decreasing pulmonary artery occlusive pressure).

Digitalis binds to a subunit of sodium potassium ATPase, producing complete inhibition of enzymatic and transport processes. Thus, intracellular sodium and calcium increase and intracellular potassium is lost. The elevated intracellular sodium increases the availability of calcium to the contractile proteins, increasing contractility. Increased intracellular calcium is associated with decreased intracellular pH, which increases inward sodium movement and outward hydrogen ion movement, further increasing intracellular sodium concentration and inotropy. Digitalis exerts its positive inotropic effect independent of catecholamine liberation. Digitalis augments both force and velocity of myocardial contraction without raising cardiac output. Ventricular end-diastolic volume and end-diastolic pressure are decreased. The positive inotropic effects of digitalis, however, are weak. The physiologic onset of action of digitalis occurs within 15–30 min following intravenous administration, with peak effects being obtained in 2–5 h. It must be kept in mind that the therapeutic plasma level "window" of digoxin is relatively narrow and substantial toxicity (heart block, enhanced automaticity) may occur.

Thyroid hormone's effects on the cardiovascular system are well established in clinical states of hyperthyroidism and hypothyroidism. Clinical studies suggest that a reduction in plasma thyroid hormone concentration may be associated with the decreased myocardial performance that occurs in certain clinical scenarios, such that occurs following exposure to cardiopulmonary bypass and in the setting of organ transplantation. However, the proper role that thyroid hormone

supplementation plays in clinical treatment of hemodynamic instability remains to be determined.

Calcium may antagonize the action of catecholamine activity, but does not alter the cardiotonic actions of phosphodiesterase inhibitors. Calcium influx during ischemia-reperfusion may increase oxygen consumption and contribute to diastolic dysfunction. However, calcium administration usually increases mean arterial pressure via an increase in systemic vascular resistance and may also improve right ventricular function.

Magnesium has a key role in cellular energy transfer and use (involving adenosine triphosphate) and in cell membrane function. It is widely used as an adjunct for the treatment of arrhythmias following myocardial infarction. Magnesium may influence hemodynamic performance through its modulation of vascular tone, intracellular calcium, catecholamine activity, and adenosine triphosphate metabolism. The potential for magnesium deficiency to affect cardiovascular performance may be particularly relevant in the presence of ischemia, and there are reports of a potential role for magnesium in enhancing hemodynamic performance in ventricular dysfunction following cardiac surgery.

Norepinephrine stimulates both alpha and beta receptors in a dose-dependent fashion. Norepinephrine, after a long period of disfavor, is experiencing a renewed popularity for management of hemodynamic instability. When used appropriately, norepinephrine increases blood pressure, increases stroke volume, increases cardiac output, and increases urine output.

Phenylephrine is a potent alpha receptor agonist devoid of beta receptor agonist activity. Thus, the physiologic effect of phenylephrine administration is an increase in systemic vascular resistance, with no effects as myocardial contractility.

Arginine vasopressin is an endogenous peptide synthesized exclusively in the hypothalamus and released from the posterior pituitary. Traditionally, arginine vasopressin release is stimulated by changes in vascular volume and vascular tone. Vasopressin is bound by two distinct types of receptors: renal (V2) and vasomotor (V1). Although under normal conditions, arginine vasopressin contributes little, if any, to blood pressure maintenance, investigations have shown the ability of arginine vasopressin to be helpful in the management of certain refractory vasodilatory states [15, 16]. In a syndrome known as post-conditioning vasodilatory shock (characterized by catecholamine resistance, low systemic vascular resistance despite norepinephrine administration), administration of arginine vasopressin is effective in restoring hemodynamic stability. Numerous investigators have explored the role of arginine vasopressin administration in the management of vasodilatory states in septic shock and following cardiopulmonary bypass. Although the precise mechanisms responsible for this vasodilatory state are unknown, patients experiencing such vasodilatory states are characterized by a significant reduction in circulating vasopressin. In these patients, infusion of arginine vasopressin in the range of 2–8 units/h results in significant hemodynamic improvements. An increase in the infusion above 8 units/h provides little added effect.

Several case reports have been described in the literature in which the guanylate cyclase inhibitor methylene blue was successfully administered intravenously to reverse norepinephrine-resistant vasoplegia after cardiopulmonary bypass [17]. The favorable effect of methylene blue in this scenario suggests refractory vasoplegia may reflect a dysregulation of nitric oxide synthesis and vascular smooth muscle cell guanylate cyclase activation. The available data have been obtained from anecdotal case reports only and the effect of methylene blue has not been examined in larger cohorts. Methylene blue has also been used to effectively treat patients with septic shock and low peripheral vascular resistance. A few adverse effects of methylene blue in the treatment of norepinephrine-refractory vasoplegia have been described, such as cardiac arrhythmias, coronary vasoconstriction, decreases in cardiac output, renal blood flow, and mesenteric blood flow, increases in pulmonary vascular pressure and resistance, and deterioration in gas exchange. However, most of these side effects are dose-dependent and do not occur when the dose of methylene blue is no >2 mg/kg.

Levosimenden is a new inotropic agent and belongs to a class of drugs known as calcium sensitizers. It prolongs the actin-myosin cross bridging time by stabilizing cardiac troponin C. It is a unique drug because it does not increase intracellular calcium unlike traditional inotropic agents, thus it increases cardiac output without increasing myocardial oxygen consumption and causing arrhythmias. It is currently clinically available in Europe and is being investigated in the United States. Studies have demonstrated utility in weaning patients off cardiopulmonary bypass (CPB) and early recovery after CPB in patients with heart failure [18, 19].

Assessment of Therapy

Assessment of therapy entails contemplation of the same physiologic parameters (heart rate/rhythm, preload, myocardial contractility, and systemic vascular resistance) that were assessed during the initial period of hemodynamic instability. This will involve reassessment of blood pressure, heart rate/rhythm, level of mental status (if applicable), urine output, central venous pressure, information from a pulmonary artery catheter, and/or information from some form of echocardiography.

Conclusions

The successful perioperative anesthetic management of patients with heart failure is complex and challenging. In order to ensure acceptable postoperative outcome, a true team approach is required by the surgeon, anesthesiologist, perfusionist, and nursing staff. Anesthesiologists managing these patients need to have extensive knowledge regarding cardiovascular physiology and pharmacology, physiologic effects of anesthetic drugs and techniques on the cardiovascular system, and rational assessment/pharmacologic treatment of hemodynamic instability. Most times, no specific drug or technique is truly indicated. Identified goals (analgesia, amnesia, muscle relaxation) can be safely attained in many ways. In the current era, anesthesiologists managing these extremely sick individuals should possess appropriate skills regarding use of transesophageal echocardiography, which simplifies hemodynamic instability assessment and may influence surgical management. Once again, identified goals (optimize preload, optimize myocardial contractility, optimize afterload) can be safely attained in many ways. Thus, there is much "art" (which requires extensive clinical experience) to the successful perioperative anesthetic management of patients with heart failure.

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Peri-operative Care, ICU Care and Fluid Management

18

Rinaldo Bellomo

Introduction

The medical component of the care of adult patients with cardiac failure undergoing cardiac surgery is likely important to their outcome as the surgery itself. As a significant proportion of patients undergoing cardiac surgery, have a degree of cardiac failure (systolic or diastolic or both) such care applies to many patients and is clinically important.

This component of patient care includes four major aspects:

1. The medical management of their cardiac failure
2. The anesthetic management of the patient
3. The management of the cardiopulmonary bypass aspect of the operation
4. The post-operative management of the patient.

The peri-operative management of the these patients is most complex in the acute phase, either when the patient is already critically ill and requires an urgent operation or immediately after the operation has been completed and the patient has been admitted to the Intensive Care Unit. This chapter will focus mostly on the aspects of peri-operative care, which relate to the acute phase or the sub-acute phase, while the patient is or remains critically ill. It will also discuss other general principles of management as they relate to fluid therapy and important aspects of the general care of the cardiac surgery patient with heart failure.

The Pre-operative Period

Patients with heart failure (acute or chronic) come to cardiac surgery through several pathways: (1) The outpatient setting; (2) The ward inpatient setting; (3) The coronary care unit (CCU); (4) The Intensive Care Unit (ICU) and (less commonly) (5) The Emergency Department (ED).

Those patients coming from [1] usually have the opportunity to be prepared for surgery in a deliberate and planned fashion. Such planning for surgery should allow the cardiologist, the anesthesiologist and the cardiac surgeon to consider several aspects of care (Table 18.1). These aspects of care should of course be considered for each patient. However, the time frame available for their assessment or the actual ability to obtain such information or manipulate such aspects of patient care is markedly affected by the presence of an acute situation (patient from source 2 to 5). In urgent situations, decisions have to be made in a hurry and in the absence of a comprehensive

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9_18

Table 18.1 Issue to be considered prior to elective surgery for cardiac failure

1. General issues
Medical history: previous problems with anesthesia including allergies and current medications; presence of conditions that might affect surgical risk (chronic lung disease, renal disease, liver disease, arrhythmias, hematological disorders, diffuse vascular disease, diabetes, early dementia etc.)
Examination: signs of other important medical conditions (see above)
Biochemistry and general tests: full blood examination, renal and liver biochemistry, group and cross match of blood, urinalysis, chest X-ray, electrocardiogram, and, in selected patients pulmonary function tests and arterial blood gases
2. Specific issues
Recent use of anticoagulants
Recent use of antiplatelet agents
Current control of heart failure symptoms and signs
Optimization of cardiac failure control with medications
Absence of any currently active infection
3. Cardiological issues
Availability and review of all appropriate imaging modalities
Careful assessment of risk/benefit ratio for the decision to operate
Need to modify medications before surgery (temporarily stop clopidogrel or aspirin or warfarin)
4. Surgical issues
Quality of leg veins as conduits
Suitability of radial arteries as conduits
If re-do surgery, suitable information of previous operation
Planning of correct approach for a given patient (off-pump vs. on-pump, number of grafts, type of valve surgery, cardioplegic strategy, etc.)

discussion with patient or family which gives them sufficient time to consider further care over weeks or months.

When the patient comes to surgery from the CCU, ICU or ED, by definition, there must have been a sudden change, which requires prompt surgical intervention. Such change may stem from unstable coronary ischemia, coronary ischemia with aggravation of heart failure, worsening of valve function, decompensation of cardiac function, endocarditis, valve rupture and so on. The treatment of such patients must, of course, include: (1) Stabilization of the physiological state in order to ensure patient safety; (2) Simultaneous management of the exacerbating condition and (3) Carefully timed surgical intervention.

No randomized controlled trials exist to specify a particular pathway of management for all conditions. Each must be dealt with using the specific knowledge, which applies to it. Thus, a given patient may just require antibiotics and optimization of cardiac failure medications, while another will require intubation, mechanical ventilation, inotropic support, intra-aortic balloon counterpulsation, continuous hemofiltration and even extra-corporeal membrane oxygenation or the use of a ventricular assist device.

In fact, the principles which apply to this period are the same as those that apply to post-operative care and will be described in detail later in this chapter.

The Immediate Post-operative Period

The most important single predictor of a safe post-operative period is the successful execution of a well-planned and correctly applied operation.

However, even when this is done, several patients with heart failure require very careful and skilled medical management. If the operation is ill-conceived or ill-executed or the patient is extremely unwell ever before surgery, the patient will experience life-threatening problems, which, sometimes require extraordinary feats of technology and great team work to achieve survival and recovery.

Monitoring and Inotropic Drugs

A patient with heart failure undergoing surgery with cardiopulmonary bypass will inevitably experience a decrease in myocardial contractility, which, combined with the pre-operative state of heart failure, often mandates the use of intropic drugs. This decrease in contractility is mediated by complex mechanisms [1, 2] and typically results in a progressive post-operative decrease in contractility with a nadir in contractile function between 8 and 24 h after cardioplegia, depending on the duration of cardiopulmonary bypass (CPB).

Accordingly, almost all of these patients require inotropic support. Although, no randomized controlled trials exist, in the opinion of the authors, it is generally best to monitor cardiac output in cardiac surgery patients and it is vital to do so in those who have surgery in the context of impaired pre-operative myocardial function (heart failure patients). Monitoring of cardiac output allows physicians to either prevent or rapidly detect and treat a low cardiac output state. Such treatment initially requires a judicious combination of three components: (1) Inotropic drugs; (2) Fluid resuscitation; (3) Control of heart rhythm and rate (pacing).

There are two major classes of inotropic drugs that can be used in patients with cardiac surgery in the setting of a postoperative heart failure and/or a low cardiac output state (LCOS): catecholamines and phosphodiesterase III inhibitors (PDEIs) [3–13] (Table 18.2). More recently, they have been joined by a new class of agents called calcium sensitizers [14]. However, experience with these new inotropic agents in cardiac surgery is limited [15]. These agents have different properties (Table 18.2) and have never been compared in suitably powered randomized controlled trials of heart failure patients having cardiac surgery to test whether the use of one or the other results in better clinical (instead of physiological) outcomes. Accordingly, they are typically used according to local (institution) and individual (physician) preferences. In addition, there is no consensus definition of what constitutes the goal of inotropic therapy. In general, however, inotropic agents are administered to deal with a low cardiac output syndrome (LCOS) in order to either prevent its occurrence or return cardiac output (CO) to adequate levels to ensure sufficient oxygen delivery to tissues.

No consensus definition of what a LCOS currently exists. However, it would be reasonable to define it as any low cardiac output state (cardiac index of <2.4 L min^{-1} m^{-2} is used as a criteria in some studies) with clinical and laboratory evidence of inadequate peripheral perfusion (e.g. a persistently elevated lactate, cool vasoconstricted hands and feet, a urine output persistently <0.5 ml h^{-1} for more than 1 h, evidence of ischemic hepatitis).

Table 18.2 Inotropic drugs

Agent	Significant features
Epinephrine	Increases CI with biphasic effect on SVRI. Produces rise in serum lactate
Dopamine	Increased SVRI at doses above 5.0 μg/kg/min. Less clinical efficacy than dobutamine, dopexamine, amrinone or enoximone. Increased incidence of adverse cardiac events than dopexamine
Dobutamine	Better efficacy than dopamine and epinephrine. Decreases SVRI. Tachycardia and tachyarrythmia (esp. AF) more common
Dopexamine	Greater tachycardia than dobutamine. More efficacious and less adverse events than dopamine
Amrinone	Improved weaning from CPB. Improves CI and decreases SVRI with minimal effects on HR. Reports of thrombocytopenia associated with use
Enoximone	Significant increase in CI without tachycardia. Decreases SVRI. As effective as dobutamine
Milrinone	Significant increase in CI without tachycardia. Decreases SVRI. As effective as dobutamine, but less AF. Lusitropic. Improves graft flow. As effective as 20 ppm of inhaled nitric oxide in pulmonary hypertension

Such LCOS can continue for several hours to days, despite optimisation of volume status, temporary pacing, exclusion of mechanical factors (e.g. cardiac tamponade or pneumothorax) and mechanical assistance with intra-aortic balloon counter pulsation (IABP). Causes for this LCOS are multifactorial but include myocardial ischemia during cross clamping, reperfusion injury, cardioplegia-induced myocardial dysfunction, activation of inflammatory and coagulation cascades and un-reversed pre-existing cardiac disease. LCOS can result in reduced oxygen delivery to vital organs. Such end-organ ischemia will lead to multiorgan failure. Initial organ dysfunction and multiple organ failure are among the main causes of prolonged hospital stay after cardiac surgery and they increase resource use and

healthcare costs as well as morbidity and mortality. Optimisation of cardiac output and oxygen delivery may, therefore, decrease morbidity and reduce length of stay and remains the cornerstone of hemodynamic management.

It must be emphasized here that a particular value for the cardiac index must always be interpreted within the clinical context. A cardiac index of 1.8 L/m^2/min may be perfectly adequate in a patient with a normal lactate, a urine output of 1 ml/kg/h and a core temperature of 35.5 °C immediately after transfer to the ICU. In such a patient, hypothermia is likely mostly responsible for decreased metabolic demand and the low value of the cardiac index. Nonetheless, in all patients the cause for the low cardiac index must be diligently sought and dealt with. In particular, one must always be vigilant about the possibility of cardiac tamponade or pneumothorax or other mechanical factors which impede cardiac output. Their diagnosis requires a high index of suspicion, regular patient examination and review and the prompt use of chest X-rays and echocardiography.

The use of inotropic drugs is often insufficient to restore cardiac output if the patient's heart rate (HR) is not optimized. Patients with cardiac failure who have been on beta-blockers until the time of surgery will often be bradycardic post-operatively and will have a LCOS because of such bradycardia in the setting of a low stroke volume, unless their hear rate is optimized. This is because CO = stroke volume (SV) × heart rate (HR). In these patients, even with inotropic drugs and optimal fluid therapy, SV can only be partially increased, therefore optimal HR is vital. This optimization is best achieved by epicardial pacing of the atria in order to maintain atrial contractility. If the patient is chronic atrial fibrillation, ventricular pacing is necessary to maintain an adequate rate. The importance of pacing in the post-operative period in patients with pre-operative heart failure cannot be overemphasized. Pacing not only provides the ability to optimize heart rate but also allows the prompt and safe treatment of tachyarrhythmias like atrial fibrillation, which so commonly occurs after cardiac surgery in these patients.

In particular, the availability of pacing makes the use of intravenous amiodarone extremely safe [16].

Post-operative Fluid Therapy

Fluid therapy is a source of incessant controversy in the post-cardiac surgery period because of the lack of randomized controlled trials. Such controversy also arises from the need to individualize care and to change such individualized care dynamically and frequently as the patient's hemodynamic state changes over hours and sometimes days following surgery [17]. However, some comments are in order.

First, there is insufficient evidence that a particular kind of fluid is better than another. A recent large randomized controlled trial in critically ill patients has shown no difference in overall outcome between patients treated with saline compared to patients treated with albumin [18]. Accordingly, both colloids or crystalloids are theoretically acceptable choices. However, there is widespread concern about inducing fluid overload states and about the capillary leak state that most cardiac surgery patients experience after CPB. Therefore, most of the fluid literature for cardiac surgery patients appears to preferentially report the use of colloidal fluid preparations. These typically include either natural colloids such as albumin or artificial colloid solutions such as starch and gelatin preparations [19].

Second, there is always controversy about "adequacy of filling" in these patients (i.e. what the optimal left or right ventricular end diastolic volume might be in a given patient at a given time). This is also due to the lack of randomized controlled trials and the dynamic nature of all measurements and physiological states. Further uncertainty is added by the fact that myocardial filling cannot be reliably assessed by currently applied forms of hemodynamic monitoring [20]. In particular standard pulmonary artery technology measures pressures, not volumes. The relationship between pulmonary artery catheter derived pressures and end diastolic filling volumes is highly unpredictable [20]. New technologies are being applied beyond the traditional pulmonary artery catheter such as pulse contour cardiac output analysis by transpulmonary thermodilution [21] and transesophageal echocardiography [22].

Their usefulness in the ICU and ability to deliver superior outcomes remain unknown. In the opinion of the author, echocardiography and thermodilution technology are complementary and should be used in unison and together with clinical and laboratory assessment of the patient's condition to help guide hemodynamic management. Importantly, however, and irrespective of echocardiographic findings if a fluid challenge (250 ml of IV colloid bolus over 10–15 min in an adult patient) fails to increase cardiac output (CO) by >15 %. Then the patient is in the flat portion of the Starling curve. Logically, in such patients, further administration of fluid will provide no benefit and will potentially induce chamber dilatation. Such dilatation and the increased intracavitary pressures that go with it will likely decreased endocardial perfusion (thus worsening cardiac output), increase the probability of pulmonary edema, myocardial edema and vital organ edema. Thus, such unnecessary fluid therapy should be avoided. In mechanically ventilated patients who do not have spontaneous respiratory effort he measurement of pulse pressure variation (the percentage change in mean arterial pressure induced by a ventilator breath) may help predict which patients will respond to a fluid challenge with a >15 % increase in cardiac output.

Particularly seductive and misleading is the appearance of an "underfilled" left ventricle on echocardiography in the setting of right ventricular dysfunction with an already enlarged right ventricle and a high right atrial pressure (>15 mmHg). Further filling will predictably result in the following: no change in left ventricular filling, septal movement into the left cavity with decreased left ventricular compliance, further right ventricular dilatation, right ventricular endocardial ischemia, increased back pressure in the liver, liver cell ischemia and no change or even a decrease in cardiac output. In this setting, the correct treatment is the use of inotropic support, pulmonary vasodilatation with nitric oxide and, if these measures appear insufficient, institution of mechanical support (IABP or extracorporeal membrane oxygenation or ventricular assist device).

Vasopressor Drugs

Hypotension is relatively common after cardiac surgery. While a degree of hypotension may be clinically unimportant, a low mean arterial blood pressure (MAP <65–70 mmHg) may be undesirable in some patients (carotid artery disease, renovascular disease) and, in general, should be prevented or treated. A very low blood pressure (MAP <60 mmHg or diastolic BP <40 mmHg) frequently causes renal dysfunction, threatens the adequacy of liver perfusion and may induce inadequate coronary blood flow with sub-endocardial ischemia, especially in the setting of high pulmonary artery occlusion pressures (PAOP). In particular, if the diastolic BP is 40 mmHg and the PAOP (a surrogate for left ventricular end diastolic pressure) is 25 mmHg, coronary perfusion pressure for the left ventricle will be 15 mmHg. This value is <25 % of normal and is likely reduce coronary blood flow significantly, especially in patients with a hypertrophic ventricle [23]. The same is true for liver blood flow in the setting of a LCOS, right ventricular dysfunction and an elevated central venous pressure [24].

The pathogenesis of hypotension after cardiac surgery in heart failure patients is typically complex and may involve a variety of factors either alone or in combination (Table 18.3). All should be considered and either excluded or identified by means of prompt clinical, radiological, hematological and hemodyamic assessment.

If the patient has an adequate or even high cardiac output and all other factors have been excluded, then one is likely dealing with an

Table 18.3 Factors potentially responsible for hypotension after cardiac surgery in heart failure patients

Low cardiac output syndrome
Relative or absolute hypovolemia
Bleeding
Tamponade
Pneumothorax
Inflammatory response to CPB
Fever
Drugs used for sedation
Use of inodilators (PDEIs)
Residual effect of pre-operative ACE inhibitors
Patient-ventilator dyssynchrony

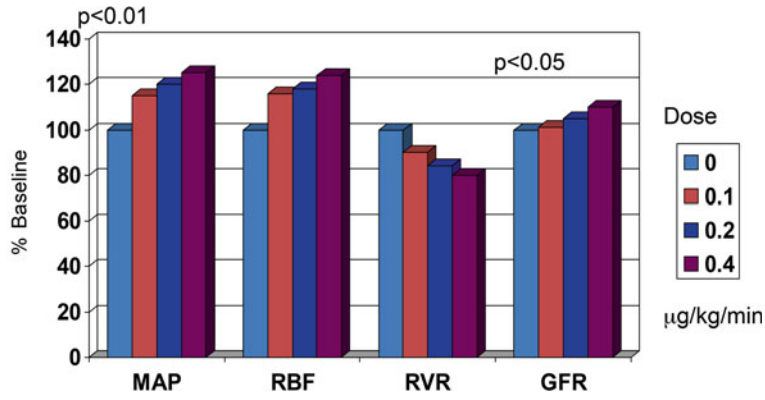


Fig. 18.1 Comparison of changes in renal function in dogs with the administration of increasing doses of norpineprhine (noradrenaline) (*MAP* mean arterial pressure, *RBF* renal blood flow, *RVR* renal vascular resistance, *GFR* glomerular filtration rate). Norepinephrine infusion up to 0.4 mcg/kg/min increases MAP, RBF and GFR and decreases RVR

"inflammatory vasodilatory state" or so-called "post-CPB vasoplegia" [25]. In these patients, if the blood pressure is too low, the use of vasopressor drugs becomes necessary.

There are several vasopressor agents, which can be used for this purpose (norepineprhine, phenyephrine, vasopressin). The agent for which there is greater clinical experience, however, is norepinephrine (noradrenaline). Despite theoretical concerns over its adverse effects on renal and mesenteric blood flow, most of the available data in fact indicate this agent is efficacious and safe under these circumstances [26], particularly from the renal functional point of view (Fig. 18.1).

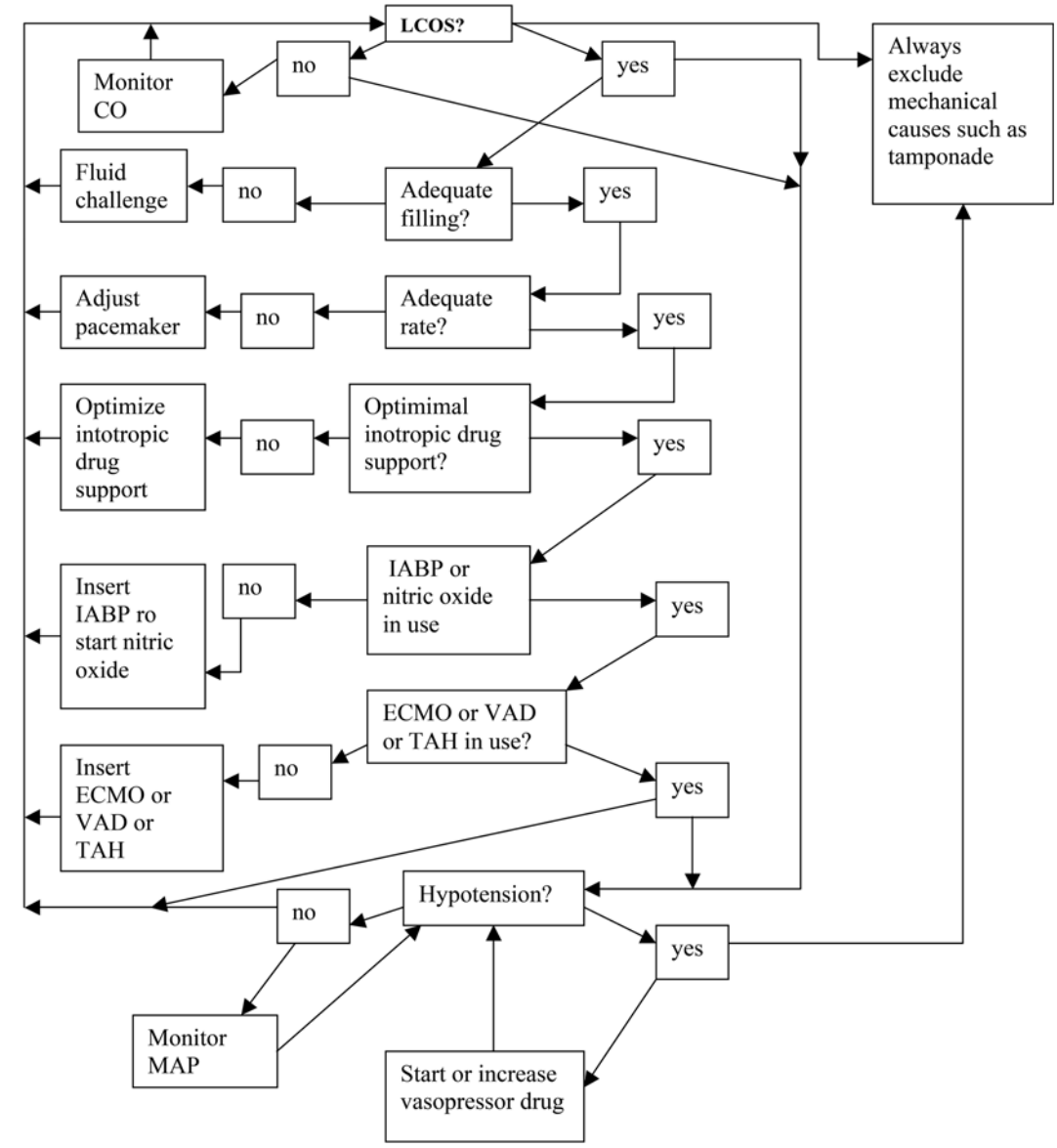
In some patients with pre-operative sepsis (e.g. endocarditis), this vasodilatory state can be dramatic and may require the addition of vasopressin [27]. Assuming that external mechanical factors have been corrected, the approach to the hemodynamic management of these patients can be summarized in a flow chart (Fig. 18.2).

Mechanical Support

Some patients with heart failure have severe cardiac functional impairment after surgery. Despite the use of inotropic agents, optimization of fluid therapy, optimization of pacing and the addition of vasopressor drugs to restore adequate vital organ perfusion pressure, and nitric oxide to decrease pulmonary vascular resistance, some of these patients continue to have either a LCOS or hypotension of both. In these patients, mechanical support should be rapidly considered and implemented.

Broadly speaking the first line of support is the implementation of intra-aortic balloon counterpulsation (IABP). The addition of IABP can sometimes bring about sufficient improvement in hemodynamics and no further mechanical support is needed. However, in general the benefits of IABP in these patients are modest and if there are continuing signs of LCOS [28], the treating team should rapidly move to more advanced mechanical support, which depending on the situation, availability and local expertise, may be in the form of a ventricular assist device, or a total artificial heart device or the institution of extracorporeal membrane oxygenation (ECMO) [29].

Such mechanical devices add another layer of complexity to the management of the patients (Fig. 18.3). The care of such patients requires consideration of a myriad of issues [29], which cannot be discussed in a general chapter. Nonetheless, it is important to note that almost all of these patients have acute renal failure and requirements for very tight fluid control especially because the administration of large amounts of blood and blood products is relatively common. As will be discussed in detail later in the chapter, the use of hemofiltration in these patients both during and particularly after surgery offers important physiological advantages [30, 31].



LCOS = low cardia output syndrome; CO = cardiac output; MAP= mean arterial pressure;
IABP = intraaoirtic balloon counterpulsation; ECMO = extracorporeal membrane oxygenation;
VAD = ventricular assist device; TAH = total artificial heart

Fig. 18.2 Flow diagram for hemodynamic management

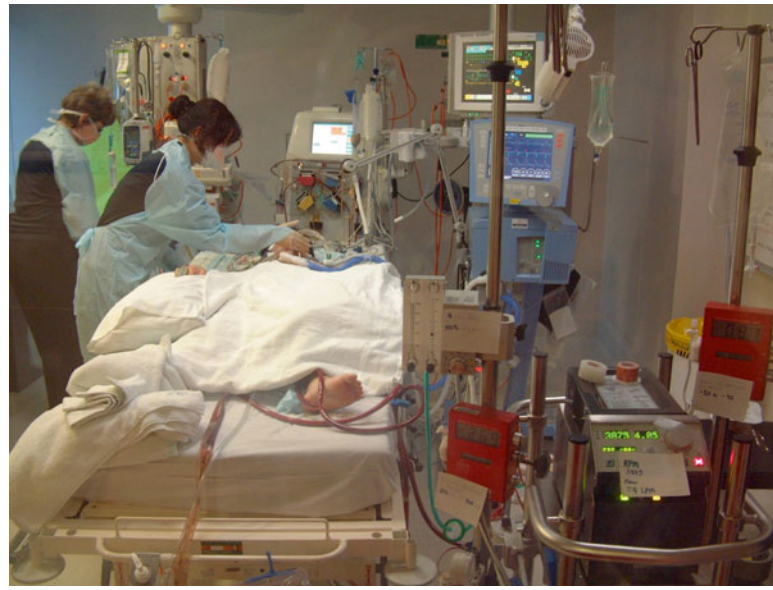


Fig. 18.3 Photograph of patient receiving mechanical support by means of an extracorporeal membrane oxygenation device. The mechanical ventilator and continuous hemofiltration machine can be seen on the right and at the back of the patient's bed

Non-hemodynamic Issues

Beyond the dominant hemodynamic issues, these patients share several other unique features. One such feature is the risk of post-operative bleeding [32]. Although a variety of steps are typically taken in the OR to prevent this complication, some patients continue to have large mediastinal drainage post-operatively. In these patients several steps should be promptly considered:

1. Measurement of INR, fibrinogen and APTT
2. Empiric administration of protamine
3. Empiric administration of platelets
4. Empiric administration of an antifibrinolytic agent
5. Empiric administration of fresh frozen plasma
6. Empiric administration of cryoprecipitate

If, despite an aggressive response, mediastinal drainage continues at a high rate (e.g. >200 ml/h) despite platelet administration and near normalization of INR, APTT and fibrinogen levels and/or there is suspicion of tamponade or evidence of an accumulating hemothorax, the patient should promptly return to the OR for surgical intervention.

Another common and unique feature of heart failure patients having cardiac surgery is their high likelihood of developing atrial fibrillation (AF). This is an undesirable complication because it removes the atrial contribution to left ventricular filling in patients who tend to have diastolic dysfunction. Furthermore, if the ventricular response rate is too fast, such ventricular filling will be further impaired by the decreased filling time. Accordingly, it is desirable to prevent AF. Although meta-analysis shows that beta-blockers may reduce the risk of post-operative AF [33], their use in patients with poor left ventricular function on inotropic agents is fraught with dangers. On the other hand, prophylactic magnesium supplementation is exceedingly safe. A meta-analysis of 17 trials using magnesium prophylaxis after cardiac surgery showed a significant 23 % reduction in the incidence of supraventricular arrhythmias [34]. Another effective agent, which is safer than beta-blockers in these patients, because it lack negative inotropic effects, is amiodarone. This agent has been repeatedly shown to be effective when given prophylactically as well as for treatment of new onset AF [16]. Amiodarone does not increase the rate of reversal of atrial fibrillation, but it does allow rate control. As this agent typically induces a degree of bradycardia, it is at its safest when coupled with the presence of epicardial pacing. Amiodarone also remains an ideal agent for the treatment of essentially all arrhythmias in the post-

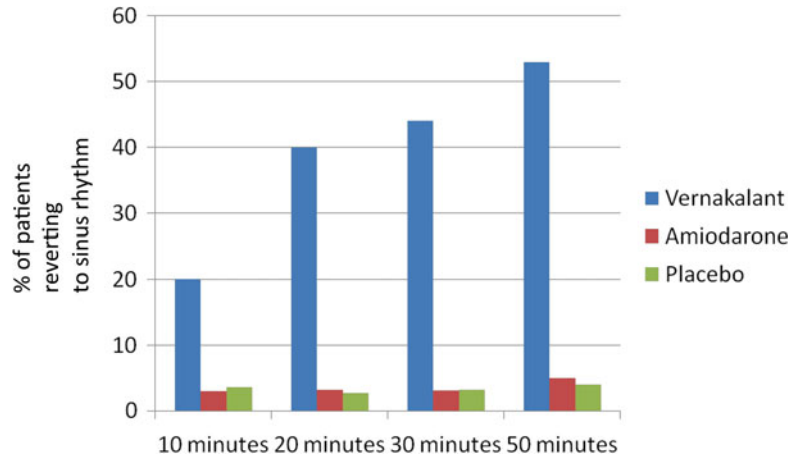


Fig. 18.4 Histogram illustrating the approximate conversion rate of new onset atrial fibrillation with different treatment. Vernakalant appears a promising agent and is clearly more effective than available alternatives

operative period. Normalization of potassium levels and administration of supplemental magnesium are, in our opinion, vital ancillary measures in these patients. More recently a new class of antiarrhytmic drugs (atrial potassium channel blockers with frequency dependent blockade of sodium channels) has emerged. One of these agents (vernakalant hydrochloride) has shown excellent safety and the ability to successfully revert new onset atrial fibrillation with 8–10 min [35, 36]. The use of these agents is likely to increase (Fig. 18.4).

In other ways, however, cardiac surgery patients with heart failure are similar to critically ill patients with other disorders. First, they require post-operative mechanical ventilation. In most cases such ventilation is straightforward and executed along conventional lines. However, in patients with co-morbidities such COPD or chronic lung disease or asthma, such ventilation may require specific adjustments. In patients with known right ventricular dysfunction and/or pulmonary hypertension, hypercarbia and acidemia should be prevented or rapidly treated by means of adjusted minute ventilation as they increase pulmonary vascular resistance and may exacerbate right ventricular failure.

Derangements of acid-base status are frequently observed in patients after cardiac surgery. Their pathogenesis is complex [37], however, the most common and important disorder is that of a non-anion gap acidosis which is secondary to the effect of the pump prime fluid on the strong ion difference [38–40]. Such acidosis slowly resolves over the first 12–24 h provided no further chloride rich fluids are given. It is wise, however, to monitor blood lactate levels on a regular basis as they are often an early indicator of clinical deterioration. It is highly desirable for ICUs providing post-cardiac surgery care to have a point of care machine that can measure arterial blood gases and lactate.

Almost all patients undergoing cardiac surgery develop hyperglycemia. A recent single center randomized controlled trial [41], which contained close to 500 cardiac surgery patients in each arm, showed that the maintenance of normoglycemia may reduce morbidy and mortality in such patients. Although these findings appeared promising, they were later contradicted by a large multicentre randomised controlled trial [42], which found that the pursuit of normoglycemia in ICU patients was associated with a higher rate of hypoglycaemia and a greater mortality rate compared with aiming for a glucose level of between 8 and 10 mmol/L (144–180 mg/dL).

Infection, especially pulmonary infection, remains an important source of morbidity in these patients and should be considered in the presence of any change in patient status, temperature or white cell count. Although, cardiac surgery patients receive peri-operative antibiotic prophylaxis and protection from chest infection is typically promoted by the application of breathing exercises and physiotherapy, no evidence of clinical benefit from chest physiotherapy could be demonstrated in a recent randomized controlled trial [43]. Central venous lines or other

invasive devices should be removed as soon as possible to prevent line-related sepsis. Finally other general measures of patient care should routinely be attended to, including pressure sore prevention, administration of prophylactic gastric acid suppression therapy, the early introduction of deep venous thrombosis prevention and, in the majority of cases, the administration of aspirin within the first 48 h. Finally, although many patients are able to rapidly resume oral intake after surgery, a significant proportion of patients cannot do so. In such patients, rapid implementation of enteral nutrition is considered important. If gastroparesis is present, the use of nasojejunal feeding may become necessary [44].

Pain relief requires detailed attention because pain may inhibit coughing and promote chest infection and because it can trigger patient anxiety, discomfort, distress and induce significant deleterious hemodynamic changes. Pain control requires the use of judicious mixture of approaches from the administration of intravenous narcotics (either under medical direction or, preferably, under patient control in the form of patient controlled analgesia), the strict use of acetaminophen, the adjunctive use of non-steroidal anti-inflammatory drugs in selected patients, the use of low-dose ketamine infusion and in some cases the use of thoracic epidural analgesia. As the use of narcotics frequently induces nausea and vomiting, prophylactic or prompt patient-responsive antiemetic treatment is also important.

The Prolonged ICU Stay of the Complicated Patient

If the critically ill cardiac failure patient survives the initial hemodynamic instability of the first 48 h after surgery and begins to improve, such improvement may be rapid and lead to ICU discharge over the ensuing day or 2. However, some patients remain critically ill, dependent on either inotropic support or mechanical support and only slowly progress to be weaned off mechanical support and then, later on also be weaned off inotropic and vasopressor support. Such patients are exposed to complications similar to those seen in other acutely ill patients who require prolonged intensive care support. Although there are many issues that require discussion, in this chapter, we will focus on some particularly important ones.

First, these patients are at high risk of infection. This is because of the highly invasive nature of both monitoring and mechanical support. These very ill patients will often have several intravenous catheters, an arterial catheter to monitor blood pressure, an intra-aortic balloon counterpulsation device and, in some cases, large cannulae for mechanical support of cardiac output. They will also have hematomas or some residual clot in the mediastinum and, sometimes, chest drains. All such breaches of skin integrity occur in patients whose immune system is highly dysfunctional as a consequence of the insults associated with repeated major surgery and a LCOS. In these patients, the onset of sepsis can be lethal. Accordingly, vigilance for possible infection must be extreme. Regular monitoring of sputum for organisms, rapid line change at even minute indications of possible infection (increase in white cell count, change in C reactive protein, increased body temperature) or even broad spectrum prophylactic antibiotic cover should all be considered.

Careful fluid management is paramount as these patients are at high risk of the Acute Respiratory Distress Syndrome. Accordingly, detailed monitoring of fluid balance and use of diuretics and/or hemofiltration are essential tools to avoid unnecessary fluid overload. Mechanical ventilation should be with low tidal volumes [44].

Almost all of these patients develop anemia. While it is obviously vital that red cell transfusion should take place in the context of continued documented blood loss during various operations, the treatment of anemia of critical illness should preferably be conservative as shown by a recent randomized controlled trial [45].

Furthermore, recent evidence suggests that the administration of red cells of older age may affect the complication rate and survival of cardiac surgery patients [46].

In addition to their other problems, these very ill patients are likely to develop a polyneuropathy of critical illness, especially if neuromuscular blocking agents are used [47]. Accordingly, such agents should be used very sparingly.

Last but not least, there remains the issue of sedation during mechanical ventilation. Once again, such sedation is necessary for patient safety and comfort as is occasionally true of neuromuscular

blockade. However, like neuromuscular blockade, it can be a double-edged sword and lead to the unnecessary prolongation of mechanical ventilation with its attendant problems [47]. Therefore, it should be used judiciously and with the understanding, that, especially in the presence of renal failure, there is significant accumulation of metabolites of sedating agents such as morphine and/or midazolam, which would further prolong the duration of sedation even after cessation of drug infusion [48]. Accordingly, it appears desirable to re-assess the patient's needs for sedation daily and to titrate such sedation according to validated sedation scales in order to avoid both under and over dosage.

In addition to these problems, cardiac surgery patients subjected to prolonged and invasive ICU treatment are a high risk of developing delirium (Fig. 18.5). Delirium is independently associated with increased duration of ICU, hospital stay and even increased mortality. It makes patient care more difficult and problematic for the patient himself/herself and for the nursing and medical personnel. Although delirium is traditionally treated with haloperidol and or diazepam, newer agents are emerging which appear to be safer and more effective (Fig. 18.6) like dexmedetomidine [49]. As haloperidol prolongs the QT interval and as many of these patients may simultaneously be on

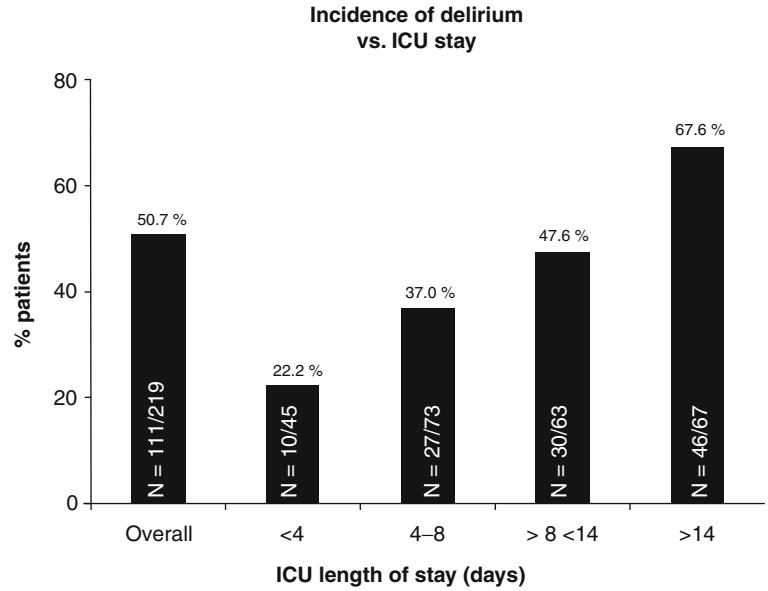


Fig. 18.5 Incidence of delirium in ICU patients according to duration of ICU stay

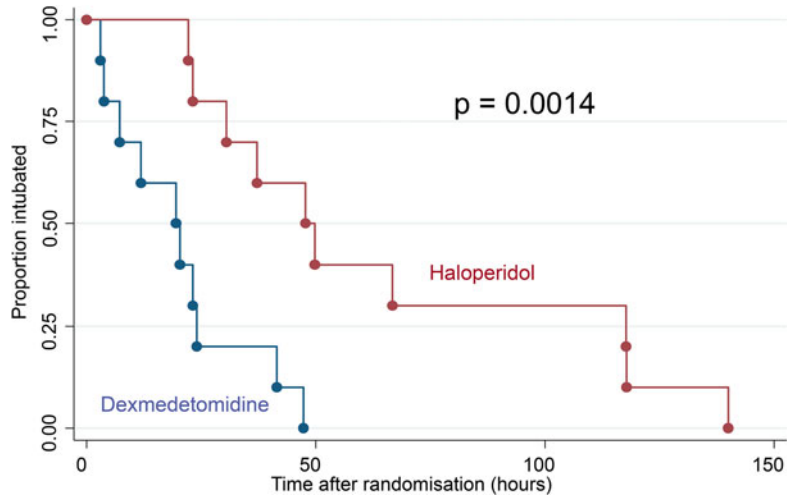


Fig. 18.6 Kaplan-Meier diagram illustrating the time to extubation for patients with delirium randomised to treatment with either haloperidol or dexmedetomidine. Treatment with dexmedetomidine was associated with faster resolution of delirium and more rapid extubation

amiodarone which also prolongs the QT interval, there is real risk of torsade. Accordingly, in these patients newer agents should be considered in preference.

Conclusions

The care of cardiac failure patients undergoing cardiac surgery is complex and multidisciplinary in nature. It is best performed as part of a team effort which includes intensivists, anesthetists, cardiac surgeons, cardiologists, highly trained nursing staff along with ancillary support staff such as physical therapists and nutritionists. Attention to detail, frequent patient review, a high index of suspicion for complication and a systematic a logical approach to care are necessary to ensure excellent outcomes.

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J. Raman (ed.), *Management of Heart Failure: Volume 2: Surgical*,
DOI 10.1007/978-1-4471-4279-9