In Clinical Practice

Doreen DeFaria Yeh · Ami Bhatt
Editors

Adult Congenital Heart Disease in Clinical Practice

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In Clinical Practice

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Adult Congenital Heart Disease in Clinical Practice

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Preface

The Adult Congenital Heart Disease Program at the Massachusetts General Hospital was established in 1974 by Dr. Richard Liberthson, a pioneer in this field who shepherded his patients from infancy through childhood and into adulthood in health and well-being. Dr. Liberthson cared for many thousands of congenital heart patients for over four decades with a highly individualized and thoughtful approach, and his patients continue to revere him as a beloved member of their families. Hundreds of adult and pediatric cardiology fellows from across the globe have joined him in his office with these patients learning the nuances of the cardiac physical exam and pearls in clinical management. Through example he would ensure that every trainee internalized the critical importance of longitudinal personalized care for this unique population. This book is dedicated to Dr. Liberthson's legacy, the decades of extraordinary teaching and mentorship he has provided to all of us, and to the many generations of cardiology fellows he has trained over his career.

Boston, MA, USA — Doreen DeFaria Yeh

Contents

Part I General Introductory Principles

1 Terminology: Defining Cardiac Position, Chamber Morphology and Van Praagh Nomenclature 3
Evin Yucel and Doreen DeFaria Yeh

2 Dextrocardias 11
Evin Yucel

Part II Shunt Lesions

3 General Principles of Simple Shunt Lesions 27
Jonathan Kochav

4 Atrial Septal Defects and Sinus Venosus Defects . . . 31
Jonathan Kochav

5 Ventricular Septal Defect 55
Jonathan Kochav

6 Atrioventricular Septal Defect 71
Jonathan Kochav

7 Patent Ductus Arteriosus 91
Jonathan Kochav

8 Miscellaneous Shunts 107
Jonathan Kochav

9 Pulmonary Hypertension and Eisenmenger Physiology 117
Jonathan Kochav

10 Persistent Left Superior Vena Cava 143
Jonathan Kochav

11 Anomalous Pulmonary Venous Return 151
Jonathan Kochav

Part III Left Heart Obstructive Lesions

12 Cor Triatriatum 167
Jonathan Kochav

13 Congenital Mitral Stenosis 175
Lucy M. Safi

14 Subaortic Stenosis 187
Lucy M. Safi

15 Congenital Valvular Aortic Stenosis 195
Lucy M. Safi

16 Supravalvular Aortic Stenosis 209
Lucy M. Safi

17 Coarctation of the Aorta 217
Akl C. Fahed

Part IV Right Heart Obstructive Lesions

18 Valvular Pulmonic Stenosis 235
Jonathan Kochav

19 Supravalvular Pulmonic Stenosis 251
Christopher Valle

20 Subvalvular Pulmonic Stenosis 265
Christopher Valle

21 Double-Chambered Right Ventricle (DCRV) 271
Christopher Valle

Part V Conotruncal Abnormalities

22 Double Outlet Right Ventricle 283
Yamini Krishnamurthy

23 Tetralogy of Fallot 295
Jonathan Kochav

24 Truncus Arteriosus 319
Christopher Valle and Michelle Hadley

25 D-Looped Transposition of the Great Arteries 331
Ada C. Stefanescu Schmidt

26 L-Loop or Congenitally Corrected Transposition of the Great Arteries (L-TGA or CCTGA) 353
Yamini Krishnamurthy

Part VI Other Complex Lesions

27 Ebstein's Anomaly of the Tricuspid Valve 371
Jonathan Kochav

28 Anatomic Variants of Univentricular Physiology and Fontan Palliation 391
Ada C. Stefanescu Schmidt

29 Left Ventricular Non-compaction 417
Evin Yucel

30 Genetic Thoracic Aortic Diseases 431
Akl C. Fahed

Part VII Coronary Abnormalities

31 Congenital Coronary Anomalies 447
Ada C. Stefanescu Schmidt

32 Kawasaki Disease 461
Yamini Krishnamurthy

Part VIII Principles in Adult Congenital Heart Disease

33 Advanced Imaging in Adult Congenital Heart Disease 477
Sandeep Hedgire, Vinit Baliyan, and Brian Ghoshhajra

34 Cardiopulmonary Exercise Testing in ACHD 511
Ada C. Stefanescu Schmidt

35 Obesity and Exercise Recommendations in Adult Congenital Heart Disease 519
Laura D. Flannery

36 Endocarditis Prophylaxis in ACHD. 525
Evin Yucel

37 Pregnancy in Adults with Congenital Heart Disease 533
Evin Yucel

38 Heart Failure and Transplant in Adult Congenital Heart Disease 551
Laura D. Flannery

39 Atherosclerosis in Adult Congenital Heart Disease 561
Laura D. Flannery

Index. 567

Part I
General Introductory Principles

Chapter 1
Terminology: Defining Cardiac Position, Chamber Morphology and Van Praagh Nomenclature

Evin Yucel and Doreen DeFaria Yeh

Cardiac Position (See Fig. 1.1)

1. Levocardia: the normal configuration of the base to apex axis of the heart is leftward.
2. Mesocardia: cardiac mass is midline and the apex is pointing to the midline.
3. Dextrocardia: the major axis of the heart points to the right of the sternum (dextrocardias are detailed in Chap. 2).

Morphology of Cardiac Chambers

1. Atrial chambers: the appendage distinguishes morphologically the right from left atrium.

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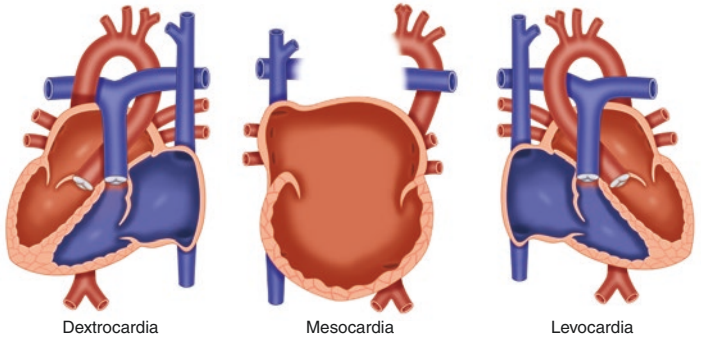

FIGURE 1.1 Cardiac position

(a) The right atrium is characterized by:

- Triangular appendage with a broad base
- Sinus node is located at the superior cavoatrial junction
- Pectinate muscles occupy the parietal wall and extend to the inferior wall towards the coronary orifice
- Muscular rim around the fossa ovalis is located on the right atrial side of the intraatrial septum

(b) The left atrium is characterized by:

- Appendage which is small and hook shaped with narrower base and multiple fingerlike projections
- Pectinate muscles within the atrial body are limited, smoother walls
- The thin septum primum (flap) is located on the left atrial side of the intraatrial septum

2. Valvular relationships:

(a) Morphologic tricuspid valve is always associated with the morphologic right ventricle.
(b) Morphologic mitral valve is always associated with the morphologic left ventricle.
(c) In the presence of a large VSD, valves may either override or straddle the septum (Fig. 1.2):

- Override: abnormal position of the valve annulus relative to the septum

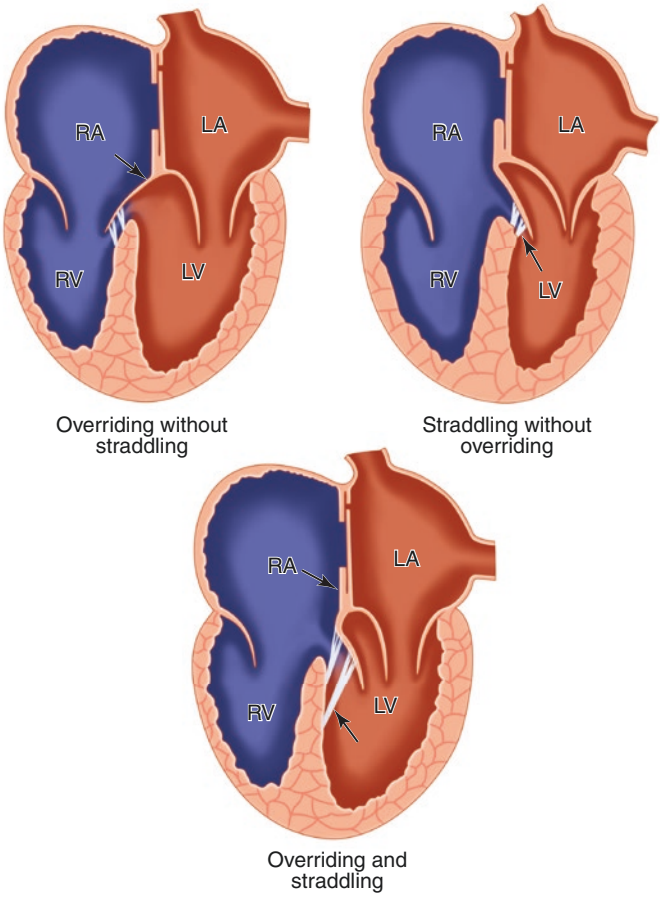

FIGURE 1.2 Straddling and overriding

  - Can apply to semilunar and atrioventricular (AV) valves

- Straddling: inappropriate attachments of chordal supports to the contralateral ventricle
  - Applies only to the AV valves

3. Ventricles:
   (a) The right ventricle is characterized by:
   - Course trabeculations that emanate from the midseptal wall
   - Morphologic tricuspid valve is always associated with the morphologic right ventricle

   (b) The left ventricle is characterized by:
   - Septal surface is smooth without protruding trabeculations
   - Aortic-mitral fibrous continuity is seen (exception is situation with a subaortic conus)
   - Morphologic mitral valve is always associated with the morphologic left ventricle

4. Great arteries – the appearance of semilunar valves will not be distinguishing:
   (a) Aorta:
   - Arch gives rises to head and neck vessels
   - Coronary arteries arise from the aortic sinuses (with rare exception: anomalous left or right coronary arising from the pulmonary artery)

   (b) Pulmonary trunk:
   - No coronary ostia at the sinuses (with the above exception)
   - Bifurcation into two pulmonary artery trunks

   (c) Common arterial trunk:
   - Seen in truncus arteriosus (Chap. 24) where one great artery is noted arising from the myocardium (avoid misdiagnosis of atretic aortic or pulmonary atresia)

   (d) Solitary arterial trunk:
   - Also termed type IV truncus where the solitary trunk does not give rise to pulmonary arteries (severe form of tetralogy of Fallot with pulmonary atresia, and

collateral arteries arise from the descending aorta to supply the lungs)

Segmental approach is essential for accurate and thorough diagnosis.

1. Visceroatrial situs (Fig. 1.3)
   - Three types of situs:
     - Solitus (S,–,–)
     - Inversus (I,–,–)

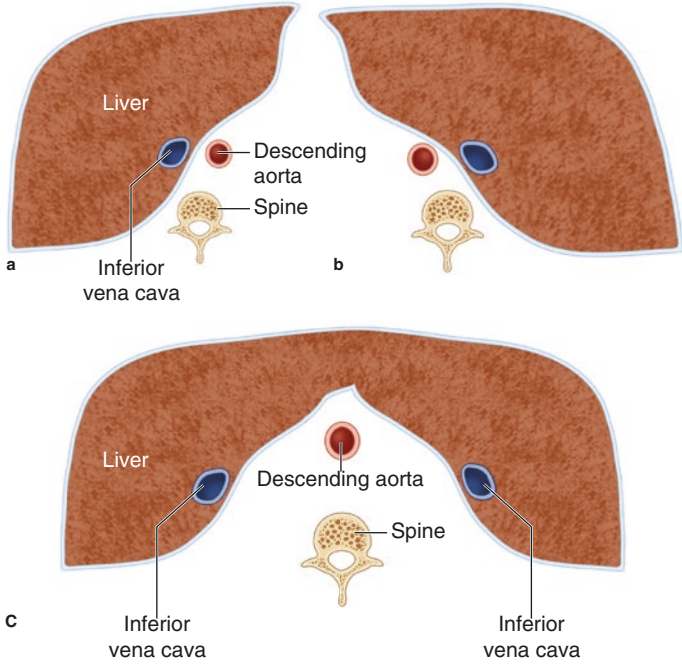

Figure 1.3 Abdominal situs. (**a**) situs solitus with the liver to the patient's right (left of the image) and the descending aorta left of midline (**b**) situs inversus with the liver to the patient's left and the descending aorta to the right of midline and (**c**) situs ambiguous with midline liver and disorganization of vascular arrangement

  - Ambiguous (A,–,–)
  - The inferior vena cava will always drain into the right atrium (unless there is interrupted IVC, which is seen in heterotaxy syndromes).
  - Identifying the atrial and visceral situs will aid in defining situs inversus (mirror-image dextrocardia), situs solitus (dextroversion) and situs ambiguous (heterotaxy syndromes)

2. Ventricular loop

- Bulboventricular loop may be (Fig. 1.4):
  - Rightward (dextro-loop, D-loop) (–,D,–): normal position of RV to the right of the LV
  - Leftward (levo-loop or L-loop) (–,L,–): the RV is to the left side and posterior to the LV
- Atrioventricular (AV) valves are always associated with their morphological ventricles (i.e. tricuspid valve in RV, mitral valve in LV)
- Morphological RV: muscular portion of the outflow tract, the presence of infundibulum, trabeculations near the apex, moderator band, septal leaflet of AV valve is

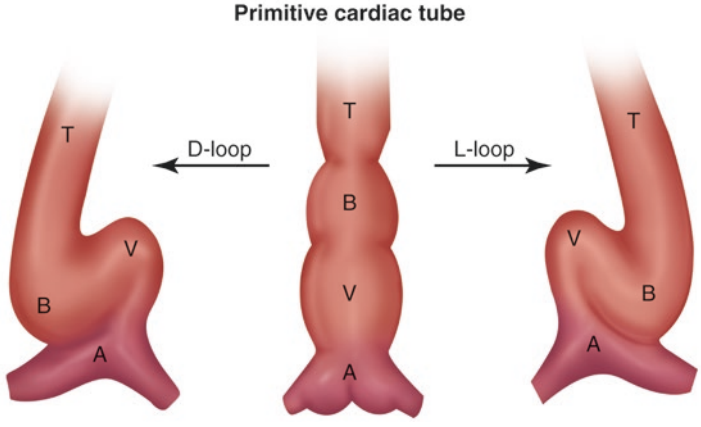

Figure 1.4 Primitive cardiac tube

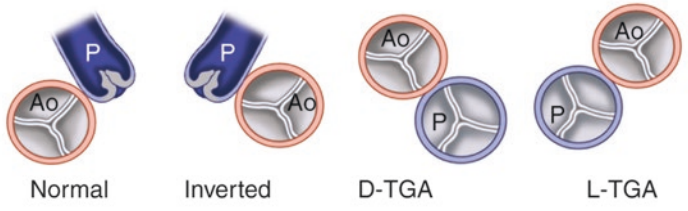

FIGURE 1.5 Relationship of great arteries

displaced slightly towards the apex and papillary muscles of the RV attached to both the interventricular septum and the free wall

- Morphological LV: smooth septal surface, fibrous continuity between inflow valve and semilunar outflow valve and two well-formed papillary muscles attached only to the free wall

3. Position of the great vessels (Fig. 1.5)

- The vessels may be in:
  - Normal position (solitus) (–,–,S)
  - Inverted position (inversus) (–,–,I)
  - D-transposition (–,–,D-TGA)
  - L-transposition (–,–,L-TGA)

- In normal D-bulboventricular loop development, pulmonic valve (PV) is anterior, superior and to the left of the aortic valve (AoV)
- In L-bulboventricular loop with a normal conotruncal development, the relationship between the great arteries is mirror image of the normal D-loop; therefore, PV is anterior, superior and to the right of the AoV
- Transposition of conotruncal development in D-loop, known as D-TGA→ AoV, is anterior and to the right of the PV
- Transposition of conotruncal development in L-loop, known as L-TGA→ AoV, is anterior and to the left of the PV

Chapter 2
Dextrocardias

Evin Yucel

Abbreviations

CHD	Congenital heart disease
IVC	Inferior vena cava
RA	Right atrium
TGA	Transposition of the great arteries
TTE	Transthoracic echocardiogram

Epidemiology

- Dextrocardia is a rare congenital abnormality with an estimated incidence of 1 in 8000–25,000 live births.
- Among patients treated by adult congenital heart disease (CHD) specialists, the prevalence is 0.5%, of which 2/3rd are situs solitus [1].
- For historical background, see Table 2.1.

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Table 2.1 Historical background

Dextrocardia, one of the first congenital malformations of the heart, was recognized in the seventeenth century by Hieronymus Fabricius and Aurelio Severino. Matthew Baillie published his experience in 1793 in a book entitled, The Morbid Anatomy of Some of the Most Important Parts of the Human Body. In 1915, Richard Paltaus described the various types of dextrocardia, and later in 1928, Mandelstam and Reinberg proposed the first classification of cardiac malpositions. Maria de la Cruz published her work on the embryologic basis of malpositions in 1931 [2].

Anatomic Definition and Pathophysiology

1. Anatomy:

   (a) The normal configuration of the base to apex axis of the heart is leftward, which is called levocardia. When the apex is pointing to the midline, it is defined as mesocardia. In dextrocardia, the major axis of the heart points to the right of the sternum.
   (b) Dextrocardia is a consequence of abnormal lateralization of the embryonic left-right axis during early development. This is contrary to *dextroposition*, where the heart is positioned in the right thorax due to mechanical considerations such as right lung hypoplasia or a space-occupying mass, with the apex still pointing leftward (Fig. 2.1).
   (c) During development, dextrocardia results from either a failure of the D-bulboventricular looped heart tube to migrate (or sweep) into the left hemithorax, which occurs generally during week 5 of gestation, or successful apical shifting of the L-bulboventricular looped heart tube to the right hemithorax.
   (d) Three configurations:

   - Situs solitus – normal asymmetrical arrangement of abdominal and thoracic organs:
     – Liver – right.
     – Stomach and spleen – left.

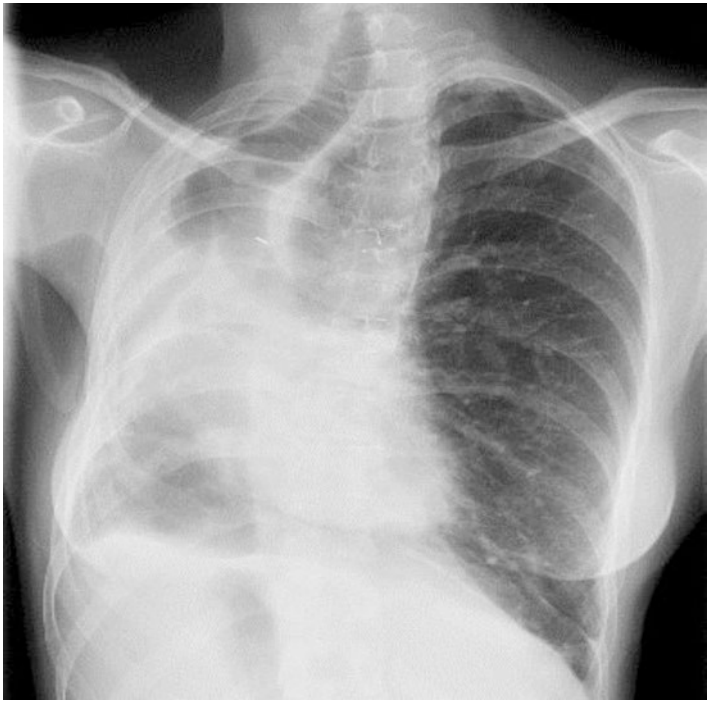

FIGURE 2.1 Chest X-ray in a patient with dextroposition due to right pneumonectomy. The cardiac apex is pointing toward left, but the cardiac silhouette and bronchus are seen on the right side of the sternum

  - Inferior vena cava (IVC) – right and flows into the right atrium (RA).
  - The right lung has three lobes, and the left lung has two lobes.
  - The left hemidiaphragm is lower than the right hemidiaphragm.
  - The aorta descends on the left.

- Situs inversus – mirror image of normal, with reversal of abdominal and thoracic structures:
  - Liver – left
  - Stomach – right

- IVC – left and flows into left-sided RA.
- The left lung has three lobes, and the right lung has two lobes.
- The right hemidiaphragm is lower than the left hemidiaphragm.
- Aorta descends on the right.

- Situs ambiguous (heterotaxy) – the relationship between atria and viscera is inconsistent:

- Asplenia syndrome – bilateral right sidedness (two morphologic right atria and two trilobed right lungs), absent spleen, associated with common atrioventricular canal, univentricular heart, transposition of the great arteries (TGA), and total anomalous pulmonary venous return
- Polysplenia – bilateral left sidedness (two morphological left atria and two bilobed left lungs), multiple small spleens that are adjacent to the stomach, commonly associated with azygous continuation of the IVC (interrupted IVC), partial anomalous pulmonary venous return, atrial septal defect, and endocardial cushion defect

(e) In adults, dextrocardia can be seen with:

- Situs inversus or situs inversus totalis, L-loop ventricles, and inverted great vessels (not transposed), known as "mirror-image dextrocardia" (most common in general population). This configuration is due to the successful sweeping of L-looped ventricles (Fig. 2.2).
- Situs solitus with D-loop ventricles and normally related great arteries, known as "dextroversion" or "isolated dextrocardia" (second most common in general population). This configuration is due to failure of the apical sweep to the left (Fig. 2.2).
- Situs solitus with L-loop ventricles and L-TGA, where there is atrioventricular and ventriculoatrial

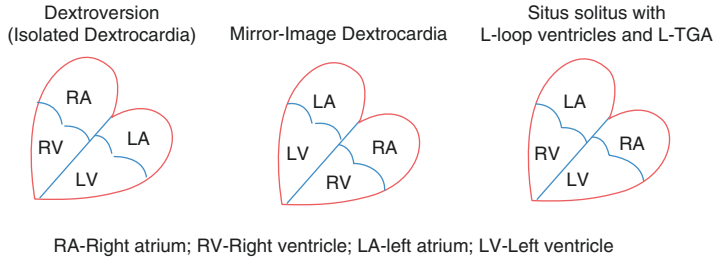

FIGURE 2.2 The configuration of dextroversion and mirror-image dextrocardia. The cardiac apex is pointing rightward of the sternum. In dextroversion, the right atrium and right ventricle are to the right of the left atrium and left ventricle, while the atria and ventricle are in their normal position in mirror-image dextrocardia. *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle

discordance. The morphological left ventricle (LV) is in subpulmonic position, and the morphological right ventricle (RV) is the systemic ventricle; however, due to dextrocardia, the LV is to the left of the RV.

- Situs inversus with D-loop ventricles and D-TGA.
- Associated with the asplenia or polysplenia syndrome.

2. Physiology:

   (a) Physiology of dextrocardias depends on the associated cardiac abnormalities.

3. Spectrum of disease*:*

   (a) Mirror-image dextrocardia and structurally normal heart is usually an incidental finding on physical exam and/or chest X-ray.
   (b) The clinical course of isolated dextrocardia (dextroversion) is dependent upon the associated CHD.
   (c) Majority of patients with heterotaxy syndrome with asplenia do not reach adult age, with a mortality rate of up to 80% by the first year of life.

4. Associated defects:
   (a) Kartagener's syndrome is seen in 25% of patients who have "mirror-image dextrocardia" and is characterized by the presence of situs inversus totalis, paranasal sinusitis, bronchiectasis, ciliary dysmotility, and infertility. Other cardiac abnormalities are rare in mirror-image dextrocardia [3].
   (b) In isolated dextrocardia (also as known as dextroversion), anomalous pulmonary venous return, tetralogy of Fallot, septal defects, pulmonic stenosis, coarctation of the aorta, and TGA can be seen. Isolated dextroversion is rare.
   (c) Pulmonary outflow obstruction, systemic atrioventricular valve dysfunction, dysplastic tricuspid valve, Ebstein's anomaly, and atrioventricular blocks are common in other forms of dextrocardia [3].
5. Genetics and maternal factors:
   (a) Maternal pregestational diabetes during pregnancy can be associated with heterotaxy syndromes in the offspring [4].
   (b) Family history of cardiac malformations and the presence of dextrocardias in twins suggest a genetic basis for these defects [5].

Diagnostics

Clinical Presentation in Adults

- Clinical presentation depends on the configuration of the dextrocardia and associated cardiac malformations. Refer to individual chapters for details on associated malformations.
- Chest pain will be on the right side with radiation to the right arm.

Physical Exam

- Cardiac dullness will be to the right of the sternum.
- In mirror-image dextrocardia, hepatic dullness will be on the left.
- In isolated dextrocardia (or dextroversion), hepatic dullness will be on the right.
- Refer to individual chapters for physical exam findings for associated cardiac malformations.

Electrocardiography

- In mirror-image dextrocardia (Fig. 2.3)
  - Predominantly negative P wave, QRS complex, and T wave in lead I.
  - Reverse R wave progression in precordial leads (low voltage of R wave in V3–V6)
  - Right axis deviation

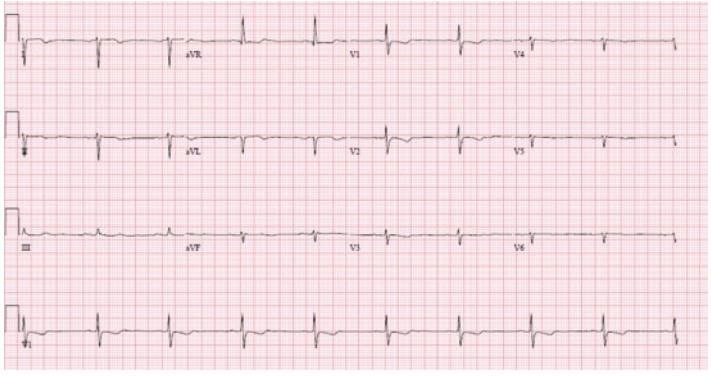

FIGURE 2.3 EKG of a patient with **mirror-image dextrocardia**. There is negative P wave, QRS, and T waves in lead I with reverse R wave progression

- In dextroversion (Fig. 2.4)
  - P wave is positive in lead I; QRS and T wave morphology depends on the type and degree of associated anomalies.
  - Anterior precordial leads (V2–V4) have small Q waves and tall R waves; QRS amplitude progressively decreases from V1 to V6.

Chest X-Ray

- In mirror-image dextrocardia (Fig. 2.5)
  - The apex of the heart is in the right hemithorax.
  - Liver shadow is on the left and stomach bubble is on the right side.
  - Elevated left hemidiaphragm.
  - Descending aorta will be on the right side of the sternum.
- Dextroversion (or isolated dextrocardia) (Fig. 2.6)
  - Apex of the heart is in the right hemithorax.
  - Liver shadow is on the right side and stomach bubble is on the left.

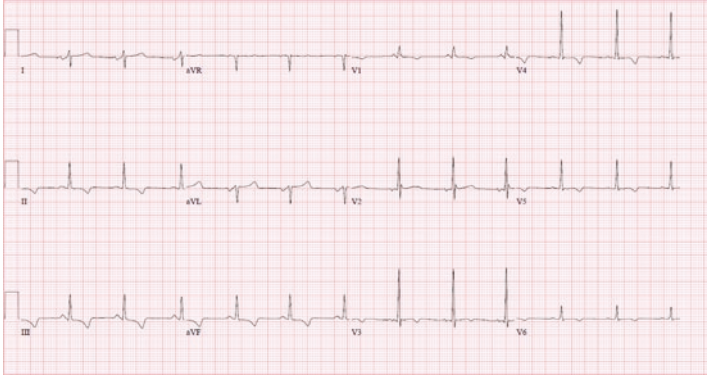

Figure 2.4 EKG of a patient with dextroversion. P wave is positive in lead I, anterior precordial leads have small Q and tall R, QRS amplitude decreases to V6

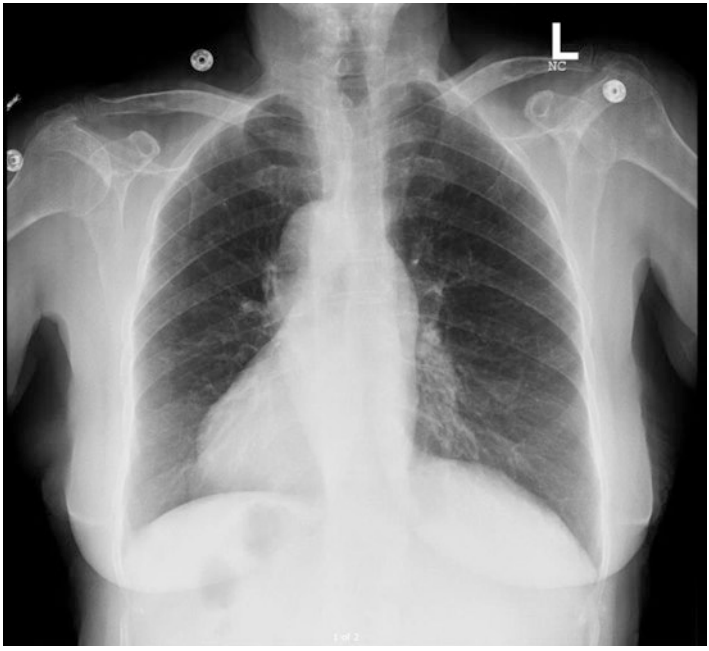

FIGURE 2.5 CXR in a patient with mirror-image dextrocardia. Cardiac silhouette is in the right chest cavity with the apex of the heart pointing rightward, there is a right-sided aorta and the left hemidiaphragm is elevated

- Elevated right hemidiaphragm.
- Descending aorta will be on the left side.

Echocardiography

- In mirror-image dextrocardia, intracardiac connections are often normal; however, the morphological right atrium and right ventricle are to the left of the morphological left atrium and left ventricle.
- In dextroversion (or isolated dextrocardia), atria are in their usual place or shifted slightly to the right.
- Table 2.2 highlights the essentials of echocardiographic assessment of patients with dextrocardia.

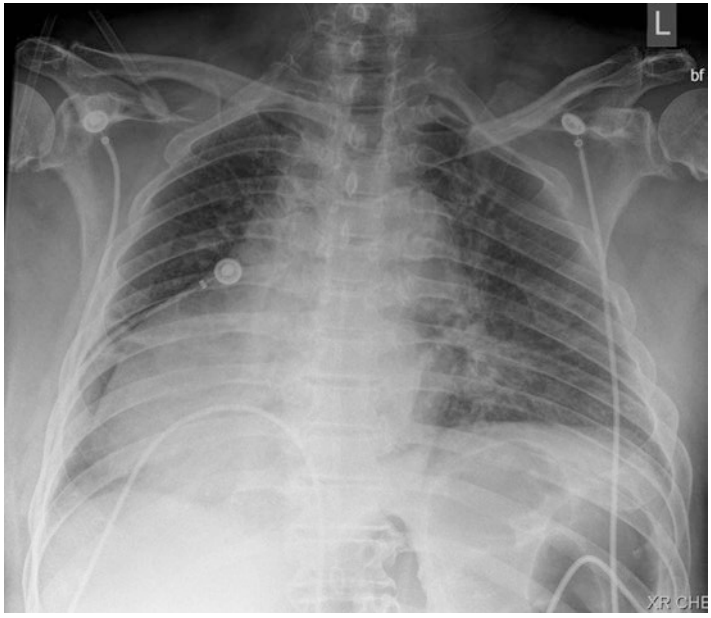

FIGURE 2.6 CXR in a patient with dextroversion. The stomach bubble is to the left and the hemidiaphragm position is ambiguous due to patient positioning.

Cardiac Catheterization

- The coronary artery course is determined by the ventricular looping. In D-loop ventricles, the anterior descending artery is supplied from the left coronary artery (originating from the left sinus of Valsalva), whereas in L-loop ventricles, the anterior descending artery is supplied by the right coronary artery (originating from the right sinus of Valsalva) [3].
- In mirror-image dextrocardia, the aorta is right sided; in dextroversion, the aorta is left sided (in the normal position).

Table 2.2 Echocardiographic essentials for assessment [6, 7]

1. Determine abdominal situs and cardiac positioning by subcostal view 2. In normal configuration, the liver is on the right side of the patient (left side of the screen), IVC is to the right of the spine, and aorta is to the left of the spine. 3. In situs inversus, the liver is on the left side of the patient, IVC is to the left of the spine, and aorta is to the right of the spine. 4. In heterotaxy syndromes, the liver is in midline, and the IVC is to the left of the spine. The IVC will be seen to the left of the spine in asplenia and will be absent in polysplenia syndrome with a dilated azygous vein posterior to the aorta. 5. Follow the segmental approach to define visceroatrial situs, ventricular looping, and great vessel connections 6. Define associated cardiac abnormalities	Tips on obtaining images: Major axis of the heart is aligned from the left shoulder toward the right hip Parasternal long-axis view should be obtained with the transducer oriented in mirror-image direction of normal (from left shoulder to right hip) Parasternal short axis can be obtained with normal orientation in dextroversion and oriented in the mirror-image direction of normal in mirror-image dextrocardia (from right shoulder to the left hip) Apical views can be obtained with the transducer oriented in a mirror-image direction of normal (notch pointing to the left)

Advanced Imaging Techniques

- Cardiac computed tomography and magnetic resonance imaging demonstrate the right-sided position of the heart apex, situs of the viscera, ventricular loop, and position of the great vessels.

Management of Adult Survivors

- There are no specific guidelines for management of patients without any other CHD.
- For management of associated cardiac abnormalities, refer to individual chapters.

Management of Pregnancy

- Patients with dextrocardias without any associated cardiac abnormalities are not at an increased risk for adverse pregnancy outcomes. However, a higher-than-expected prevalence of small for gestational age infants has been reported in patients with mirror-image dextrocardias (5).
- In the setting of other associated cardiac abnormalities, the modified World Health Organization classification of maternal cardiovascular risk stratification should guide the management of pregnant women. (See Chap. 37 for Management of Pregnancy in Adult Congenital Heart Disease).

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Part II
Shunt Lesions

Chapter 3
General Principles of Simple Shunt Lesions

Jonathan Kochav

Introduction

There are several congenital abnormalities that cause blood flow to deviate from the normal circuit. While they may differ in regard to size, location with respect to the tricuspid valve and pressure gradient across the shunt, there are several unifying concepts that are useful in understanding the pathophysiology of simple shunt lesions.

General Features of Shunt Lesions

Defining the Size of the Shunt

- The shunt volume generally determines the physiologic impact of a shunt.
- The shunt volume can be quantified by the Qp/Qs ratio, where Qp is an estimate of pulmonary blood flow and Qs an estimate of systemic blood flow.
  - A Qp/Qs ratio of 1:1 is normal and indicates an absence or balance of shunting.

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- A Qp/Qs ratio of >1 indicates that pulmonary blood flow exceeds systemic blood flow and the presence of left-to-right shunting.
- Conversely a Qp/Qs ratio of <1 indicates right-to-left shunting.

- Qp and Qs can be estimated by echocardiography or phase-contrast cardiac MRI measurements of stroke volume. The gold standard is cardiac catheterization with measurement of oxygen saturations of the various circulations [1].
  - The Qp/Qs is derived from the shunt fraction calculation, which examines the ratio of the oxygen-carrying capacity of blood in various circulations.

    Oxygen obtained in the pulmonary capillaries = $(CpvO_2–CpaO_2) \times Qp$
    Oxygen delivered to systemic tissues = $(CaO_2–CvO_2) \times Qs$
  - where CaO_2, CvO_2, $CpaO_2$, and $CpvO_2$ represent systemic arterial, systemic venous, pulmonary arterial, and pulmonary venous oxygen content.
  - Using the assumption that oxygen delivered to the systemic tissues is equal to the oxygen obtained in the pulmonary capillaries:

    $Qp/Qs = (CaO_2–CvO_2)/(CpvO_2–CpaO_2)$
  - The oxygen content of each of the circulations can be determined by the following relationship between hemoglobin (Hgb), oxygen saturation (Sat), and partial pressure of oxygen:

    $CO_2 = (1.34 \times Sat \times Hgb) + (PO_2 \times 0.003)$
  - Because hemoglobin is fixed across all circulations and the partial pressure of dissolved oxygen is negligible, the Qp/Qs equation can be simplified into the following formula:

    $Qp/Qs = [(SaO_2–SvO_2)/(SpvO_2–SpaO_2)]$
  - where SaO_2 is the systemic arterial oxygen saturation, SvO_2 is the central venous oxygen saturation, $SpvO_2$ is the pulmonary venous oxygen saturation (obtained as a pulmonary capillary wedge saturation), and $SpaO_2$ is the pulmonary arterial oxygen saturation.

Volume Overload and Chamber Enlargement

- Shunt lesions will lead to volume overload and chamber enlargement.
- The magnitude of chamber enlargement will depend on the size of the shunt.
  - Pre-tricuspid lesions will result in volume overloading of the right atrium (RA) and right ventricle (RV).

    Atrial septal defects and sinus venosus defects
    Anomalous pulmonary venous return
    The Gerbode defect: left ventricle (LV) to RA shunt
  - Post-tricuspid lesions will lead to an increased pulmonary venous return and volume overloading of the left atrium (LA) and LV.

    Ventricular septal defects
    Patent ductus arteriosus
  - *Mechanism of LV volume loading:*

    With a left-to-right shunt, the LV output into the systemic circulation is reduced by the volume of the shunt.
    The patient will compensate by increasing intravascular volume until LV end-diastolic volume is sufficient to generate both a normal cardiac output and the proportionate left-to-right shunt. The result is LV volume overload [2].

Right-Sided Pressure Overload

- Right-sided pressure overload occurs as a consequence of both direct transmission of pressure from the higher-pressure left-sided circuit to the right heart, and increased afterload.
  - Direct transmission of pressure:

    A large unrestricted ventricular septal defect will elevate (RV) pressures irrespective of pulmonary vascular remodeling.

Similarly, a large patent ductus arteriosus will elevate pulmonary arterial pressures.

– Increased afterload:

Over time, pulmonary over-circulation leads to vascular remodeling in the form of medial hypertrophy of the pulmonary arterioles [3].

The consequence is increased pulmonary vascular resistance, resulting in elevated right-sided pressures as the RV aims to maintain cardiac output.

If right-sided pressures approximate and then exceed left-sided pressures, the shunt direction can reverse, resulting in systemic cyanosis (see Chap. 9 **Eisenmenger Physiology**).

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Chapter 4
Atrial Septal Defects and Sinus Venosus Defects

Jonathan Kochav

Epidemiology

- Atrial septal defects (ASD) are quite common with an incidence of about 1 per 400–800 live births, accounting for around 13% of all congenital heart disease (CHD) [1, 2]. As a whole, these lesions occur in nearly equal proportion in males and females [1] though differences are seen among subtypes.
- See Table 4.1 for historical background.

Anatomic Definition and Pathophysiology

1. Anatomy:

   (a) There are several subtypes of ASDs, including primum, secundum, and although not technically defects of the

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Table 4.1 Historical background

Leonardo da Vinci's description in 1513 of a "perforating channel" in the atrial septum is believed to be the first recorded account of a congenital malformation of the human heart [3].
In 1948 Gordon Murray reported the first surgical closure of an ASD by externally suturing the septum through the atrial wall [4].
In 1952 John Gibbon closed a large secundum atrial septal defect in an 18-year-old woman marking the first open-heart cardiac surgery performed on the cardiopulmonary bypass machine he developed [5].
A successful transcatheter closure was first reported by T.D. King and N.L. Mills in 1976, revolutionizing the management of patients with secundum defects and amenable anatomy [6].

atrial septum, inferior or superior sinus venosus defects and coronary sinus defects which demonstrate similar shunt physiology and are therefore included in this section (Fig. 4.1).

- Ostium primum defect (10–15%): component of partial or complete atrioventricular (AV) canal defects:
  - Typically associated with mitral valve deformities such as cleft mitral valve.
  - They are defects low in the atrial septum bounded posteriorly by mitral and tricuspid valves. These defects occur as a result of abnormal development of the endocardial cushions and therefore lie on an embryologic continuum with atrioventricular canal defects.
  - The Rastelli classification is used to describe AV septal defects:
    - With Rastelli type A the superior bridging leaflet is divided equally across the ventricular septum. It is commonly associated with outflow tract obstruction due to LVOT elongation.

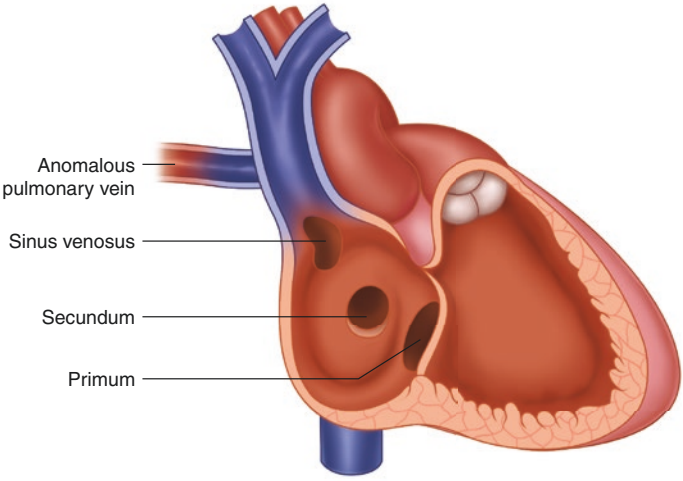

FIGURE 4.1 Depiction of types of atrial septal defects [7]

- Rastelli type C has a few floating superior bridging leaflet and is associated with Down syndrome.

- Ostium secundum defect (65%): most common ASD due to deficiency of the septum primum in the region of the fossa ovalis
  - Vary widely in size.
  - Located at the site of the fossa ovalis.
  - Occur more commonly in females in a ~2:1 ratio [1, 8]
- Sinus venosus defect (10–15%): located at the juncture of the superior or inferior vena cava with the atrial septum (Fig. 4.2):
  - Technically they are not atrial septal defects, as the defect is that of the great veins meeting the atrial septum

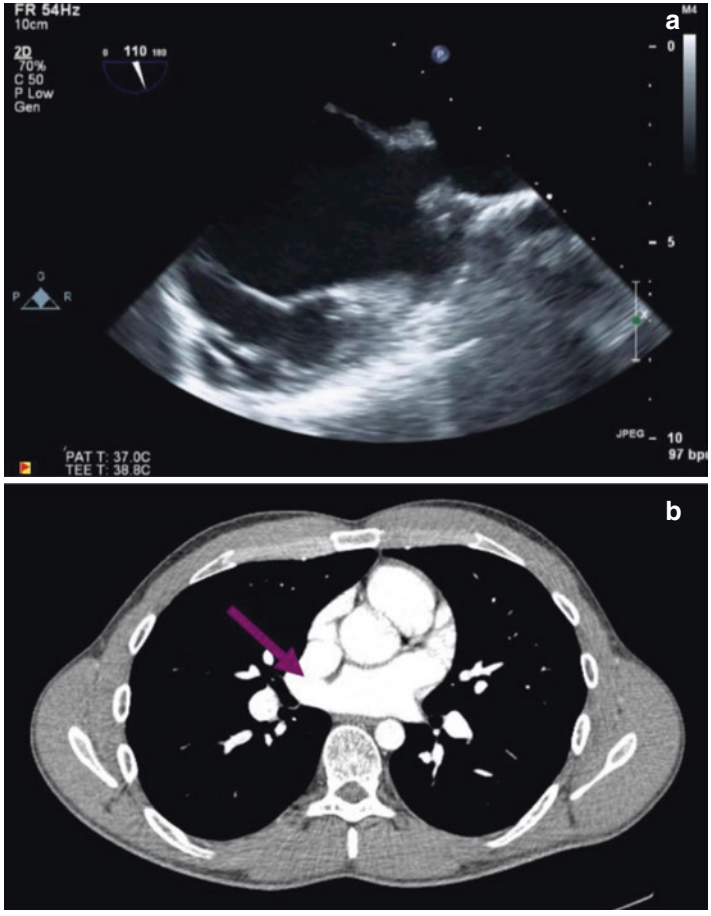

FIGURE 4.2 (**a**) Transesophageal echocardiography of a superior sinus venosus defect. The SVC is to the right of the image. (**b**) Cardiac CT angiogram axial image depicting a superior sinus venosus defect

- Coronary sinus defect: very rare, associated with complex cardiac lesions

2. Physiology:

   (a) An ASD initially results in a left-to-right atrial shunt due to increased compliance of the right heart

(b) Right-sided volume overload eventually leads to right atrial, right ventricular (RV), and pulmonary artery enlargement
(c) Reduced left ventricular (LV) preload results in reduced maximal cardiac output
(d) Patients are often asymptomatic for decades before developing atrial arrhythmias and RV dilation/dysfunction
(e) Rarely with large unrepaired ASDs, pulmonary arterial hypertension (PAH) may develop and progress, resulting in shunt reversal (right-to-left) and systemic hypoxemia (see Chap. 9 on Eisenmenger Syndrome). Of note, 6–8% of patients with an ASD may develop pulmonary hypertension (in the absence of Eisenmenger syndrome).

3. Spectrum of disease:

(a) The size of the lesion and severity of associated defects define the disease spectrum
(b) Larger lesions result in higher-volume shunting (higher Qp/Qs):

- Patients develop exercise intolerance, failure to thrive, recurrent respiratory infections, or arrhythmia in childhood
- Exercise intolerance, arrhythmia (atrial fibrillation), right heart failure, RV dysfunction, paradoxical emboli, stroke, and pulmonary hypertension can all present in adulthood in association with ASDs

(c) Most patients with moderate-sized defects develop symptoms before the age of 40
(d) Patients with small defects, <1 cm in size, may remain asymptomatic into the fourth and fifth decade of life [9]

4. Associated defects:

(a) Associated abnormalities are frequently present with ASD [10]:

- Ostium primum defect (atrioventricular canal-type defect):
  - Associated with a cleft mitral valve, with cleft directed toward the mid-ventricular septum.

  - Left ventricular outflow tract obstruction may develop over time with contribution from an elongated LVOT, abnormal chordal attachments to the LV side of the ventricular septum, discrete subaortic stenosis, septal hypertrophy, anomalous anterolateral papillary muscles, and aneurysm of the membranous septum into the LVOT.

- Ostium secundum defect:
  - Valvular pulmonary stenosis
  - Bicuspid aortic valve
  - Rarely associated with superior sinus venosus defects and/or partial anomalous pulmonary venous drainage of the right pulmonary veins
  - Late mitral valve degeneration and mitral regurgitation [11]
- Sinus venosus defect:
  - Often associated with partial anomalous pulmonary venous drainage of the right pulmonary veins
- Coronary sinus defect:
  - Associated with complex cardiac lesions
  - Partial anomalous pulmonary venous drainage
  - Persistent left superior vena cava draining to the coronary sinus
- Various types of ASDs frequently coexist (e.g. important to screen for sinus venosus defects before percutaneously closing a secundum defect).
- Atrial septal aneurysms, defined by an excursion of 15 mm due to redundant atrial septal tissue, are commonly associated.

5. Genetic and maternal factors:
   (a) Several specific genes such as homeobox transcription factor gene NKX2.5 [12], GATA4 [13], and MYH6 [14] have been implicated in families with autosomal dominant pattern of inheritance.
   (b) Patients who have ASDs associated with an NKX2.5 mutation may be at risk for complete heart block.
   (c) Parents with sporadic ASDs have an increased likelihood (~10%) of having offspring with CHD, including ASDs [15].
   (d) Both ostium primum and ostium secundum defects have been associated with trisomy 21 (Down syndrome). Importantly, 75% of patients with a complete AVSD have trisomy 21.
   (e) ASDs have been associated with the autosomal dominant Holt-Oram syndrome (absent radial bone, ASD, and first-degree heart block) [16]. These individuals may have a mutation in the TBX5 gene.

Diagnostics

Clinical Presentation in Adults

- Patients most commonly present with symptoms of dyspnea on exertion and palpitations.
- Patients may be diagnosed after auscultation of an abnormal cardiac exam, observation of cardiomegaly on routine chest imaging, or incidentally during cardiac imaging.
- Alternatively, patients may present with stroke or systemic ischemic event due to a paradoxical embolism.
- In rare circumstances, patients may present with the platypnea-orthodeoxia syndrome:
  - Characterized by dyspnea and deoxygenation when changing from a recumbent to an upright position

  - In these patients, assuming an upright position leads to an increase in blood flow from the inferior vena cava (IVC) through the septal defect resulting in an increased right-to-left shunting of blood
  - Often associated with a prominent persistent Eustachian valve, which functions to direct flow from the IVC toward the foramen ovale in the developing fetus

- Patients who have undergone repair early in childhood are usually free of symptoms and complications for the duration of their lives. However, older adult patients may have dyspnea on exertion related to exercise-induced pulmonary hypertension, which may occur despite remote defect closure.

Physical Exam

- Unrepaired adult:
  - Right-sided volume overload:
    - May result in a fixed split S2, due to delayed closure of the pulmonary valve that does not vary with inspiration
    - A pulmonary outflow murmur may be heard over the left upper sternal border due to increased flow over the pulmonary valve
    - With very large shunts, a diastolic flow murmur may be heard across the tricuspid valve
    - RV heave
  - Platypnea-orthodeoxia:

    Peripheral oxygen saturations will demonstrate hypoxemia when moved from a recumbent to an upright position in patients with position-dependent right-to-left shunting through the ASD.

- Repaired patient:
  - Exam should be normal, with return of normal physiologic splitting of S2; however, sometimes pulmonary outflow murmurs may persist, and a right bundle branch block (RBBB) may affect the S2 split. A holo-

systolic murmur of mitral regurgitation may be present in individuals with a residual mitral cleft in AVSD. Later in life a holosystolic, or midsystolic, click and murmur may develop in secundum ASD patients who evolve mitral regurgitation or mitral valve prolapse with regurgitation, respectively.

- Eisenmenger exam:
  - See Chap. 9 for further details on the Eisenmenger exam.

Electrocardiogram

- Right atrial enlargement
- Incomplete RBBB
- Lesion-specific electrocardiographic abnormalities:
  - Ostium primum defects (Fig. 4.3a):

    Left axis deviation, likely due to a congenitally anomalous or hypoplastic left anterior fascicle [18]. S wave in lead III and R wave in lead AVR
  - Ostium secundum ASD (Fig. 4.3b):

    Incomplete RBBB
    Right axis deviation due to RV hypertrophy
  - Sinus venosus defect (Fig. 4.3c):

    Abnormal P wave axis may be seen with superior sinus venosus defects due to displacement of the sinoatrial node.
    Abnormal conduction pattern or an ectopic atrial pacemaker may occur as the defect approaches the sinus node and may disrupt normal conduction.

Chest Radiograph

- Right atrial and right ventricular enlargement
- Prominent pulmonary arteries, with increased pulmonary vasculature

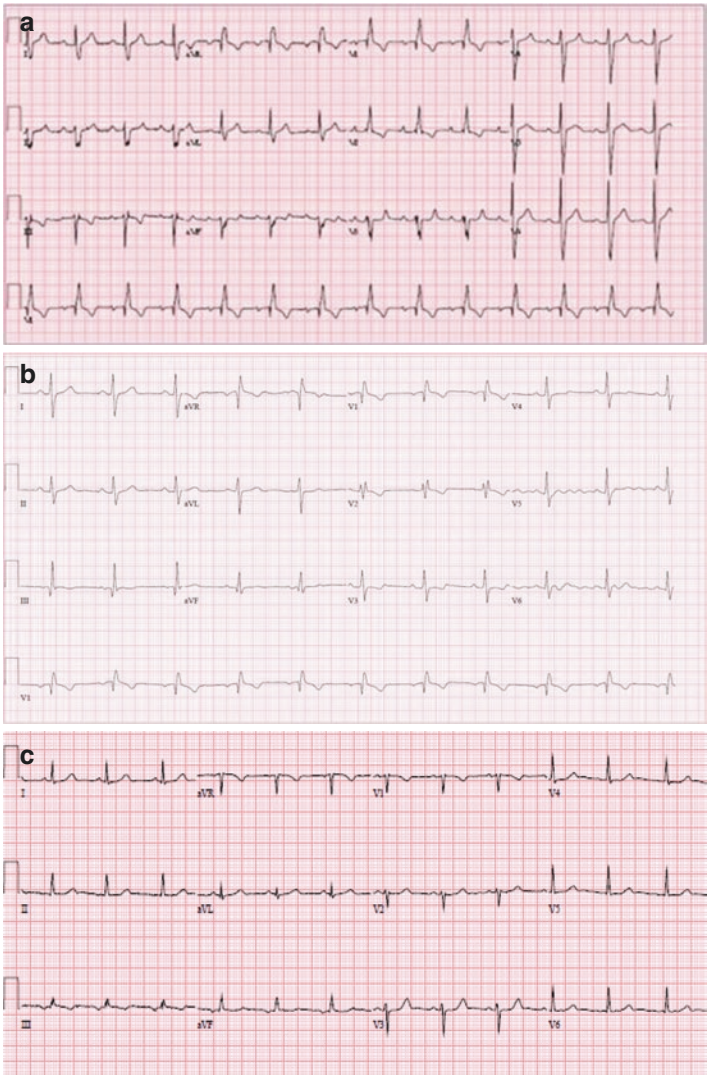

Figure 4.3 (**a**) ECG tracing of patient with primum ASD (partial AV canal defect). Note RBBB with left axis deviation. (**b**) ECG tracing of a patient with a secundum ASD. Note RBBB with rightward axis. (**c**) ECG tracing of patient with sinus venosus defect. Note low atrial focus (inverted P waves in leads III, aVF). (**d**) Movies: Echo images. Apical four-chamber view of adult patient with unrepaired primum ASD

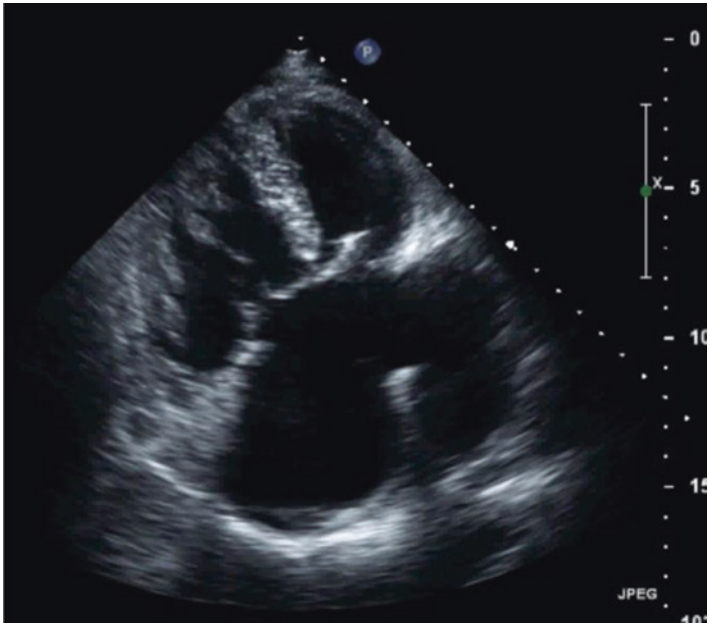

FIGURE 4.3 (continued)

Echocardiography

- Standard 2D transthoracic echocardiogram with color Doppler will generally make the diagnosis of an ASD:
  - When color Doppler is inconclusive, contrast echocardiography with intravenous agitated saline may be useful in making the diagnosis of an intra-atrial right-to-left shunt
  - Tilt-table testing may show position-dependent right-to-left shunting, consistent with a diagnosis of platypnea-orthodeoxia
  - Sinus venosus or coronary sinus defects can be challenging to see on routine transthoracic imaging. A transesophageal approach is indicated if suspicion is high (e.g., RV dilation without an obvious secundum or primum defect).

If an inferior sinus venosus defect is suspected, injection of agitated saline should be administered using the lower extremity.

- Assessment of right atrial and RV volumes is essential, as enlargement of these chambers is an indication for defect closure.
- It is important to define the margins of the defect in consideration for device closure and to identify other associated pretricuspid lesions if present. More advanced imaging techniques such as transesophageal echocardiogram, cardiac CT, or cardiac MRI are often utilized for this purpose and may be helpful in identifying associated pulmonary venous anomalies.
- Table 4.2 highlights the essentials of echocardiographic assessment of patients with ASD, both pre and post complete repair.

Cardiac Catheterization

- Routine diagnostic right heart catheterization is generally not needed for diagnosis or risk stratification of patients with atrial septal defects, particularly if noninvasive echocardiographic assessment demonstrates no significant elevation in pulmonary pressures.
- A coronary evaluation is reasonable in patients with planned operative management who have an increased risk of coronary artery disease.
- In select cases of patients with pulmonary hypertension, preoperative right heart catheterization with inhaled nitric oxide (iNO) may be useful to assess for reversibility of severe pulmonary hypertension, as this may influence the decision for defect closure. Similarly, assessment of hemodynamics during a temporary test occlusion may assist in the decision-making. If cardiac output declines with test balloon occlusion, the defect should not be closed.

Table 4.2 Echocardiographic essentials for assessment [17]

Atrial septal defects	Postoperative ASD	Post device closure ASD
1. ASD size and location from multiple windows 2. Size of septal rims 3. RV size and function 4. Estimated RV and pulmonary arterial pressure from tricuspid and pulmonary regurgitation jet velocities 5. Associated lesions—pulmonic stenosis, mitral valve prolapse, cleft mitral valve, anomalous pulmonary veins, and persistent left superior vena cava	1. Evidence of residual shunting 2. Residual pulmonary hypertension 3. Persistent RV enlargement and dysfunction 4. RV or right atrial thrombus 5. Mitral regurgitation from cleft mitral valve or mitral valve prolapse 6. Superior vena cava or pulmonary vein stenosis after sinus venosus ASD repair	1. Device position 2. Evidence of residual shunting 3. Device impingement upon systemic or pulmonary venous inflow 4. Device impairment of aortic, mitral, or tricuspid valve function 5. Device impingement upon posterior aortic wall 6. Thrombus or vegetation on right or left atrial device facets

Advanced Imaging Techniques

- Cardiac CT angiography performed at an ACHD center is useful for:
  - Direct visualization of the septal defect
  - Complete definition of the defect borders
  - Sizing of the surrounding rim
  - Identification of associated pulmonary venous abnormalities (Fig. 4.4).

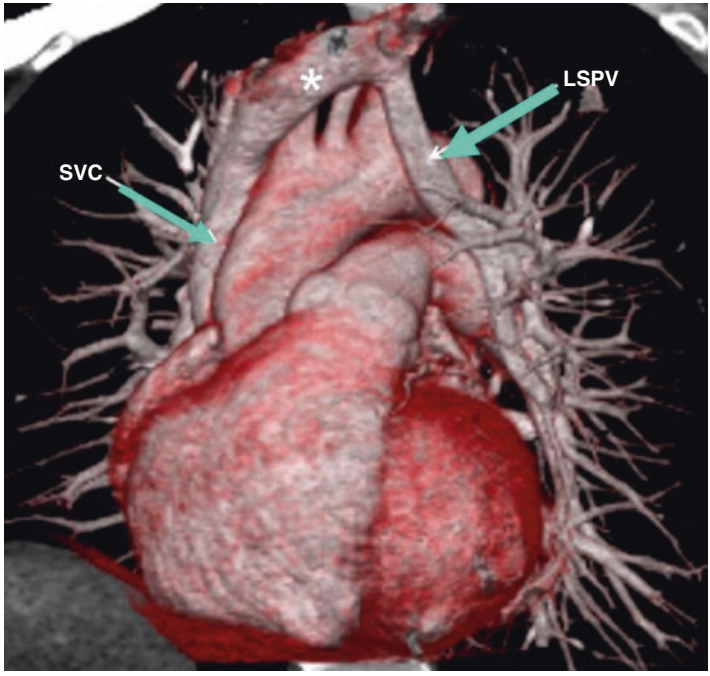

FIGURE 4.4 Three-dimensional CT angiography of anomalous left upper pulmonary venous drainage to the innominate vein

Use of this modality is limited by radiation exposure concerns in young patients, although the amount of radiation has significantly decreased with evolving scan protocols [19]:

- Cardiac MRI provides similar diagnostic delineation, without exposing patients to ionizing radiation:
  - Phase contrast imaging through the LV and RV outflow tracts can be used for defining Qp/Qs and shunt fraction.

Management of Adult Survivors

See Table 4.3 for summary of most recent guidelines.

Table 4.3 ACC/AHA guidelines 2008 [10]

Recommendations for evaluation of the unoperated patient	Recommendations for postintervention follow-up
Class I 1. ASD should be diagnosed by imaging techniques with demonstration of shunting across the defect and evidence of RV volume overload and any associated anomalies (*Level of Evidence: C*) 2. Patients with unexplained RV volume overload should be referred to an ACHD center for further diagnostic studies to rule out obscure ASD, partial anomalous venous connection, or coronary sinoseptal defect (*Level of Evidence: C*) *Class IIa* 1. Maximal exercise testing can be useful to document exercise capacity in patients with symptoms that are discrepant with clinical findings or to document changes in oxygen saturation in patients with mild or moderate PAH (*Level of Evidence: C*) 2. Cardiac catheterization can be useful to rule out concomitant coronary artery disease in patients at risk because of age or other factors (*Level of Evidence: B*)	*Class I* 1. Early postoperative symptoms of undue fever, fatigue, vomiting, chest pain, or abdominal pain may represent postpericardiotomy syndrome with tamponade and should prompt immediate evaluation with echocardiography (*Level of Evidence: C*) 2. Annual clinical follow-up is recommended for patients postoperatively if their ASD was repaired as an adult and the following conditions persist or develop: (a) PAH (*Level of Evidence: C*) (b) Atrial arrhythmias (*Level of Evidence: C*) (c) RV or LV dysfunction (*Level of Evidence: C*) (d) Coexisting valvular or other cardiac lesions (*Level of Evidence: C*) 3. Evaluation for possible device migration, erosion, or other complications is recommended for patients 3 months to 1 year after device closure

(continued)

TABLE 4.3 (continued)

Class III

1. In younger patients with uncomplicated ASD for whom imaging results are adequate, diagnostic cardiac catheterization is not indicated (*Level of Evidence: B*)
2. Maximal exercise testing is not recommended in ASD with severe PAH (*Level of Evidence: B*)

Recommendations for medical therapy

Class I

1. Cardioversion after appropriate anticoagulation is recommended to attempt restoration of the sinus rhythm if atrial fibrillation occurs (*Level of Evidence: A*)
2. Rate control and anticoagulation are recommended if sinus rhythm cannot be maintained by medical or interventional means (*Level of Evidence: A*)

Recommendations for interventional and surgical therapy

Class I

1. Closure of an ASD either percutaneously or surgically is indicated for right atrial and RV enlargement with or without symptoms (*Level of Evidence: B*)
2. A sinus venosus, coronary sinus, or primum ASD should be repaired surgically rather than by percutaneous closure (*Level of Evidence: B*)
3. Surgeons with training and expertise in CHD should perform operations for various ASD closures (*Level of Evidence: C*)
4. Device erosion, which may present with chest pain or syncope, should warrant urgent evaluation (*Level of Evidence: C*)

Recommendations for pregnancy

Class III

1. Pregnancy in patients with ASD and severe PAH (Eisenmenger syndrome) is not recommended owing to excessive maternal and fetal mortality and should be strongly discouraged (*Level of Evidence: A*)

Class IIa

1. Surgical closure of secundum ASD is reasonable when concomitant surgical repair/replacement of a tricuspid valve is considered or when the anatomy of the defect precludes the use of a percutaneous device (*Level of Evidence: C*)
2. Closure of an ASD, either percutaneously or surgically, is reasonable in the presence of:
   (a) Paradoxical embolism (*Level of Evidence: C*)
   (b) Documented platypnea-orthodeoxia (*Level of Evidence: B*)

Class IIb

1. Closure of an ASD, either percutaneously or surgically, may be considered in the presence of net left-to-right shunting, pulmonary artery pressure less than two thirds systemic levels, PVR less than two thirds systemic vascular resistance, or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect (patients should be treated in conjunction with providers who have expertise in the management of pulmonary hypertensive syndromes) (*Level of Evidence: C*)
2. Concomitant Maze procedure may be considered for intermittent or chronic atrial tachyarrhythmias in adults with ASDs (*Level of Evidence: C*)

Class III

1. Patients with severe irreversible PAH and no evidence of a left-to-right shunt should not undergo ASD closure (*Level of Evidence: B*)

Intracardiac Shunting Through Atrial Septal Defect

1. Indications for intervention [10]:
   (a) Right atrial and RV enlargement, with or without symptoms (Class I)
   (b) Paradoxical embolism (Class IIa)
   (c) Documented platypnea-orthodeoxia (Class IIa)
   (d) Any defect with left-to-right shunting as long as pulmonary vascular resistance (PVR) is less than two thirds of systemic resistance, pulmonary arterial pressures are less than two thirds of systemic pressures, or PVR is responsive to pulmonary vasodilator testing (Class IIb)
   (e) Concomitantly during open-heart surgery for a separate lesion (Class IIa)
2. Contraindications for intervention:
   (a) Severe irreversible pulmonary arterial hypertension (PAH) due to the risk of inducing right-sided pressure overload (Class III):
      - As discussed previously, pre-procedural right heart catheterization with iNO may be helpful to risk stratify patients who might be able to tolerate defect closure.
3. Options for intervention:
   (a) Surgical repair:
      - Preferred in patients who require surgical correction of associated defects, such as tricuspid valve insufficiency or anomalous pulmonary venous return
      - A sinus venosus defect, coronary sinus defect, or septum primum ASD must be repaired surgically by a surgeon with sufficient experience with these defects:
        – Superior sinus venosus repair may be complicated postoperatively by the development of superior vena cava (SVC) stenosis and the SVC syndrome

- Direct suture closure or pericardial patch closure can be used, depending on the size and location of the defect

(b) Percutaneous repair:

- The procedure of choice for secundum defects with 360° of sufficient bordering rim due to an equivalent success rate with a reduced complication rate and hospital stay duration as compared to surgical repair [20]
- Currently approved devices include the Amplatzer septal occluder, Gore Helex, and CardioSEAL devices (Fig. 4.5)
- Requires follow-up echocardiogram immediately post-procedure and subsequently at regular intervals to assess for potential complications:
  - Residual shunting
  - Device erosion/migration and/or aortic erosion
  - Thrombus formation

Complications Specific to Repaired Atrioventricular Septal Defect

- Indications for reoperation in AVSD (Class I) include:
  - Left AV valve stenosis, regurgitation or prosthesis dysfunction which causes symptoms, arrhythmias, increased LV dimensions, or decreased LVEF
  - LVOT obstruction with a mean gradient of >50 mmHg or peak gradient >70 mmHg or a mean gradient <50 mmHg with significant Left AV valve regurgitation or aortic regurgitation
  - Presence of residual or recurrent ASD or ventricular septal defect which meet criteria for closure

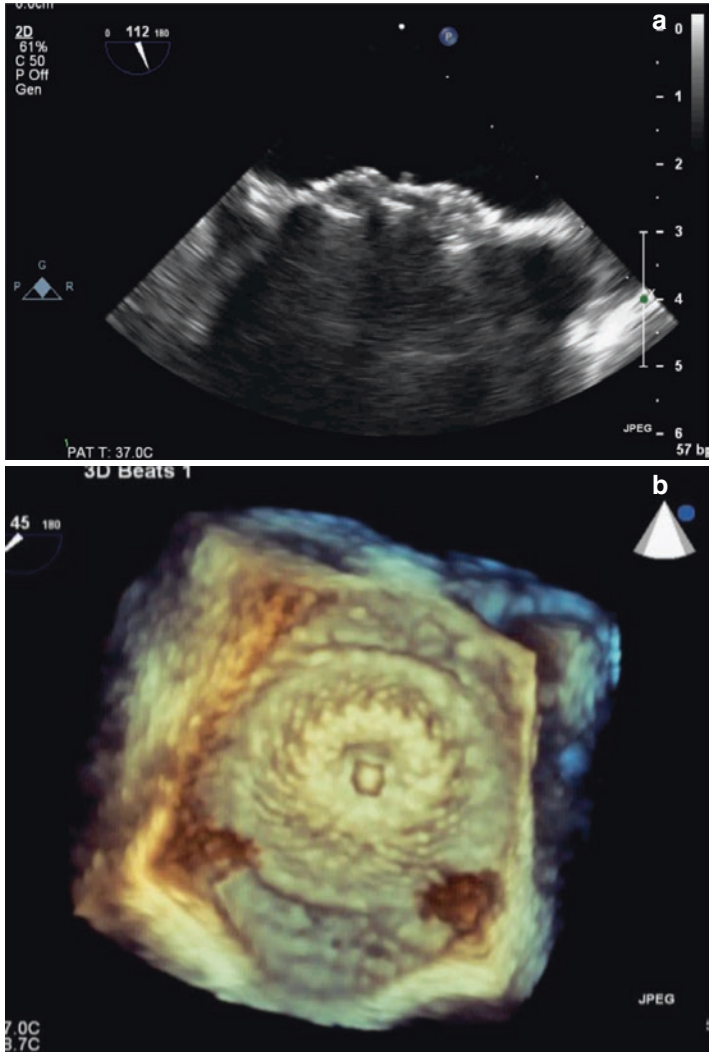

FIGURE 4.5 (**a**) Transesophageal bicaval view of well-seated secundum ASD closure device. (**b**) 3D TEE imaging of ASD closure device en face

Pulmonary Hypertension and Eisenmenger Syndrome

- Please see Chap. 9 for a full discussion of Eisenmenger syndrome
- Compared to higher-pressure shunts, such as a ventricular septal defect or patent ductus arteriosus, the flow across an ASD shunt is usually lower, and pulmonary hypertension will develop much more slowly. Development of Eisenmenger syndrome is therefore rare with pretricuspid shunts.
- In patients for whom ASD closure is contraindicated, due to irreversible PAH, medical management for pulmonary hypertension should be initiated.

Arrhythmia

- Atrial fibrillation, atrial flutter, and sick sinus syndrome are common and should be treated in standard fashion with medical therapy, catheter ablation, and pacemaker therapy as indicated.
- Concomitant Maze procedure may be considered in patients with atrial fibrillation or atrial flutter (Class IIa) [8].

Paradoxical Embolization

- With scuba diving and also during pregnancy, there is increased right-to-left shunting and therefore an increased risk of paradoxical embolization or stroke
- Patients with residual shunts should have all IV infusions filtered
- Paradoxical embolism is an indication for repair

Management of Pregnancy

- Pregnancy is an absolute contraindication in patients with Eisenmenger syndrome due to the high risk of maternal mortality [21, 22]
- Pregnancy is well tolerated in patients with pretricuspid shunt lesions without pulmonary hypertension
- Right heart volume and pressure overload may progress during pregnancy in unrepaired patients (with the development of symptoms of dyspnea or arrhythmia) due to increased left-to-right shunting in the setting of increased intravascular volume and cardiac output
- Women may be at an increased risk of paradoxical embolism due to:
  - Thrombophilic state of pregnancy
  - Increased risk of right-to-left shunting due to the decrease in systemic vascular resistance (starting in the second trimester of pregnancy) and during Valsalva in labor.

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Chapter 5
Ventricular Septal Defect

Jonathan Kochav

Epidemiology

- Ventricular septal defects (VSD) are among the most common congenital heart entities in early childhood with an incidence of about 1 per 250–300 live births [1, 2].
- Two-thirds of VSDs close spontaneously by early school age [3] or are repaired in childhood; therefore, the prevalence is much lower in adults.
- For historical background, see Table 5.1.
- Acquired VSDs, such as post-myocardial infarction VSDs, will not be discussed in the chapter.

Anatomic Definition and Pathophysiology

1. Anatomy:

   (a) There are several types of VSDs (Figure 5.1), the most common being in the perimembranous region. Less frequently, they may be found in the inlet region at the level of the atrioventricular valves, the muscular region, or the outlet (supracristal).

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Table 5.1 Historical background

- In 1879 French physiologist Henri Rogers described the characteristic murmur and clinical findings of six acyanotic patients with a holosystolic murmur. After identifying an isolated VSD in an autopsy of a young child, he inferred that this defect was responsible for their clinical picture. The isolated restricted VSD became known as the "maladie de Roger" and the characteristic murmur the "bruit du Roger" [4].
- Lellehie and Varco reported the first successful surgical VSD closure in 1954. The first percutaneous VSD device closure was performed by Lock in 1989.

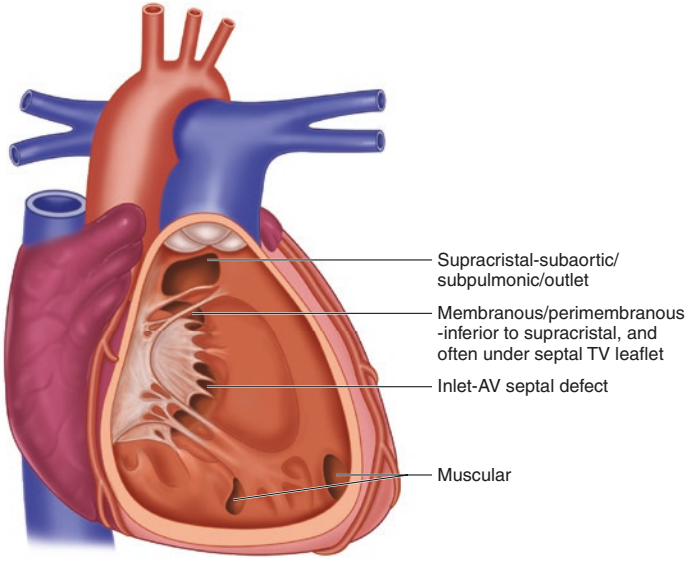

Figure 5.1 Depiction of type of ventricular septal defects [5]

- Supracristal (5%): Also known as type I or outlet defect (Video 5.1)
  - Deficiency of the septum inferior to the aortic and pulmonary valves
  - The aortic valve cusp (typically right or noncoronary) can prolapse into the VSD leading to progressive aortic regurgitation and occasionally sinus dilation

  - This defect is more common in the Asian population occurring in up to 30% of patients in Asian series [6]

- Perimembranous (60–70%): Also known as type II or membranous defect (Video 5.2)
  - Most common defect
  - Deficiency of the septal wall adjacent to the septal leaflet of the tricuspid valve on the right and aortic valve on the left
  - The septal leaflet of the tricuspid valve may become adherent to the septal wall obstructing and thereby limiting left-to-right shunting in some circumstances; a membranous septal aneurysm may develop
- Inlet (5%): Also known as type III or canal type defect (Video 5.3)
  - Results from deficiency of the inlet septum located beneath both mitral and tricuspid valves
  - Does not result in mitral or tricuspid regurgitation as an isolated defect but is often seen as a component of an atrioventricular septal defect (associated with Down's syndrome)
- Muscular (10%): Also known as type IV defect (Video 5.4)
  - Occurs due to excessive fetal muscular resorption
  - May be small or large and single or multiple
  - May occur at any area of the muscular septum
  - In adults they are generally small and restrictive
  - Spontaneous closure of these defects in children is quite common [3]

2. Physiology and spectrum of disease:
   (a) A VSD results in shunting of blood from one ventricle to the other
   (b) Small (restrictive) defects are generally <40% of the size of the aortic annulus and will result in high-velocity, low-volume left-to-right shunting that does not result in left-sided volume overload

(c) With moderate-sized defects, the left atrium (LA) and left ventricle (LV) will progressively dilate due to increased pulmonary venous return

- The larger the defect size, the faster this process will progress
- Increased pulmonary blood flow over time results in pulmonary arteriolar medial hyperplasia that increases pulmonary vascular resistance (PVR), and significant right ventricular (RV) and pulmonary arterial pressure overload may develop
- If uncorrected, this may lead to severe pulmonary hypertension and the potential for right-to-left flow reversal (Eisenmenger syndrome)

(d) Patients with large VSDs (i.e., >80% of the size of the aortic annulus) can present with congestive heart failure in infancy

- If an infant is very ill and/or has a large complex VSD that is technically difficult to surgically repair, a pulmonary artery band may be placed to provide distal RV outflow tract obstruction and limit left-to-right shunting
- Once the patient's anatomy is amenable to surgical repair, a second operation is performed during which the pulmonary band is removed and the defect is closed

3. Associated defects:

(a) Most often isolated, however VSDs are a common component of complex abnormalities, particularly conotruncal (e.g., tetralogy of Fallot, transposition of the great arteries)

(b) Can be associated with valvular override or straddling (see Chap. 1) depending on the degree of septal annular misalignment (Figure 5.2)

(c) Defects [7]:

- Membranous ventricular septal aneurysm
- Sinus of Valsalva aneurysm (risk of rupture and formation of fistula)

- Aortic valve prolapse into the VSD with aortic insufficiency (specifically in supracristal VSD)
- Conal septal malalignment with RV or LV outflow obstruction
- Double-chamber RV
- Right-sided obstruction
  - Valvular pulmonary stenosis
  - Acquired infundibular hypertrophy with right ventricular outflow tract obstruction

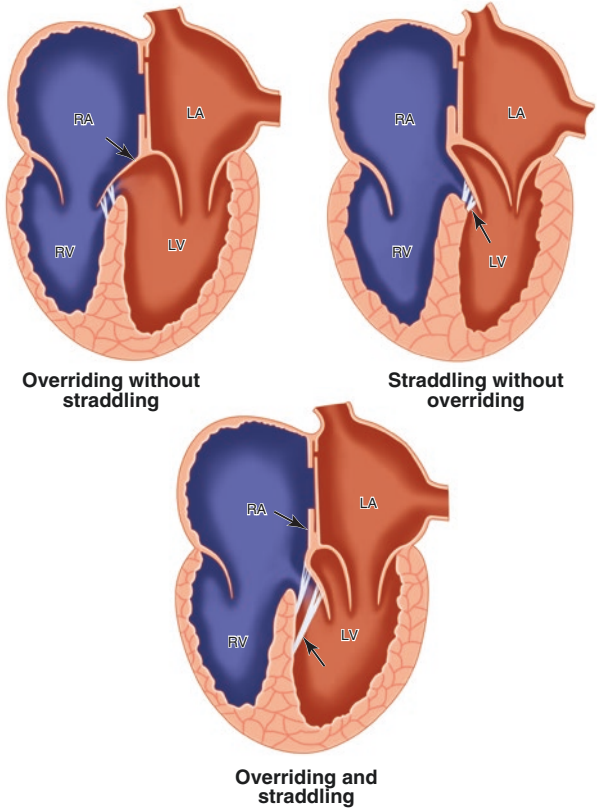

FIGURE 5.2 Valvular "straddling" and "overriding" of a ventricular septal defect

- Left-sided obstruction
  - Coarctation of the aorta
  - Bicuspid aortic valve
  - Discrete subaortic membrane
  - Mitral valve anomaly (such as parachute mitral valve)

4. Maternal and genetic factors
   (a) VSDs are the most common lesion associated with many chromosomal disorders such as trisomy 13, 18 (Edwards syndrome), and 21 (Down's syndrome).
   (b) Parents with sporadic VSDs have an increased likelihood (~10%) of having offspring with CHD, including a VSD [8].

Diagnostics

Clinical Presentation in Adults

- Patients repaired earlier in life are typically asymptomatic
- Residual VSDs are usually small and hemodynamically restricted
- Because large nonrestricted shunts in children usually present clinically and are repaired, the adult presenting with a VSD will usually present with a small restrictive defect
- Adults may present with new exercise intolerance as a result of LV dilation due to a moderate VSD with associated left-to-right shunting
  - With age the LV becomes less compliant, LA pressures rise, and symptoms develop
- Young adults with large defects who have had limited exposure to medical care can present late into disease progression with severe pulmonary hypertension and systemic cyanosis consistent with Eisenmenger syndrome

- Rarely, adults will present with a large defect that is restricted by a distal RV outflow tract obstruction (may be apical RV muscle bundle if apical muscular defect)

Physical Exam

- Ventricular septal defect
  - Restrictive defects will produce a loud, holosystolic, high-pitched murmur

    Augments with isometric maneuvers due to increased afterload on the outflow tract and therefore increased proportion of blood flow through the shunt
  - If RV pressure increases as a consequence of pulmonary hypertension, the duration of the murmur decreases, and the pitch drops
  - Small muscular septal defects may occupy only early systole if the defect closes with systolic contraction
  - Large defects may produce only a soft or absent murmur due to laminar, nonturbulent flow
- Aortic cusp prolapse in patients with supracristal defect
  - Diastolic murmur of aortic insufficiency is best heard at the left lower sternal border
- Prior pulmonary banding complicated by supravalvular pulmonic stenosis
  - Loud systolic ejection murmur best heard over the left upper sternal border
- Eisenmenger exam
  - See Chap. 9 for further details on the Eisenmenger exam

Electrocardiogram

- Patients with restrictive small VSDs may have a normal electrocardiogram

- Left-sided pressure/volume overload
  - Left ventricular hypertrophy
  - Left atrial enlargement
- Right-sided pressure overload
  - Right bundle branch block
  - Right ventricular hypertrophy
  - Right axis deviation
  - Right atrial enlargement

Chest Radiography

- Patients with restrictive small VSDs will usually have a normal chest radiograph
- Left-sided volume overload
  - Left atrial enlargement
  - Left ventricular enlargement
- Pulmonary hypertension
  - Prominent pulmonary artery
  - Distal pulmonary vascular pruning

Echocardiography

- Standard 2D transthoracic echocardiography with color Doppler will generally make the diagnosis of a VSD
  - Color Doppler must be interrogated over the entire ventricular septum, as small defects may be easily missed with incomplete interrogation
- Table 5.2 highlights the essentials of echocardiographic assessment of patients with VSDs, both pre- and post-complete repair
  - Transesophageal echocardiography is often necessary when VSD endocarditis is in question or pre-operatively for surgical planning

Table 5.2 Echocardiographic essentials for assessment [9]

Native ventricular septal defect	VSD: following surgical repair
• Size and location of VSD • Direction of shunt flow; LV to RV shunting, LV to right atrial shunting • Left atrial size • LV size, mass, and function • VSD gradient by continuous waveform Doppler • Estimated RV and pulmonary arterial pressure from tricuspid regurgitation and pulmonary regurgitation jet velocity • Presence and degree of RV outflow tract obstruction—double-chamber right ventricle infundibular, valvular, or branch PS • Associated lesions—membranous septal aneurysm, aortic valve prolapse, or discrete subaortic membrane	• Residual VSD shunt • Residual pulmonary hypertension • LV dysfunction • Tricuspid regurgitation due to surgical distortion of the septal leaflet • Aortic valve prolapse with aortic insufficiency • Aortic valve distortion and dysfunction due to VSD patch placement • Discrete subaortic membrane and double-chamber right ventricle

Cardiac Catheterization

- Simultaneous right heart and left heart catheterization with oximetry can be utilized to define Qp/Qs and shunt fraction (see Chap. 3)
- In select cases, preoperative right heart catheterization with inhaled nitric oxide (iNO) may be useful to assess for reversibility of severe pulmonary hypertension
- A coronary evaluation is reasonable in patients with planned operative management who have risk of coronary disease because of age or other risk factors

Advanced Imaging Techniques

- May aid in defining the anatomy of patients with apical muscular or inlet lesions that are not well characterized by echocardiography

- Useful if percutaneous or surgical intervention is planned, or for assessment of complex associated lesions
- Cardiac MRI with phase-contrast imaging through the LV and RV outflow tracts can be used for defining Qp/Qs and shunt fraction

Management of Adult Survivors

See Table 5.3 for summary of guidelines.

Intracardiac Shunting Through Ventricular Septal Defect

- Indications for intervention [7]:
  - Qp/Qs > 2.0 with clinical evidence of LV volume overload (Class I)
  - A history of infective endocarditis (Class I)
  - Qp/Qs > 1.5 with PA pressure less than two-thirds of systemic pressure and PVR less than two-thirds of systemic vascular resistance (SVR) (Class IIa)
  - Qp/Qs >1.5 in the presence of LV systolic or diastolic failure (Class IIa)
- Contraindications for intervention:
  - Patients with severe irreversible pulmonary hypertension should not undergo VSD closure due to risk of inducing overwhelming right-sided pressure overload (Class III). Pre-procedural right heart catheterization with iNO may be helpful to risk stratify patients who might be able to tolerate defect closure
- Options for intervention:
  - Surgical
    - Patch closure with synthetic material (e.g., Gore-Tex, Dacron).
    - Primary suture closure for smaller defects.

Table 5.3 ACC/AHA guidelines 2008 [7]

Recommendations for cardiac catheterization:

Class I

- Cardiac catheterization to assess the operability of adults with VSD and pulmonary arterial hypertension (PAH) should be performed in an ACHD regional center in collaboration with experts (*level of evidence: C*)

Class IIa

- Cardiac catheterization can be useful for adults with VSD in whom noninvasive data are inconclusive and further information is needed for management. Data to be obtained include the following:
  - Quantification of shunting (*level of evidence: B*)
  - Assessment of pulmonary pressure and resistance in patients with suspected PAH. Reversibility of PAH should be tested with various vasodilators (*level of evidence: B*)
  - Evaluation of other lesions such as AR and double-chamber right ventricle (*level of evidence: C*)
  - Determination of whether multiple VSDs are present before surgery (*level of evidence: C*)
  - Performance of coronary arteriography is indicated in patients at risk for coronary artery disease (*level of evidence: C*)
  - VSD anatomy, especially if device closure is contemplated (*level of evidence: C*)

Recommendations for surgical ventricular septal defect closure:

Class I

- Surgeons with training and expertise in CHD should perform VSD closure operations (*level of evidence: C*)
- Closure of a VSD is indicated when there is a Qp/Qs (pulmonary-to-systemic blood flow ratio) of 2.0 or more and clinical evidence of LV volume overload (*level of evidence: B*)
- Closure of a VSD is indicated when the patient has a history of infective endocarditis (*level of evidence: C*)

Class IIa

- Closure of a VSD is reasonable when net left-to-right shunting is present at a Qp/Qs greater than 1.5 with pulmonary artery pressure less than two-thirds of systemic pressure and PVR less than two-thirds of systemic vascular resistance (*level of evidence: B*)
- Closure of a VSD is reasonable when net left-to-right shunting is present at a Qp/Qs greater than 1.5 in the presence of LV systolic or diastolic failure (*level of evidence: B*)

Class IIb

- Device closure of a muscular VSD may be considered, especially if the VSD is remote from the tricuspid valve and the aorta, if the VSD is associated with severe left-sided heart chamber enlargement, or if there is PAH (*level of evidence: C*)

(continued)

Table 5.3 (continued)

Recommendation for medical therapy:

Class IIb

- Pulmonary vasodilator therapy may be considered for adults with VSDs with progressive/severe pulmonary vascular disease (refer to Chapter XX on pulmonary hypertension/ Eisenmenger physiology) (*level of evidence: B*)

Recommendation for reproduction:

Class III

- Pregnancy in patients with VSD and severe PAH (Eisenmenger syndrome) is not recommended, owing to excessive maternal and fetal mortality and should be strongly discouraged (*level of evidence: A*)

Class III

- VSD closure is not recommended in patients with severe irreversible PAH (*level of evidence: B*)

Recommendations for surgical and catheter intervention follow-up:

Class I

- Adults with VSD with residual heart failure, shunts, PAH, AR, or RV outflow tract or LV outflow tract obstruction should be seen at least annually at an ACHD regional center (*level of evidence: C*)
- Adults with a small residual VSD and no other lesions should be seen every 3 to 5 years at an ACHD regional center (*level of evidence: C*)
- Adults with device closure of a VSD should be followed up every 1 to 2 years at an ACHD center depending on the location of the VSD and other factors (*level of evidence: C*)

- Post-repair intraoperative transesophageal echocardiography should be performed to rule out additional VSDs not previously identified, as the closure of a large VSD may unmask smaller shunts.
- Associated defects (e.g., LV outflow tract obstruction, RV outflow tract obstruction, aortic regurgitation) should be repaired as part of a combined procedure.
- Postoperative heart block may occur early or late after surgical repair.

– Transcatheter

- Some muscular VSDs may be closed percutaneously if they are remote from valvular apparatus
- United States Food and Drug Administration approval for percutaneous closure is limited
- Percutaneous closure of perimembranous VSD is more challenging due to the proximity of the tricuspid and aortic valves and the proximity to the conduction system.
- Be useful to close residual defects after attempts at surgical repair, poorly accessible defects, or VSDs with multiple defects in close proximity.
- Complications include arrhythmia and new conduction defects.

Pulmonary Hypertension and Eisenmenger Syndrome

- Please see Chap. 9 for a full discussion of the Eisenmenger syndrome.
- VSD closure is indicated for patients in early stages of pulmonary hypertension or for patients with more advanced pulmonary hypertension that is deemed reversible by right heart catheterization iNO.
- In patients for whom VSD closure is contraindicated due to irreversible pulmonary hypertension, medical management for pulmonary hypertension with pulmonary vasodilators should be attempted.

Paradoxical Embolization

- With increased right-to-left shunting, there is an increased risk of paradoxical embolization
- This risk increases with RV pacer or implantable cardioverter-defibrillator leads which should be avoided if possible in patients who have unrepaired VSD

Infective Endocarditis Prophylaxis

- Infective endocarditis prophylaxis is indicated in many patients with VSD. Please see Chap. 36 for further details.

Management of Pregnancy

- Pregnancy is an absolute contraindication in patients with Eisenmenger syndrome due to high risk of maternal mortality [10, 11].
- Pregnancy is well tolerated in patients without pulmonary hypertension.
- Right heart volume and pressure overload may progress during pregnancy in unrepaired patients (with the development of symptoms of dyspnea or arrhythmias) due to increased left-to-right shunting in the setting of increased intravascular volume and cardiac output.
- Women are at an increased risk of paradoxical embolism due to:
  - The thrombophilic state of pregnancy
  - An increased risk of right-to-left shunting secondary to the decrease in SVR starting in the second trimester of pregnancy and during Valsalva in labor

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Chapter 6
Atrioventricular Septal Defect

Jonathan Kochav

Epidemiology

- Atrioventricular septal defects (AVSD) account for ~4–5% of congenital heart disease (CHD), with a prevalence of about 1 per 4500 live births [1, 2].

Anatomic Definition and Pathophysiology

1. Anatomy and spectrum of disease:
   (a) AVSD are also termed atrioventricular canal defects or, in reference to the embryologic etiology, endocardial cushion defects. They result from abnormal development of the endocardial cushion at the crux of the heart, resulting in the absence of the atrial and ventricular septum at the crux, and abnormalities of the atrioventricular (AV) valves (Fig. 6.1). Out of conven-

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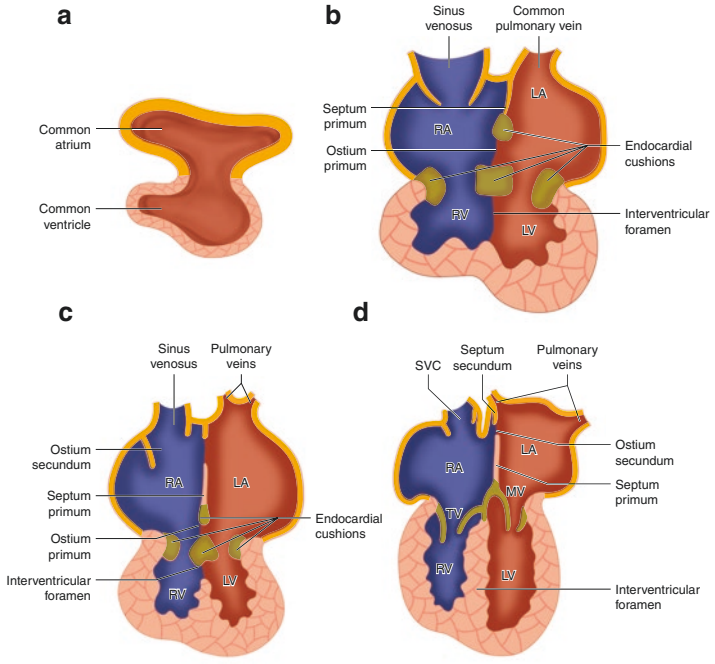

FIGURE 6.1 Normal fetal cardiac development: (**a**) the primitive common atrium and ventricle. (**b**) the four endocardial cushions form at the crux of the heart. (**c**) the endocardial cushions grow toward each other, contributing to the development of the atrial and ventricular septa and to the seperate atrioventricular valves. (**d**) the normal fetal heart. Green colored areas represent anatomic structures formed by the endocardial cushions that are susceptible to malformation in atrioventricular septal defects

tion, the AV valves are termed right and left AV valves instead of the tricuspid and mitral valves, in the presence of an AVSD.

(i) Features shared by all forms of AVSD

- A septum primum atrial septal defect (ASD).
- AV valve leaflets insert at the same level at the cardiac crux as opposed to the normal relationship where the

tricuspid valve inserts more apically in the interventricular septum (Fig. 6.2).

- Elongated left ventricular (LV) outflow tract with anterior displacement of the aortic valve, often referred to as "goose necking" of the LV outflow tract (Fig. 6.3).
- Counterclockwise rotation of the LV papillary muscles.
- Cleft left AV valve component, directed toward the ventricular septum.

(b) AVSD lie along a continuum with isolated septum primum ASDs that do not involve the AV valves or ventricular septum. AV valve involvement results in a common AV valve annulus that spans across both ven-

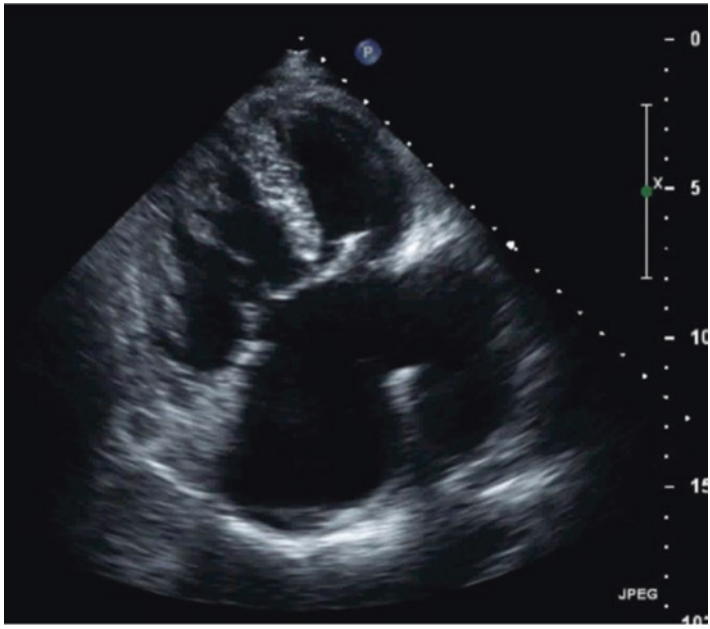

FIGURE 6.2 Four-chamber view (apex up) of a patient with an uncorrected AVSD demonstrating a large primum atrial septal defect and equiplanar AV valves

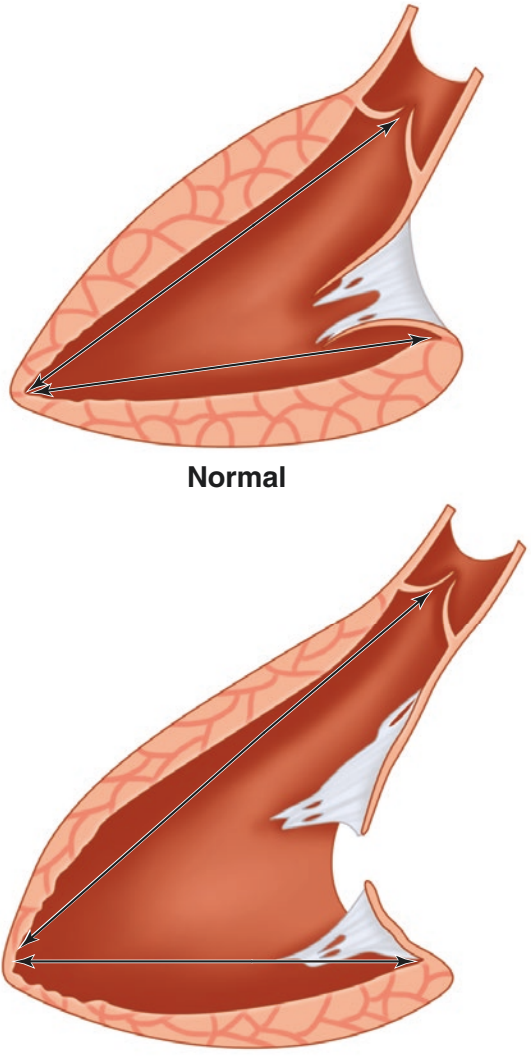

FIGURE 6.3 Left ventricular outflow elongation with anterior displacement of the aorta, commonly seen in patients with AVSD

tricles. The size of the associated inlet interventricular defect can vary (Fig. 6.4).

(i) **Partial AVSD:** Primum ASD with a cleft left AV valve, with the cleft directed toward the ventricular septum; distinct right and left AV valve annuli remain, and a ventricular septal defect (VSD) is not present.

(ii) **Transitional AVSD:** Primum ASD with a cleft left AV valve. A common AV valve is divided by a tongue of tissue into right and left orifices. An inlet VSD is usually small and covered by aneurysmal membraneous septal tissue.

(iii) **Intermediate AVSD:** Primum ASD, a common AV valve divided by a tongue of tissue into right and left orifices, and a large hemodynamically significant VSD.

(iv) **Complete AVSD:** Primum ASD, a common AV valve without dividing tissue, and large hemodynamically significant VSD.

(c) In addition to left AV valve cleft, patients may have a double-orifice left AV valve, due to additional tissue

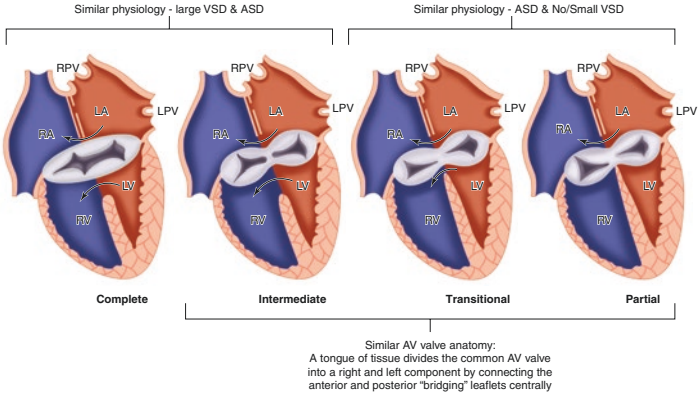

FIGURE 6.4 Schematic of the subtypes of atrioventricular septal defects

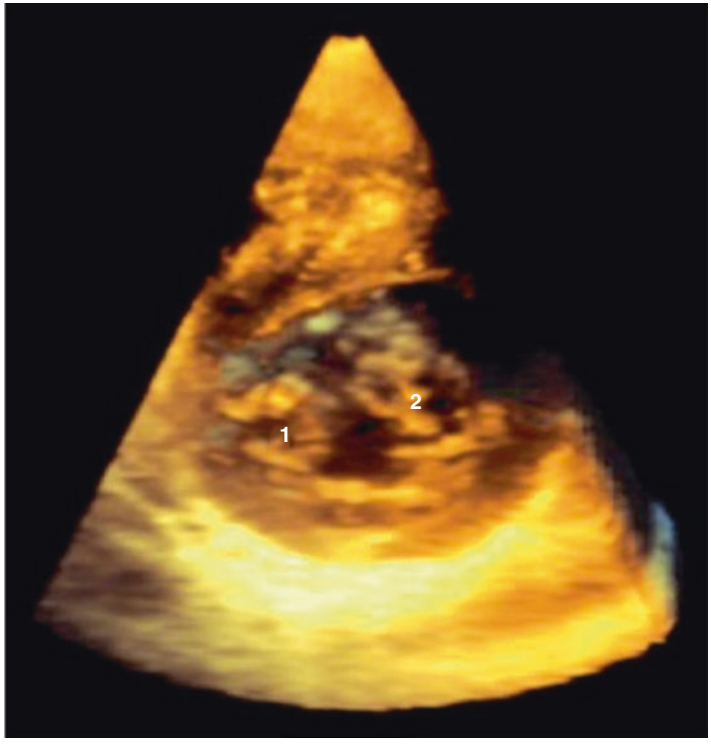

Figure 6.5 Parasternal short axis of 3D echocardiogram image from a patient with a transitional atrioventricular canal defect and a double-orifice left AV valve, with number marking each orifice, (used with permission from DeFaria Yeh D, King. Cardiovascular Imaging Repo (2013)6:454–466)

that subdivides the left AV valve orifice. This results in decreased valve area, and mitral stenosis physiology (Fig. 6.5).

- The common AV valve is composed of five leaflets: three free-wall leaflets (two right-sided, one left-sided) and two bridging leaflets, with five associated papillary muscles.

- The LV papillary muscles are rotated counterclockwise and sit closer together than in the usual anatomic relationship, sometimes forming a "parachute" left AV valve with a single LV papillary muscle.
- There can be variability in the anterior bridging leaflet, which is often defined using the Rastelli classification.

Rastelli type A: divided and attached to the crest of the ventricular septum with multiple chordae

Rastelli type B: Partly divided; not attached to the crest of the septum. Chordae attach to the right ventricular (RV) papillary muscle

Rastelli type C: Not divided and not attached to the crest of the septum ("free floating"). Chordae attach to the RV papillary muscle

- Unbalanced AVSD:

- The AV valve inflow may be malaligned over the ventricular septum, which results in underdevelopment of either the RV or LV (see Chap. 5).

2. Physiology

(a) Partial AVSD:

(i) Physiology is defined by a large left-to-right atrial shunt with progressive RV volume and subsequently pressure overload. Patients may also have significant left AV valvular regurgitation as a result of cleft left AV valve.

(b) Transitional AVSD:

(i) Physiology is defined by a large left-to-right atrial shunt and a smaller, usually restricted, left-to-right VSD. As in a partial AVSD, the hemodynamics are driven primarily by the atrial level shunt, with progressive RV volume and subsequently pressure overload.

(c) Intermediate or complete AVSD:

(i) Large left-to-right atrial and ventricular shunts quickly progress to pulmonary hypertension and congestive biventricular heart failure, usually requiring repair early in infancy.

3. Associated defects:

(a) Partial AVSD

(i) Persistent left superior vena cava
(ii) Coarctation of the aorta
(iii) Patent ductus arteriosus

(b) Complete AVSD

(i) Tetralogy of Fallot
(ii) Double outlet right ventricle
(iii) Ebstein's anomaly

(c) LV outflow tract obstruction

(i) More common in patients with partial AVSD.
(ii) Can be due to the anteriorly displaced, elongated, and narrowed LV outflow tract.
(iii) Can be due to subaortic membrane.
(iv) Left AV valve chordal insertion to the ventricular septum can result in flow acceleration across the LV outflow tract, but significant obstruction from this defect is uncommon.

(d) Heterotaxy syndromes

4. Genetic or maternal factors:

(a) AVSD is seen in patients with trisomy 21 (Down's syndrome) [3].

(i) Most complete AVSD are seen in patients with Down's syndrome (>75%).
(ii) Most partial AVSD occur in patients without Down's syndrome (>90%).

Childhood Repairs

Pulmonary Artery Banding

- In this procedure, a band is placed around the pulmonary artery to introduce resistance to pulmonary blood flow. Left-to-right shunting is reduced, and the pulmonary vascular remodeling that occurs with excessive pulmonary blood flow is limited.
- Pulmonary artery banding is a palliative procedure that has been employed with decreasing frequency in recent decades in lieu of primary repair.
- In rare circumstances when an infant is very ill or has a large, complex defect that is technically difficult to surgically repair, a pulmonary artery band may be placed until the child grows and primary repair can be performed.

Surgical Repair of AVSD

- The primary repair consists of patch repair of the central AVSD and subdivision of the AV septal bridging leaflet with approximation of the cleft in the left AV valve using either a one-patch or two-patch technique (Fig. 6.6).

Diagnostics

Clinical Presentation in Adults

- Most adult patients present post surgical repair in childhood.
- Rarely, patients with more mild disease will present in late childhood or early adulthood with congestive heart failure, pulmonary hypertension with Eisenmenger syndrome, infective endocarditis, or arrhythmia.

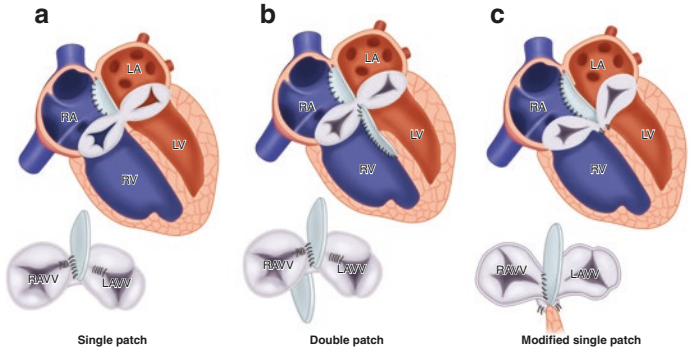

FIGURE 6.6 Schematic of the surgical techniques for AVSD repair: (**a**) The Single-Patch technique: a single prosthetic patch is used to close both atrial and ventricular septal defects, with the divided AV valve sutured to the patch. (**b**) The Double-Patch techinque: Individual patches are used to close the atrial and ventricular septal defects, with the divided AV valves sutured to each patch individually. (**c**) The Modified Single-Patch technique: The divided AV valve is pulled down and sutured to the crest of the ventricular septum, and a patch is used to close the remaining defect

Physical Exam

- Repaired patient
  - Exam should be normal.
  - Listen for systolic murmurs associated with residual left AV valve regurgitation or left ventricular outflow tract obstruction.
  - Listen for diastolic rumbling murmur that may be indicative of left AV valve stenosis.
  - Right bundle branch block is common, so wide split S2 may be heard.
- Unrepaired adult
  - ASD

  May result in a fixed and split S2 due to delayed closure of the pulmonary valve that does not vary with inspiration.

A pulmonary flow murmur may be heard over the left upper sternal border due to increased flow over the pulmonary valve. With very large shunts, a diastolic flow murmur may be heard across the tricuspid valve.

RV heave.

– VSD

Small restrictive VSD: loud, holosystolic, high-pitched murmur; augments with isometric maneuvers due to increased systemic afterload and subsequent increased shunt.

Large, unrestrictive VSD: there may be no murmur associated with the VSD.

As the RV pressure increases with progression of disease, the duration of the murmur decreases and the pitch drops.

– AV valve regurgitation or stenosis

Holosystolic blowing murmur best heard at the apex and left lower sternal base.

Diastolic rumbling murmur that may be indicative of left AV valve stenosis.

– LV outflow tract obstruction

Systolic crescendo-decrescendo murmur.

– Severe pulmonary arterial hypertension with Eisenmenger syndrome

See Chap. 9 on the Eisenmenger syndrome.

Electrocardiogram

- In AVSD, the AV node is inferiorly and posteriorly displaced to where the posterior rims of the atrial and ventricular septae unite [4]. The His bundle extends along the lower rim of the ventricular septum and the left anterior fascicle is hypoplastic, resulting in a left axis deviation with a superior QRS axis [5].

- Right bundle branch block morphology is classically seen, though this is thought to reflect aberrant conduction along a longer-than-normal right bundle branch that comes off of the inferiorly displaced His bundle [6].
- First-degree AV block is found in >50% of patients, due to progressive conduction disease or postoperative injury.
- Right ventricular volume and pressure overload.
  - Right atrial enlargement
  - RV hypertrophy

Chest Radiography

- Cardiomegaly
- Pulmonary hypertension
  - Prominent main pulmonary artery segments
  - Distal pruning of pulmonary vessels

Echocardiography

- Transthoracic echocardiography is the gold standard for evaluation of patients with repaired or unrepaired AVSD.
- Table 6.1 highlights the essentials of echocardiographic assessment of patients with ASVD, both pre- and post-complete repair.

Cardiac Catheterization

- Cardiac catheterization serves a limited role in AVSD.
- In select cases, preoperative right heart catheterization with inhaled nitric oxide (iNO) may be useful to assess for reversibility of severe pulmonary hypertension.
- A coronary evaluation is reasonable in patients with planned operative management who have risk of coronary disease because of age or other risk factors.

Table 6.1 Echocardiographic essentials for assessment [10]

Unrepaired atrioventricular septal defect	Postoperative AVSD
1. Size and location of atrial and ventricular defects 2. Presence, direction, and size of ASD and VSD shunt 3. Estimate of RV and pulmonary arterial pressure from tricuspid and pulmonic regurgitant velocities 4. Specifics of atrioventricular valve anatomy—common AV valve, septal attachments of anterior and posterior bridging leaflets (Rastelli type A, B, or C); unbalanced alignment 5. Degree of left or right AV valve regurgitation 6. Papillary muscle anatomy and chordal attachments 7. LV size, mass, and function 8. RV size, wall thickness, and function 9. Associated defects—patent ductus arteriosus, coarctation, subaortic obstruction	1. Residual atrial or ventricular shunt; possible LV-right atrial shunting 2. Residual pulmonary hypertension 3. AV valve regurgitation 4. Discrete subaortic stenosis 5. Assessment of other coexisting preoperative issues

Advanced Imaging Techniques

- Cardiac MRI and CT can be useful for evaluation of associated vascular lesions.
- 3D images may be useful for delineating leaflet morphology if echocardiographic images are equivocal.

Management of Complications in Adult Survivors

See Table 6.2 for summary of guidelines.

Table 6.2 ACC/AHA guidelines 2008 [3]

Recommendation for heart catheterization:
Class IIa
1. Cardiac catheterization is reasonable to assess PAH and test vasoreactivity in patients with repaired or unrepaired AVSD (*level of evidence: B*)

Recommendations for surgical therapy:
Class I
1. Surgeons with training and expertise in CHD should perform operations for AVSD (*level of evidence: C*)
2. Surgical reoperation is recommended in adults with previously repaired AVSD with the following indications:
   (a) Left AV valve repair or replacement for regurgitation or stenosis that causes symptoms, atrial or ventricular arrhythmias, a progressive increase in LV dimensions, or deterioration of LV function (*level of evidence: B*)
   (b) LV outflow tract obstruction with a mean gradient greater than 50 mm hg or peak instantaneous gradient greater than 70 mm h, or a gradient less than 50 mm hg in association with significant mitral regurgitation or aortic regurgitation (*level of evidence: B*)
   (c) Residual/recurrent ASD or VSD with significant left-to-right shunting

Recommendations for endocarditis prophylaxis:
Class IIa
1. Antibiotic prophylaxis before dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa is reasonable in patients with CHD with the highest risk for adverse outcome from IE, including those with the following indications:
   (a) Prosthetic cardiac valve or prosthetic material used for cardiac valve repair (*level of evidence: B*)
   (b) Previous IE (*level of evidence: B*)
   (c) Unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits (*level of evidence: B*)
   (d) Completely repaired CHD with prosthetic materials, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure (*level of evidence: B*)
   (e) Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device that inhibit endothelialization (*level of evidence: B*)

Recommendations for pregnancy:

Class I

1. All women with a history of AVSD should be evaluated before conception to ensure that there are no significant residual hemodynamic lesions that might complicate the management of pregnancy (*level of evidence: C*)
2. The issue of pregnancy risk and preventive measures should be discussed with women with Down's syndrome and their caregivers (*level of evidence: C*)

2. It is reasonable to consider antibiotic prophylaxis against IE before vaginal delivery at the time of membrane rupture in select patients with the highest risk of adverse outcomes. This includes patients with the following indications:
   (a) Prosthetic cardiac valve or prosthetic material used for cardiac valve repair (*level of evidence: C*)
   (b) Unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits (*level of evidence: C*)

Class III

1. Prophylaxis against infective endocarditis is not recommended for nondental procedures (such as esophagogastroduodenoscopy or colonoscopy) in the absence of active infection (*level of evidence: C*)

Unrepaired AVSD

- Surgical repair is indicated unless there is proven irreversible pulmonary hypertension. Right heart catheterization with iNO may be useful to assess for reversibility.
- Surgical repair is not recommended for patients with severe irreversible pulmonary hypertension due to complete or intermediate AVSD that remain unrepaired into adulthood. Please see Chap. 9 for a full discussion of congenital heart disease associated pulmonary arterial hypertension and the Eisenmenger syndrome.
- Among adult patients for whom AVSD repair is contraindicated due to irreversible pulmonary hypertension, medical management for pulmonary hypertension with pulmonary vasodilators should be attempted.

Residual/Recurrent ASD or VSD

- Suture or patch closure is indicated for patients with significant left-to-right shunting. See Chaps. 4 and 5 for a more detailed discussion on indications for ASD or VSD closure.

LV Outflow Tract Obstruction

- Open operation for resection of the obstruction Warnes is indicated if the mean gradient is greater than 50 mmHg, peak gradient is greater than 50 mmHg, or a for a gradient less than 50 mm Hg in association with significant mitral or aortic regurgitation [3].
- If surgical resection is not possible, a Konno or Konno-Rastan aortoventriculoplasty may be necessary.

Symptomatic AV Valve Regurgitation or Stenosis

- *Surgical management:* valve repair or replacement is indicated in patients with severe AV valve regurgitation who

are symptomatic, have atrial or ventricular arrhythmia, or have a progressive increase in LV dimensions or deterioration of LV function [3].

- *Medical management:* ACE inhibitors and diuretics may be used for medical management of heart failure symptoms.

Arrhythmia

- Atrial arrhythmia:
  - Atrial fibrillation and flutter are common and should be treated in standard fashion with medical therapy, catheter ablation, and pacemaker therapy as indicated.
  - Maze procedure should be considered in patients with arrhythmia who are undergoing open surgical repair.
  - Persistent hemodynamic abnormalities should be identified, and surgical correction should be considered.
  - Periodic Holter monitoring should be considered to assess for subclinical rhythm abnormalities.
- Complete heart block:
  - Occurs in about 2% of patients with AVSD [7].
  - The AV node and bundle of His are inferiorly displaced in patients with ASVD, and patients are at risk of progressive conduction disease over time. They are at particular risk of injury during and following surgical repair.
  - Periodic Holter monitoring should be considered to assess for subclinical heart block.

Infective Endocarditis Prophylaxis

- Infective endocarditis prophylaxis is indicated in many patients with ASVD. Please see Chap. 35 for further details.

Management of Pregnancy

- Pregnancy is well tolerated in patients without pulmonary hypertension, but right heart volume and pressure overload may progress during pregnancy in unrepaired patients (with the development of symptoms of dyspnea or arrhythmia).
- Women with unrepaired defects may be at increased risk of paradoxical embolism due to thrombophilic state of pregnancy and increased risk of right-to-left shunting due to decrease in systemic vascular resistance starting in the second trimester of pregnancy and during Valsalva in labor.
- Reproductive counseling should be offered to patients and family of patients with Down's syndrome who are at risk of transmitting this genetic defect to offspring.
- Pregnancy is an absolute contraindication in patients with Eisenmenger syndrome due to high risk of maternal mortality [8, 9].

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Chapter 7
Patent Ductus Arteriosus

Jonathan Kochav

Epidemiology

- The reported incidence of patent ductus arteriosus (PDA) is about 1 per 1200–3500 live births [1, 2] or about 10% of all patients with congenital heart disease [1], with a ~2:1 female to male predominance [2].
- See Table 7.1 for historical background.

Anatomic Definition and Pathophysiology

- Embryology:
  - In normal cardiovascular development, the ventral portion of the right and left sixth aortic arch form the right and left pulmonary artery. While the dorsal portion of the right sixth aortic arch involutes, the dorsal portion of the left sixth aortic arch persists as the ductus arteriosus

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Table 7.1 Historical background

Although the existence of the ductus arteriosus was known by the Greek anatomist Galen as early as the second century AD, the ductus arteriosus was first described in modern medicine by Italian anatomist Leonardo Botallo in 1564 and was often referred to as the "Ductus Botalli" [3].
Dr. John Strieder attempted the first ductus ligation at the Massachusetts General Hospital in 1937, however the patient died a few days later. Robert Gross reported the first successful ligation of a patent ductus arteriosus in 1938 [4] at Boston Children's Hospital. Following this revolutionary procedure, Helen Taussig approached Dr. Gross to ask whether he could effectively reconstruct a ductus for her cyanotic patients with tetralogy of Fallot. When he declined, she approached Alfred Blalock, who agreed to perform this operation; thus the Blalock-Taussig-Thomas shunt was developed [3]. Transcatheter methods of closure were first reported by Portsman in 1967 [5], and techniques have since developed to the point where transcatheter closure has become the procedure of choice.

(DA) and connects to the descending thoracic aorta. The aortic connection is typically just distal to the left subclavian artery [6] (Fig. 7.1).

- The DA remains as a fetal vascular connection between the main pulmonary artery and the aorta and functions to divert blood from the fetal pulmonary circulation.
- The DA typically closes within 12 h after delivery in a process highly dependent on circulating prostaglandin levels and arterial oxygen tension. PGE_2 is present at high levels in the fetus due to high levels of production by the placenta and decreased pulmonary clearance. PDE_2 acts as a smooth muscle vasodilator of the DA and maintains its patency through fetal development. After delivery of the fetus, oxygenation of pulmonary blood flow leads to an increase in the arterial oxygen tension, which leads to oxygen-dependent vasoconstriction. Simultaneously, loss of the placenta, and increased blood flow to the lungs, leads to an acute decrease in PGE_2 levels, eliminating the opposing vasodilatory action [6].

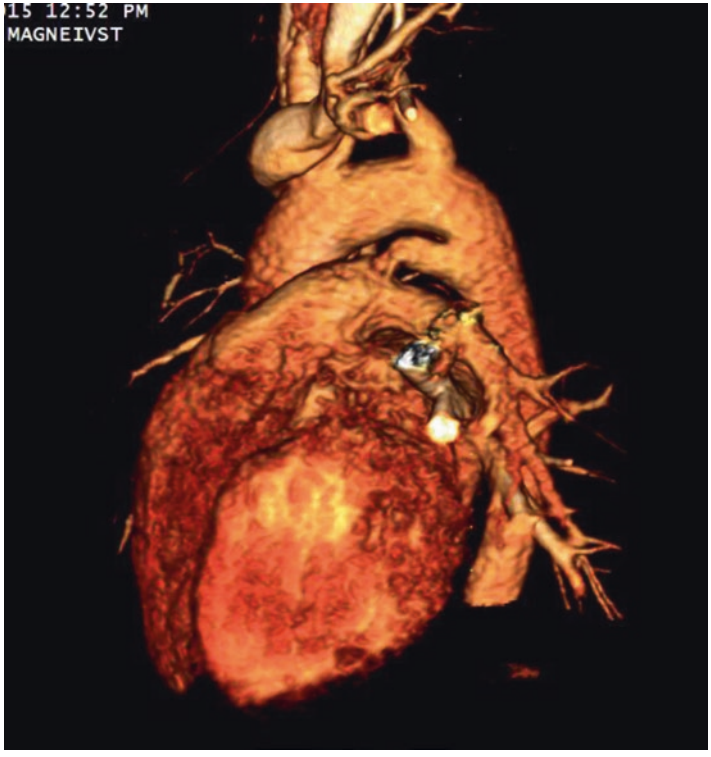

FIGURE 7.1 3-dimensional rendered image of a patent ductus arteriosus by CT angiography. The aortic connection is distal to the left subclavian artery

  - There are clinical factors that contribute to persistent patency of the DA. There is a higher incidence in premature infants [7] and those living at higher altitudes [8], likely related to decreased arterial oxygen tension in these populations. PDAs are more commonly seen among patients with in prenatal infections including the congenital rubella syndrome [9] and prenatal exposure to valproic acid as part of the fetal valproate syndrome [10].

- Anatomy:
  - Variations of anatomy can be described by the Krichenko classification [11] (Fig. 7.2).

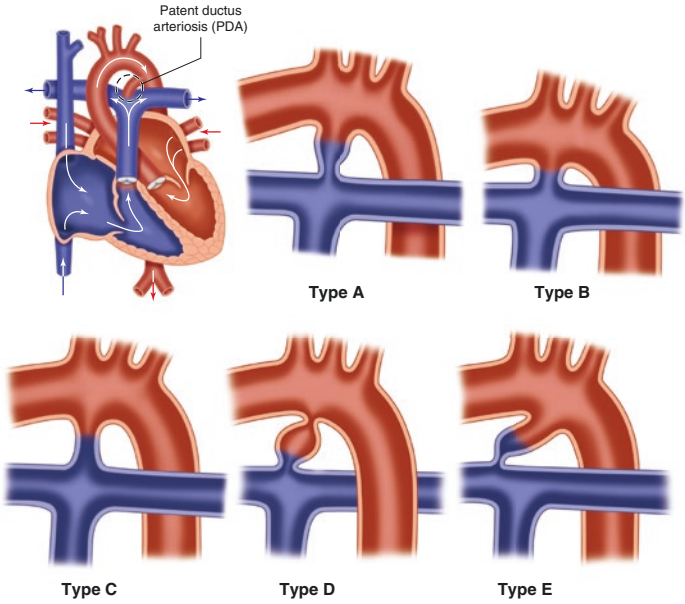

FIGURE 7.2 The Krichenko classification: Type A - well-defined aortic ampulla with constriction at the pulmonary insertion; Type B - short and narrow; Type C - tubular ductus without constriction; Type D - multiple constrictions: Type E - enongated conical appearance with constriction remote from the anterior border of the trachea (when viewed on lateral angiogram)

- Physiology and spectrum of disease:
  - A PDA results in shunting of blood from the aorta to the pulmonary artery. **Small,** hemodynamically restricted defects (defined by Qp:Qs <1.5) will result in high-velocity, low-volume left-to-right shunting that usually does not result in left-sided volume overload.
  - With **moderate**-sized defects (Qp:Qs <1.5–2.2), the left atrium (LA) and left ventricle (LV) will progressively dilate due to increased pulmonary venous return and may hypertrophy to reduce wall stress. The larger the size of the defect, the faster this process will progress. Increased pulmonary blood flow over time results in structural vascular changes that increase pulmonary vascular resistance.

  - Patients with **large** PDAs (Qp:Qs > 2.2) may present with congestive heart failure in infancy. Overtime uncorrected large defects will result in significant right ventricular and pulmonary artery pressure overload, and severe pulmonary hypertension may lead to shunt reversal with right to left flow (Eisenmenger syndrome).

- Associated defects:
  - Often associated with atrial septal defects (ASD), ventricular septal defects (VSD), or additional abnormalities of the aortic arch.
  - Can be seen in many cases of complex congenital heart disease.

- Genetic factors:
  - PDA has been observed at increased frequency among those with well-defined genetic mutations such as single gene mutations (e.g., Holt-Oram syndrome) and chromosomal abnormalities (e.g., trisomy 21 and 4p syndrome) [6].
  - The development of sporadic PDA is likely due to a multifactorial inheritance. Parents with sporadic PDA have an increased likelihood (~8%) of having offspring with congenital heart disease [12], and for each patient with sporadic PDA, there is a 3% likelihood of PDA occurring in a subsequent sibling [6, 13].

Diagnostics

Clinical Presentation in Adults

- Small PDAs
  - Occasionally, asymptomatic patients will be identified later in life based on the characteristic continuous flow murmur or incidentally on cardiac imaging studies performed for another indication.
  - Rarely discovered during a presentation of infective endocarditis.

- Moderate or large PDA
  - Most patients with moderate or large unrestricted PDAs will be diagnosed in infancy or childhood based on cardiac exam or clinical progression of disease, but patients with limited healthcare exposure may present in adulthood.
  - Patients may present with left-sided volume overload and congestive heart failure, often unmasked by the onset of atrial fibrillation or ischemic heart disease.
  - Patients with a large PDA who present to care late may have already progressed to severe pulmonary hypertension and the Eisenmenger syndrome (see Chap. 9).

Physical Exam

1. Murmur
   (a) Soft, continuous, infraclavicular "machinery" murmur that radiates to the left sternal border and left upper back.
      - A continuous flow murmur can be caused by a handful of solitary defects other than PDA:
        - Coronary arteriovenous fistula
        - Aortopulmonary window
        - Pulmonary AV malformation
        - Combined aortic stenosis and regurgitation

   (b) When shunting is still left-to-right, the murmur will augment with isometrics due to increased systemic peripheral resistance and therefore increased shunt through the PDA.
2. Displaced PMI
   (a) May occur in the context of left ventricular volume overload
3. Eisenmenger exam
   (a) See Chap. 9 for further details.
   (b) Importantly because deoxygenated blood enters the aorta distally to the left subclavian artery, cyanosis

and other sequelae of hypo-oxygenation (e.g. clubbing) may affect the lower extremities predominantly.

Electrocardiogram

- Small, restrictive PDA
  - Usually associated with a normal electrocardiogram
- Moderate-sized PDA [14]
  - LA enlargement
  - PR prolongation
  - LV hypertrophy with nonspecific repolarization changes
  - Atrial fibrillation
- Large, uncorrected PDA
  - Signs of RV hypertrophy and right heart strain may be present

Chest Radiography

- Left-sided volume overload
  - LA enlargement
  - LV enlargement
- Pulmonary hypertension
  - Prominent pulmonary artery with increased pulmonary vascular markings.
  - Distal pulmonary vascular pruning may occur late in the progression of pulmonary arterial hypertension.
- Calcification of the PDA may be seen

Echocardiography

- Standard 2D transthoracic echocardiography with color Doppler will generally make the diagnosis of a PDA.

  - Left to right color Doppler flow can be seen in the main PA in parasternal short axis views with focus on the main PA and branches. This generally originates near the origin of the left pulmonary artery
  - In the suprasternal notch views, color flow can also be seen from the proximal descending aorta into the PA
  - The peak PDA jet velocity gives a good indication of aortopulmonary pressure gradient and may decrease with time as the pulmonary pressures increase and approximate systemic pressures. Under these circumstances, the PDA may become more difficult to detect. In these circumstances, contrast echocardiography with injection of agitated saline may demonstrate bubbles in the descending aorta but not the ascending aorta.

- Table 7.2 highlights the essentials of echocardiographic assessment of patients with PDA.

Cardiac Catheterization

- A diagnostic cardiac catheterization may be considered if PDA is suspected and echocardiographic imaging is equivocal due to decreased transductal flow in patients with severe pulmonary hypertension.
- In select cases of patients with pulmonary hypertension, preoperative right heart catheterization with inhaled nitric

Table 7.2 Echocardiographic essentials for assessment [15]

1. Size and shape of the ductal channel
2. Size and direction of shunt
3. Aortopulmonary gradient from peak systolic PDA jet velocity
4. LA and LV chamber size; LV function
5. RV hypertrophy, RV septal flattening, and RV systolic pressure from peak tricuspid regurgitant jet velocity
6. Main PA and branch PA dimensions
7. Aortic arch and isthmus anatomy
8. Device or coil position with specific attention to residual shunt, branch PA stenosis, or aortic protrusion

oxide (iNO) may be useful to assess for reversibility of severe pulmonary hypertension, as this may influence the decision for defect closure. Similarly, assessment of hemodynamics during a temporary test occlusion may assist in the decision-making.

- A coronary evaluation is reasonable in patients with planned operative management who have risk of coronary disease because of age or other risk factors.

Advanced Imaging Techniques

- Cardiac CTA or MRI can be similarly considered if PDA is suspected and echocardiographic imaging is equivocal due to decreased transductal flow in patients with severe pulmonary hypertension.
- Can be useful in defining PDA anatomy prior to intervention (Fig. 7.3).

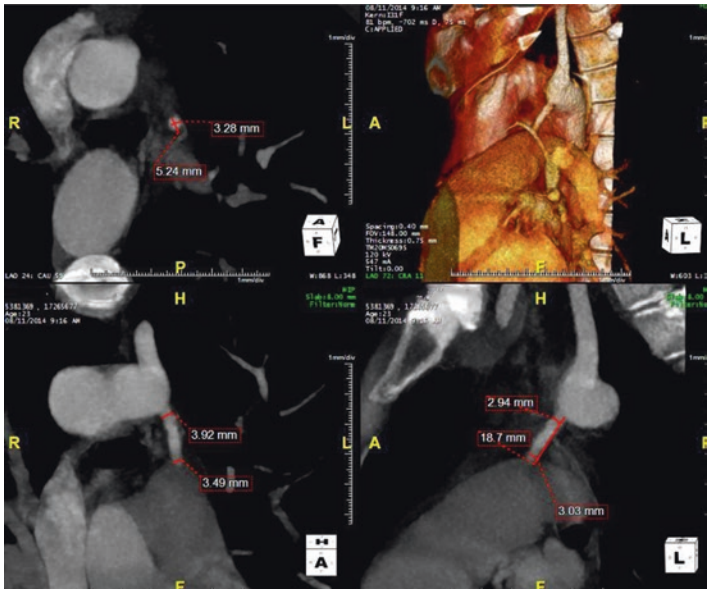

FIGURE 7.3 Cardiac CT can be useful to fully define the anatomy of a patent ductus arteriosus in preparation for surgical or percutaneous closure

Management of Complications in Adult Survivors

See Table 7.3 for summary of guidelines.

Shunt Flow Through an Unrepaired PDA

1. Indications for intervention [16]:
   (a) Left atrial and/or LV enlargement, or if pulmonary hypertension is present in the presence of net left-to-right shunting (Class I)
   (b) History of infective endocarditis (Class I)
   (c) Asymptomatic small PDA only if catheter-based device closure is possible (Class IIa)
2. Contraindications for intervention [16]:
   (a) Patients with pulmonary hypertension with net right-to-left shunt should not undergo PDA closure due to risk of inducing overwhelming right-sided pressure overload (Class III)
3. Options for intervention:
   (a) Transcatheter
      - This is the technique of choice for patients with isolated PDA and appropriate anatomy. The Amplatzer Duct Occluder® is currently the most commonly used device, but coil embolization can be used for smaller PDAs <2–3 mm in size or for small residual leaks following initial attempts at occlusion (Fig. 7.4).
   (b) Surgical
      - Surgical closure is most appropriate when the PDA is too large for percutaneous closure device, when the PDA is aneurysmal, or when there is ongoing endarteritis.

Table 7.3 ACC/AHA guidelines 2008 [12]

Recommendations for evaluation of the unoperated patient:

Class I

1. Definitive diagnosis of PDA should be based on visualization by imaging techniques and demonstrations of the shunting across the defect (with or without evidence of clinically significant LV volume overload) (*level of evidence: C*)

Class III

1. Diagnostic cardiac catheterization is not indicated for uncomplicated PDA with adequate noninvasive imaging (*level of evidence: B*)
2. Maximal exercise testing is not recommended in PDA with significant pulmonary arterial hypertension (*level of evidence: B*)

Recommendations for medical therapy:

Class I

1. Routine follow-up is recommended for patients with a small PDA without evidence of left-sided heart volume overload. Follow-up is recommended every 3–5 years for patients with a small PDA without evidence of left heart volume overload (*level of evidence: C*)

Class III

1. Endocarditis prophylaxis is not recommended for those with a repaired PDA without residual shunt (*level of evidence: C*)

Recommendations for closure of patent ductus arteriosus:

Class I

1. Closure of a PDA either percutaneously or surgically is indicated for the following:
   (a) Left atrial and/or LV enlargement or if pulmonary arterial hypertension is present or in the presence of net left-to-right shunting (*level of evidence: C*)
   (b) Prior endarteritis (*level of evidence: C*)
2. Consultation with ACHD interventional cardiologists is recommended before surgical closure is selected as the method of repair for patients with a calcified PDA (*level of evidence: C*)
3. Surgical repair by a surgeon experienced in CHD surgery is recommended when:
   (a) The PDA is too large for device closure (*level of evidence: C*)
   (b) Distorted ductal anatomy precludes device closure (e.g., aneurysm or endarteritis) (*level of evidence: B*)

Class IIa

1. It is reasonable to close an asymptomatic small PDA by catheter device (*level of evidence: C*)
2. PDA closure is reasonable for patients with pulmonary arterial hypertension with a net left-to-right shunt. (*level of evidence: C*)

Class III

1. PDA closure is not indicated for patients with PAH and net right-to-left shunt (*level of evidence: C*)

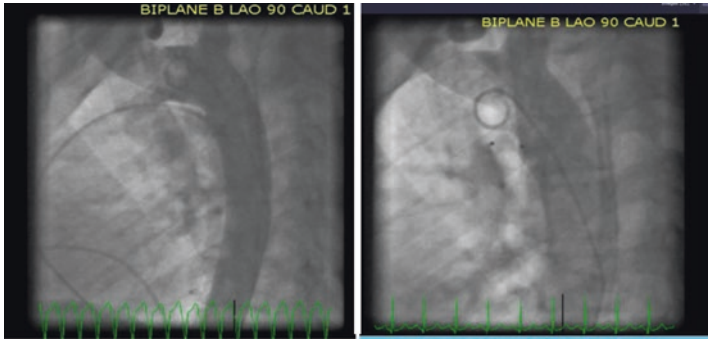

FIGURE 7.4 Closure of a PDA using an Ampltazer Duct Occluder®. Panel A demonstrates a catheter in the main PA crossing through the PDA into the descending aorta. Panel B demonstrates the position of the closure device (Amplatzer ADO I)

- Usually accomplished by simple off-pump surgical ligation of the PDA via thoracotomy
  - Surgical ligation is more challenging in adults than it is in children due to calcification of the PDA, and the development of tissue friability in the area that increases risk of rupture or dissection. In fact, transcutaneous closure of the PDA is sometimes performed *prior* to cardiac surgery performed for other reasons, rather than performing surgical ligation concurrently.
  - Patch closure from inside the aorta or pulmonary artery may be performed in cases where a transcatheter approach is not possible but calcification precludes ligation.
  - Surgical ligation may be complicated by injury to the nearby recurrent laryngeal nerve and result in vocal cord paralysis.

Infective Endocarditis

- As the risk of endocarditis appears to correlate with size of PDA, with small lesions being at lower risk, there is little

evidence to support closure of a small PDA for the sole purpose of preventing infective endocarditis [17].

- Antibiotic prophylaxis is not recommended for uncorrected PDA but is recommended for 6 months after surgical or transcatheter PDA closure or indefinitely for those with residual shunt [16].
- Please refer to Chap. 36 for discussion regarding infective endocarditis prophylaxis.

Management of Pregnancy

- Pregnancy is an absolute contraindication in patients with Eisenmenger syndrome due to high risk of maternal mortality [18, 19].
- Pregnancy is well tolerated in patients without pulmonary hypertension (WHO pregnancy risk category I) [20].
- Left heart volume overload may progress during pregnancy in unrepaired patients (with the development of symptoms of dyspnea or arrhythmia). Monitoring for signs and symptoms of left heart failure in the third trimester and peri-partum is important.

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Chapter 8
Miscellaneous Shunts

Jonathan Kochav

In addition to atrial level defects, ventricular septal defects, atrioventricular septal defects, and persistent patent ductus arteriosus, there exist several other congenital left-to-right shunts that are rare enough not to warrant their own chapter or set of guidelines, but still deserve mention.

Sinus of Valsalva Fistula (To Right Atrium or Right Ventricle)

Anatomy and Physiology

1. The sinus of Valsalva fistula (SVF) occurs as a result of spontaneous rupture of a sinus of Valsalva aneurysm (SVA) [1].
   (a) SVA:
      - Rare congenital disorder with an incidence between 0.14% and 0.96% of all patients undergoing open-

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heart surgical procedures [2], with higher prevalence in the East Asian population [3].

- The majority of SVAs originate from the right sinus of Valsalva (80%):
  - SVAs originating from the noncoronary sinus are less common (20%).
  - Those arising from the left sinus are exceedingly rare [4].
- The etiology of the congenital SVA is a defect of the elastic lamellae of the media:
  - Commonly associated with connective tissue abnormality, such as Marfan syndrome.
  - Non-congenital SVA is often attributed to trauma or mycotic aneurysm secondary to infection.
- Prior to rupture a SVA is usually asymptomatic
- Associated with:
  - Supracristal or perimembranous ventricular septal defects (30–60% of patients)
  - Aortic valve abnormalities, such as bicuspid aortic valve [3, 5].

(b) Rupture and formation of SVF:

- Rupture usually occurs spontaneously.
- Occasionally precipitated by strenuous isometric exertion or trauma.
- Fistulization may occasionally establish a communication with the right atrium but more commonly will cause shunting from the aortic sinus to the right ventricle [1].

Diagnosis

- Presentation:
  - Patients may present acutely with chest pain or heart failure or subacutely with progressive dyspnea.
  - Patients with small defects may be asymptomatic with a murmur noted on exam.
- Physical exam:
  - New onset prominent continuous murmur throughout both systole and diastole, similar to that heard in patent ductus arteriosus.
- Imaging:
  - Cardiac MRI and CT are the more sensitive modalities for identifying sinus of Valsalva aneurysm.
  - Transthoracic echocardiography with color Doppler is the technique of choice for identifying a ruptured SVA with SVF.

Management

- In the acute setting, medical management with inotropes and afterload reduction may be required in order to augment cardiac output.
- Urgent surgical repair is usually warranted in a large-volume fistula and may require aortic root reconstruction or replacement.
- Asymptomatic patients with a small volume fistula may be corrected on an elective basis.
- Transcatheter closure has been successfully performed in selected patients who are unable to tolerate open cardiac surgery [6].

Gerbode Defect (Left Ventricle to Right Atrium Defect)

Anatomy and Physiology

- A congenital Gerbode defect is caused by a membranous ventricular septal defect (VSD).
- The deficiency occurs in the space where the membranous septum separates the left ventricle from the right atrium (Fig. 8.1).

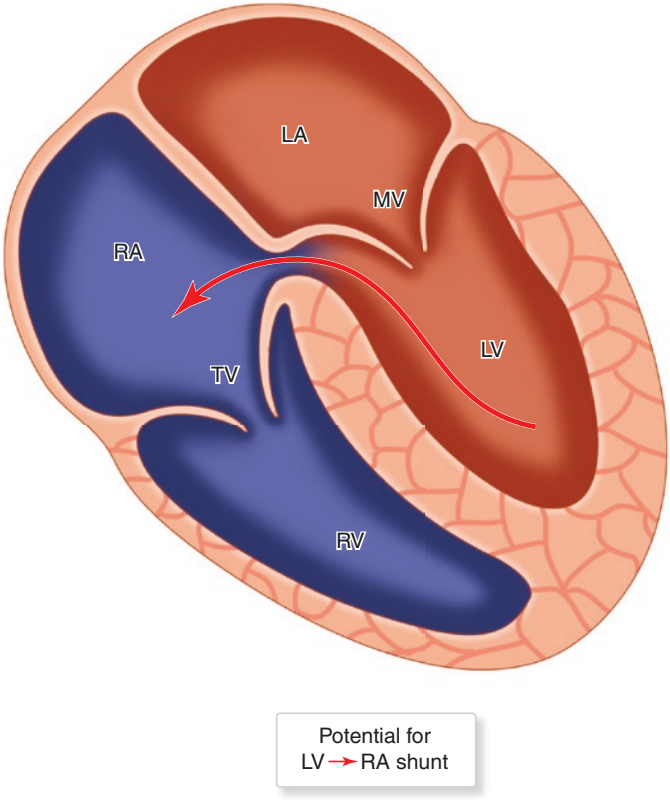

FIGURE 8.1 Gerbode defect

  - This space exists as a result of the relative apical displacement of the tricuspid valve as compared to the mitral valve.

- The Gerbode defect is most frequently acquired (~75% of patients) often in the setting of infective endocarditis or iatrogenically after aortic valve replacement. Only 25% of cases are congenital [7].

Diagnosis

- Presentation:
  - Presentation in adults is dependent on the size of the lesion.

    Patients with small lesions may be identified incidentally.
    Those with large defects can present with congestive heart failure and right heart volume overload.

- Physical exam:
  - Holosystolic murmur, quiet in diastole due to relative equilibration of left ventricular and right atrial pressures.

- Imaging:
  - Transthoracic echocardiogram will show:

    A high velocity systolic flow from the left ventricle to the right atrium with a very high Doppler gradient.
    This is commonly confused for a very high-velocity tricuspid regurgitation jet, but occurs without other clinical or echocardiographic evidence for pulmonary hypertension.
    Right atrial enlargement is often present.
  - Transesophageal echocardiogram or cardiac MRI can be used to visualize the shunt, which can be very difficult to image directly by transthoracic echocardiogram.

Management

- Surgical closure is reasonable in patients who have not developed significant pulmonary hypertension [8].
- Although percutaneous closure has been reported in patients who are high risk for surgery, [9] this is not standard of care due to the risk of disrupting atrioventricular valve competency or inducing complete atrioventricular block [10].

Aortopulmonary Window

Anatomy and Physiology

- An aortopulmonary window is caused by the failure of complete fusion of the conotruncal ridges responsible for separating the truncus arteriosus into the aorta and pulmonary artery (Fig. 8.2).
- While the defect can be small and restrictive, the majority of lesions are quite large with hemodynamic abnormalities similar to those seen in a large PDA or unrestrictive VSD [11].

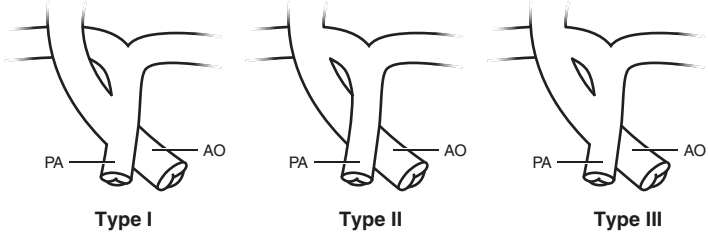

Figure 8.2 Aortopulmonary window. Schematic drawing of the anatomical types of aortopulmonary window Type I—proximal defect; Type II—distal defect; Type III—complete defect (I+II) (Adapted from Mori K et al. [13])

- Associated with additional lesions in 47–77% of cases, most commonly coarctation of the aorta or an interrupted arch, both of which exacerbate left-to-right shunting [12].

Diagnosis

- Presentation:
  - Presentation with unrepaired defect in adulthood is rare.
  - The majority of unrepaired patients will progress to Eisenmenger syndrome within the first year of life if uncorrected.
- Physical exam:
  - In uncorrected patients the exam reveals:

    A systolic murmur, which may diminish over time as pulmonary pressures rise and approximate systemic pressures

    Unlike in patients with a patent ductus arteriosus, a diastolic murmur is rare due to relative equilibration of aortic and pulmonary arterial pressures

Management

- Surgical repair should be considered in any patient without significant pulmonary hypertension (see Chap. 9 for more information on the decision to perform shunt closure in patients with pulmonary hypertension and/or Eisenmenger syndrome).
- Adults who have previously undergone repair require echocardiographic monitoring to screen for progressive aortic dilation and the development of pulmonary artery or branch pulmonary artery stenosis [11].

Coronary AV Fistula to Right Atrium

- Please refer to Chap. 31 for more information on the presentation, diagnosis, and management of patients with congenital coronary anomalies.

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Chapter 9
Pulmonary Hypertension and Eisenmenger Physiology

Jonathan Kochav

Epidemiology

- It is estimated that 10% of patients with repaired and up to 30% of patients with unrepaired congenital heart disease (CHD) with left-to-right shunting also have pulmonary arterial hypertension (CHD-PAH) [1]. The frequency and rate of progression to Eisenmenger syndrome (ES) depend on the degree of volume and pressure shunting across the lesion.
- For historical background, see Table 9.1.

Anatomy and Physiology

1. CHD-PAH may occur for several reasons. This chapter will focus on the first two etiologies [4, 5]:

   (a) Left-to-right shunts:

   - Correctable: Dynamic pulmonary hypertension occurs as a result of high left-to-right shunt flow and, in its early stages, will reverse with surgical reduction of the shunt.

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Table 9.1 Historical background

In 1897, the Viennese physician Victor Eisenmenger, while working as personal physician to the Archduke Franz Ferdinand, published a report on a patient with a ventricular septal defect and cyanosis [2]. However, it was London cardiologist Paul Wood who in the 1950s recognized that the clinical syndrome could present with various lesions including atrial septal defect, atrioventricular septal defect, patent ductus arteriosus, persistent truncus arteriosus, and aortopulmonary window [3]. He proposed that the term "Eisenmenger syndrome" be used to define the syndrome of pulmonary hypertension due to a high pulmonary vascular resistance with reversed or bidirectional shunt at the aortopulmonary, ventricular, or atrial level.

- Non-correctable: If left uncorrected, high shunt flow can lead to irreversible vascular remodeling and progressive pulmonary hypertension.

(b) Eisenmenger syndrome:

- If left-to-right shunts are left uncorrected and vascular remodeling is allowed to progress, pulmonary pressures may eventually exceed systemic pressures and lead to shunt reversal. Closure of the defect is contraindicated.

(c) PAH with coincidental CHD:

- Defined by a marked elevation in pulmonary vascular resistance (PVR) in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH, and patients do nearly as poorly [6].

(d) Postoperative PAH:

- Pulmonary hypertension can acutely worsen immediately following cardiac surgery due to pulmonary vascular reactivity caused by an endothelial inflammatory reaction.

- Pulmonary hypertension may develop months/years after surgery likely due to shunt repair that occurs too late into the pulmonary vascular remodeling phase.

(e) Secondary to lesions that cause pulmonary venous hypertension:

- Pulmonary vein stenosis and pulmonary veno-occlusive disease
- Left-sided obstructive disease: atrioventricular valve stenosis or atresia, aortic stenosis, and coarctation of the aorta
- Left-sided systolic or diastolic dysfunction

2. Associated anatomic lesions:

(a) Unrepaired, medium-to-large simple shunts such as those caused by atrial septal defects (ASD), ventricular septal defects (VSD), atrioventricular septal defects (AVSD), and patent ductus arteriosus (PDA) account for the majority of cases of CHD-PAH [4]. However, complex lesions with ventricular or arterial level shunting may also result in the development of PAH if not corrected early.

3. Pathophysiology:

(a) The rate of progression and natural course of CHD-PAH is dependent on both the location and size of the anatomic defect:

- Patients with post-tricuspid ventricular (e.g., VSD, AVSD) or arterial shunts (e.g., PDA, truncus arteriosus) are at higher risk of progressing to ES than patients with similarly sized pre-tricuspid, lower-pressure, lower-volume shunts, such as ASD:

  – Patients with VSD are more than twice as likely to develop ES as are those with an ASD [7].

  – ES in pre-tricuspid shunts presents later in life compared to post-tricuspid shunts, but patients with pre-tricuspid lesions tend to have lower

exercise tolerance, more advanced right ventricular (RV) dilation and systolic/diastolic dysfunction, and increased mortality once ES is diagnosed [8, 9]. One potential explanation for this is that the post-tricuspid right-to-left shunt allows for RV offloading during systole, whereas a pre-tricuspid shunt does not.

- In patients with large central shunts, ES can occur as early as the first year or first decade of life. In uncorrected medium or large ASDs, ES appears later in life (symptoms may be first recognized during pregnancy).

(b) The mechanisms underlying the development of CHD-PAH are incompletely elucidated. It is thought that endothelial shear stress and circumferential stretch lead to local release of inflammatory mediators and subsequent structural changes including smooth muscle cell proliferation, increase in extracellular matrix, and capillary and arteriolar occlusion, all of which act to increase the pulmonary vascular resistance (PVR) [10]:

- Pulmonary vascular histology resembles that described in idiopathic pulmonary arterial hypertension with medial thickening and plexiform lesions in severe cases [4, 11].

Diagnostics

Clinical Presentation in Adults

- Adults presenting with progressive CHD-PAH and ES will typically have a history of normal childhood, but will gradually become more cyanotic during their second or third decade with a subsequent progressive decline in physical abilities, followed by the development of congestive heart failure in the fifth decade.

- Rarely, they may present initially with hemoptysis, syncope, arrhythmia, or sudden cardiac death.

Physical Exam

- Pulmonary hypertension and RV failure:
  - RV heave, loud P2, and right-sided S4.
  - Holosystolic murmur associated with functional tricuspid regurgitation secondary to RV dilation.
    - Diastolic decrescendo murmur secondary to pulmonary regurgitation.
    - Peripheral edema and hepatomegaly may occur when RV failure develops.
    - Jugular venous pressure may or may not be elevated due to increased compliance of the right atrium (RA).
- Primary lesion:
    - The shunt murmur related to the original anatomic defect becomes progressively quieter as pulmonary and systemic pressures approximate.
- Reversal of shunt flow in Eisenmenger syndrome:
    - Central cyanosis
    - Clubbing of nail beds of the fingers and toes (Fig. 9.1)

Electrocardiogram (Fig. 9.2)

- RV hypertrophy with right axis deviation
- P-pulmonale
- May show abnormalities related to the underlying cardiac defect

Chest Radiography

- Will often show a large main pulmonary artery (PA) with rapid tapering ("peripheral pruning") (Fig. 9.3).

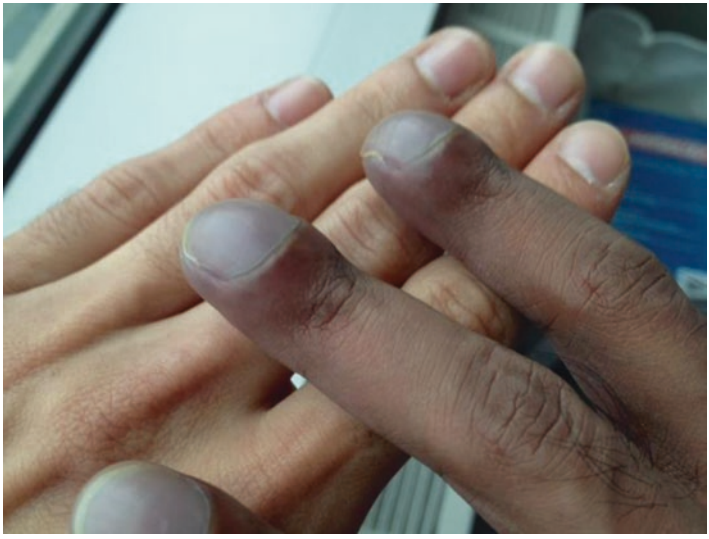

FIGURE 9.1 Clubbing of fingers (right) associated with the Eisenmenger syndrome compared to normal patient (left)

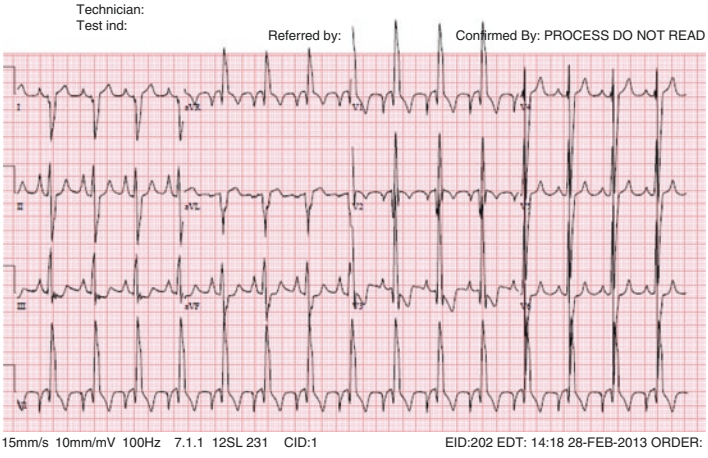

FIGURE 9.2 Typical electrocardiogram of a patient with Eisenmenger syndrome with marked right ventricular hypertrophy and atrial enlargement

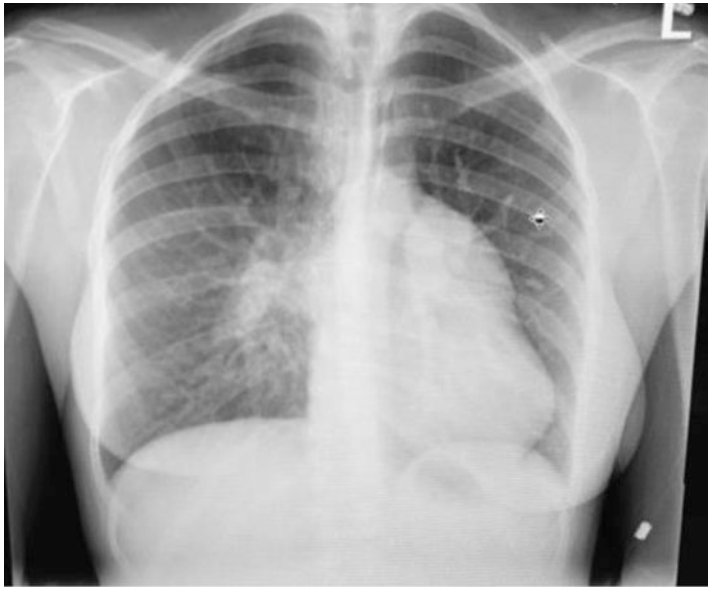

FIGURE 9.3 Typical chest radiograph of a patient with uncorrected double outlet right ventricle and Eisenmenger syndrome with marked prominence of the pulmonary arteries

- Calcification of the PA may be seen in advanced cases.
- Patients with pre-tricuspid lesions will usually have advanced RA and RV dilation, while those with post-tricuspid lesions may have normal or only modestly enlarged cardiothoracic ratio.

Echocardiography

- Transthoracic echocardiography is the first-line imaging modality for patients presenting with suspected CHD-PAH and/or ES and is used to identify the underlying lesion if unknown, assess biventricular function and chamber size, and estimate pulmonary arterial pressures by measuring the tricuspid regurgitant Doppler jet velocity.

Cardiac Catheterization

- Right heart catheterization (RHC) should be performed at least once, with potential for vasodilator testing or anatomic intervention.
- Pulmonary hypertension is confirmed by a mean pulmonary artery pressure greater than 25 mmHg and a PVR greater than 3 Woods units (WU).
- Pulmonary vasoreactivity can be assessed during RHC by the use of 100% oxygen to determine whether PVR is oxygen responsive, or the administration of chemical vasodilators such as inhaled nitric oxide (iNO), prostacyclin, or adenosine. These maneuvers help to identify patients who may still benefit from surgical repair, and prognosticate the potential benefit from advanced therapies [12].

Advanced Imaging Techniques

- If an underlying lesion is suspected but not identified on echocardiography, cardiac MRI or cardiac CT should be performed to fully define the anatomy.
- CT angiography can also be useful for the evaluation of the pulmonary arterial anatomy, assessment for potential contribution of pulmonary arterial thrombus, and for a global assessment of pulmonary parenchyma.

Exercise Testing

- A 6-minute walk test (6MWT) or a nonmaximal cardiopulmonary exercise test is reasonable to perform as part of the functional assessment of patients with CAD-PAH [4]. Maximal cardiopulmonary exercise tests are of limited utility in patients who have progressed to ES, since peak oxygen consumption may be limited by right-to-left shunting and arterial hypoxemia rather than failure of cardiopulmonary mechanics [13].

- The 6-minute walk test is a common end point used in trials of advanced therapy and can be used to follow response to therapy.

Pulmonary Hypertension Workup

- Alternate etiologies of pulmonary hypertension should be pursued as the congenital lesion, particularly if small or pretricuspid, may be coincidental:
  - Consider sending for HIV and/or rheumatologic serologies (e.g., lupus, scleroderma).
  - Consider performing pulmonary evaluation with pulmonary function tests with volumes and diffusion capacity, high-resolution CT scan, and polysomnography.
  - Consider performing nuclear lung scintigraphy to rule out chronic thromboembolic pulmonary hypertension.

Management of Complications in Adult Survivors

See Table 9.2 for summary of guidelines.

Pulmonary Arterial Hypertension, Right Heart Failure, and the Eisenmenger Syndrome

1. Morbidity:
   (a) Compared to patients with idiopathic PAH, adults with ES have significantly improved cardiac indices, lower right atrial pressures, and improved survival, despite a trend toward greater pulmonary artery pressures [14]:

Table 9.2 ACC/AHA guidelines 2008 [4]

Recommendations for evaluation of the patient with congenital heart disease-pulmonary arterial hypertension

Class I

1. Care of adult patients with CHD-related PAH should be performed in centers that have shared expertise and training in both ACHD and PAH (*Level of Evidence: C*)
2. The evaluation of all ACHD patients with suspected PAH should include noninvasive assessment of cardiovascular anatomy and potential shunting, as detailed below:
   (a) Pulse oximetry, with and without administration of supplemental oxygen, as appropriate (*Level of Evidence: C*)
   (b) Chest X-ray (*Level of Evidence: C*)
   (c) Diagnostic cardiovascular imaging via transthoracic echocardiography, transesophageal echocardiography, MRI, or CT as appropriate (*Level of Evidence: C*)
   (d) Complete blood count and nuclear lung scintigraphy (*Level of Evidence: C*)
3. If PAH is identified but its causes are not fully recognized, additional testing should include the following:
   (a) Pulmonary function tests with volumes and diffusion capacity (diffusing capacity of the lung for carbon monoxide) (*Level of Evidence: C*)
   (b) Pulmonary embolism protocol CT with parenchymal lung windows (*Level of Evidence: C*)

Recommendations for reproduction

Class I

1. Women with severe CHD-PAH, especially those with Eisenmenger physiology, and their partners should be counseled about the absolute avoidance of pregnancy in view of the high risk of maternal death, and they should be educated regarding safe and appropriate methods of contraception (*Level of Evidence: B*)
2. Women with CHD-PAH who become pregnant should:
   (a) Receive individualized counseling from cardiovascular and obstetric caregivers collaborating in care and with expertise in management of CHD-PAH (*Level of Evidence: C*)
   (b) Undergo the earliest possible pregnancy termination after such counseling (*Level of Evidence: C*)

(c) Additional testing as appropriate to rule out contributing causes of PAH (*Level of Evidence: C*)
(d) Cardiac catheterization at least once, with potential for vasodilator testing or anatomic intervention, at a center with expertise in catheterization, PAH, and management of CHD-PAH (*Level of Evidence: C*)

Class IIa

1. It is reasonable to include a 6-minute walk test or similar nonmaximal cardiopulmonary exercise test as part of the functional assessment of patients with CAD-PAH (*Level of Evidence: C*)

Recommendations for medical therapy of Eisenmenger physiology

Class I

1. It is recommended that patients with Eisenmenger syndrome avoid the following activities or exposures, which carry increased risks:
   (a) Pregnancy (*Level of Evidence: B*)
   (b) Dehydration (*Level of Evidence: C*)
   (c) Moderate and severe strenuous exercise, particularly isometric exercise (*Level of Evidence: C*)
   (d) Acute exposure to excessive heat (e.g., hot tub or sauna) (*Level of Evidence: C*)
   (c) Surgical sterilization carries some operative risk for women with CHD-PAH but is a safer option than pregnancy. In view of advances in minimally invasive techniques, the risks and benefits of sterilization modalities should be discussed with an obstetrician experienced in management of high-risk patients, as well as with a cardiac anesthesiologist (*Level of Evidence: C*)

Class IIb

1. Pregnancy termination in the last two trimesters of pregnancy poses a high risk to the mother. It may be reasonable, however, after the risks of termination are balanced against the risks of continuation of the pregnancy (*Level of Evidence: C*)

(continued)

TABLE 9.2 (continued)

Recommendations for evaluation of the patient with congenital heart disease-pulmonary arterial hypertension

(e) Chronic high-altitude exposure, because this causes further reduction in oxygen saturation and increased risk of altitude-related cardiopulmonary complications (particularly at an elevation greater than 5000 ft above sea level) (*Level of Evidence: C*)

(f) Iron deficiency (*Level of Evidence: B*)

2. Patients with Eisenmenger syndrome should seek prompt therapy for arrhythmias and infections (*Level of Evidence: C*)
3. Patients with Eisenmenger syndrome should have hemoglobin, platelet count, iron stores, creatinine, and uric acid assessed at least yearly (*Level of Evidence: C*)
4. Patients with Eisenmenger syndrome should have assessment of digital oximetry, both with and without supplemental oxygen therapy, at least yearly. The presence of oxygen-responsive hypoxemia should be investigated further (*Level of Evidence: C*)
5. Exclusion of air bubbles in intravenous tubing is recommended as essential during treatment of adults with Eisenmenger syndrome (*Level of Evidence: C*)

Recommendations for reproduction

Class III

1. Pregnancy in women with CHD-PAH, especially those with Eisenmenger physiology, is not recommended and should be absolutely avoided in view of the high risk of maternal mortality (*Level of Evidence: B*)
2. The use of single-barrier contraception alone in women with CHD-PAH is not recommended owing to the frequency of failure (*Level of Evidence: C*)
3. Estrogen-containing contraceptives should be avoided (*Level of Evidence: C*)

Recommendations for follow-up

Class I

1. Patients with CHD-related PAH should:
   (a) Have coordinated care under the supervision of a trained CHD and PAH provider and be seen by such individuals at least yearly (*Level of Evidence: C*)

6. Patients with Eisenmenger syndrome should undergo noncardiac surgery and cardiac catheterization only in centers with expertise in the care of such patients. In emergent or urgent situations in which transportation is not feasible, consultation with designated caregivers in centers with expertise in the care of patients with Eisenmenger syndrome should be performed and sustained throughout care (*Level of Evidence: C*)

Class IIa

1. All medications given to patients with Eisenmenger physiology should undergo rigorous review for the potential to change systemic blood pressure, loading conditions, intravascular shunting, and renal or hepatic flow or function. (*Level of Evidence: C*)
2. Pulmonary vasodilator therapy can be beneficial for patients with Eisenmenger physiology because of the potential for improved quality of life (*Level of Evidence: C*)
   (b) Have yearly comprehensive evaluation of functional capacity and assessment of secondary complications (*Level of Evidence: C*)
   (c) Discuss all medication changes or planned interventions with their CHD-related PAH caregiver (*Level of Evidence: C*)

Class III

1. Endocardial pacing is not recommended in patients with CHD-PAH with persistent intravascular shunting, and alternative access for pacing leads should be sought (the risks should be individualized) (*Level of Evidence: B*)

- Potential explanations for this include superior RV compensation due to a PVR that rises slowly over time starting in infancy, and the physiologic benefit of the right-to-left shunt acting as a pop-off pressure valve for the RV, allowing left ventricular cardiac output to be sustained as pulmonary flow becomes increasingly limited at the expense of cyanosis.

(b) Characteristics associated with increased mortality include younger age at presentation (which is associated with complex anatomy), functional class, and the development of supraventricular arrhythmia [15].

2. Surgical or catheter-based therapy:

(a) Surgical or catheter-based shunt closure can be considered in cases where pulmonary hypertension is thought to be dynamic and reversible, although this exact threshold is not entirely clear:

- The 2015 European Society of Cardiology [16] and the 2013 Fifth World Symposium on Pulmonary Hypertension [5] guidelines recommend repair when PVR <2.3 WU or PVRi (PVR indexed to body surface area) <4 WU/m^2, no repair when PVR >4.6 WU or PVRi >8 WU/m^2, and individualized decision-making when PVR 2.3–4.6 WU or PVRi 4–8 WU/m^2:
  - The treatment decision is particularly challenging for patients with moderately elevated PVR (2.3–4.6 WU or 4–8 WU/m^2) because outcomes are extremely poor among those who do not have improvement in PVR post-closure (i.e., PAH after defect correction), perhaps worse than if they had never been corrected [6, 17].
  - A PVR to systemic vascular resistance (SVR) ratio of >2/3 is often used as an additional criterion for surgical inoperability [4].
  - Cardiac catheterization with assessment of hemodynamics during a temporary test

occlusion of the shunt may assist in the decision-making.
  - Importantly, the use of medical therapy to achieve PVR criteria for defect correction is not currently recommended, though this strategy has been successfully utilized [18, 19].

- Given the paucity of data in this controversial area, thresholds may vary by institution, or depending on the associated lesion.

(b) Shunt closure is contraindicated for those who have progressed to ES and for whom the only surgical option is a heart-lung transplant:

- Survival for ES patients posttransplant is similar to those who undergo cardiac transplant for other reasons [20].
- However, patients with ES who are listed for transplant generally survive longer than do patients with idiopathic PAH while awaiting transplant (77% vs. 35% 3 year survival) [14]. This makes optimal timing of the decision to proceed with transplant quite challenging.

3. Medical therapy:

(a) Pulmonary arterial vasodilators:

- Contraindicated in patients with pulmonary hypertension due to left heart disease and significant pulmonary venous hypertension:
  - Worsening pulmonary vascular congestion and hypoxia may occur, as the left heart is unable to accommodate increased pulmonary venous return.
  - In cases where the degree of contribution of left heart failure to CHD-PAH is unclear, right heart catheterization with vasodilator testing may be helpful. Significant increases in pulmonary capillary wedge pressure with pulmonary

vasodilators suggest that these medications should probably be avoided.

- Among ES patients, pulmonary arterial vasodilators significantly improve survival [21] (Fig. 9.4).
- Among patients with positive vasodilatory testing, agents to consider include:
  - Phosphodiesterase-5 (PDE-5) inhibitors:

    Sildenafil [22, 23] and tadalafil [24, 25]:

    The use of PDE-5 inhibitors has been shown to decrease PVR both acutely and long-term, with associated improvement in 6MWT and functional class.
    Nonrandomized retrospective data has suggested improvement mortality compared to conventional therapy.
  - Oral endothelin antagonists:

    Bosentan [26, 27] and ambrisentan [28]:
    Endothelin antagonists have been shown to reduce PVR, improve resting and exercise oxygen saturation, and improve both exercise capacity by 6MWT and functional class.
  - Guanylate cyclase inhibitor:

    Riociguat improved 6MWT, PVR, functional class, and time to clinical worsening among patients with persistent PAH after correction of CHD [29].
  - Prostacyclin inhibitors:

    Selexipag is an oral prostacyclin inhibitor that has been approved for patients who have ongoing PAH following CHD repair, but has not been extensively studied in other CHD-PAH contexts [30].
    Inhaled (treprostinil or iloprost) [31] or subcutaneous (treprostinil) prostacyclin inhibitors may be used, but are generally not first line given challenges of administration.

IV epoprostenol or treprostinil may be used in patients with WHO class IV symptoms [32] but is otherwise not first line in ES with uncorrected shunt lesions due to the prohibitive risks of thrombus, paradoxical embolism, and infection with central lines. May be considered among patients with PAH and repaired lesions (and no residual right-to-left shunt).

– Calcium channel blockers:

A reasonable option for patients with CHD-PAH and positive vasodilator testing

Contraindicated in patients with ES due to risk of decreased SVR more than PVR, thus worsening right-to-left shunting

– Combination therapy (generally with endothelin receptor antagonists and PDE-5 inhibitors):

Recommended when treatment goals are not met [33, 34]

(b) Oral anticoagulants:

- The use of oral anticoagulants in ES is controversial:
  - Pulmonary arterial thrombus is often seen and is associated with worse disease [35], but at the same time, patients are at higher risk of hemoptysis.
- In the absence of reliable data, oral anticoagulant therapy may be considered in patients with severe disease and no prior episodes of hemoptysis, but is generally reserved for patients with true indications.

(c) General recommendations [4]:

- Significant volume shifts (dehydration, or volume overload) should be avoided.
- The initiation of any medications that can affect hemodynamics should be done carefully and with very close monitoring.

- Unnecessary procedures, surgery, or anesthesia should be avoided in patients with ES, and if a procedure with anesthesia is necessary, cardiac anesthesia should be involved.
- Strenuous activity, in particular isometric exercise, should be avoided in patients with severe PAH.
- Excessive heat (i.e., sauna, hot tub) should be avoided due to risks associated with dehydration and systemic vasodilation which can worsen right-to-left shunt flow.
- Prompt workup and treatment for infection is essential, as patients may not have the cardiac reserve to support a septic physiology, and systemic vasodilation will worsen right-to-left shunt flow.

Hypoxemia

- Can be seen in ES due to right-to-left shunting.
- Oxygen responsiveness should be tested and treated, particularly if catheterization demonstrates oxygen-responsive decrement in PVR. Notably, oxygen therapy has not been shown to modify survival in this population [36].
- Intubation should be avoided for temporary hypoxemia that may occur in the setting of anesthesia.

Erythrocytosis

- Erythrocytosis is an appropriate physiologic response to chronic hypoxemia, resulting in increased oxygen carrying capacity.
- Hyperviscosity syndrome may contribute to the increased risk of neurovascular events.
- Common masqueraders of hyperviscosity include hypovolemia, endocarditis, brain abscess, depression, hypothyroidism, and gout/hyperuricemia.
- Phlebotomy should not be performed routinely. Should be performed only when neurologic symptoms are attributed

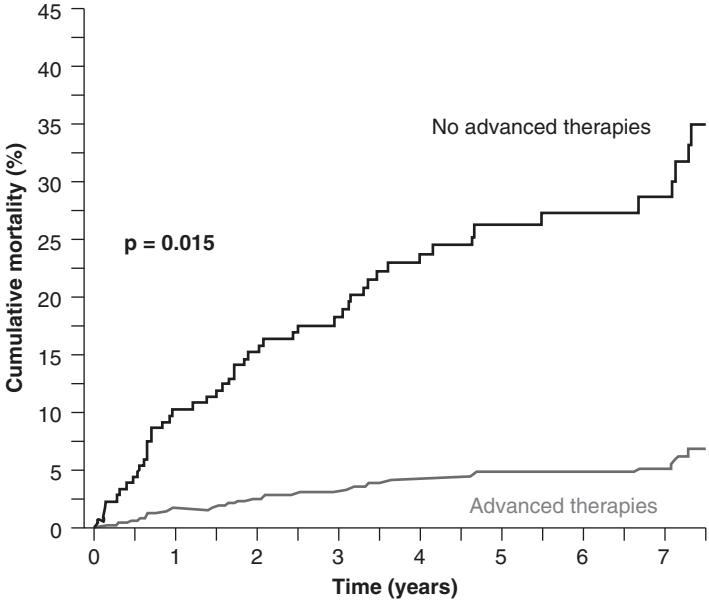

FIGURE 9.4 Survival rate curves, adjusted by propensity scoring, of patients with and without advanced therapy. Retrospective study of patients with Eisenmenger physiology under active follow-up at Royal Brompton Hospital in London. Patients on advanced therapies (i.e., pulmonary vasodilators) were at a significantly lower risk of death (hazard ratio, 0.16; 95% confidence interval 0.04–0.71; *p*, 0.015) [21]

to hyperviscosity, volume depletion has been excluded, and hemoglobin is >20 g/dL or hematocrit is >65%.

- Iron deficiency worsens intravascular sludging and increases risk of stroke [37].
  - Iron stores should be checked yearly and deficiencies repleted.

Paradoxical Emboli

- Risk can be reduced by filtering of intravenous tubing to exclude bubbles that could potentially embolize systemically.

- Avoidance of central lines and endocardial pacer leads is encouraged to reduce risk of venous thromboembolism and paradoxical stroke.
- Right-to-left shunting also allows bacteria in venous blood to bypass the lungs and deposit systemically, resulting in an increased risk of cerebral abscess [15].

Hemoptysis

- Hemoptysis occurs frequently in patients with ES, but is only rarely the cause of death (3–15% of contemporary cases, up to 29% in index case series) [3, 15], and otherwise does not seem to modify survival [38]. It may occur due to rupture of the pulmonary arteries, rupture of aortopulmonary collaterals, or due to pulmonary infarct from pulmonary artery thrombosis.

Arrhythmia or Sudden Death

- Patients are at increased risk of both atrial and ventricular tachyarrhythmias.
- Arrhythmia may be very destabilizing and requires immediate attention.
- Endocardial pacing is not recommended in patients with intravascular shunting due to risk of paradoxical emboli and infection.
- Significant isometric effort can cause sudden hemodynamic collapse and sudden death.

Hyperuricemia

- Increased uric acid levels are common in patients with cyanotic CHD and are thought to be due to both increased production and decreased renal clearance.
- Serum uric acid increases in proportion to hemodynamic severity in adults with ES [39] and is associated with long-term mortality.

- Uric acid levels should be assessed annually, and treatment of hyperuricemia should be initiated in patients who develop gout.
- Complications can include urate nephropathy, gallstones, cholecystitis, and renal dysfunction.

Pregnancy

- Pregnancy is high risk in individuals with pulmonary hypertension and is absolutely contraindicated in patients with ES, where maternal mortality rates approach 30–50% [40]. Mechanisms that contribute to poor clinical outcomes include the following [41]:
  - Pulmonary vascular disease prevents the fall in PVR normally associated with pregnancy, leading to a further rise in pulmonary artery pressure when cardiac output increases.
  - The RV is unable to augment output to accommodate the plasma volume increase associated with pregnancy.
  - The decrease in the SVR of pregnancy, particularly midsecond trimester, augments right-to-left shunting (increasing the risk of paradoxical embolic event), worsening hypoxia and cyanosis.
  - During labor and delivery, the risk of cardiovascular collapse increases as a result of hemodynamic perturbations, including volume shifts caused by blood loss and uterine contractions, withdrawal of sympathetic tone, or RV failure.
  - The prothrombotic changes of pregnancy may contribute to the development of pulmonary arterial thrombosis, which will further worsen PVR.
- Termination of pregnancy is safest in the first trimester before the significant fluid shifts of pregnancy develop.
- There is significant fetal risk with live birth rate of only 12% among women with oxygen saturation less than 85%.

- Contraception decisions are complicated. Estrogen-containing contraceptives should be avoided because of the increased risk of venous thrombosis, but progesterone-only contraceptives have lower birth prevention efficacy. With those caveats, the best contraceptive option may be a long-acting progesterone-only preparation (depot or implant) or a Mirena intrauterine device (IUD). The IUD should generally be inserted in a tertiary care setting because of the risk of significant vagal episodes which may suddenly alter hemodynamics or lead to syncope in these patients.
- Those women who choose to proceed with pregnancy should be referred to a tertiary center with a multidisciplinary team that includes a pulmonary hypertension specialist for intensive prenatal monitoring, admission for bed rest in the third trimester, and an intensively managed delivery in an intensive care setting [40].

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Chapter 10
Persistent Left Superior Vena Cava

Jonathan Kochav

Epidemiology

- Persistent left superior vena cava (PLSVC) is the most common congenital thoracic venous anomaly with a prevalence of ~0.5% in the population and up to 10% of those with established congenital heart disease [1, 2].

Anatomic Definition and Pathophysiology

1. Anatomy and Embryology: (Fig. 10.1)
   (a) In the developing fetus, the bilateral anterior cardinal veins provide systemic venous return from the cephalic aspect of the body.
   (b) The most cephalic portions of the cardinal veins forms the internal jugular veins, and the caudal portion of

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the right superior cardinal vein forms the right-sided superior vena cava.

(c) The caudal portion of the left superior cardinal vein forms the coronary sinus but otherwise regresses proximal to the brachiocephalic vein forming the "ligament of Marshall".

(d) When the regression of the ligament of Marshall does not occur, a PLSVC results.

2. Spectrum of disease:

(a) Subtypes (Fig. 10.2):

- Presence of both left and right SVCs is seen in ~90% of cases [3].
  - A brachiocephalic bridging vein may be present in ~30% of patients with bilateral SVC [4].
- PLSVC with an absent right SVC occurs in ~10% of cases:
  - The PLSVC provides all venous return from the cranial aspect of the body, draining into the right atrium via the coronary sinus.
  - In 10–20% cases, the PLSVC will drain into the left atrium through an unroofed coronary sinus or through the left superior pulmonary vein, resulting in a right-to-left shunt and possibly neonatal cyanosis [5].

3. Physiology:

(a) Typically PLSVC is an incidental anomaly with little physiologic significance unless the PLSVC drains into the left atrium or if there are significant associated abnormalities.

4. Associated defects [6–8]:

(a) Atrial septal defects or coronary sinus defect more commonly.

(b) Bicuspid aortic valve.

(c) Coarctation of the aorta.

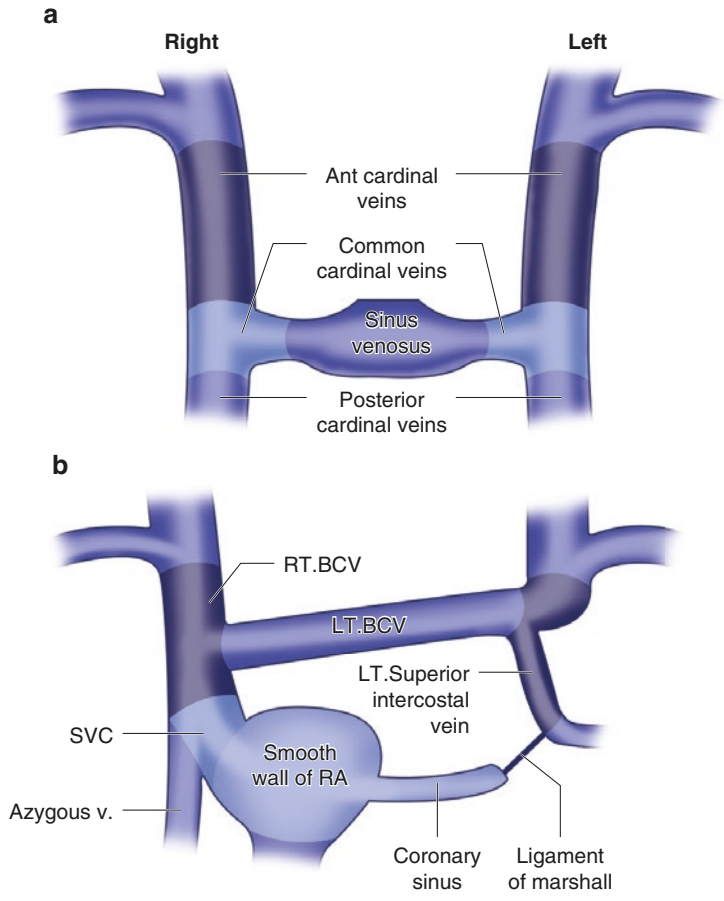

FIGURE 10.1 Normal embryologic development of the anterior cardinal vein. (**a**) Early embryologic development and (**b**) Adult anatomy

(d) Cor triatriatum.
(e) Coronary sinus ostial atresia.
(f) Note that these associated defects are more commonly seen in patients with an absent right SVC.

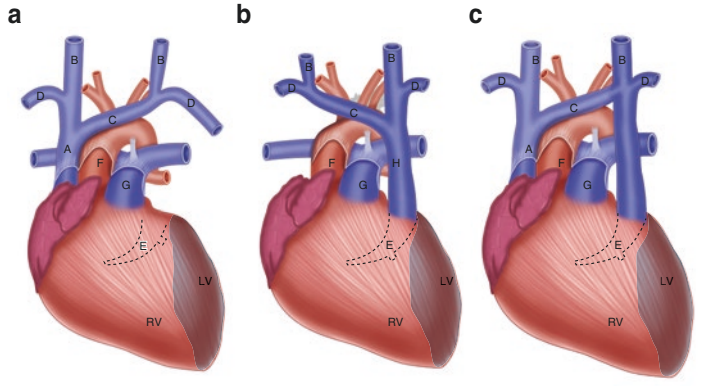

FIGURE 10.2 Three major subtypes of the SVC anatomy. (**a**) Normal anatomy, (**b**) Left SVC with absent right SVC, and (**c**) double SVC. A bridging brachiocephalic vein may be present in 30% of cases. *RSVC* right superior vena cava, *IJ* internal jugular vein, *LBCV* left brachiocephalic vein, *Subclav* subclavian vein, *CS* coronary sinus, *Ao* aorta, *MPA* main pulmonary artery, *LSVC* left superior vena cava, *RV* right ventricle, *LV* left ventricle

Diagnostics

Clinical Presentation in Adults

- The diagnosis is generally made as an incidental finding during cardiovascular imaging or during attempts at placement of central venous catheters.

Physical Exam

- If PLSVC occurs as an isolated defect, the physical exam should be normal.

Electrocardiogram

- The electrocardiogram may show a leftward P-wave axis with normal PR interval [4].

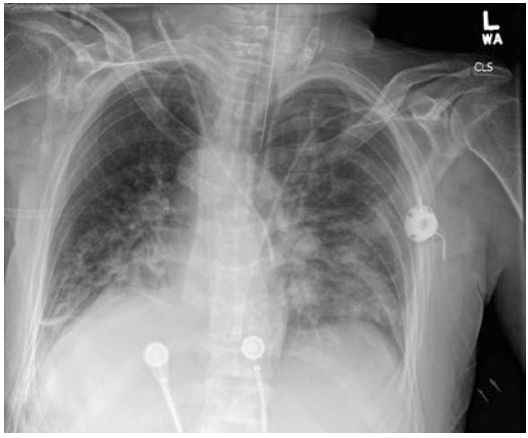

FIGURE 10.3 Chest radiograph of a patient with persistent left superior vena cava, following placement of a left internal jugular central venous catheter

Chest Radiograph

- Chest radiography may demonstrate a crescentic vascular shadow extending from the upper left border of the aortic arch to the middle third of the left clavicle [5].
- Chest radiograph may demonstrate anomalous course of a catheter placed for central venous access (Fig. 10.3).

Echocardiography

- Transthoracic echocardiography will reveal a dilated coronary sinus in the absence of elevated right-sided filling pressures:
  - The differential for a dilated coronary sinus also includes [2]:

    Total anomalous pulmonary venous return with coronary sinus drainage
    Coronary arteriovenous fistula with drainage into the coronary sinus
    Coronary sinus defect

- Contrast echocardiography may show enhancement of the coronary sinus before the right atrium when contrast is injected into the left arm and normal transit of contrast when injected into the right arm, though this may vary based on anatomy.
- Echocardiography should be performed in all patients diagnosed with PLSVC by different modalities, for the purpose of screening of the various associated congenital abnormalities.

Cardiac Catheterization

- Not routinely performed as part of the diagnostic workup.
- PLSVC may be diagnosed when left-sided (jugular or subclavian) access is used for right heart catheterization, permanent pacemaker, or implantable cardioverter defibrillator placement.
- Contrast venography can be performed to define the venous anatomy and determine the drainage site of the anomalous vessel.

Advanced Imaging Techniques

- Tomographic imaging with MRI or CT is useful for making the diagnosis, identifying associated defects, and to differentiate between the variations of venous drainage.

Management of Adult Survivors

Arrhythmia

- PLSVC has been associated with an increased risk of arrhythmia [9, 10]. Anatomic abnormalities of conduction tissue are thought to occur as a result of dilation of the coronary sinus and/or through electrical communications with the atria through the vein of Marshall:

  - Atrial fibrillation
  - Supraventricular tachyarrhythmias
  - Atrioventricular block due to distortion of the AV node or bundle of His

Access Considerations

- PLSVC may complicate the use of left-sided access points (subclavian or internal jugular veins) for right heart catheterization, placement of a pacemaker, or implantable cardioverter defibrillator leads. This is particularly true among patients with an absent right SVC.
- Complications associated with accessing the right heart through the coronary sinus include:
  - Coronary sinus perforation causing hemorrhagic pericardial effusion and tamponade.
  - Coronary sinus thrombosis causing effective "SVC syndrome."
  - As previously discussed, 10–20% of patients will have drainage into the left atrium, and these patients are at risk of systemic embolization of thrombus or air with the use of catheters that drain into this circuit. For this reason, the vascular anatomy must be fully defined using one of the above imaging modalities prior to use of a central venous catheter that is suspected to be draining into an anomalous vessel.

Surgical Considerations

- PLSVC may complicate the ability to perform standard retrograde infusion of cardioplegia solution into the coronary sinus in patients undergoing cardiopulmonary bypass [11].
- PLSVC may complicate anastamosis venous return in patients who are undergoing heart transplantation.

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Chapter 11
Anomalous Pulmonary Venous Return

Jonathan Kochav

Epidemiology

- The incidence of partial anomalous pulmonary venous return (PAPVR) is estimated to be at least 7 per 1000 individuals [1].
- The incidence of total anomalous pulmonary venous return (TAPVR) is lower, at about 0.8 per 10,000 live births [2].

Anatomic Definition and Pathophysiology

1. Embryology [3]:
   (a) Standard pulmonary venous anatomy consists of four veins, two on each side, each draining into the left atrium.
   (b) Anomalous pulmonary venous return occurs when a pulmonary vein drains directly into the right heart or into a systemic vein resulting in a left-to-right shunt.

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(c) In normal fetal development, the lung buds are formed from the primitive foregut and share a common vascular splanchnic plexus that initially drains into both the cardinal and umbilicovitelline systems. The cardinal system will develop into the superior vena cava (SVC) and coronary sinus (see Chap. 10), while the umbilicovitelline system will develop into the inferior vena cava, the ductus venosus, and the portal vein. At around 30 days of development, a cranial outpouching known as the common pulmonary vein develops in the sinoatrial region of the primordial left atrium. The common pulmonary vein extends towards the vascular splanchnic plexus of the lung bud, forming four pulmonary veins that drain in conjunction with the cardinal and umbilicovitelline systems that preceeded them. Over time, the pulmonary-cardinal and pulmonary-umbilicovitelline connections regress, and the common pulmonary vein incorporates into the left atrium.

2. Anatomy and spectrum of disease:

(a) Total anomalous pulmonary venous return (TAPVR) occurs when the common pulmonary vein fails to incorporate into the left atrium or the connection between the common pulmonary vein and left atrium becomes atretic [4].

(i) Anatomic variants:

- Supracardiac (~50%): Retained connection of the common pulmonary vein to the cardinal system via the vertical vein results in drainage into the brachiocephalic vein, SVC, right atrium (RA), or azygos vein.
- Cardiac (~15%): Retained connection of the common pulmonary vein to the cardinal system via the vertical vein can also result in drainage into the coronary sinus or directly to the RA.
- Infracardiac (~25%): Retained connection of the common pulmonary vein to the umbilicovitelline

system via the vertical vein results in drainage into the IVC, portal vein, or hepatic vein.

(ii) This defect is not compatible with neonatal life unless there is a concomitant central defect to allow for right-to-left blood flow (e.g., intracardiac septal defect or patent ductus arteriosus (PDA).

(b) Partial anomalous venous return (PAPVR) occurs when (up to three) individual pulmonary veins retain their connection to the cardinal or umbilicovitelline system.

(i) Right lung drainage to:

- SVC
- RA
- Coronary sinus
- Azygos vein
- Inferior vena cava (IVC)—This lesion is known as the "Scimitar syndrome" due to the radiographic appearance, which resembles a Turkish sword or "scimitar." Usually drains the entire right lung

(ii) Left lung drainage to:

- Brachiocephalic vein
- Coronary sinus
- Hemiazygos vein

(iii) In pediatric populations, 90% of anomalous pulmonary veins originate from the right lobe [5].

(iv) In adult populations 20–67% of veins originate from the right lobe [6–8].

3. Physiology:

(a) Physiology varies widely depending on the volume of shunt flow.

(i) TAPVR:

- Patients with TAPVR will have left-to-right shunting of the entire pulmonary circulation.
- Pulmonary blood flow returns to the RA through the anomalous vascular connection, having mixed with deoxygenated blood from the systemic vascular return.
- The mixed blood must be shunted back into the left system through a concomitant intracardiac shunt or PDA.
- These patients will be cyanotic in the neonatal stage and require early surgical intervention.

(ii) PAPVR:

- PAPVR results in a left-to-right, low-pressure, variable-volume shunt.
- If shunt flow is large enough, right-sided volume overload will lead to RA, RV, and pulmonary artery enlargement; generally an isolated anomalous vein will not cause right heart enlargement.
- Pulmonary arterial hypertension and RV failure may subsequently develop.
- In the absence of an additional central shunt, Eisenmenger syndrome can not develop as right-to-left flow reversal through this shunt is not possible.

(b) Associated defects:

(i) PAPVR:

- Right upper lobe PAPVR is associated with:
  - Superior sinus venosus defect:

    Up to 90% of pediatric cases [5]
    Less frequently in adults [7, 8]

  - Septum secundum atrial septal defects are seen in up to 15% of cases [5].

- "Scimitar syndrome" is associated with [3, 9–11]:
  - Right lung and right pulmonary artery hypoplasia
  - Systemic arterial blood supply to the right lower lung from the branches of the abdominal aorta
  - PDA
  - Coarctation of the aorta
  - Sinus venosus defects or septum secundum ASD (~70% of cases)
  - Complex congenital heart disease:

    Hypoplastic left heart syndrome
    Tetralogy of Fallot
- Cor triatriatum

(ii) TAPVR:

- Complex cardiac malformations including:

  Functional single ventricle
  Heterotaxy [12, 13]

Childhood Repairs

- Neonatal surgery is required for patients with TAPVR with the surgical approach dependent on the anatomy of the lesion.
  - Supracardiac drainage to the SVC:

    When the pulmonary vein drains into the SVC, an intracardiac baffle may be used to channel blood from the SVC through the RA into the LA.
  - Cardiac drainage to the coronary sinus:

    When the pulmonary vein drains in the coronary sinus, the sinus is unroofed into the left atrium and atrial septal connections are closed.

- All other lesions:

  The anomalous vertical vein is ligated, and an anastomosis of the pulmonary venous confluence and the left atrium is created.

Diagnostics

Clinical Presentation in Adults

- PAPVR:
  - Presentation is dependent on the volume of the shunt and the presence and significance of associated cardiac defects.
  - With large-volume shunt lesions, patients may present early in childhood.
  - With moderate-volume lesions, patients may present in adulthood with dyspnea on exertion, palpitations, and symptoms of pulmonary hypertension and right heart failure.
  - With low-volume shunt lesions, patients may never develop symptoms, and PAPVR may be discovered as an incidental finding on chest or cardiac imaging.
  - PAPVR should be considered in patients with unexplained RV enlargement and no intracardiac shunt identified by echocardiography.
- TAPVR:
  - There have been rare case reports of patients presenting in early-to-late adulthood with unrepaired TAPVR [14].
  - The majority of adult patients will present with a history of childhood repair.
  - In the absence of the development of pulmonary venous stenosis or stenosis of the anastomosis, functional capacity should be normal in patients with repaired isolated TAPVR.

Physical Exam

- Unrepaired PAPVR:
  - Right-sided volume overload:

    May result in a fixed split S2 due to delayed closure of the pulmonary valve that does not vary with inspiration. This is particularly pronounced in patients with concomitant sinus venosus defect.

    A pulmonic flow murmur and less frequently a tricuspid diastolic flow murmur may be heard over the left upper sternal boarder due to increased flow through the right heart.

    RV heave
- Repaired PAPVR:
  - Exam should be normal with the return of normal physiologic splitting of S2.
- Repaired TAPVR:
  - Exam may be normal or show evidence of progressive pulmonary hypertension and right heart failure.

Electrocardiogram

- Right-sided volume and pressure overload:
  - Right atrial enlargement
  - Right axis deviation
  - RV hypertrophy
- Supraventricular arrhythmias may be seen.
- Abnormal P wave axis may be seen in association with sinus venosus defects, typically low atrial focus.

Chest Radiography

- Unrepaired PAPVR:
  - Right-sided pressure and volume overload:

    RA and right ventricular enlargement.
    Prominent pulmonary artery with an increase in pulmonary vasculature.
  - In patients with right lower lobe PAPVR with anomalous connection to the IVC, a "Scimitar vein" may be seen along the right heart border (Fig. 11.1):

    Dextroposition of the right heart may be seen in the case of right lung hypoplasia associated with the scimitar syndrome.

Echocardiography

- Transthoracic echocardiography:
  - Usually unable to assess for correct insertion of the pulmonary veins [8].

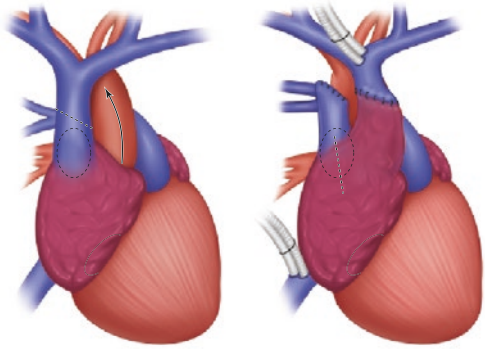

FIGURE 11.1 "Scimitar syndrome" as seen on chest radiography

  - Useful for assessment of right-sided volumes, pressures, and RV function.
  - May also identify dilated SVC or IVC.
- Transesophageal echocardiography is highly sensitive for the diagnosis of PAPVR [15].

Cardiac Catheterization

- Right heart catheterization with delayed phase pulmonary angiography may rarely identify anomalous venous drainage but has limited sensitivity [10].
- Patients with uncorrected disease should undergo hemodynamic assessment of pulmonary pressures with vasoreactivity and Qp/Qs flow ratios if repair is being considered.

Advanced Imaging Techniques

- CT or MRI is the modality of choice and is able to definitively define the anatomy of the anomalous venous return [3].
  - Benefits of MRI include lack of ionizing radiation and the ability to assess Qp/Qs through phase-contrast imaging.

Management of Adult Survivors

PAPVR

1. Left-to-right shunting through unrepaired PAPVR
   (a) Indications for surgery: No major guidelines exist at this time and indications are controversial.
      (i) RA and right ventricular enlargement.
      (ii) Hemodynamically significant left-to-right shunting, Qp/Qs >1.5–2.
      (iii) During surgical repair of other cardiac lesions.

(iv) Asymptomatic patients with single, isolated PAPVR with low shunt flow and without right-sided overload can be followed without intervention [16].

(b) Surgical techniques:

(i) Depends on the site of the anomalous veins

- PAPVR to the SVC [17]
  - An internal patch with baffle to the left atrium (through the sinus venosus defect) with or without SVC enlargement (Fig. 11.2a).

    Patients who have undergone this repair must be monitored for SVC syndrome, obstruction of the anomalous pulmonary vein, and arrhythmias such as sinus node dysfunction or supraventricular tachycardia.
  - Alternative techniques include caval division with atriocaval anastomosis (also known as the Warden technique). This technique is

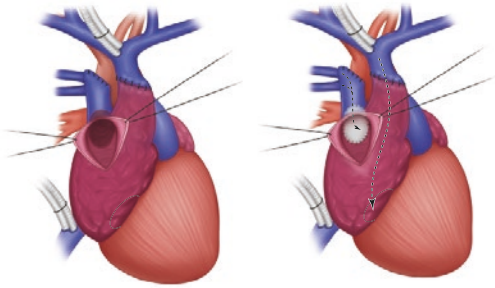

FIGURE 11.2 (**a**) The internal patch tecnique. A right atriotomy is created and an intra-atrial baffle is placed, redirecting the anomalous pulmonary venous return to the left atrium through the sinus venosus defect. (**b**) The Warden procedure. The superior vena cava, superior to the site of anomalous pulmonary venous return, is transposed to the right atrial appendage. A right atriotomy is created and an intra-atrial baffle is placed, redirecting the anomalous pulmonary venous return to the left atrium through the sinus venosus defect [17]

often used when the anomalous pulmonary veins have a high insert point (i.e., >2 cm above the cavoatrial junction) (Fig. 11.2b).

- Surgical technique will vary greatly depending on the anatomy of the anomalous pulmonary venous return and associated cardiac abnormalities.
  - If a left upper pulmonary vein without associated ASD needs to be intervened upon, it can be approached via L thoracotomy or median sternotomy and anastomosis LUPV to left atrial appendage.

(c) Percutaneous techniques:

(i) In patients who are not surgical candidates, transcatheter occlusion can be considered to reduce shunting [18].

2. Arrhythmia:

(a) Atrial fibrillation, atrial flutter, and sick sinus syndrome are common and should be treated in standard fashion with medical therapy, catheter ablation, and pacemaker therapy as indicated.

TAPVR

- Stenosis of individual pulmonary veins or anastomosis:
  - Patients may present with symptoms of pulmonary hypertension due to pulmonary venous hypertension. Reoperation is indicated in these cases.
- Arrhythmia
  - Atrial fibrillation, atrial flutter, and sick sinus syndrome are common and should be treated in standard fashion.
  - Periodic Holter monitoring can be considered in asymptomatic adults.

Management of Pregnancy

- Pregnancy is absolutely contraindicated in patients with Eisenmenger syndrome due to the high risk of maternal mortality.
- Pregnancy is well tolerated in patients without pulmonary hypertension.
- Right heart volume and pressure overload may progress during pregnancy in unrepaired patients (with the development of symptoms of dyspnea or arrhythmia) due to increased left-to-right shunting in the setting of increased intravascular volume and cardiac output.

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Part III
Left Heart Obstructive Lesions

Chapter 12
Cor Triatriatum

Jonathan Kochav

Epidemiology

- Cor triatriatum, also referred to as cor triatriatum sinister (CTS), is defined by a separating membrane within the left atrium (LA). It is a very uncommon congenital heart condition and is identified in only 0.1–0.4% of patients with congenital heart disease [1, 2].
- Cor triatriatum dexter, a separating membrane within the right atrium, is even more rare, and incidences have not been reported.

Anatomic Definition and Pathophysiology

- Embryology:
  - In normal fetal development, the lung buds are formed from the primitive foregut and share a common vascular splanchnic plexus that initially drains into both the cardi-

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nal and umbilicovitelline systems. The cardinal system will develop into the superior vena cava and coronary sinus (see Chap. 10), while the umbilicovitelline system will develop into the inferior vena cava, the ductus venosus, and the portal vein. At around 30 days of development, a cranial outpouching known as the common pulmonary vein develops in the sinoatrial region of the primordial left atrium. The common pulmonary vein extends towards the vascular splanchnic plexus of the lung bud, forming four pulmonary veins that drain in conjunciton with the cardinal and umbilicovitelline systems that preceeded them. Over time, the pulmonary-cardinal and pulmonaryumbilicovitelline connections regress, and the common pulmonary vein incorporates into the left atrium [3].

  - In circumstances where the connection between the common pulmonary vein and left atrium becomes stenotic, the common pulmonary vein dilates, and the CTS results.

- Anatomy:
  - In CTS, the left atrium is divided into a superior and inferior chamber. The superior, or accessory chamber, receives the pulmonary inflow. The inferior, or true chamber, contains the left atrial appendage and the mitral valve orifice. This is in contrast to a supramitral membrane, in which the separating membrane is found inferior to the left atrial appendage (Fig. 12.1).
- Physiology:
  - The physiology of flow-restricting CTS is similar to that of mitral stenosis, with elevated pulmonary venous pressures leading to pulmonary congestion and pulmonary arterial hypertension.
  - Turbulent flow at the level of the mitral valve can over time cause mitral valve degeneration, with subseqeunt valvular stenosis and/or regurgitation.

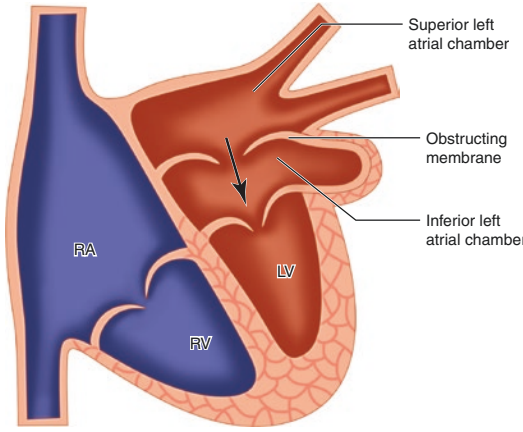

FIGURE 12.1 The membrane in CTS separates the superior chamber receiving pulmonary venous inflow from the inferior chamber containing the left atrial appendage and the mitral valve orifice

- Spectrum of disease:
  - CTS membranes are classified anatomically into one of three groups [4]:

    Group 1: No connection between the two chambers—survival is dependent on anomalous pulmonary venous drainage to the inferior chamber or to the right heart with subsequent interatrial shunting to the inferior chamber through an atrial septal defect (ASD).

    Group 2: One or multiple small openings in the intra-atrial membrane.

    Group 3: One single large opening in the intra-atrial membrane.
- Associated defects [5]: Associated defects are seen in a majority of patients.
  - ASD or ventricular septal defect (VSD)
  - Pulmonary vein stenosis
  - Patent ductus arteriosus
  - Anomalous pulmonary venous return
  - Persistent left superior vena cava

Diagnostics

Clinical Presentation in Adults

- Patients with Group 1 or Group 2 anatomy are usually highly symptomatic and diagnosed in infancy or childhood.
- Patients with Group 3 anatomy are likely to survive into adulthood and are often diagnosed only incidentally.
  - Patients with more severe stenosis will present with symptomology similar to that of mitral stenosis: [6–8]

    Palpitations and atrial arrhythmia
    Dyspnea on exertion due to pulmonary vascular congestion and pulmonary hypertension
    Hemoptysis
  - Patients are theorized to be at increased risk of thromboembolism due to increased frequency as atrial fibrillation, as well as stasis of flow in the partitioned left atrium [9].

Physical Exam [10]

- Diastolic rumbling murmur may be heard due to turbulent flow through the membrane.
  - In contrast to mitral stenosis, S1 is normal and there is no opening snap.
- A loud P2 may be heard where pulmonary hypertension is present.

Electrocardiogram [11, 12]

- LA enlargement
- Right atrial enlargement

- Right ventricular hypertrophy
- Atrial fibrillation is common

Chest Radiography

- Increased pulmonary vascular markings [11]

Echocardiography

- Echocardiography usually confirms the diagnosis.
  - A thin, mobile, intra-atrial membrane can be identified.
  - Doppler echocardiography can be used to estimate the gradient across the membrane.

Advanced Imaging Techniques

- Advanced imaging techniques with CT **(**Fig. 12.2**)** and MRI are generally not required in cases of CTS, unless additional congenital defects are suspected and need to be characterized.

Management of Adult Survivors

Obstruction by a Flow Restricting Intra-Atrial Membrane

- Indications for intervention:
  - Consensus guidelines for intervention do not exist for CTS, and thus it seems reasonable to reserve invasive intervention for those patients who are symptomatic.

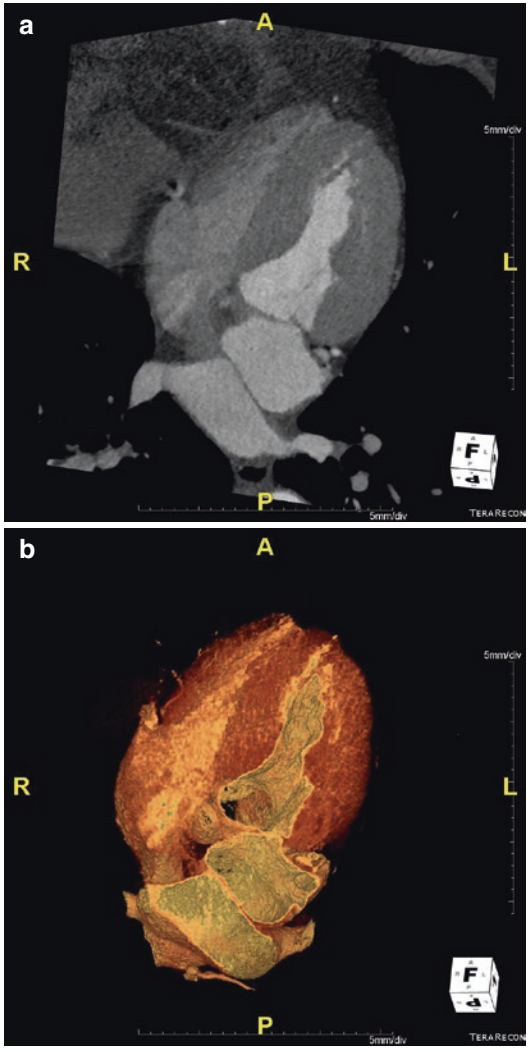

FIGURE 12.2 (**a**) Axial reconstruction of the gated CT showing cor triatriatum sinister with the usual configuration at the mid left atrial level. (**b**) 3D imaging of the same

- Options for intervention:
  - Surgical management:

    Consists of simple resection of the membrane and correction of any associated defects.
    This approach has demonstrated an 85% survival rate without recurrence of disease [2, 12].
  - Percutaneous management:

    Percutaneous balloon dilation with rupture of intra-atrial membrane has been described [13] and may be considered as an alternative to surgical approach in the high-risk patient. However, as only case reports have been described at this time, neither the procedural risk profile nor the durability of the dilation can be compared to surgical excision.

Pulmonary Hypertension

- Patients with a flow-restricting lesion may develop pulmonary venous hypertension with subsequent hypertrophy of the pulmonary arterioles. Response of pulmonary arterial pressures to resection of the membrane is variable [14].
- Patients who have had membrane resection in childhood may develop progressive pulmonary hypertension as adults. Pulmonary hypertension should be considered in the dyspnea evaluation of patients with prior resection.

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Chapter 13
Congenital Mitral Stenosis

Lucy M. Safi

Abbreviations

LA	Left atrium
NYHA	New York heart association
MVA	Mitral valve area

Epidemiology

- Congenital mitral stenosis can occur at the valvular, supravalvular, or subvalvular levels and is associated with developmental abnormalities in the mitral valve leaflets, mitral valve annulus, and/or the subvalvular apparatus.
- Congenital mitral stenosis is rare and occurs in 0.4–0.6% of autopsied patients with congenital heart disease [1, 2].
- For historical background, see Table 13.1.

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Table 13.1 Historical background

Shone and colleagues described Shone's complex in 1963 which includes multiple levels of left-sided obstruction. The paper was entitled "parachute mitral valve, supravalvular ring of the left atrium, subaortic stenosis and coarctation or the aorta" [3].

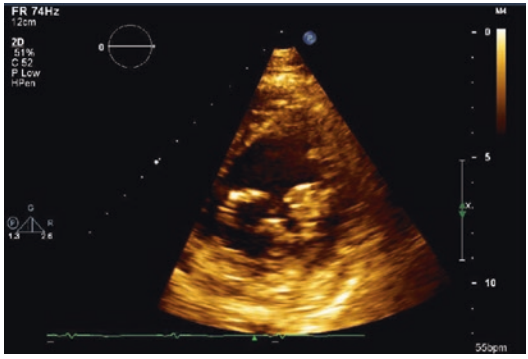

Figure 13.1 Echocardiographic imaging of a mitral valve showing a double orifice mitral valve

Anatomic Definition and Pathophysiology

1. Anatomy
   (a) Valvular mitral stenosis
      - Valvular mitral stenosis can occur from multiple etiologies including hypoplastic annulus, commissure fusion, or double orifice mitral valve.
      - Double orifice mitral valve occurs when a fibrous bridge or tissue separates the mitral valve orifice into two (Fig. 13.1). It is possible that insufficient endocardial cushion fusion during embryogenesis is what leads to mitral stenosis, mitral regurgitation or both. There are three overall types of double orifice mitral valve [4].

  - Incomplete bridge: small strand of tissue connects the anterior and posterior mitral valve leaflet edges.
  - Complete bridge: fibrous bridge connects the anterior and posterior mitral valve leaflets dividing the orifice into two equal or unequal orifices.
  - Hole type: additional orifice seen at the posterior commissure of the mitral valve.

(b) Supravalvular mitral stenosis

- Supravalvular stenosis also called a "mitral ring" is a shelf-like ridge of fibrous tissue on the atrial surface of the mitral valve that may or may not adhere to the mitral valve leaflets restricting their movement at the base.
- The stenosis is located superior to the mitral valve annulus but inferior to the left atrial appendage (whereas the membrane of cor triatriatum inserts at the level between the pulmonary veins and the left atrial appendage).
- The tissue is variable in size and may be partial or circumferential around the mitral valve annulus.
- A second type of supravalvular mitral stenosis may occur due to a thin membrane located within the mitral valve leaflets referred to as an "intramitral ring." Restriction with this lesion occurs at the base of the mitral valve leaflets—this differs from rheumatic heart disease where restriction occurs at the mitral valve leaflet tips.
- Supravalvular mitral stenosis rarely occurs as an isolated defect.

(c) Subvalvular mitral stenosis

- The subvalvular apparatus of the mitral valve includes the chordae tendineae and the papillary muscles.

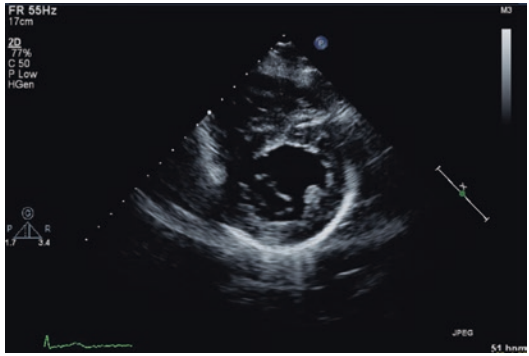

FIGURE 13.2 Echocardiographic imaging of a mitral valve showing the single papillary muscle of a patient with a parachute mitral valve

- A parachute mitral valve occurs when all chordae tendineae insert into a single papillary muscle (Fig. 13.2) leading to subvalvular obstruction [5].
  - A second papillary muscle may be present but small and/or have no chordal attachment.
  - Often seen with other left-sided obstructive lesions such as coarctation of the aorta.
  - Echocardiographic short axis view shows deviation of the mitral valve orifice toward the single papillary muscle.

2. Physiology

(a) The physiologic effect of mitral stenosis is based on the severity of mitral stenosis and obstruction.
(b) Stenosis of the mitral valve leads to diastolic flow obstruction and elevated left atrial filling pressures. This restricts pulmonary venous emptying into the left atrium resulting in pulmonary congestion.
(c) Pulmonary congestion triggers compensatory pulmonary vasoconstriction leading to elevation in pulmonary artery pressure or secondary pulmonary hypertension.
(d) The long-standing increase in pulmonary pressure increases the work load on the right ventricle that may lead to failure.

3. Spectrum of disease
   (a) The severity of mitral stenosis may vary from mild to severe.
   (b) Severe stenosis may lead to heart failure and cardiogenic shock immediately after birth without intervention.
   (c) If left untreated, severe isolated congenital mitral stenosis leads to death within the first 5 years of life [6].
4. Associated defects
   (a) Most commonly associated cardiac lesions are coarctation of the aorta, aortic valve stenosis, subvalvular aortic stenosis, ventricular septal defect, and patent ductus arteriosus.
   (b) Shone complex is rare and refers to multiple levels of left-sided cardiac obstruction including: supravalvular mitral ring, parachute mitral valve, subvalvular or valvular aortic stenosis, and aortic coarctation [7].

Diagnostics

Clinical Presentation

- Patients with congenital mitral stenosis may present as children with dyspnea with exertion, recurrent pulmonary infections, failure to thrive, pulmonary edema, or congestive heart failure. Older children may present with exercise limitation.
- Occasionally mitral stenosis is found on echocardiography and assumed to be rheumatic heart disease in etiology. Careful examination of the subvalvular apparatus is important to distinguishing between the two disease states as the treatment varies.
- Occasionally congenital mitral anomalies such as parachute mitral valves are incidentally found as associated lesions with other congenital heart defects such as coarctation of the aorta.
- Adults with well-repaired congenital mitral stenosis in childhood may present with pulmonary hypertension or exercise-related pulmonary hypertension later in life and pulmonary vasodilators may be necessary [8].

Physical Exam

- A loud S_1 due to mitral valve closure may be heard. In the setting of pulmonary hypertension, the P_2 component of the second heart sound may increase in intensity, and a right ventricular heave may be palpitated.
- A diastolic murmur is heard at the apex, and the timing is associated with the severity of the stenosis.

Electrocardiography

- Patients with mitral stenosis are prone to atrial arrhythmias, specifically atrial fibrillation, which may be seen on the electrocardiogram.
- Left atrial abnormality due to elevated left atrial pressures, right axis deviation, and right ventricular hypertrophy (in the setting of pulmonary hypertension) are nonspecific findings that may also be seen.

Chest X-Ray

- Straightening of the left heart border can be seen on chest radiograph due to left atrial enlargement.
- Other findings such as pulmonary congestion and dilated pulmonary arteries may be seen in patients with advanced disease.

Echocardiography

- 2D and Doppler echocardiography is able to assess the mitral valve noninvasively in both children and adults. Echocardiography is critical in distinguishing between rheumatic and congenital forms of mitral stenosis.
- Table 13.2 highlights the essentials of echocardiographic assessment of patients with congenital mitral stenosis in comparison to rheumatic heart disease.

Table 13.2 Echocardiographic essentials for assessment

Diagnosis of congenital mitral stenosis	Diagnosis of rheumatic mitral stenosis
1. Evaluate the short axis view of the mitral valve at multiple levels for the presence of a supravalvular membrane, subvalvular membrane, and double orifice mitral valve 2. Evaluate subvalvular apparatus for single papillary muscle/parachute mitral valve 3. Determine the mitral valve area, mean, and peak transmitral Doppler pressure gradients (note heart rate) 4. Exclude associated congenital defects: Coarctation of the aorta, aortic valve stenosis, subvalvular aortic stenosis, ventricular septal defect, and patent ductus arteriosus	1. Short axis view of the mitral valve shows commissural fusion and a narrowed mitral valve orifice area 2. Thickened, shortened, and calcified subvalvular apparatus is often seen 3. Direct planimetry at the mitral valve leaflet tips or pressure halftime can be used to determine the mitral valve orifice area and assess the severity of stenosis 4. The mitral valve leaflet tips are thickened and/or calcified and have a doming "hockey stick" appearance in diastole 5. Exclude rheumatic valve involvement of the other heart valves

- Table 13.3 highlights the ACC/AHA classification of mitral valve severity written for patients with acquired mitral stenosis. This classification, although not studied in the congenital population, is often extrapolated to the congenital population.

Cardiac Catheterization

- The use of cardiac catheterization in patients with congenital mitral stenosis is limited.
- Although rarely required, transeptal punctures for direct measurement of left atrial pressures in patients whose echocardiographic findings are inconclusive can be performed.

Table 13.3 ACC/AHA: guideline for the management of patients with valvular heart disease (Executive summary 2014) [9]

Stages of mitral stenosis	Hemodynamic findings on echocardiography
(a) At risk	(a) Normal transmitral flow velocity
(b) Progressive MS	(b) MVA > 1.5 cm^2 and a diastolic pressure halftime <150 ms
(c) Asymptomatic severe mitral stenosis	(c) MVA ≤ 1.5 cm^2 and a diastolic pressure halftime ≥150 ms; very severe MVA <1.0 cm^2 and diastolic pressure halftime ≥ 220 ms
(d) Symptomatic severe mitral stenosis	(d) MVA ≤ 1.5 cm^2 and a diastolic pressure halftime ≥150 ms; very severe MVA <1.0 cm^2 and diastolic pressure halftime ≥220 ms

Advanced Imaging Techniques

- Stress echocardiography may be indicated in those patients with clinical symptoms that are disproportionate to resting echocardiographic findings. Stress echocardiography is able to also assess for exercise-induced pulmonary hypertension.

Management of Patients with Congenital Mitral Stenosis

- Many infants with mild stable congenital mitral stenosis are responsive to medical management [10].
- In those patients with hemodynamically significant disease, surgical intervention is delayed as long as possible to avoid placement of mitral valve prosthesis in a young child.
- American guidelines do not address the timing of surgical intervention for patients with congenital mitral stenosis; however, the Canadian Cardiovascular Society published surgical guidelines for management of congenital mitral stenosis which are summarized in Table 13.4.

Table 13.4 Canadian Cardiovascular Society: surgical management of valvular heart disease (Guidelines 2004) [11]

Recommendations for mitral valve surgery in patients with congenital mitral stenosis
Class I
1. Small children with intractable NYHA class III or IV symptoms despite maximal medical treatment
2. Failure to thrive despite maximal medical treatment
3. Older children with symptomatic NYHA class III or IV
4. Adolescents or young adults with symptomatic NYHA class III or IV and mean mitral valve gradient >10 mmHg on Doppler echocardiography

- Percutaneous mitral balloon valvotomy is generally not recommended among patients with congenital mitral stenosis.
- Despite surgical intervention, the long-term mortality of patients with congenital mitral stenosis is still elevated.
- Symptoms of dyspnea among patients with history of congenital mitral stenosis, even if well repaired in early life, may reflect pulmonary vascular disease, and adult clinicians should be vigilant about screening for pulmonary hypertension.

Management of Pregnancy

- The most common etiology leading to mitral stenosis in women of childbearing age is from rheumatic heart disease and less likely from congenital mitral stenosis.
- Increase in plasma volume to the left atrium (LA) may not be tolerated given fixed mitral orifice area.
- The physiologic increase in heart rate (and resultant shortening of diastole) in pregnancy may precipitate LA hypertension.
- The increased heart rate and cardiac output required for pregnancy may cause patients with moderate or severe mitral stenosis to decompensate and lead to pulmonary edema.

- Beta blockers and diuretics may be prescribed to patients with mitral stenosis with attempts to control heart rate and reduce LA hypertension.
- Severe mitral stenosis carries an increased maternal risk with pregnancy, and pregnancy is not recommended without prior intervention [12, 13].
- Percutaneous valvuloplasty intervention is generally not an option for congenital mitral stenosis.

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Chapter 14
Subaortic Stenosis

Lucy M. Safi

Abbreviations

ACHD	Adult congenital heart disease
CT	Computed tomography
LOE	Level of evidence
LVOT	Left ventricular outflow tract
MRI	Magnetic resonance imaging

Epidemiology

- The prevalence of subaortic stenosis is 6.5% among patients with adult congenital heart disease and occurs predominantly in men.
- Subaortic stenosis can be acquired or familial with an occurrence of congenital LVOT obstruction of ~ 15% among primary relatives [1].

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Anatomic Definition and Pathophysiology

- Anatomy
  - Subaortic stenosis is often caused by obstruction in the left ventricular outflow tract (LVOT) due to a discrete membrane (type I) or less commonly by diffuse and tunnel-like obstruction (type II).
  - Discrete membranes are fibrous or fibromembranous and attach circumferentially (either partially or completely) in the LVOT. The membrane attaches medially to the upper interventricular septum and laterally to the LVOT wall and may extend to the base of the anterior mitral valve leaflet.
  - Membranes vary in distance below the aortic valve annulus as well as thickness.
  - Diffuse subvalvular stenosis is a more significant form of subvalvular obstruction and often limited to children.
- Physiology
  - Increased LVOT shear forces lead to progressive LVOT fibrosis and injury to the aortic valve.
  - Injury to the aortic valve is hypothesized to occur from increased subvalvular velocities leading to fibrous tissue encroachment of the membrane toward the aortic valve leaflets causing aortic regurgitation. Similarly, this fibrous tissue may encroach upon the anterior mitral valve leaflet.
  - Obstruction of the LVOT overtime may lead to compensatory left ventricular concentric hypertrophy.
- Spectrum of disease
  - The amount of the obstruction may vary from mild to severe and may progress overtime.
  - Individuals with mild or moderate LVOT obstruction may be asymptomatic, and as obstruction worsens, patients may present with signs and symptoms of left-sided obstruction.
    - Left ventricular hypertrophy may develop due to long-standing increased LVOT obstruction.

- Associated defects
  - Discrete subaortic membranes are occasionally associated with premium atrial septal defects, membranous ventricular septal defects, coarctation of the aorta, double outlet right ventricle, and tetralogy of Fallot.
  - Diffuse subvalvular stenosis is associated with hypoplasia of the aortic annulus, dysplasia of the aortic valve, mitral stenosis, and a small, thick left ventricle.

Diagnostics

Clinical Presentation in Adults

- Individuals with subaortic stenosis may present with dyspnea with exertion, chest pain with exertion, fatigue, endocarditis, arrhythmia, or heart failure.

Physical Exam

- Systolic crescendo-decrescendo murmur with an absence of an ejection sound is heard best in the mid-left sternal border.
- A diastolic murmur of aortic regurgitation is heard in over 50% of patients.
- The intensity of the subaortic stenosis murmur usually decreases with the Valsalva maneuver.

Electrocardiography

- Increased QRS voltage may be seen on electrocardiogram in those patients who have developed left ventricular hypertrophy as a result of the LVOT obstruction.

Chest X-Ray

- The chest radiograph is usually normal in patients with subaortic stenosis.

Echocardiography

- The location of the subaortic membrane in relation to the aortic valve, mitral valve, and the severity aortic insufficiency (if any) can be evaluated by transthoracic echocardiography (Figs. 14.1 and 14.2).
- LVOT turbulence by color Doppler below the level of the aortic valve should raise suspicion for a subaortic membrane.
- Peak and mean instantaneous gradients can be measured noninvasively using Doppler.
- Table 14.1 highlights the essentials of echocardiographic assessment of patients with subaortic stenosis.

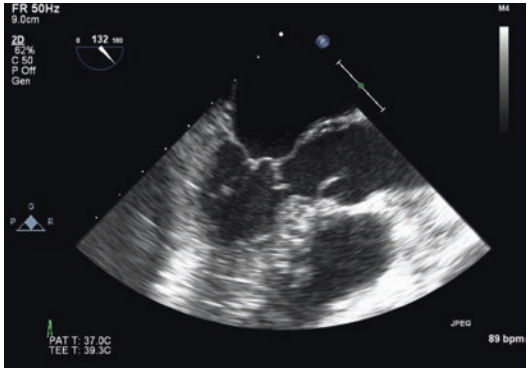

Figure 14.1 Transesophageal image of a subaortic membrane located in the left ventricular outflow tract and also attached to the base of the anterior mitral valve leaflet

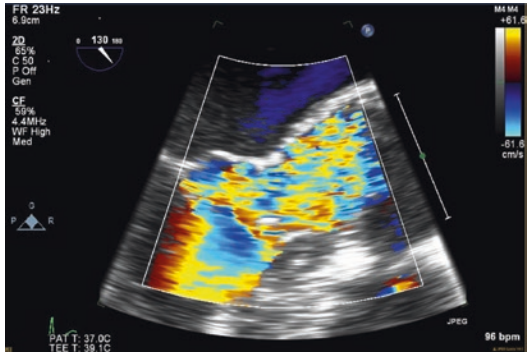

Figure 14.2 Transesophageal image showing turbulence using color Doppler in the left ventricular outflow tract that begins subvalvular at the level of the subaortic membrane

Table 14.1 Echocardiographic essentials for assessment [3]

1. Identify the nature and location of the membrane
2. Evaluate the degree of LVOT stenosis by Doppler
3. Evaluate aortic annular dimension, aortic valve morphology, and severity of aortic regurgitation
4. Evaluate left ventricular size, mass, and function
5. Exclude associated defects including septal defects and double-chambered right ventricle

Cardiac Catheterization

- Invasive hemodynamic assessment of the subaortic stenosis can be performed by measuring a peak-to-peak gradient proximal and distal to the subaortic stenosis.
- Direct gradient measurement by cardiac catheterization is helpful in those individuals with serial stenosis—such as with concomitant aortic valve stenosis.

Advanced Imaging Techniques

- Advanced imaging techniques such as computed tomography or cardiac magnetic resonance imaging are usually not indicated for diagnosis.

Management of Adult Survivors

- Surgical resection of discrete subaortic membranes are able to be performed without compromise to the native aortic valve. However, intervention on the aortic valve is usually performed in the setting of significant aortic regurgitation at the time of surgery.
- Diffuse subaortic stenosis usually requires a more extensive resection and enlargement of the LVOT with a Konno operation.
- Percutaneous intervention (balloon dilation) of the membrane is usually not successful [2] and not recommended.
- Approximately 15% of patients develop endocarditis [1], and endocarditis precautions should be discussed with the patient.
- Surgical indications for subaortic stenosis intervention are stated in Table 14.2.
- Postoperative complications include damage to the aortic or mitral valve (if the subaortic membrane extends toward the anterior mitral valve leaflet), heart block, iatrogenic VSD, and infectious endocarditis.
- After resection ~15% of subaortic membranes may recur [1], and lifelong follow-up is recommended.

Management of Pregnancy

- Left ventricular outflow obstruction is a maternal risk factor for with pregnancy.

Table 14.2 ACC/AHA guidelines 2008 [4]

Recommendations	Recommendations
Class I	1. Lifelong cardiology follow-up, including evaluation by an ACHD specialist, is recommended for all patients with repaired or unrepaired subaortic stenosis (*LOE: C*) 2. An unoperated, asymptomatic adult with subaortic stenosis and stable LVOT obstruction (mean gradient <30 mmHg) without left ventricular hypertrophy or significant aortic regurgitation should be monitored at yearly intervals for increasing obstruction, the development or progression of aortic regurgitation, and the evaluation of left ventricular systolic and diastolic function (*LOE: B*) 3. Surgical intervention is recommended for individuals with subaortic stenosis and peak Doppler gradient of 50 mmHg or a mean Doppler gradient of 30 mmHg by echocardiography (LOE: C) 4. Surgical intervention is recommended for subaortic stenosis with peak gradient <50 mmHg or mean gradient <30 mmHg by Doppler who have progressive aortic regurgitation and a left ventricular end-systolic diameter of >50 mm or left ventricular ejection fraction of less than 55%. (*LOE:C*)

- ACC/AHA Guidelines state that surgical resection may be considered in women with subaortic stenosis and a peak Doppler gradient of <50 mmHg or a mean Doppler gradient <30 mmHg if pregnancy is being planned.
- Unlike with valvular aortic stenosis, catheter balloon dilation is not an option during pregnancy for women with subaortic stenosis.

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Chapter 15
Congenital Valvular Aortic Stenosis

Lucy M. Safi

Abbreviations

AR	Aortic regurgitation
AS	Aortic stenosis
AV	Aortic valve
BA	Bicuspid aortic valve
CT	Computed tomography
LOE	Level of evidence
LV	Left ventricle
MRA	Magnetic resonance angiogram

Epidemiology

- Congenital valvular aortic stenosis has multiple morphologic variations including unicuspid aortic valve (AV), bicuspid aortic valve (BAV), or quadricuspid AV (Fig. 15.1).

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- BAV is the most common congenital heart lesion, is estimated to occur in 1–2% of the general population, may be inherited, and has a male predominance.

Anatomic Definition and Pathophysiology

- Anatomy **(**Fig. 15.1**)**:
  - BAV occurs when there is fusion of two cusps of the AV—forming a raphe at the site of fusion. The fusion may be partial or complete.
  - The most commonly fused leaflets are the right and the left leaflet (horizontal commissure) in which the commissures are oriented anteriorly and posteriorly. Fusion of the right and noncoronary leaflets (vertical commissure) is the second most common orientation and fusion of the left, and noncoronary leaflets are the least common [1].

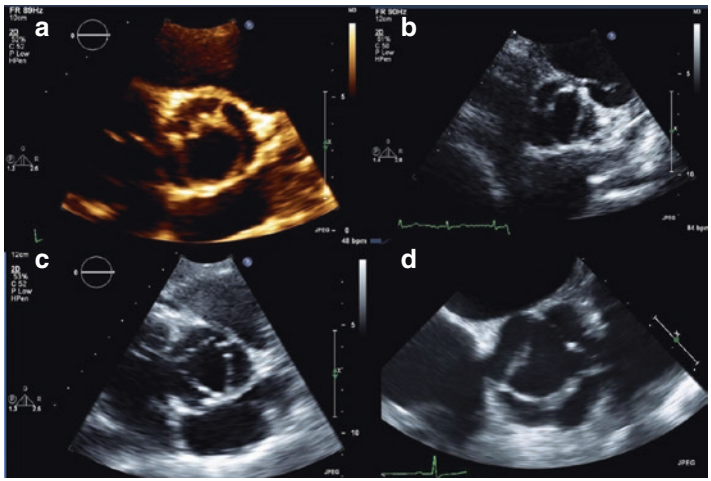

Figure 15.1 Echocardiographic short-axis images of the aortic valve. (**a**) Unicuspid aortic valve (note the open commissure between the left and the non-cusps). (**b**) Bicuspid aortic valve. (**c**) Tricuspid aortic valve. (**d**) Quadricuspid aortic valve

  - BAV can also be classified by types [2]: type 0, no raphe; type 1, one raphe; and type 2, two raphe—followed by description of spatial position and function.
  - Progressive valvular calcification leading to stenosis of the aortic valve may make it difficult to identify the individual leaflets.
  - Unicuspid valve has a "keyhole" appearance with a single commissure usually located between the left and noncoronary leaflets. Patients with unicuspid aortic valves rarely present in adulthood.
  - Quadricuspid aortic valves are very rare. Fibrous thickening leading to incomplete coaptation is more common than valvular stenosis. Hurwitz and Roberts classified quadricuspid aortic valves into seven types (types A–G) based on the size of the aortic leaflets [3]. Quadricuspid aortic valves are associated with truncus arteriosus.

- Physiology:
  - Left ventricular outflow obstruction increases ventricular afterload over time leading to increased left ventricular pressure and secondary concentric left ventricular hypertrophy.
  - Leaflet fusion limits the mobility of the aortic valve leaflets leading to fibrosis and calcification.
  - Patients with congenital valvular anomalies (BAV, unicuspid aortic valve, quadricuspid aortic valve) are at risk for aortic stenosis or regurgitation.

- Spectrum of disease:
  - The spectrum of aortic stenosis is variable and can vary from aortic sclerosis without stenosis to mild, moderate, or severe aortic stenosis.
  - Critical aortic stenosis in a fetus limits systemic blood flow and can lead to hypoplastic left heart or hypoplastic aorta. Without prostaglandin E intervention immediately following birth, infants will be at risk for cardiovascular collapse.
  - Individuals with mild stenosis may be asymptomatic until discovered during routine physical examinations later in life.

  - Individuals with BAV leading to stenosis traditionally require intervention at younger ages than those with tricuspid aortic valves.

- Associated defects:
  - BAV is associated with aortopathies where abnormalities of the smooth muscle, extracellular matrix, elastin, and collagen of the ascending aorta may lead to ascending aortic dilation and an increased risk of aortic dissection over time.
  - BAV is also associated with subaortic stenosis, atrial septal defects, ventricular septal defects, mitral valve prolapse, and aortic coarctation.
  - Importantly, the Ross procedure may be an option for some valvular aortic disease patients; however, it is not indicated in the presence of associated right ventricular outflow tract abnormalities. Therefore, though a less common association, the RVOT should be thoroughly evaluated.

- Genetics and maternal factors:
  - BAV may occur sporadically or with familial inherence and variable penetrance. A mutation in the NOTCH pathway has been associated with BAV.
  - Certain genetic syndromes and diseases have an association with BAV including Turner syndrome, Loeys-Dietz syndrome, Shone's complex, and aortic coarctation. Echocardiography to exclude the presence of a BAV is usually indicated if diagnosed with one of these syndromes.

Diagnostics

Clinical Presentation in Adults

- The clinical presentation is variable and is based on the amount of aortic regurgitation or aortic stenosis present.

- Symptoms can vary from asymptomatic to severe left ventricular outflow obstruction leading to heart failure, syncope, angina, or ventricular dysfunction.
- In women, the first presentation of disease may be in the setting of pregnancy.
- Aortic stenosis may be progressive and require intervention later in life.

Physical Exam

- A prominent mid-systolic ejection click may be heard with or without the murmur of aortic stenosis or regurgitation in young patients with a BAV.
- If a concomitant aortic coarctation is present, auscultation of the left scapular region may identify the murmur.

Electrocardiography

- There are no specific electrocardiographic findings to suggest congenital aortic stenosis.
- Secondary effects from aortic stenosis may be seen on ECG including increased QRS voltage due to left ventricular hypertrophy.

Chest X-Ray

- The chest radiograph of a patient with congenital valvular disease can be normal; however, associated findings like aortic root dilation may be visualized as a prominent right mediastinum.
- Late stages of aortic stenosis may show cardiomegaly and pulmonary vascular congestion.

Echocardiography

- The gold standard of diagnosis and follow-up of congenital aortic stenosis is Doppler echocardiography.
- Findings suggestive of congenital aortic stenosis on echocardiography include systolic aortic valve leaflet doming, eccentric aortic valve leaflet closure, aortic regurgitation, aortic stenosis, and ascending aortic dilatation.
- Ascending aorta root dilatation may be seen with BAV (Fig. 15.2). In patients with BAV, aortic root dimensions at the sinus of Valsalva, sinotubular junction, and ascending aorta should be reported.
- Table 15.1 highlights the essentials of echocardiographic assessment of patients with valvular aortic stenosis.
- It is recommended that those patients with BAV undergo routine follow-up with echocardiography. The frequency of the echocardiograms is based on the severity of the disease; see Table 15.2.

Cardiac Catheterization

- Cardiac catheterization may be indicated in those patients whose echocardiographic Doppler measurements do not correlate with the patient's symptoms.

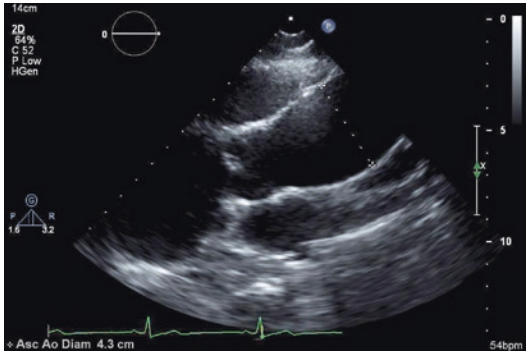

Figure 15.2 Transthoracic echocardiographic imaging of a patient with a unicuspid aortic valve showing a dilated ascending aorta

Table 15.1 Echocardiographic essentials for assessment [4]

1. Morphologic aortic valve features and location of commissural fusion (raphe)
2. Degree of stenosis and/or regurgitation
3. Estimated aortic valve area, peak, and mean Doppler aortic valve gradients
4. Dimensions of the aortic annulus, sinuses of Valsalva, and ascending aorta
5. LV size, mass, and function
6. Exclude associated congenital lesions including aortic coarctation, subaortic stenosis, supramitral ring, atrial septal defects, ventricular septal defects, and mitral valve abnormalities

Table 15.2 Echocardiographic assessment of valvular stenosis

	Peak Doppler velocities (m/s)	**Mean Doppler velocities (mmHg)**	**Follow-up echocardiogram (year)**
At risk	Vmax < 2	$\Delta P < 20$	As clinically indicated
Progressive (mild)	Vmax = 2–2.9	$\Delta P < 20$	3–5
Progressive (moderate)	Vmax = 3–3.9	$\Delta P \geq 20$–40	1–2
Severe	Vmax ≥ 4	$\Delta P \geq 40$	0.5–1

- "Pullback" aortic valve gradients (peak-to-peak aortic valve gradient) correlate with echocardiographic mean Doppler gradients.
- Invasive direct measurement of gradients may be needed in the setting of serial left-sided stenosis to better differentiate the gradients at each level of obstruction.

Advanced Imaging Techniques

- Echocardiography is usually the first imaging modality ordered to diagnose and follow patients with congenital aortic stenosis. When assessment of the aortic root is unclear by echocardiography or if imaging of the entire aorta is needed, advanced imaging modalities such as computerized tomography (CT) angiography or cardiac magnetic resonance (CMR) imaging can be used.
- CMR offers no radiation to young patients who need serial imaging of the aorta to follow aortic dimensions (Fig. 15.3) and is also able to calculate left ventricular ejection fraction and regurgitant volume of heart valves.

Management of Adult Survivors

See Table 15.3 for summary of Valvular Guidelines.

- Adults with BAV leading to stenosis may require intervention earlier in life than those with tricuspid aortic valves.
- Aortic stenosis is defined as a transaortic valve gradient greater than 2 m/s. A transaortic valve velocity greater

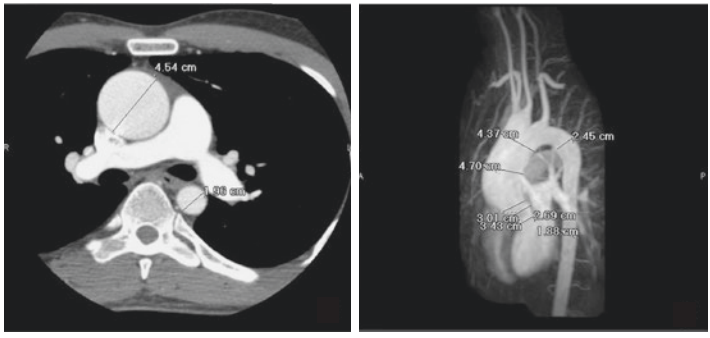

FIGURE 15.3 CMR of a patient with a bicuspid aortic valve showing a dilated ascending aorta

Table 15.3 ACC/AHA valvular guidelines 2014 [5]

Recommendations	Recommendations
Class I	1. Echocardiography is recommended for those with known BAV to evaluate valve morphology, AS/AR severity, shape and diameter of the aortic sinuses and ascending aorta for prediction of clinical outcome and to determine timing of intervention (LOE:B)
	2. Aortic MRA or CT angiography is indicated in patients with BAV when morphology of the aortic sinuses, sinotubular junction, or ascending aorta cannot be assessed accurately or fully by echocardiography (LOE: C)
	3. Serial evaluation of the size and morphology of the aortic sinuses and ascending aorta by echocardiography, CMR, or CT angiography is recommended in patients with a BAV and an aortic diameter greater than 4.0 cm, with the examination interval determined by the degree and rate of progression of aortic dilation and by family history. In patients with an aortic diameter greater than 4.5 cm, this evaluation should be performed annually (LOC: C)
	4. Operative intervention to repair the aortic sinuses or replace the ascending aorta is indicated in patients with a BAV if the diameter of the aortic sinuses or ascending aorta is >5.5 cm (LOC: B)

(continued)

Table 15.3 (continued)

Recommendations	Recommendations
Class IIa	1. Operative intervention to repair the aortic sinuses or replace the ascending aorta is reasonable in patients with BAV, and the diameter of the aortic sinuses or ascending aorta is >5.0 cm, and a risk factor for dissection is present (family history of aortic dissection or if the rate of increase in diameter is ≥0.5 cm/year) (LOE: C)
	2. Replacement of the ascending aorta is reasonable in patients with a bicuspid aortic valve who are undergoing aortic valve surgery because of severe AS or AR if the diameter of the ascending aorta is greater than 4.5 cm (LOE: C)

than 4 m/s and an aortic valve area of less than 1 cm^2 are consistent with severe aortic stenosis.

- Importantly young patients with aortic stenosis may tolerate much higher gradients prior to symptom development compared to older patients with a less compliant left ventricle.
- Surgical or transcatheter aortic valve replacement (TAVR) is recommended for symptomatic severe aortic stenosis.
- Percutaneous valvuloplasty may be therapeutic in a young patient with a stenotic BAV and no significant calcification or aortic regurgitation.
  - Risk factors associated with the percutaneous valvuloplasty procedure include resulting significant aortic insufficiency (~10%) [6] and embolic phenomenon such as stroke.
- Isolated aortic insufficiency from a BAV occurs less frequently than aortic stenosis:
  - The etiology of the aortic insufficiency in these patients may be due to leaflet redundancy or prolapse, leaflet thickening, aortic root dilation, post-valvuloplasty procedure, or endocarditis leading to leaflet perforation or destruction.

- BAV and aortopathy:
  - Medical therapy is recommended for blood pressure control. There is no proven benefit from beta blocker or losartan.
  - Serial aortic measurements are recommended to evaluate and follow aortic dilatation.
  - Surgical intervention is reasonable for those patients with a BAV and ascending aortic measurement of >5.5 cm, BAV and an ascending aorta measurement of ≥5.0 cm, and risk factor for dissection (e.g., family history of dissection or growth rate ≥ 0.5 cm/year) [7].
  - For those patients with a BAV already referred for surgical intervention, it is reasonable to also replace the ascending aorta when the aorta diameter is ≥4.5 cm [7].
- Prophylaxis for endocarditis (such as for dental procedures or labor) is not recommended unless there is a prior history of endocarditis.
- Screening echocardiogram of first-degree family members is recommended for those with a BAV.

Management of Pregnancy

- Women with severe aortic stenosis are at increased risk for cardiac complications with pregnancy [8, 9].
- Fixed left heart stenotic lesions make it difficult for pregnant patients to be able to obtain the required cardiac output and tolerate the volume load associated with pregnancy.
- The fetus can also be affected because of fixed stroke volume leading to decreased placental flow.
- Maternal risk during pregnancy is related to the severity of the stenosis as well as the presence of symptoms. Class I indications for intervention in valvular AS prior to pregnancy include symptoms at rest or with exertion, LVEF <50%, and an aortic diameter ≥ 5.0 cm.
- BAV is the most common cause of aortic stenosis in women of childbearing age.

- Prepregnancy:
  - Prepregnancy counseling is recommended for those patients with congenital aortic stenosis.
  - Aortic stenosis is highly heritable with rates of 10–40% in offspring.
  - A baseline echocardiogram is usually preferred prior to pregnancy to evaluate severity of aortic valve disease as well as assess the size of the aorta.
  - Importantly, transvalvular aortic valve gradients are expected to increase along with cardiac output during pregnancy.
  - Exercise stress testing can be used to evaluate heart rate and blood pressure response with exercise, evaluate for arrhythmia, and confirm asymptomatic state prior to pregnancy.
- Peripartum management:
  - Patients should be followed generally each trimester by a cardiologist experienced in managing cardiac disease in pregnancy for signs and symptoms of severe aortic stenosis including angina, syncope, and heart failure. Often multidisciplinary team (obstetrics, cardiology, anesthesia, etc.) management is required.
  - Strict blood pressure control while pregnant is strongly recommended. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are contraindicated during pregnancy due to teratogenic effects on the fetus.
  - In mild or moderate stenosis, assisted vaginal delivery with regional analgesia is generally tolerated [10]. Minimizing the hemodynamic effects of the Valsalva maneuver using a facilitated second stage of labor (forceps or vacuum extraction) may be performed.
  - Percutaneous balloon valvotomy may be considered in patients with severe aortic stenosis who develop symptoms refractory to medical management during pregnancy.

- Pregnant patients with a BAV and aortic dilation are at increased risk for aortic dissection:
  - BAV with an aortic dilatation of 45–50 mm carries a significantly increased maternal morbidity and mortality risk with pregnancy [10].
  - A prophylactic aortic root replacement should be considered in those with BAV and a dilated aorta (>50 mm) who are contemplating pregnancy.
  - Cesarean section is reasonable for pregnant patients with a BAV and a dilated aorta [11].
- In individuals who undergo a mechanical valve replacement prior to surgery, options for anticoagulation in pregnancy are evolving and enumerated in Chap. 37.

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Chapter 16
Supravalvular Aortic Stenosis

Lucy M. Safi

Abbreviations

ACHD	Adult congenital heart disease
CMR	Cardiac magnetic resonance
LOE	Level of evidence
LV	Left ventricle
MRA	Magnetic resonance angiography

Epidemiology

- Supravalvular aortic stenosis is rare and may occur sporadically (most common) or be inherited or related to a genetic disorder such as Williams syndrome [1].
- See Table 16.1 for historical background.

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Table 16.1 Historical background

John Cyprian Phipps Williams, a New Zealand cardiologist, published a case report in 1961 of four patients with supravalvular aortic stenosis who also shared multiple physical and mental characteristics. A year later, Beuren et al. also published a case series of five patients with similar findings [1]. Due to these publications, the syndrome including supravalvular stenosis, mental retardation, abnormal facies, and hypercalcemia has been referred to as Williams syndrome or Williams-Beuren syndrome

Anatomic Definition and Pathophysiology

- Anatomy:
  - Supravalvular aortic stenosis is a narrowing or a fixed obstruction of variable length that occurs superior to the sinus of Valsalva usually in the location of the sinotubular junction. Varying amount of accompanying stenosis or hypoplasia may occur in the ascending aorta, aortic arch, and aortic arch vessels.
  - The obstruction appears as an hourglass deformity of the aorta due to a discrete membrane or from a diffuse tubular narrowing of the aorta.
  - The origin of the coronary arteries is usually proximal to the obstruction. The coronary artery ostia may be dilated, tortous, and rarely there may be partial ostial coronary artery obstruction.
- Physiology:
  - Left-sided outflow obstruction from supravalvular stenosis increases afterload on the left ventricle (LV) and over time may lead to LV hypertrophy.
  - Narrowing of the ascending aorta causes increased LV outflow velocities, increased systolic blood pressure, and dilation of the aorta proximal to the stenosis. In the presence of ostial coronary artery stenosis, limited diastolic blood flow into the coronary arteries may lead to exertional ischemia.

- Spectrum of disease:
  - There is a wide spectrum of clinical disease seen with supravalvular stenosis. Patients with sporadic or familial varieties may have isolated supravalvular stenosis, whereas individuals with Williams syndrome may have multilevel obstruction.
- Associated defects:
  - Supravalvular aortic stenosis is commonly seen with Williams syndrome. Other defects associated with Williams syndrome include: aortic hypoplasia, large branch aortic artery stenosis (e.g. renal artery stenosis), and long segment pulmonary artery stenosis.
  - Other defects associated with supravalvular stenosis include: valvular aortic stenosis, ostial aortic coarctation, pulmonary artery or branch pulmonary artery stenosis, and ostial head and neck artery stenosis (off of the aorta).
- Genetics and maternal factors:
  - Williams syndrome is an autosomal dominant syndrome associated with deletion in the elastin gene on chromosome 7q11.23. Patients with Williams syndrome have supravalvular aortic stenosis, abnormal facies, mental retardation, and hypercalcemia.
  - In those patients with homozygous familial hypercholesterolemia, acquired supravalvular obstruction may occur from atheroma deposition and calcification.

Diagnostics

Clinical Presentation in Adults

- Unrepaired supravalvular stenosis may present in adulthood with symptoms of left ventricular outflow obstruction, hypertension, or ischemia.

Figure 16.1 This figure demonstrates a patient with the "elfin facies" of Williams syndrome. Note the broad forehead, flat nasal bridge, long philtrum, and full lips with wide mouth. (Photos courtesy of the Williams Syndrome Association)

Physical Exam

- The physical exam findings of a patient with Williams syndrome include short stature, "elfin" facies (broad forehead, flat nasal bridge, long philtrum, and full lips with wide mouth; Fig. 16.1), mental retardation, and hypertension.
- Supravalvular aortic stenosis may direct blood flow predominately toward the right innominate artery leading to higher blood pressure in the right arm compared to the left arm.
- A systolic ejection murmur is usually heard in the right-sided first intercostal space with no associated opening click.

Electrocardiography

- The electrocardiogram of patients with supravalvular stenosis may be normal or show increased QRS voltage with strain pattern in those who have developed LV hypertrophy.

Chest X-Ray

- The chest radiograph of a patient with supravalvular stenosis is usually normal.

Echocardiography

- Evaluation of the aorta including the aortic valve, ascending aorta, and aortic arch by color and spectral Doppler is recommended to evaluate for the presence and severity of supravalvular stenosis [2] (Fig. 16.2).
- Multiple echocardiographic imaging planes are recommended to best align the Doppler probe with the gradient and obtain the maximal instantaneous gradient. Careful evaluation of the arch and arch vessels with Doppler is recommended into order to exclude stenosis.
- Table 16.2 highlights the essentials of echocardiographic assessment of patients with supravalvular aortic stenosis.

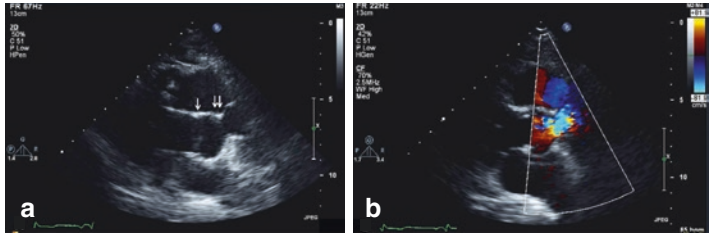

FIGURE 16.2 Echocardiographic imaging showing a supravalvular stenosis. In image (**a**), the single arrow is pointing to the aortic valve annulus, and the double arrow is pointing to the supravalvular stenosis. Image (**b**) shows turbulence in the ascending aorta in the location of the supravalvular stenosis

Table 16.2 Echocardiographic essentials for assessment [2]

1.	Evaluate the location and degree of the supravalvular stenosis
2.	Determine the dimensions of the aortic root and ascending aorta
3.	Determine the aortic arch anatomy and evaluate for stenosis
4.	Evaluation of left ventricular size, function, and mass

Cardiac Catheterization

- Cardiac catheterization may be performed to measure a direct gradient across the stenosis. This may be helpful in the setting of concomitant valvular stenosis.

Advanced Imaging Techniques

- Magnetic resonance angiography imaging may be used to supplement echocardiographic imaging to diagnose and follow supravalvular aortic stenosis.

Management of Adult Survivors

See Table 16.3 for summary of guidelines.

- Adult patients with supravalvular stenosis are usually followed by or in collaboration with ACHD specialists.
- Endocarditis prophylaxis for supravalvular stenosis is usually not recommended unless the patient has a history of endocarditis or aortic repair that required prosthetic material or device.

Management of Pregnancy

- An increase in cardiac output and blood volume occurs with pregnancy. Individuals with fixed left heart stenotic lesions may not be able to tolerate the required hemodynamic changes associated with pregnancy.

Table 16.3 ACC/AHA guidelines 2008 [3]

Recommendations	Recommendations of management and treatment
Class I	1. Patients with supravalvular aortic stenosis should be followed at a regional ACHD center annually (LOE:C) 2. In patients with discrete or diffuse supravalvular obstruction and symptoms and/or echocardiographic peak Doppler gradient >70 mmHg or mean Doppler gradient >50 mmHg, operative intervention should be performed (LOE: B) 3. Operative intervention is recommended with lesser degree of obstructions in the setting of: (a) Symptoms (e.g., angina, dyspnea, or syncope) (*LOE: B*) (b) Left ventricular hypertrophy (LOE:C) (c) Planned pregnancy or limited exercise tolerance (LOE:C) (d) Left ventricular dysfunction (LOE:C) 4. Coronary artery intervention for patients with supravalvular aortic stenosis and coronary artery obstruction should have interventions performed at ACHD-experienced centers (*LOE: C*)

- The peripartum management of patients with supravalvular aortic stenosis is similar to those patients with congenital valvular aortic stenosis.
- Preconception counseling is advised to patients with supravalvular obstruction, and usually an echocardiogram is ordered to evaluate the severity of the obstruction.

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Chapter 17
Coarctation of the Aorta

Akl C. Fahed

Abbreviations

AS	Aortic stenosis
BAV	Bicuspid aortic valve
CHD	Congenital heart disease
CT	Computed tomography
MR	Magnetic resonance
MV	Mitral valve
PDA	Patent ductus arteriosus
VSD	Ventricular septal defect

Epidemiology

- Coarctation of the aorta constitutes 6–8% of congenital heart disease and occurs at a frequency of 4 in 10,000 live births [1]. It is two times more common in males than in females.

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Table 17.1 Historical background

The first description of coarctation of the aorta was in 1760 by Morgagni. In 1832, a reported case of coarctation of the aorta was published in an autopsy report on Julia the daughter of the French poet Alphonse de Lamartine in Beirut. The manuscript still exists in the one of the Maronite monasteries of Mount Lebanon. The preductal vs. postductal types were first distinguished by Bonnet in 1903. It was not until 1944 that Crawford performed the first surgical repair of coarctation.

Historical Background

- For historical background, see Table 17.1.

Anatomic Definition and Pathophysiology

- Anatomy:
  - Coarctation of the aorta is a narrowing in the region of the ligamentum arteriosum near the origin of the left subclavian artery. The narrowing may be a discrete membranous shelf or a long segment of hypoplasia of the distal transverse arch and isthmus. The origin of the left subclavian artery may be involved.
- Physiology:
  - Obstruction to outflow occurs due to the narrowing, with systolic flow acceleration through the narrow segment and significant pressure gradient across it. As a consequence, the coronary arteries and cerebral vasculature are exposed to a high pressure that is not transmitted to the lower body. Collateral vessels may develop from arteries in the upper chest (proximal to the coarctation) to the descending aorta (distal to the coarctation) to offload this elevated pressure. If these collaterals are large, they may reduce the measured gradient across the coarctation.
  - Blood pressure in the upper extremities is usually higher than the lower extremities. In a small percentage

of cases, the right subclavian artery originates distal to the coarctation, and right arm pressures may reflect the post-coarctation pressure.

- Spectrum of disease—There are two types of coarctation of the aorta:
  - *Preductal*: This constitutes 70% of cases and is generally diagnosed in infancy. The narrowing is proximal to the ductus arteriosus. Perfusion of the lower body is dependent on the patent ductus arteriosus.
  - *Postductal*: This constitutes ~30% of cases and may present in adulthood. The narrowing is distal to the ductus arteriosus.
- Associated defects:
  - *Bicuspid aortic valve* (*BAV*): 50–60% of the cases in adults are associated with BAV [2].
  - *Shone's complex*: Describes the occurrence of coarctation with multiple left heart obstructive lesions (subaortic stenosis, BAV, parachute mitral valve, or supramitral ring). It is often detected in childhood and requires surgical correction prior to the occurrence of secondary pulmonary hypertension. Treatment delay is associated with poor outcomes and need for heart-lung transplant [3]. Recurrent need for surgical intervention may be common in adulthood and lead to late presentation of pulmonary arterial hypertension.
  - *Circle of Willis* (*berry*) *aneurysms*: One-time screening of the intracranial vessels using MR or CT is recommended in all patients with coarctation (ACC/AHA Class I recommendation).
  - *Turner syndrome*: Preductal coarctation is seen in 5% of individuals with Turner syndrome.
  - *Other*: Several associations are seen in the infantile type of coarctation, including PDA (70%), arch hypoplasia (45%), malalignment VSD (30%), subvalvular AS (25%), mitral valve abnormalities (25%), complete transposition of the great arteries (10%), complete atrioventricular septal defects (5%), and aortic stenosis or atresia (5%) [4].

- Genetics:
  - Familial clustering as well as autosomal dominant inheritance has been reported in coarctation of the aorta. Similar to most congenital heart disease, there is often incomplete penetrance and co-occurrence of other CHD phenotypes. Overall, the recurrence rate in siblings is 0.5% for coarctation and 1% for any form of CHD [5]. Some of the single gene defects associated with coarctation in familial studies are *VEGF*, *NOTCH1*, *NKX2-5*, and *LEFTY2* [6].

Diagnostics

Clinical Presentation in Adults

- The majority (85%) are diagnosed in childhood. Recoarctation following surgical repair or balloon dilation and/or stenting could occur in adulthood. Adult presentation is typically associated with resting or exercise-related hypertension [7].
- Factors associated with recoarctation include small patient size, younger age at operation, and transverse arch hypoplasia.
- If untreated, the median survival of adults with coarctation is 31 years [8].

Physical Exam

- The pulse and blood pressure should be evaluated in all four extremities. Radial-femoral delay may be present. Upper-extremity hypertension (arm-to-leg gradient of >20 mmHg) is the characteristic but not always present. An arm-to-leg blood pressure differential of >35 mmHg is likely to be a severe coarctation.

- A systolic bruit may be heard over the upper left back.
- If BAV is also present, a systolic ejection sound, a precordial outflow murmur, or an aortic regurgitation murmur might be heard.

Electrocardiography

- The ECG may show signs of left ventricular hypertrophy.

Chest X-ray

- Aortic indentation at the site of the coarctation is referred to as the "3 sign."
- Notching on the underside of the ribs reflects collateral vessel formation (Fig. 17.1).

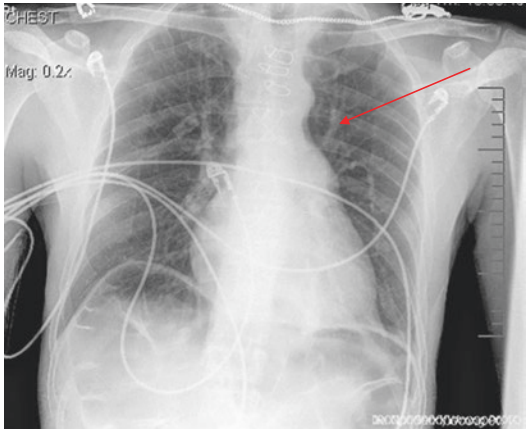

FIGURE 17.1 Classical CXR with the three sign (*red arrow*) and subtle rib notching (Adopted with permission from [2])

Echocardiography

- The anatomic narrowing is best visualized in the suprasternal notch view or high left parasternal view on (2D) echo imaging. If the coarctation occurs over a long segment of the arch, there would be systolic flow acceleration. Doppler estimates of the pressure gradient from the peak velocity, however, are often unreliable due to the pressure recovery phenomenon [2].
- Doppler flow patterns in the descending thoracic aorta are seen best on subcostal imaging. There is typically delay in systolic upstroke, turbulent high-velocity flow in systole, and anterograde flow in diastole (Fig. 17.2). It is essential to perform subcostal imaging as distal coarctation of tortuous or serpentine aortic narrowing may be missed by Doppler estimation at the suprasternal notch.
- Table 17.2 highlights the essentials of echocardiographic assessment of patients with coarctation of the aorta.

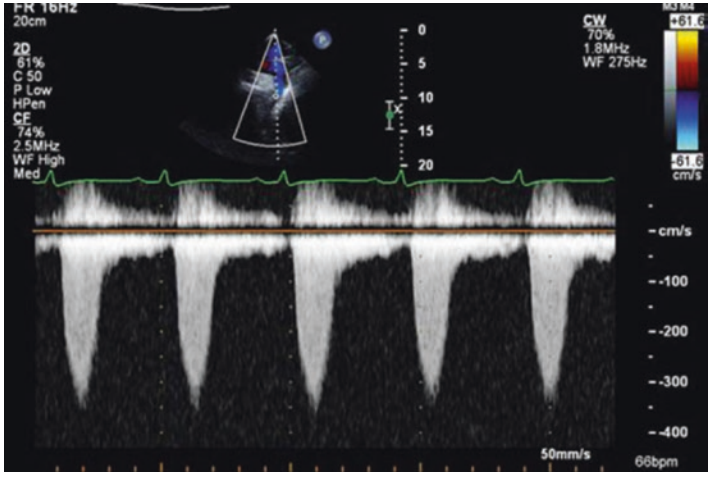

Figure 17.2 2D echocardiogram, Doppler profile of anterograde diastolic flow in the abdominal aorta (Adopted with permission from [2])

Table 17.2 Echocardiographic essentials for assessment [2]

Suprasternal notch
• Visualization of the coarctation • Visualization of the collateral vessel flow
Descending aorta
• Anterograde diastolic flow • Delay in systolic upstroke • Turbulent systolic flow

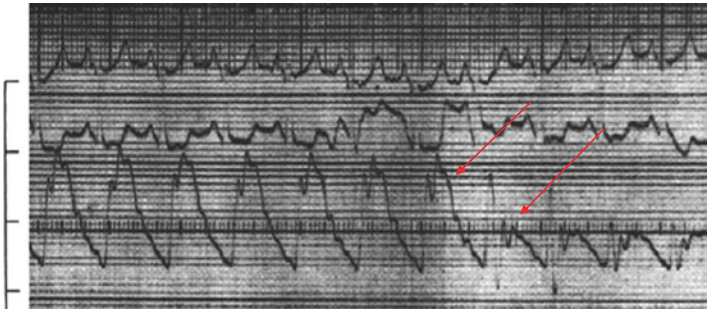

Figure 17.3 Invasive hemodynamics with catheter pullback across the coarctation site demonstrating significant drop in pressure (approximately 50 mmHg) distal to the area of coarctation (*red arrows*) (Adopted with permission [2])

Cardiac Catheterization

- Cardiac catheterization is rarely used to measure the gradient across the coarctation in cases in which the significance of the coarctation is unclear based on clinical exam and/or noninvasive evaluation (Fig. 17.3).
- Catheterization could also be used to perform percutaneous balloon dilation or stent placement in the coarctation, which is an acceptable alternative to surgical repair depending on the anatomy (Fig. 17.4).

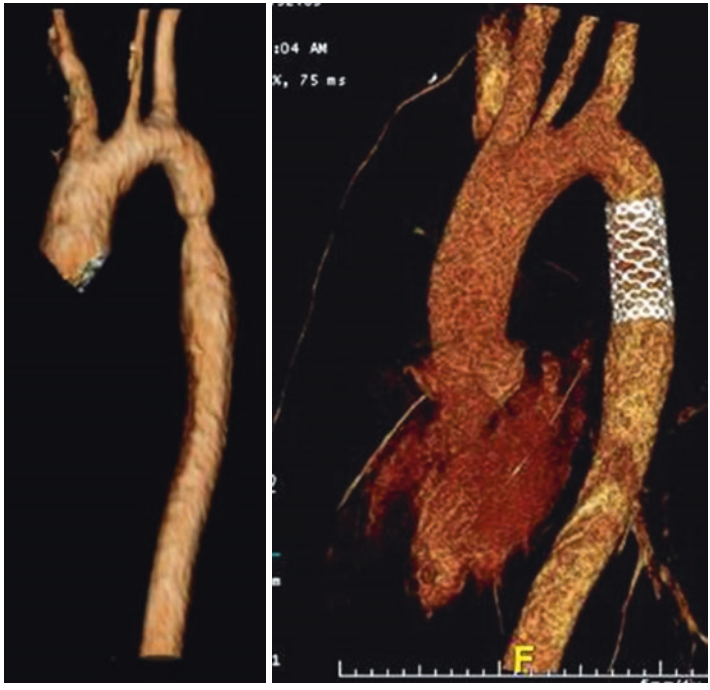

Figure 17.4 (*Left*) 3D-reconstructed CT angiography showing post-ductal coarctation in an adult patient who presented with exertional headaches and HTN. (*Right*) CTA showing the coarctation following percutaneous stenting

- Postsurgical restenosis of coarctation is often managed by percutaneous balloon dilation or stenting.
- The advent of covered stents to address coarctation and recoarctation may favor percutaneous intervention over surgical intervention in select cases.

Advanced Imaging Techniques

- CT angiography or cardiac MRI is necessary to fully characterize the location and extent of the severity of the coarctation, to define the involvement of the brachiocephalic

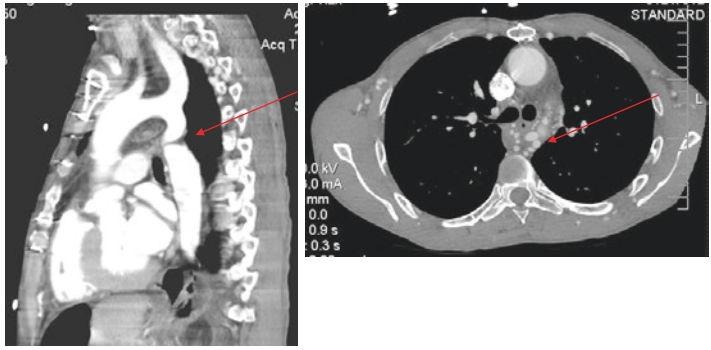

FIGURE 17.5 (*Left*) Depiction of discrete coarctation (*red arrow*) anatomy by CT angiography, sagittal section. (*Right*) Chest CTA, axial section, demonstrating prominent collateral flow axial imaging, small proximal descending aorta (*red arrow*) [2]

branches, and to identify associated lesions and collateral vessels (Fig. 17.5).

- CT and MR are also used to follow patients after repair. Current guidelines recommend imaging every 5 years to monitor for late complications such as recurrence of narrowing, formation of an aneurysm, or dissection [7].

Management of Adult Survivors

See Table 17.3 for summary of guidelines.

- Management and screening for systemic hypertension are critically important. Figure 17.6 highlights the pathophysiological changes and their related clinical consequences over the lifespan of a patient with coarctation of the aorta [9].
- Indications for intervention:
  - Peak-to-peak gradient of 20 mmHg (catheter-derived gradient) or greater regardless of hypertension.
  - Lesser gradient in the presence of imaging evidence of significant coarctation and collateral flow [7].

Table 17.3 ACC/AHA Guidelines 2008 [7]

Recommendations for clinical evaluation and follow-up

Class I

1. Every patient with systemic arterial hypertension should have the brachial and femoral pulses palpated simultaneously to assess timing and amplitude evaluation to search for the "brachial-femoral delay" of significant aortic coarctation. Supine bilateral arm (brachial artery) blood pressures and prone right or left supine leg (popliteal artery) blood pressures should be measured to search for differential pressure. (*Level of Evidence: C*)
2. Initial imaging and hemodynamic evaluation by TTE, including suprasternal notch acoustic windows, are useful in suspected aortic coarctation. (*Level of Evidence: B*)
3. Every patient with coarctation (repaired or not) should have at least one cardiovascular MRI or CT scan for complete evaluation of the thoracic aorta and intracranial vessels. (*Level of Evidence: B*)

Recommendations for interventional and surgical treatment

Class I

1. Intervention for coarctation is recommended in the following circumstances:
   (a) Peak-to-peak coarctation gradient greater than or equal to 20 mmHg. (*Level of Evidence: C*)
   (b) Peak-to-peak coarctation gradient less than 20 mmHg in the presence of anatomic imaging evidence of significant coarctation with radiological evidence of significant collateral flow. (*Level of Evidence: C*)
2. Choice of percutaneous catheter intervention versus surgical repair of native discrete coarctation should be determined by consultation with a team of ACHD cardiologists, interventionalists, and surgeons at an ACHD center. (*Level of Evidence: C*)
3. Percutaneous catheter intervention is indicated for recurrent, discrete coarctation and a peak-to-peak gradient of at least 20 mmHg. (*Level of Evidence: B*)

Table 17.3 (continued)

4. Surgeons with training and expertise in CHD should perform operations for previously repaired coarctation with the following indications:

   (a) Long recoarctation segment. (*Level of Evidence: B*)

   (b) Concomitant hypoplasia of the aortic arch. (*Level of Evidence: B*)

Class IIb

1. Stent placement for long-segment coarctation may be considered, but the usefulness is not well established, and the long-term efficacy and safety are unknown. (*Level of Evidence: C*)

Recommendations for key issues to evaluate and follow up

Class I

1. Lifelong cardiology follow-up is recommended for all patients with aortic coarctation (repaired or not), including an evaluation by or consultation with a cardiologist with expertise in ACHD. (*Level of Evidence: C*)

2. Patients who have had surgical repair of coarctation at the aorta or percutaneous intervention for coarctation of the aorta should have at least yearly follow-up. (*Level of Evidence:* C)

3. Even if the coarctation repair appears to be satisfactory, late postoperative thoracic aortic imaging should be performed to assess for aortic dilatation or aneurysm formation. (*Level of Evidence: B*)

4. Patients should be observed closely for the appearance or reappearance of resting or exercise-induced systemic arterial hypertension, which should be treated aggressively after recoarctation is excluded. (*Level of Evidence: B*)

5. Evaluation of the coarctation repair site by MRI/CT should be performed at intervals of 5 years or less, depending on the specific anatomic findings before and after repair. (*Level of Evidence: C*)

Class IIb

1. Routine exercise testing may be performed at intervals determined by consultation with the regional ACHD center. (*Level of Evidence: C*)

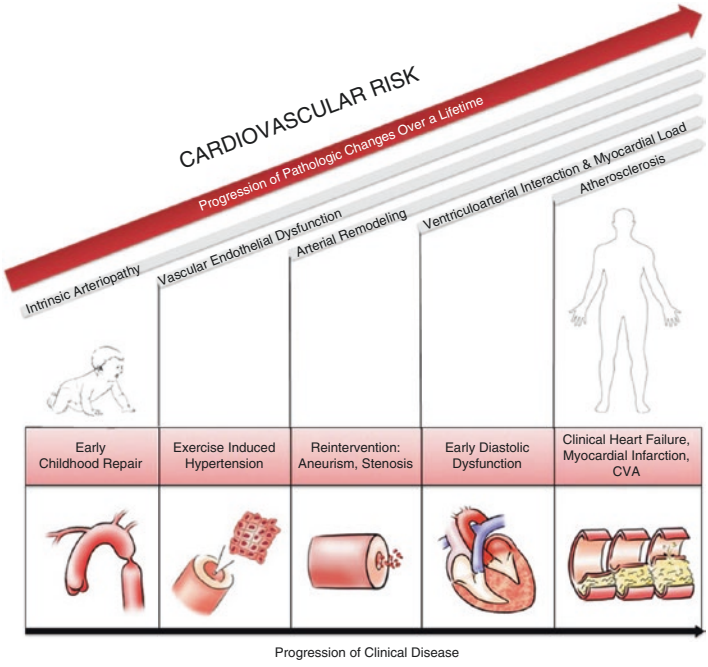

FIGURE 17.6 Superimposed pathophysiological changes and related clinical consequences over the lifespan of a patient with coarctation of the aorta (Adopted with permission from [9])

- Symptoms such as exertional headaches or claudication of the legs and refractory hypertension are clinical markers for significant disease.
- Exercise-induced hypertension and left ventricular hypertrophy are also important clinical parameters in the decision to intervene.
- Aortic events need prompt attention; however, aortic aneurysms, especially those at a repair site, are a sometimes overlooked and significant complication with high morbidity. Dacron patch aortoplasty carries the highest risk of aneurysm formation and should be assessed for with active surveillance imaging as detailed below.

- Choice of intervention:
  - Advanced imaging (CT and MRI) can help guide the appropriate interventional modality.
  - Surgical intervention is most appropriate for complex anatomy, long-segment tubular narrowing, and presence of an aneurysm, calcification, or poor compliance of the artery.
  - For complex coarctation (long-segment hypoplasia, associated arch anomalies, etc.), bypass grafting from the left subclavian (assuming there is no ostial involvement of the subclavian) or ascending aorta to the descending aorta could also be performed (Gott shunt).
  - Percutaneous intervention is appropriate if the narrowed side is short and amenable and does not involve the subclavian ostium. It is also commonly used in re-repair of coarctation after prior surgery.
  - Post-procedure complications could include aortic dissection, aortic rupture, or formation of an aneurysm, pseudoaneurysm, or rarely mycotic aneurysm at sites of anastomoses.
- Long-term follow-up:
  - Patients must be followed lifelong by adult congenital cardiology to assess for resting- or exercise-induced hypertension, complications of prior intervention, systolic and diastolic heart failure, and premature coronary artery disease.
  - In the absence of signs and symptoms, MRI/CT to evaluate the site of prior coarctation repair should be performed once every 5 years or less depending on the anatomy of repair (ACC/AHA Class I) to assess for late aneurysm formation or residual obstruction.
- The median age of death in untreated adults with coarctation of the aorta is 31 years. With intervention, survival is now 97% at 10 years.

- Causes of death include:
  - Rupture or dissection of the aorta
  - Rupture of a circle of Willis aneurysm
  - Congestive heart failure due to HTN, aortic stenosis, and/or coronary artery disease
  - Infective endocarditis or endarteritis
- Causes of late death are predominantly coronary artery disease, followed by sudden cardiac death and increasing incidence of heart failure.

Management of Pregnancy

Most of the data is from case reports or case series. There are three concerns for women with coarctation that desire to become pregnant:

- *Risk of dissection*: In the case of unrepaired or postoperative recurrent coarctation as well as in the presence of aneurysm, there is an increased risk of dissection in the third trimester or peripartum. This has specifically been reported in cases of Turner syndrome [10]. Pre-pregnancy imaging is recommended in all cases of coarctation to inform the risk of dissection.
- *Hypertension and preeclampsia*: Women with coarctation are at increased risk of developing hypertension or preeclampsia during pregnancy and as such require appropriate counseling and frequent monitoring [10].
- *Genetic transmission*: The risk of genetic transmission should be discussed. Fetal echocardiography for screening of CHD is recommended.

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Part IV
Right Heart Obstructive Lesions

Chapter 18
Valvular Pulmonic Stenosis

Jonathan Kochav

Epidemiology

- Valvular pulmonic stenosis (PS) is a relatively common congenital lesion occurring in about 5.5 of 10,000 live births [1] or approximately 7% of all patients with congenital heart disease (CHD) [2]; isolated PS is the second most common congenital cardiac defect. It represents the overwhelming majority (80–90%) of the lesions which cause RV outflow obstruction [3].
- For historical background, see Table 18.1.

Anatomic Definition and Pathophysiology

1. Anatomy:

   (a) The anatomy of valvular PS is defined by three morphologic subtypes [6]:

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Table 18.1 Historical background

Pulmonary valve commissurotomies were among the first cardiac surgeries performed in the closed-heart era of modern cardiac surgery. In June of 1948, the same month and year that Charles Bailey performed the first successful digital commissurotomy of the mitral valve in Philadelphia, T. Holmes Sellors performed the first pulmonary valve commissurotomy using a blind approach through the infundibulum [4]. Techniques improved in the era of cardiopulmonary bypass and open heart surgery, and by the mid-1950s, surgical commissurotomy was routinely performed with good results. Since the early 1980s [5], balloon valvotomy has supplanted surgery as the intervention of choice for a majority of patients with suitable anatomy.

- Typical **dome-shaped pulmonic valve** is the most common variant, with preserved and mobile valve mechanism. The central opening is narrowed as a result of incomplete division of the leaflets at the commissures.
  - Associated with pulmonary arterial medial abnormality, and pulmonary truncal dilation can occur. The jet of flow acceleration from the valve is often directed toward the left pulmonary arterial branch, causing preferential dilation of this artery [7].
- **Dysplastic pulmonic valve** with myxomatous thickening and with incomplete commissural division.
  - Frequently seen as a component of the Noonan syndrome and often associated with hypoplasia of the pulmonic valvular annulus or supravalvular narrowing. Often associated with pulmonic regurgitation and very large pulmonary arteries.
- **Unicuspid or bicuspid pulmonic valve**
  - Usually seen in the context of the tetralogy of Fallot (TOF).

2. Physiology:
   (a) Physiology is defined by right ventricular outflow tract obstruction, with subsequent right ventricular pressure overload, and the potential to progress to right-sided heart failure.
   (b) Varies significantly in severity and clinical presentation depending on the degree of obstruction.
   (c) Stenosis severity:
      - Mild PS: peak transvalvular gradient of less than 30 mmHg
      - Moderate PS: peak gradient of 30–50 mmHg
      - Severe PS: peak gradient greater than 50 mmHg
3. Associated defects [8, 9]:
   (a) Atrial septal defect, ventricular septal defect, patent ductus arteriosus
   (b) TOF
   (c) Other complex CHD (e.g., Ebstein's anomaly, double outlet right ventricle, transposition of the great arteries or other conotruncal abnormalities)
4. Genetics and maternal factors:
   (a) Noonan syndrome
      - Dysplastic pulmonic valve is associated with the Noonan syndrome (autosomal dominant, variably penetrant syndrome).
      - Around 60% of patients with Noonan syndrome have some degree of pulmonic valvular stenosis [10].
   (b) Among all patients with pulmonary stenosis, around 20% will have a congenital cardiovascular defect in offspring, with 4–10% of offspring having recurrence of pulmonic stenosis [11].

Diagnostics

Clinical Presentation in Adults

- Isolated PS:
  - Patients with mild or moderate valvular PS will usually present with an asymptomatic systolic click and murmur.
  - Patients with severe PS may present with exertional dyspnea, but progression to frank right ventricular (RV) failure from this lesion alone is rare.

Physical Exam

- Cardiovascular exam:
  - Systolic ejection murmur

    Duration is usually shorter than that of a corresponding aortic stenosis murmur, due to more rapid equilibration of RV pressures with lower pulmonary arterial pressures.

    A systolic ejection click may be heard, which may *decrease* with inspiration due to early opening of the pulmonic valve when an augmented atrial systole occurs against a hypertrophic RV. This is the only right heart sound that decreases with inspiration.
  - Low-pitched diastolic murmur of pulmonic valve regurgitation may be heard
  - P2 decreases in volume, with augmented split from A2 with increasing severity of stenosis
  - Jugular venous a-waves may be present due to a noncompliant hypertrophic RV
  - RV hypertrophy may manifest as an RV heave, right-sided S4

Electrocardiogram [12]

- May be normal in patients with mild or moderate disease
- Patients with severe PS and RV pressure overload may develop:
  - Right atrial enlargement, with high-amplitude peaked P-waves
  - Right axis deviation
  - RV hypertrophy

Chest Radiograph

- May show prominent main and left pulmonary artery dilation
- May show right atrial enlargement

Echocardiography

- Transthoracic echocardiography will generally make the definitive diagnosis, and Doppler gradients can be used to grade severity.
- Usually able to distinguish among the anatomic variants of PS in children, may be more challenging in adults given the technical challenges in imaging the valve.
- Recommendations are to repeat echocardiography every 5 years for asymptomatic patients with peak transvalvular gradients <30 mmHg and every 2–5 years for asymptomatic patients with gradients >30 mmHg [6].
- Note that the pulmonary hypertension and RV dilation are not expected to occur in patients who have isolated PS and should spur investigation for left-to-right shunt lesions or pulmonary regurgitation.
- Table 18.2 highlights the essentials of echocardiographic assessment of patients with valvular PS.

Table 18.2 Echocardiographic essentials for assessment [3]

1.	Pulmonary valve leaflet morphology and thickness
2.	Annular, main pulmonary artery, and branch dimensions
3.	Continuous wave Doppler peak and mean gradient
4.	Degree of regurgitation
5.	Subvalvular hypertrophy or obstruction
6.	Right ventricular size, wall thickness, and function
7.	Doppler tricuspid regurgitant peak velocity
8.	Associated atrial septal defect, patent foramen ovale, ventricular septal defect, other RV outflow obstruction

Cardiac Catheterization

- Can be useful for measuring RV pressures and transvalvular gradients
- Not recommended as a necessary part of the diagnostic workup for patients who are not undergoing consideration of percutaneous repair (Class III recommendation) [6]
- PA pullback into the RV among patients with isolated valvular PS will show a simultaneous rise in the systolic pressure and drop in diastolic pressure as the obstruction is crossed at the level of the valve [13]

Advanced Imaging Techniques

- MRI and CT are rarely required to diagnose valvular PS or its associated anomalies but may be useful for imaging of dilated or stenotic pulmonary arteries if these lesions are suspected, or for precise quantification of pulmonic regurgitation and serial assessment of RV size and function in patients with regurgitant lesions (see Chap. 23 on the tetralogy of Fallot for further discussion on assessment and management of pulmonic regurgitation).

Management of Adult Survivors

See Table 18.3 for summary of guidelines.

Table 18.3 ACC/AHA guidelines 2008 [6]

Recommendations for evaluation of the unoperated patient	Recommendations for intervention in patients with valvular pulmonary stenosis
Class I	*Class I*
1. Two-dimensional echocardiography-Doppler, chest X-ray, and ECG are recommended for the initial evaluation of patients with valvular PS. (*level of evidence: C*)	1. Balloon valvotomy is recommended for asymptomatic patients with a domed pulmonary valve and a peak instantaneous Doppler gradient greater than 60 mmHg or a mean Doppler gradient greater than 40 mmHg (in association with less than moderate pulmonic valve regurgitation). (*level of evidence: B*)
2. A follow-up physical examination, echocardiography Doppler, and ECG are recommended at 5-year intervals in the asymptomatic patient with a peak instantaneous valvular gradient by Doppler less than 30 mmHg. (*level of evidence: C*)	2. Balloon valvotomy is recommended for symptomatic patients with a domed pulmonary valve and a peak instantaneous Doppler gradient greater than 50 mmHg or a mean Doppler gradient greater than 30 mmHg (in association with less than moderate pulmonic regurgitation). (*level of evidence: C*)
3. A follow-up echocardiography Doppler is recommended every 2–5 years in the asymptomatic patient with a peak instantaneous valvular gradient by Doppler greater than 30 mmHg. (*level of evidence: C*)	

Class III

1. Cardiac catheterization is unnecessary for diagnosis of valvular PS and should be used only when percutaneous catheter intervention is contemplated. (*level of evidence: C*)

   Recommendation for clinical evaluation and follow-up after intervention

Class I

1. Periodic clinical follow-up is recommended for all patients after surgical or balloon pulmonary valvotomy, with specific attention given to the degree of pulmonary regurgitation; RV pressure, size, and function; and TR. The frequency of follow-up should be determined by the severity of hemodynamic abnormalities but should be at least every 5 years. (*level of evidence: C*)
3. Surgical therapy is recommended for patients with severe PS and an associated hypoplastic pulmonary annulus, severe pulmonary regurgitation, subvalvular PS, or supravalvular PS. Surgery is also preferred for most dysplastic pulmonary valves and when there is associated severe TR or the need for a surgical maze procedure. (*level of evidence: C*)
4. Surgeons with training and expertise in CHD should perform operations for the RVOT and pulmonary valve. (*level of evidence: B*)

Class IIb

1. Balloon valvotomy may be reasonable in asymptomatic patients with a dysplastic pulmonary valve and a peak instantaneous gradient by Doppler greater than 60 mmHg or a mean Doppler gradient greater than 40 mmHg. (*level of evidence: C*)

2. Balloon valvotomy may be reasonable in selected symptomatic patients with a dysplastic pulmonary valve and peak instantaneous gradient by Doppler greater than 50 mmHg or a mean Doppler gradient greater than 30 mmHg. (*level of evidence: C*)

Class III

1. Balloon valvotomy is not recommended for asymptomatic patients with a peak instantaneous gradient by Doppler less than 50 mmHg in the presence of normal cardiac output. (*level of evidence: C*)
2. Balloon valvotomy is not recommended for symptomatic patients with PS and severe pulmonary regurgitation. (*level of evidence: C*)
3. Balloon valvotomy is not recommended for symptomatic patients with a peak instantaneous gradient by Doppler less than 30 mmHg. (*level of evidence: C*)

Valvular Intervention

1. Indications for intervention [6, 14]:
   (a) Symptomatic patients:
      (i) Peak Doppler gradient >50 mmHg or mean gradient >30 mmHg
   (b) Asymptomatic patients:
      (i) Peak Doppler gradient >60 mmHg or mean gradient >40 mmHg
2. Contraindications for intervention [6]:
   (a) Asymptomatic patients with peak Doppler gradient <50 mmHg, unless there is decreased cardiac output (low-flow, low-gradient)
   (b) Symptomatic patients with peak Doppler gradient <30 mmHg
3. Choice of intervention:
   (a) Balloon valvuloplasty:
      (i) Balloon valvuloplasty has supplanted surgery as the intervention of choice for a majority of patients with suitable anatomy.
      (ii) This procedure is more effective in patients with domed valve, where the balloon reliably splits along the commissures. In dysplastic valves, the efficacy of valvotomy is more variable and if significant pulmonic regurgitation is present valvuloplasty should not be undertaken [15].
      (iii) Complications:
         - Periprocedural complications are very rare (~2%) and include arrhythmia, RV perforation and tamponade, and atrioventricular nodal block [15].
         - Cardiogenic pulmonary edema can occur acutely post-procedure if the RV output is significantly increased to a degree that the left ventricle is not able to accomidate the increased flow.

(iv) Contraindications:

- Moderate or more pulmonary regurgitation is a contraindication, as the valvotomy procedure may worsen valvular insufficiency.

(v) Follow-up:

- Unlike in balloon valvuloplasty for aortic stenosis, restenosis is very uncommon, occurring in <5% of patients over 6+ years of follow-up [16, 17], but can be addressed with attempt at repeat valvuloplasty.

(b) Surgical therapy:

(i) May be necessary if valve leaflets are heavily calcified or dysplastic, or if there is moderate or more pulmonary regurgitation. Surgical or percutaneous valve replacement may be necessary for prosthesis dysfunction.

(ii) Surgical options:

- Pulmonary valve replacement:
  - Intervention of choice among patients who have moderate or greater pulmonary regurgitation.
  - Bioprosthetic valves are generally preferred due to higher risk of thrombosis with mechanical valves in the low-pressure, slow-flow pulmonic position.

    Options for bioprosthetic valves include bovine jugular valve or porcine bioprosthetic valve. Porcine valves appear to have the longest durability and are preferred [18].

    Uncommonly, pulmonary homograft has been performed.

  - Bioprosthetic valves have good durability in this position, with 90% freedom from reoperation over 10 years of follow-up.

  - Transcatheter pulmonic valve replacement (Melody Valve®) may be an option for some with increased surgical risk and suitable anatomy [19].

- Valvectomy:
  - Historically, patients with dysplastic valves often required total or partial valvectomies, with transannular patch performed for severe annular hypoplasia.
  - Pulmonary valve regurgitation of variable degree is expected with this procedure and, for this reason, is rarely preferable to balloon valvuloplasty or valve replacement [20].

(c) Follow-up:

(i) If there is significant infundibular hypertrophy, removing the valvular obstruction can increase flow and associated Venturi forces, causing acute dynamic outflow tract obstruction and even cardiogenic shock.

- As in acute exacerbations of hypertrophic obstructive cardiomyopathy, this is treated by volume expansion and medications that increase ventricular filling time and decrease contractility, such as beta-blockers, calcium channel blockers, or disopyramide.

(ii) Repeat echocardiograms should be performed at least every 5 years to follow for worsening of pulmonic regurgitation and consequent RV dilation or dysfunction (Class I recommendation) [6].

(iii) Among patients with progressive pulmonary regurgitation, pulmonary valve replacement may prevent irreversible RV remodeling (see Chap. 23 on the tetralogy of Fallot for further discussion on assessment and management of pulmonic regurgitation).

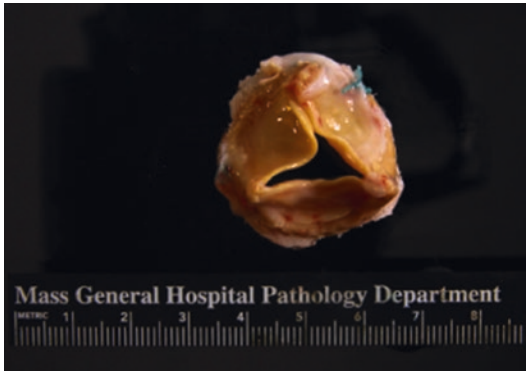

Figure 18.1 Pathology specimen of excised bioprosthetic pulmonic valve with stiff and restricted pericardial leaflets resulting in a prosthesis stenosis due to fixed orifice and severe pulmonary regurgitation

Pulmonary Artery Dilation

- Generally related to the associated arteriopathy that accompanies valvular PS [7].
- Risk of rupture is remarkably low, even with markedly dilated pulmonary arteries, because of the low-pressure pulmonary circuit. As such, there are no recommendations to perform intervention for patients with pulmonary artery dilation or aneurysm to prevent rupture unless there is associated compression of an adjacent structure.
- Patients may experience symptoms due to compression of the surrounding structures (e.g., rarely chest pain from compression of the coronary arteries [21]) or pulmonic regurgitation from dilation of the pulmonic valve annulus, and pulmonary arterioplasty of pulmonary artery replacement may be considered in these circumstances.

Management of Pregnancy

- RV obstructive lesions are generally well tolerated, and an intervention to relieve pulmonary stenosis is rarely necessary during pregnancy in the absence of RV failure or symptoms of RV pressure overload [22].
- Percutaneous valvotomy can be performed during pregnancy if necessary [23].

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Chapter 19
Supravalvular Pulmonic Stenosis

Christopher Valle

Abbreviations

AHA	American Heart Association
AS	Aortic stenosis
ASD	Atrial septal defect
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PDA	Patent ductus arteriosus
PS	Pulmonary stenosis
RV	Right ventricle
RVH	Right ventricular hypertrophy
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiography
VSD	Ventricular septal defect
WHO	World Health Organization

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Epidemiology

- Supravalvular pulmonic stenosis (PS), encompassing both branch PS and peripheral PS, is relatively uncommon, occurring as a pathologic entity in about 2–3% of all patients with congenital heart disease [1].
- See Table 19.1 for historical background.

Anatomic Definition and Pathophysiology

- Anatomy:
  - Supravalvular PS can occur as an isolated finding at single or multiple sites within the pulmonary artery (PA) or in conjunction with other malformations.
  - The lesion can be classified according to pathogenesis as:

Congenital—see below for associated congenital syndromes.

Acquired—most commonly seen in patients following cardiac surgery (e.g., prior pulmonary artery banding or from systemic pulmonary palliative shunts), but also rarely in conditions that cause external compression (e.g., fibrosing mediastinitis, mediastinal tumors).

Table 19.1 Historical background

In Baltimore in 1938, Oppenheimer first described an anomaly characterized by stenosis of the portions of the pulmonary arteries distal to the pulmonic valve [2]. Since this initial description, it has been variously labeled pulmonary coarctation, peripheral PS, branch PS, supravalvular PS, and multiple peripheral stenoses of the pulmonary artery.
The first operative treatment for supravalvular stenosis was described in 1960, in the era of cardiopulmonary bypass and open-heart surgery [3]. Similar to valvular PS, transcatheter approaches using balloon valvotomy and stenting supplanted surgery as the intervention of choice in the 1980s.

  - Four types of stenosis are defined by location:

Stenosis of the pulmonary trunk
Stenosis of the PA bifurcation with extension into the right and/or left branch PA
Multiple peripheral PA stenoses
Stenoses of both the pulmonary trunk and peripheral arteries

- Physiology:
  - If only one PA is stenotic, there is typically no right ventricular (RV) hypertension, and the affected artery may become hypoplastic with time.
  - If multiple PA branch stenoses are present, there will be proximal pulmonary arterial hypertension (PAH) and RV pressure overload, sometimes severe enough to cause right ventricular hypertrophy (RVH) and even congestive heart failure.
  - Typically, the stenoses are stable over time, with only a few case reports describing progression of the severity of stenosis over time [4].
  - Due to the normally low vascular resistance in the pulmonary circuit, significant obstruction is required to result in PAH.
  - By convention, a lesion greater than 50% diameter narrowing is defined as angiographically significant and would be expected to cause a pressure gradient resulting in hypertension in the more proximal portions of the PA system.
- Associated defects:
  - The most common associated defects are valvular PS, atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA).
  - Supravalvular PS often presents in combination with supravalvular aortic stenosis (AS), as reported in nearly 40% of patients with Williams Syndrome [5].

- Genetics and maternal factors:
  - Williams-Beuren syndrome

Contiguous gene deletion at chromosome 7q11.23 that includes the elastin gene (*ELN*) and affects elastin formation [6, 7]

Sporadic multisystem disorder that is characterized by abnormal facies and dentition, hyperacusis, some degree of mental retardation, and near universal involvement of the cardiovascular system

Patients most commonly present with supravalvular AS, although 30–80% are reported to have peripheral PS with rare cases of isolated supravalvular main PA stenosis reported as well [8]

  - Alagille syndrome (arteriohepatic dysplasia)

Autosomal dominant syndrome with variable expression due to heterozygous mutation of *JAG1* gene on chromosome 22

Multisystem disease characterized by cholestasis from paucity of intrahepatic bile ducts, characteristic facies, skeletal and ocular abnormalities, and stenosis or hypoplasia of peripheral pulmonary arteries [9]

  - Congenital rubella syndrome

Characterized by cataracts, deafness, hypotonia, retinopathy, and mental disability with peripheral PS being not uncommon [10]

  - Keutel syndrome

Rare autosomal recessive disorder characterized by diffuse calcification of cartilage, short stubby fingers, hearing loss, and peripheral PS [11]

  - Takayasu or Behcet arteritis and other systemic vasculitides

Diagnostics

Clinical Presentation in Adults

- The clinical symptom complex is similar to that of valvular PS—a spectrum from an asymptomatic murmur in patients with mild disease to exertional dyspnea and angina seen with severe disease, which is uncommon.
- Most patients seen in adulthood are referred for workup of suspected primary PAH or chronic pulmonary thromboembolic disease.
- Patients with peripheral PS may have increased risk of pneumonia in the lung with low flow distal to the stenosis and may also have lung hypoplasia noted incidentally on imaging if a lung develops under low flow.

Physical Exam

- Patients with stenosis involving the main PA and main branches will have a systolic ejection murmur (intensity, time to peak, and duration vary with severity).
- Patients with primarily peripheral PS will have peripheral bruits best heard over either lateral aspect of the posterior chest.
    - These bruits are typically systolic only but may be continuous and increase with inspiration.
- Low-pitched diastolic murmur of pulmonary regurgitation (PR) may be heard.
- Prominent jugular venous *a* waves may be present in severe stenosis due to a noncompliant, hypertrophic RV as well as an RV heave and right-sided S4.
- Cyanosis may occur if elevated right atrial pressures result in right-to-left shunting across an atrial defect.

Electrocardiography

- May be normal for patients with mild or moderate disease.
- Patients with severe PS and RV pressure overload may develop RVH with strain and right axis deviation.

Chest X-Ray

- Lung fields may show varying shadows of post-stenotic peripheral arterial dilatations in patients with peripheral PS.
- As described above, may demonstrate pneumonia or lung hypoplasia in patients with peripheral PS in the appropriate clinical setting.

Echocardiography

- Transthoracic echocardiography (TTE) with Doppler may be able to define proximal pulmonary branch stenosis as well as to confirm presence of RV systolic hypertension and any pulmonary valve regurgitation.
- TTE is less helpful for peripheral PS.
- Table 19.2 highlights the essentials of echocardiographic assessment of patients with supravalvular PS.

Cardiac Catheterization (Fig. 19.1)

- Definitive and provides additional information regarding the extent of lesions, angiographic severity, pressure drop across lesions, and degree of associated PAH.
- Helpful for planning catheter-based interventions.

Advanced Imaging Techniques (Fig. 19.2)

- Cardiac magnetic resonance imaging (MRI) and computed tomography (CT) with pulmonary angiography are much superior to echocardiography Doppler and can help confirm the diagnosis (Fig. 19.2).

Table 19.2 Echocardiographic essentials for assessment [12]

1.	Pulmonary valve morphology
2.	Annular, main PA, and branch dimensions
3.	Continuous wave Doppler peak and mean gradient
4.	Degree of pulmonary regurgitation
5.	RV size, wall thickness, and function
6.	Doppler tricuspid regurgitation (TR) peak velocity
7.	Associated ASD, VSD, and other RV outflow obstruction

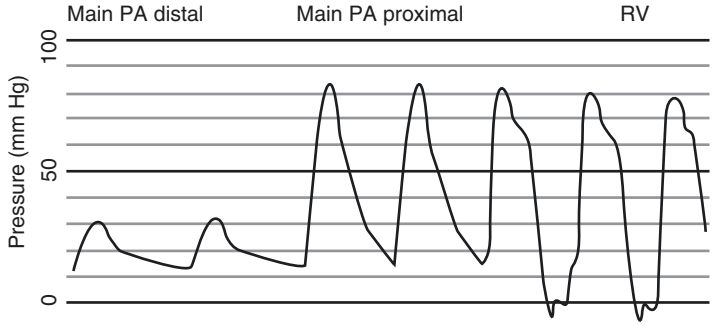

Figure 19.1 Right ventricular angiographic characterization of supravalvular pulmonic stenosis. Pullback through main PA to RV in patient with branch or supravalvular PA stenosis. Pullback from the distal PA (first two beats) to main PA demonstrates elevation in systolic pressure without change in diastolic pressure (indicating catheter remains distal to pulmonic valve). Further pullback from (from beat four to five) shows lack of obstruction at the valve as the catheter is drawn into the ventricle, where diastolic pressure falls

Management of Adult Survivors

See Table 19.3 for summary of Guidelines.

1. Indications for intervention [13]:

   - RV systolic pressure (RVSP) >50 mmHg
   - Focal branch and/or peripheral pulmonary artery stenosis with >50% diameter narrowing
   - And/or symptoms not attributed to another cause

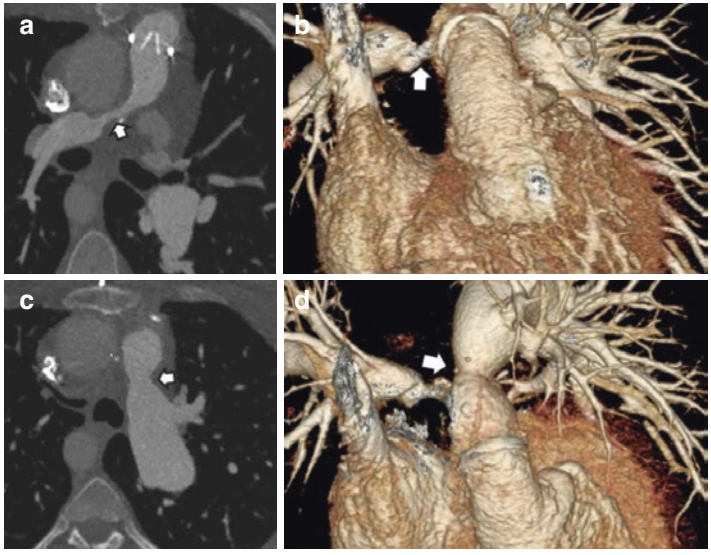

FIGURE 19.2 Computed tomography (CT) imaging of severe bilateral branch pulmonary stenosis in 27-year-old woman with history of truncus arteriosus status postoperative intervention in neonatal period. (**a**) Coronal images demonstrate severe narrowing of the main right pulmonary artery over a 2.1 cm-long segment (white arrow). The diameter of the narrowest area measures 4 mm. (**b**) Three-dimensional reconstruction shows the same severe narrowing of the main right PA (white arrow). (**c**) There is a focal narrowing at the origin of the left main PA to a diameter of 10 mm (white arrow), with poststenotic dilation of the left main PA. (**d**) Three-dimensional reconstruction of stenotic left main PA

2. Choice of intervention:

   (a) Transcatheter intervention

   - Balloon valvuloplasty and stenting has supplanted surgery as the intervention of choice for patients with suitable anatomy.
   - Initial studies using balloon angioplasty demonstrated success rates (decreased systolic pressure gradient

Table 19.3 ACC/AHA guidelines 2008 [13]

Recommendations for evaluation of patients with supravalvular, branch, and peripheral pulmonary stenosis	Recommendations for interventional therapy in the management of branch and peripheral pulmonary stenosis
Class I 1. Patients with suspected supravalvular, branch, or peripheral PS should have baseline imaging with echocardiography Doppler plus 1 of the following: MRI angiography, CT angiography, or contrast angiography (*level of evidence: C*) 2. Once the diagnosis is established, follow-up echocardiography Doppler to assess RV systolic pressure should be performed periodically, depending on severity (*level of evidence: C)*	*Class I* 1. Percutaneous interventional therapy is recommended as the treatment of choice in the management of appropriate focal branch and/or peripheral pulmonary artery stenosis with greater than 50% diameter narrowing, an elevated RV systolic pressure greater than 50 mmHg, and/or symptoms (*level of evidence: B*) 2. In patients with the above indications for intervention, surgeons with training and expertise in CHD should perform operations for management of branch pulmonary artery stenosis not anatomically amenable to percutaneous interventional therapy (*level of evidence: B)*
Recommendations for evaluation and follow-up *Class I* 1. Patients with peripheral PS should be followed up every 1–2 years, on the basis of severity, with a clinical evaluation and echocardiography Doppler to evaluate RV systolic pressure and function (*level of evidence: C)* 2. Discussion with a cardiac surgeon with expertise in CHD should take place before percutaneous peripheral pulmonary artery interventions are undertaken *(level of evidence: C)*	

across stenosis by 50% or widening of stenotic region by >50%) of only 38–64% [14].

- In many cases, an apparently successful dilatation was often followed by return to severe stenosis within days because of the highly compliant nature of the pulmonary arteries leading to transient dilatation.
- Consequently, the addition of stents was used to good effect with success rates approaching 90% [15].
- For stenoses not amenable to stenting or surgical intervention, a cutting balloon can be used with improved outcomes with no greater complication rate than using a simple balloon [16].
- *Complications*:
  - Less severe complications occur ~6–10% of the time and include femoral vein thrombosis, localized hemorrhage around stenosed segment, aneurysm of artery distal to stenosis, and segmental pulmonary edema, typically lasting 72 h post-procedure [1].
  - The risk of death from rupture of the pulmonary artery or cardiac arrest in patients with poor RV function is ~1–2% [1].
- *Follow-up:*
  - Restenosis from intimal proliferation post-stenting appears to occur in only 5% of patients [15].
  - The current recommended follow-up is a TTE with Doppler every 1–2 years or sooner if symptoms recur (ACC/AHA Class I recommendation) [13].

(b) Surgical therapy:

- The primary indication for surgery is the need to repair other cardiac abnormalities at the same time.
- Other relative indications include:
  - An isolated supravalvular stenosis involving the main PA, especially near the pulmonary valve to minimize risk of pulmonary regurgitation [17].
  - Severe stenosis at the bifurcation of the branch PAs [18].

  - Treatment of stenosis secondary to prior pulmonary artery banding or pulmosystemic shunt due to extensive fibrosis that is typically present.
  - Involvement of long segments or an entire PA.
  - If transcatheter intervention has failed.

- The operative procedure typically involves longitudinal incision of the stenotic segment with placement of a patch or, less commonly, resection of the entire affected segment with subsequent end-to-end anastomosis.
- *Follow-up*:

  - Reported rates of restenosis approach 50–60% at 5 years [1].
  - The current recommended follow-up is a TTE with Doppler every 1–2 years or sooner if symptoms recur (ACC/AHA Class I Recommendation) [13].

(c) Combined approach:

- Patients with pathology involving both ventricles (e.g., tetralogy of Fallot variants) may benefit from an approach that combines both transcatheter and surgical approaches.

Management of Pregnancy

- The risk to the woman and fetus in pregnancy depends on the degree of RV obstruction. Per the most recent American Heart Association (AHA) scientific statement, women with mild pulmonary stenosis are World Health Organization (WHO) Pregnancy Risk Category I (no detectable increase in morbidity/mortality). Women with greater degrees of obstruction will fall in WHO Pregnancy Risk Class II–III with a moderate increase in maternal morbidity mortality risk [19]. Among women with severe stenosis and RVH, there is a small increased risk of right heart failure in third trimester and peri-delivery and possible need for diuretics to manage volume overload.

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Chapter 20
Subvalvular Pulmonic Stenosis

Christopher Valle

Abbreviations

DCRV	Double-chambered right ventricle
HCM	Hypertrophic cardiomyopathy
PS	Pulmonic stenosis
RVOT	Right ventricular outflow tract
TOF	Tetralogy of Fallot

Epidemiology

- Subpulmonic stenosis is overwhelmingly seen as one of the primary features of tetralogy of Fallot (TOF).
  - TOF is defined embryologically by the underdevelopment of the subpulmonary infundibulum from malseptation of the arterial segment of the developing heart.
  - Please see Chap. 23 for a more in-depth discussion of TOF and the management of subpulmonic stenosis in this setting.

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- Sub-infundibular subvalvular pulmonic stenosis is limited to the entity of double-chambered right ventricle (DCRV) and covered entirely in Chap. 23.
- Isolated subvalvular stenosis is exceedingly rare, accounting for less than 0.5% of congenital heart disease requiring surgical intervention [1].

Anatomic Definition and Pathophysiology

- Embryology [2]
  - The heart develops as a tubular structure with a solitary lumen when the embryo is 20 days old, differentiating into a sequential pulsatile pump by 28 days.
  - By 30 days, partial separation has occurred, creating a chambered structure with interatrial and interventricular communications.
  - Remodelling of the outflow tract produces two vessels, each with its own arterial valve.
  - Initial septation is produced by ingrowth of mesenchyme, derived from the neural crest into the cushions developing throughout the outflow tract, which then fuse with each other, and also with the back wall of the aortic sac.
  - This process achieves separation of the intrapericardial components of the aorta and the pulmonary trunk.
  - The proximal part of the outflow tract remains encased in a sleeve of outflow myocardium (*developmental basis of the infundibulum*).
  - It is the division of the distal part of this persisting muscular outflow tract, again by the cushions packed with cells from the neural crest, which produces the primordia of the developing aortic and pulmonary valves.
- Anatomy
  - The infundibulum is the sleeve of free-standing musculature that supports the leaflets of the pulmonary valve and lifts the trunk of the pulmonary artery away from the base of the right ventricular mass.

- It is virtually indistinguishable from the remainder of the muscular ventricular septum in normal hearts.
- Part of the free-standing subpulmonary infundibular sleeve interposes between the leaflets of the pulmonary and tricuspid valves, an area referred to as the supraventricular crest.
- Subpulmonic stenosis can be divided anatomically into processes involving hypertrophy of the muscular infundibulum (infundibular stenosis) and rarer etiologies that have led to obstruction of the subvalvular right ventricular outflow tract (RVOT).
- Causes of infundibular stenosis:

The most common is TOF (see Chap. 23).

The next most common is reactive myocardial hypertrophy secondary to valvular pulmonic stenosis (see Chap. 19).

Much less common is hypertrophic cardiomyopathy (HCM) involving the right ventricle [3].

- Rarer causes of non-infundibular subvalvular pulmonic stenosis:

Spinnaker syndrome, in which the valve of embryonic venous sinus persists, becomes aneurysmal and extends down through the tricuspid valve [4].

Fibrous tags from the inferior vena cava or coronary sinus.

Aneurysm of the membranous septum or sinus of Valsalva [5].

Intra- and extra-cardiac mass lesions extending into RVOT [6].

The physiology and management of subpulmonic stenosis from causes other than TOF are virtually indistinguishable from valvular PS. Table 20.1 reviews echocardiographic features and Table 20.2 reviews summary of guidelines. For a more in-depth discussion of the physiology, diagnosis, and management of subpulmonic stenosis, please refer to Chap. 19 on valvular PS.

Table 20.1 Echocardiographic essentials for assessment [7]

1. Pulmonary valve leaflet morphology and thickness
2. Annular, main PA, and branch dimensions
3. Continuous wave Doppler peak and mean gradient
4. Degree of regurgitation
5. Subvalvular hypertrophy or obstruction
6. RV size, wall thickness, and function
7. Doppler TR peak velocity
8. Associated ASD, PFO, VSD, and other RV outflow obstruction

Table 20.2 ACC/AHA Guidelines 2008 [8]

Recommendations for evaluation of the unoperated patient	Recommendations for intervention in patients with valvular pulmonary stenosis
Class III 1. A follow-up physical examination, echocardiography Doppler, and ECG are recommended at 5-year intervals in the asymptomatic patient with a peak instantaneous valvular gradient by Doppler less than 30 mmHg (*level of evidence: C*) 2. A follow-up echocardiography Doppler is recommended every 2–5 years in the asymptomatic patient with a peak instantaneous valvular gradient by Doppler greater than 30 mmHg (*level of evidence: C*)	*Class I* 1. Surgical therapy is recommended for patients with severe PS and an associated hypoplastic pulmonary annulus, severe pulmonary regurgitation, subvalvular PS, or supravalvular PS. Surgery is also preferred for most dysplastic pulmonary valves and when there is associated severe TR or the need for a surgical maze procedure (*level of evidence: C*) 2. Surgeons with training and expertise in CHD should perform operations for the RVOT and pulmonary valve (*level of evidence: B*)

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Chapter 21
Double-Chambered Right Ventricle (DCRV)

Christopher Valle

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
ASD	Atrial septal defect
DCRV	Double-chamber right ventricle
MRI	Magnetic resonance imaging
RV	Right ventricle
RVSP	Right ventricular systolic pressure
TEE	Transesophageal echocardiography
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiography
VSD	Ventricular septal defect
WHO	World Health Organization

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Epidemiology

- Double-chambered right ventricle (DCRV) is uncommon, occurring in approximately 1% of patients with congenital heart disease [1].
- DCRV is alternatively referred to in the literature as subinfundibular obstruction, so as to distinguish it from subpulmonic/infundibular obstruction and its attendant causes (Chap. 20).
- For historical background, see Table 21.1.

Anatomic Definition and Pathophysiology

- Anatomy
  - The right ventricle (RV) is divided by anomalous muscle bundles into a higher-pressure proximal chamber and lower-pressure distal chamber (see Fig. 21.1).
- Physiology
  - Various mechanisms have been proposed to explain the underlying pathophysiology of DCRV:

The earliest theory suggests the obstruction is the result of increased blood flow among patients with ventricular septal defect (VSD) leading to hypertrophy of the supraventricular crest [4].

Alternatively, it has been proposed that superior displacement of the septomarginal trabecula (moderator band)

Table 21.1 Historical background

In 1858, Thomas Peacock first described subinfundibular stenosis or double-chambered right ventricle as a rare form of congenital obstruction to right ventricular outflow [2]. Some five decades later, obstructing muscle bundles within the right ventricular cavity were the subject of Sir Arthur Keith's Hunterian lecture in 1909 [3].

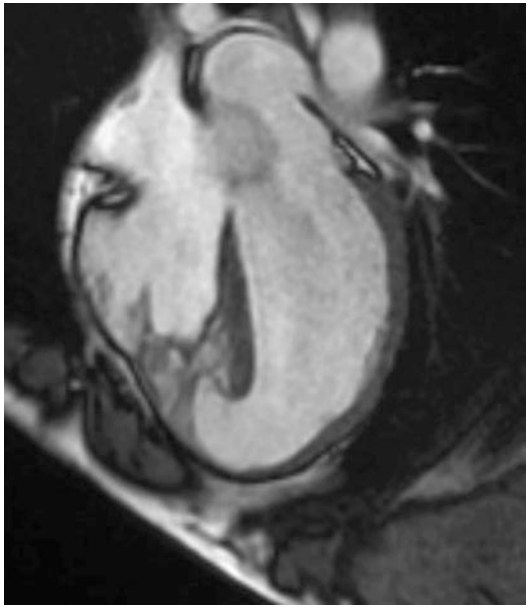

FIGURE 21.1 CT angiography demonstrating DCRV with apical VSD

predisposes to hypertrophy over time leading to obstruction [5].

Others have suggested that the anomalous muscle bundles originate from the accentuation of septoparietal trabeculations via a muscular shelf that extends toward the apical RV [6].

- Ultimately, the physiology is defined by right ventricular pressure overload of the RV inflow chamber and, in rare cases, the progression to RV failure.
- Depending on the degree of obstruction, the clinical course varies significantly in severity and clinical presentation with most cases presenting to medical attention before adulthood.
- Although the substrate is congenital, the degree of RVOT obstruction is progressive with time.

In one study, the mid-ventricular gradient increased 6 ± 3 mmHg annually [7].

- Associated defects
  - DCRV is exceptionally rare to occur as an isolated lesion [8].
  - In ~90% of cases, there is an associated membranous-type VSD [9].
  - DCRV has been shown to develop in 3% of patients with repaired tetralogy of Fallot [10].
  - Less common associations are varied and include subaortic stenosis, pulmonary valvular stenosis, double outlet right ventricle, anomalous pulmonary venous drainage, complete or corrected transposition of the great arteries, pulmonary atresia with intact ventricular septum, and Ebstein anomaly [11].
- Genetics and maternal factors
  - As of yet, no genetic associations have been identified.

Diagnostics

Clinical Presentation in Adults

- Most patients will present in childhood and undergo subsequent repair.
- Patients may occasionally present in adulthood with symptoms mimicking coronary disease (angina), pulmonary hypertension or congestive heart failure (dyspnea); or after undergoing evaluation for increasing intensity of systolic murmur previously ascribed to functional murmur.
- The combination of elevated right ventricular systolic pressure (RVSP) and intracavitary gradient on echocardiography should prompt the consideration of the diagnosis of DCRV.

Physical Exam

- Physical exam findings will vary depending on the degree of obstruction.
- Right ventricular impulse may be present at the lower left sternal border or subxiphoid area.
- There may be a mid-systolic murmur best heard below the third left intercostal space with the absence of an ejection sound.
- The murmur of an associated VSD may be appreciated if present.
- If a VSD is proximal to the membrane or there is an associated atrial septal defect (ASD), the patient may appear cyanotic once right-to-left shunting develops.

Electrocardiography

- Typically suggests RV hypertrophy, though less than may be expected for degree of stenosis appreciated on exam.
- Right-sided lead placement can help confirm diagnosis with upright T-waves in V_3R in 40% of patients [12].

Chest X-Ray

- May show right atrial enlargement in severe cases.

Echocardiography

- Transthoracic echocardiography (TTE) is diagnostic, demonstrating RV hypertrophy with Doppler/color flow evidence of a mid-ventricular gradient.
- However, the region between the RV inflow sinus and outflow tract is often poorly visualized in standard planes, requiring a high index of suspicion.
- A membranous VSD may be noted.

- One must carefully evaluate for other associated defects, specifically subaortic membrane.
- Transesophageal echocardiography (TEE) is typically not needed for diagnosis.
- Table 21.2 highlights the essentials of echocardiographic assessment of patients with DCRV.

Cardiac Catheterization

- Confirmatory and can provide relevant imaging, hemodynamic, and shunt information.
- Patients with anginal symptoms may require cardiac catheterization to exclude coronary disease.

Advanced Imaging Techniques

- Cardiac magnetic resonance imaging (MRI) is useful in addition to TTE to define the right ventricular anatomy.

Management of Adult Survivors

- Indications for intervention from 2008 ACC/AHA guidelines [14] (Table 21.3).

Table 21.2 Echocardiographic essentials for assessment [13]

1. Determination of mid-cavity flow acceleration and quantification of gradients across anomalous muscle bundles
2. Continuous-wave Doppler peak and mean gradient across mid-ventricular obstruction (this may be best done in the subcostal short-axis imaging)
3. RV size, wall thickness, and function
4. Doppler tricuspid regurgitation (TR) peak velocity
5. Associated VSD, subaortic membrane, ASD, and other RV outflow obstruction

Table 21.3 ACC/AHA guidelines 2008 [14]

Category I recommendations	Category IIb recommendations
1. Surgery is recommended for patients with a peak mid-ventricular gradient by Doppler greater than 60 mmHg or a mean Doppler gradient greater than 40 mmHg, regardless of the symptoms (*Level of Evidence: B*)	1. Symptomatic patients with a peak mid-ventricular gradient by Doppler greater than 50 mmHg or a mean Doppler gradient greater than 30 mmHg may be considered for surgical resection if no other cause of symptoms can be discerned (*Level of Evidence: C*)

  - Symptomatic patients

Peak Doppler gradient >50 mmHg or mean gradient >30 mmHg

  - Asymptomatic patients

Peak Doppler gradient >60 mmHg or mean gradient >40 mmHg

- Choice of intervention
  - Surgical therapy

Open surgery remains the intervention of choice for patients.

Most patients do extremely well with surgical intervention, and the recurrence of re-obstruction after adequate surgical repair is quite rare [11, 15].

  - Transcatheter intervention

At this time, there are only isolated case reports of the use of percutaneous strategies for repair (balloon, stenting, alcohol ablation) and no comparative long-term data versus surgical repair [16, 17].

- Medical therapy
  - Patients who do not meet criteria for consideration of surgical intervention may be trialed on

beta-blockers and calcium channel blockers as there may be a degree of dynamic obstruction, though there is no data on their efficacy.

- Risk of arrhythmia
  - Three case reports have described the development of ventricular tachycardia in patients with repaired DCRV [18–20].
  - DCRV is presumed to predispose to ventricular arrhythmias through inherent structural abnormalities of the hypertrophied muscle and/or scar from prior interventions.
  - One group described the implantation of a cardioverter-defibrillator [19], and another successfully identified the substrate of the arrhythmia and performed ablation [20].
  - At this time, the existing literature is too limited to comment on the utility of screening for arrhythmias in this population or on the optimum strategy for management (i.e., medical management vs. cardioverter-defibrillator placement vs. ablation).
- Follow-up
  - Serial TTE or cardiac MRI can be used for follow-up postoperatively.
  - There are typically no activity limitations post-repair and no need for endocarditis prophylaxis.

Management of Pregnancy

There is limited data on the course of DCRV in pregnancy, with a single case report of a woman who was followed without intervention to a successful term delivery [21]. The risk to the woman and fetus in pregnancy depends on the degree of RV obstruction. Per the most recent American Heart Association (AHA) guidelines, women with mild pulmonary stenosis belong to World Health Organization (WHO) Pregnancy Risk Category I (no detectable increase in morbidity/mortality).

Women with greater degrees of obstruction will fall in WHO Pregnancy Risk Categories II–III with a moderate increase in maternal morbidity and mortality risk [22].

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Part V
Conotruncal Abnormalities

Chapter 22
Double Outlet Right Ventricle

Yamini Krishnamurthy

Abbreviations

DORV	Double outlet right ventricle
D-TGA	D-loop transposition of the great arteries
MRI	Magnetic resonance imaging
PS	Pulmonary stenosis
TOF	Tetralogy of Fallot
VSD	Ventricular septal defect

Epidemiology

- Double outlet right ventricle (DORV) is a rare malformation that accounts for about 1–3% of all congenital heart disease. The reported incidence ranges from 3 to 14 per 100,000 live births [1].
- For historical background, see Table 22.1.

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Table 22.1 Historical background

Braun et al. first reported the term "double outlet ventricle" in 1952 [2]. The first biventricular repair for this entity was reported by Sakakibara et al. in 1967 [3]. In 1972, Lev et al. used the relationship of the VSD to the great arteries as the basis for his classification of DORV, and a subsequent description of DORV was published 1973 by John Abernethy [4, 5].

Anatomic Definition and Pathophysiology

- Anatomy and physiology:
  - The definition of DORV is that the pulmonary artery and aorta arise from the morphologic right ventricle. DORV is almost always associated with a ventricular septal defect (VSD).
  - DORV can be associated with a large spectrum of congenital heart defects, including but not limited to ventricular septal defect, balanced and unbalanced atrioventricular canal defect, hypoplastic right or left ventricle, heterotaxy syndrome, abnormalities of cardiac position (mesocardia or dextrocardia), pulmonary stenosis, and coarctation of the aorta.
  - There is a wide spectrum of anatomic variants in DORV. DORV is classified into four types based on the relationship between the great arteries and the VSD. This classification system is typically discussed in the setting of patients with two good-sized ventricles, to reflect the underlying physiology. The type of DORV depends on the location of the VSD in relation to the great arteries (Fig. 22.1).

    DORV with a subaortic VSD (50%): The aorta is in closer proximity to the VSD than the pulmonary artery, such that oxygenated blood flows from the left ventricle through the VSD and into the aorta. Oxygen-poor blood from the right ventricle flows primarily into the pulmonary artery. If both the aorta and pulmonary artery are normal in size, the physiology of this lesion resembles a VSD with

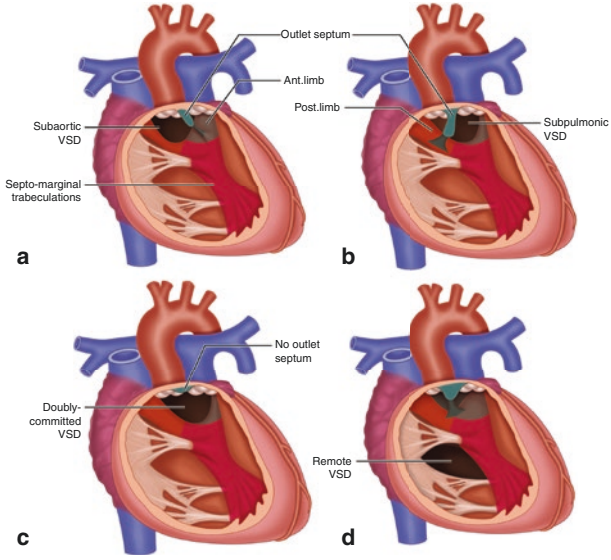

FIGURE 22.1 Classifying double outlet right ventricle [6]. (**a**) DORV with a subaortic VSD. (**b**) DORV with a subpulmonic VSD. (**c**) DORV with a doubly committed VSD. (**d**) DORV with a remote VSD

excessive pulmonary blood flow. If there is subpulmonic narrowing, the physiology resembles that of tetralogy of Fallot (TOF). In this setting, the degree of subpulmonic or valvular stenosis determines the direction of VSD flow and the degree of cyanosis (please see Chaps. 5 and 23 for details regarding VSD and TOF physiology).

DORV with a subpulmonic VSD (30%): The pulmonary artery is in closer proximity to the VSD than the aorta so that oxygenated blood preferentially flows from the left ventricle, through the VSD and into the pulmonary artery. Oxygen-poor blood from the right ventricle flows preferentially into the aorta. Because of this, the physiology often resembles D-loop transposition of the great arteries (D-TGA) (please see Chap. 25 for details regarding D-TGA physiology). With a subpulmonic VSD, the subaortic infundibulum may be

narrowed, resulting in subaortic obstruction, aortic valve, and aortic arch hypoplasia. If subaortic obstruction is present, the physiology resembles D-TGA with coarctation of the aorta.

The Taussig-Bing variant refers to DORV with a large subpulmonary VSD, side-by-side semilunar valves at approximately the same height, bilateral conus with equally developed muscular subaortic and subpulmonary conal free walls, and absence of pulmonary-mitral continuity.

DORV with a doubly committed VSD: The VSD is found below both the aortic and pulmonary arteries and communicates with both outflow tracts. The physiology can vary in regard to how much cardiac output from each ventricle/each great vessel receives. If both the aorta and pulmonary artery are normal in size, the physiology resembles a VSD with excessive pulmonary blood flow.

DORV with a remote VSD: The VSD is remote from both the pulmonary artery and the aorta. In this case, a biventricular repair may not be feasible, and a staged single ventricle-type palliation resulting in the Fontan procedure may be performed (please see Chap. 28 for details regarding single ventricle physiology). This is the least common type of DORV.

- Spectrum of disease:
  - Many patients with DORV are diagnosed prenatally and are managed surgically before the onset of severe symptoms.
  - The symptoms of DORV vary according to the degree of pulmonary and systemic blood flow and the oxygen saturation. Symptoms may include tachypnea, sweating, fatigue, cyanosis, cardiogenic shock, and failure to thrive. Symptoms may appear immediately at birth or may take days to weeks to manifest. Patients with pulmonary stenosis and/or subpulmonary ventricular septal defects are more likely to present with cyanosis. Patients with aortic stenosis are

more likely to present in shock secondary to inadequate systemic perfusion. Those with uncontrolled pulmonary blood flow will present with signs and symptoms of congestive heart failure.

- With few exceptions, adult patients will have undergone surgical repair during infancy. A biventricular repair is possible in most patients. In those with remote VSDs, often the only surgical therapy is single ventricle-type palliation and eventually a Fontan operation.
- The range of potential surgical complications depends on the underlying anatomy and surgery performed. Complications may include residual VSD, evidence of re-coarctation, conduit stenosis, valvular stenosis or regurgitation, complete heart block, atrial arrhythmias, and ventricular arrhythmias. Sudden cardiac death may occur as well and has been found to be more common in patient operated on later in life, those with ventricular ectopy and third-degree atrioventricular block [7]. In those with single ventricle palliation, complications of the Fontan operation include ventricular dysfunction, progressive cyanosis, atrial arrhythmias, and hepatic dysfunction, among others.
- Because the anatomy of DORV varies so widely, outcome studies are difficult to interpret [6].

- Associated defects:
  - DORV is almost always associated with a VSD.
  - Other common anomalies associated with DORV include:

    Subpulmonary/pulmonary stenosis
    Atrial septal defects
    Patent ductus arteriosus
    Subaortic/aortic stenosis
    Mitral valve abnormalities
    Abnormal origins of the right and left coronary arteries

  - In patients with DORV with a subpulmonic VSD, 50% will also have an aortic coarctation or aortic arch hypoplasia [6].

- Genetics and maternal factors:
  - No specific genetic mutation has been identified as the causal agent for DORV.
  - A study found chromosomal anomalies in 61 of 149 cases of DORV. Trisomies 13 and 18 and del 22q11 were the most commonly associated genetic lesions. Animal studies implicate maternal diabetes and prenatal exposure to ethanol, retinoids, theophylline, and valproate as teratogenic factors for DORV [1].

Diagnostics

Clinical Presentation in Adults

- Most patients present and undergo surgical intervention during infancy.
- Unrepaired adult patients may present with signs and symptoms of cyanosis, congestive heart failure, pulmonary hypertension, and/or Eisenmenger physiology (see Chap. 9 for details on Eisenmenger physiology).

Physical Exam

- In patients with DORV, systemic and pulmonary blood flow dictates physical exam findings.
  - In those with increased pulmonary blood flow:

    Cyanosis is mild or absent.
    Congestive heart failure signs such as tachypnea, tachycardia, hepatomegaly, and failure to thrive are likely.
    The precordium is hyperactive.
    A loud single second heart sound.
    Harsh systolic murmur may be present from flow across the VSD, though if the VSD is large, it may not be audible (see Chap. 5 for physical exam signs of a VSD).
  - In those with decreased pulmonary blood flow:

Cyanosis is present and may lead to late findings of digital clubbing if unrepaired.
A systolic murmur from PS may be present.

– In those with aortic obstruction:

Pulmonary over-circulation and heart failure symptoms may be present.
If obstruction is severe, then poor pulses and hypoperfusion are possible.

Electrocardiography

- Electrocardiography is rarely diagnostic for DORV.
- Electrocardiography reflects the presence of right ventricular and/or left ventricular hypertrophy.
- Right bundle branch block and right axis deviation are often seen.
- Operated patients are susceptible to heart block, bundle branch block, atrial arrhythmias, and ventricular arrhythmias notable on electrocardiography.

Chest X-Ray

- Chest radiography demonstrates cardiac position, chamber enlargement, and cardiomegaly.
- Diminished pulmonary vasculature suggests severe PS.
- In the absence of PS, the pulmonary artery may be enlarged, and increased pulmonary vascularity will be present.

Echocardiography

- Echocardiography is used to diagnose DORV.
- Echocardiography should demonstrate the following:
  - The commitment of the pulmonary artery and aorta to the right ventricle.
  - The relationship of both great arteries to each other.

  - The location of the VSD and its relationship to the great arteries.
  - The presence of associated anomalies.
- Multiple views, sometimes including 3D echocardiography, are necessary to accurately determine the relationship between the VSD and great arteries.

Cardiac Catheterization

- Cardiac catheterization may be performed to document hemodynamic status before or after repair, define aberrant coronary anatomy, and define pulmonary vascular abnormalities.

Advanced Imaging Techniques

- Magnetic resonance imaging (MRI) may serve as an adjuvant to echocardiography in defining anatomy and may provide additional information on the relationship of the VSD to the great arteries [8].
- Computed tomography angiography can also aid in defining the anatomy, of the VSD, outflow tracts, and coronary artery origins (Fig. 22.2).
- 3D printing of MRI or CT images is particularly useful in the preoperative planning for DORV surgery because it gives the surgeon a visual understanding of the relationship of the VSD to the great arteries.

Management of Adult Survivors

Follow-Up

- It is rare for primary presentation of DORV to occur in adults. Additionally, the surgical management of DORV is so varied that follow-up depends on the patient's condition,

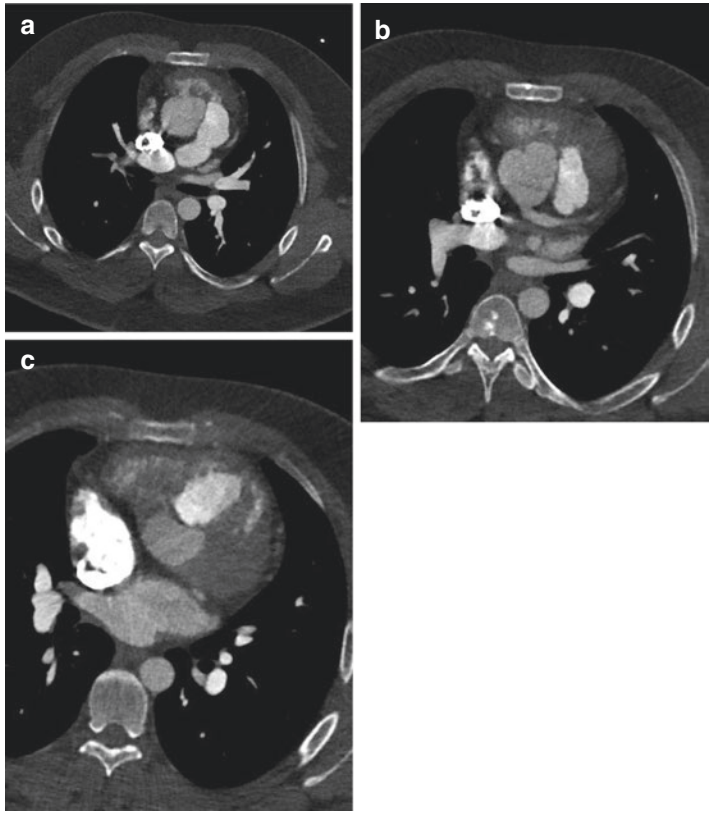

FIGURE. 22.2 CT angiography images of double outlet right ventricle. Axial CTA images from the aortic and pulmonic root to the RVOT level (**a–c** serially in craniocaudal direction) showing both the aorta and pulmonary artery arising from RV

type of repair, and residual lesions. The American College of Cardiology/American Heart Association published guidelines for the management of adults with a VSD, D-TGA, TOF, and single ventricle with a Fontan repair; [9] thus adults with DORV should be managed according to the lesion-specific guidelines that most reflect their anatomy [10].

- Periodic follow-up with a specialized adult congenital heart disease cardiologist is recommended, though interval of follow-up and interval of additional testing are determined by severity of symptoms.
- Follow-up may include studies such as electrocardiography, echocardiography, MRI, cardiopulmonary exercise testing, and cardiac catheterization.

Unrepaired Patients

- The benefits of surgical intervention depend on the anatomy and physiology of each individual patient. Unrepaired adult patients without severe pulmonary hypertension or Eisenmenger physiology will likely benefit from a biventricular repair or Fontan palliation.
- Preoperative evaluation with MRI and echocardiography is important for determining anatomy. Cardiac catheterization is performed to assess hemodynamics to ensure that repair is feasible (pulmonary hypertension may preclude repair), as well as determine coronary anatomy.

Repaired Patients

- Complications after repair depend on the underlying anatomy and type of surgery performed.
- During follow-up, the status of both ventricles, residual valvular or subvalvular stenosis or insufficiency, the presence of a residual VSD, evidence of coarctation or re-coarctation, and evidence of conduit stenosis or regurgitation should be evaluated. Imaging studies such as echocardiography and MRI are beneficial for this evaluation.
- Electrocardiography is warranted to assess for heart block, atrial arrhythmias, or ventricular arrhythmias.
- If a Fontan was performed, hemodynamic assessment is important as elevated pulmonary vascular resistance will impede Fontan physiology [6]. See Chap. 28 on late Fontan management.

Arrhythmias and Sudden Cardiac Death

- Adult patients with DORV, both repaired and unrepaired, are at risk for atrial and ventricular arrhythmias as well as sudden cardiac death [7].
- Previous intracardiac surgery and stenosed conduits are additional risk factors for repaired patients.
- Arrhythmias in this patient population may reflect abnormal hemodynamic status associated with chamber dilation, hypertrophy, and/or dysfunction.

Infective Endocarditis Prophylaxis

- Infective endocarditis prophylaxis is indicated in most patients with DORV. In particular, endocarditis prophylaxis is warranted in those with:
  - Prosthetic cardiac valve
  - Previous endocarditis
  - Unrepaired patients
  - Repaired patients with prosthetic material or device during first 6 months following procedure
  - Repaired patients with residual defects at the site or adjacent to the site of a prosthetic patch/device

Management of Pregnancy

- Most patients with DORV who have had successful biventricular repair can carry a pregnancy to term, as long as the patient does not have severe pulmonary insufficiency, pulmonary hypertension, severe aortic stenosis, or left ventricular dysfunction [6].
- The risk of pregnancy is significantly higher in those who have had a Fontan operation, though there are reported cases of successful pregnancies in patients who underwent a Fontan operation [11].

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Chapter 23
Tetralogy of Fallot

Jonathan Kochav

Epidemiology

- Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart lesion after infancy, with an incidence of 4–5 per 10,000 live births [1, 2]. It accounts for about ~5% of cases of congenital heart disease worldwide [2].
- For historical perspective, see Table 23.1.

Anatomic Definition and Pathophysiology

- Anatomy:
  - The pathologic description by Fallot included four distinct abnormalities (Fig. 23.1):
    - Pulmonic stenosis (PS)
    - Large, nonrestrictive ventricular septal defect (VSD)
    - Overriding aorta
    - Right ventricular (RV) hypertrophy

      This constellation results from a single embryologic malformation, anterior deviation of the conal septum

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Table 23.1 Historical background

Tetralogy of Fallot was first described in by Danish scientist Nicolaus Steno in a 1673 case report of an infant with omphalocele, sternal cleft, and an unusual cardiac anatomy (this syndrome is now referred to as the pentalogy of Cantrell). In 1888, Etienne-Louis Arthur Fallot described a series of cyanotic patients as having a "tetralogy" of defects that produced their cyanosis. In an era when it was believed that all instances of cyanotic heart disease were result of patent foramen ovale, it was he who first identified that the tetralogy of Fallot was the most common cause of cyanosis post infancy [3].
In 1944, Surgeon Alfred Blalock and his assistant Vivien Thomas, in association with pediatric cardiologist Helen Taussig, performed the first Blalock-Taussig-Thomas shunt (subclavian artery to pulmonary artery anastomosis) on 15-month-old girl with tetralogy of Fallot. This revolutionary event ushered in the modern era of cardiac surgery [4]. This was followed in 1954 by the first open repair of the tetralogy of Fallot by Walton Lillehei on controlled cross-circulation [5]. Percutaneous pulmonic valve replacement was first reported by Bonhoeffer in a human patient with a dysfunctional RVOT conduit [6].

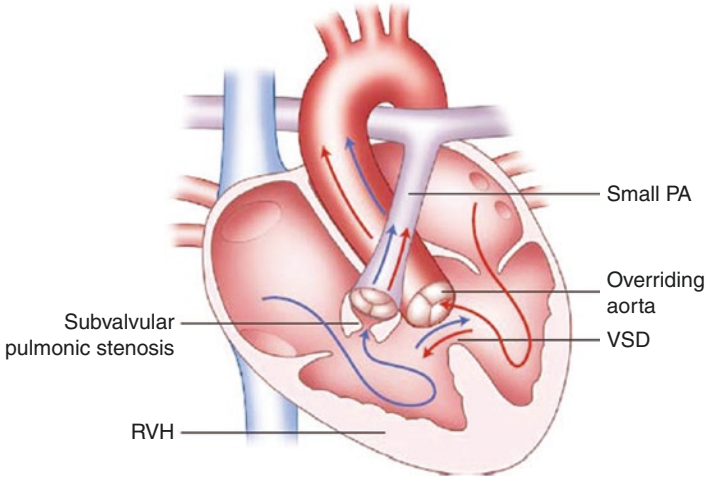

Figure 23.1 Schematic diagram showing the anatomy of unrepaired tetralogy of Fallot [7]

separating the aorta and pulmonary artery, leading to a diminutive pulmonary artery/annulus, and a VSD, which the anteriorly displaced aorta overrides. The RV outflow tract is crowded, and infundibular PS is typical, but valvular and supravalvular PS can also be seen. Due to the increased afterload on the RV induced by the PS, RV hypertrophy ensues.

- Physiology:
  - The resultant physiology is that of a right-to-left shunt through the ventricular septal defect, resulting in a diminished Qp/Qs ratio as well as systemic cyanosis. Contraction or spasm of the infundibulum can produce dynamic increases in RV outflow resistance, acutely increasing right-to-left shunt flow, and resulting in episodic worsening of systemic cyanosis ("tet spells"). Patients will instinctively squat to increase systemic vascular resistance and reduce the right-to-left shunt fraction. These episodes can be life threatening if prolonged and are treated with intravenous beta-blockers to reverse infundibular spasm or vasopressors to pharmacologically increase systemic vascular resistance and restore the balance of flow.
- Spectrum of disease:
  - Depending on the extent of deviation of the conal septum, a wide spectrum of morphology and severity can exist. On the least severe end of the spectrum are patients with minimal infundibular stenosis, who initially manifest a left-to-right shunting pattern through the VSD (often referred to as "pink tets"). On the more severe end are patients with pulmonary atresia who are dependent on a patent ductus arteriosus for pulmonary arterial blood flow.
- Associated defects:
  - Aorta:
    - Right aortic arch is associated in 25% of cases
    - Approximately 15% patients have ascending aortic dilation, which is associated with moderate or severe

aortic regurgitation in 13% of cases. Most common in patients with severe pulmonary stenosis or who had palliative shunts [8]

- Coronary artery [9]:
  - Anomalous coronary origin occurs in 8% of patients
  - ~5% of TOF patients have aberrant course of the left anterior descending (LAD) or left main (LM) arising from the proximal right coronary artery (RCA) traversing the RV outflow tract (RVOT) (Fig. 23.2). This anatomy is important to define prior to TOF repair as discussed below
- Other associated abnormalities [10–12]:
  - Atrial septal defect in 10% ("pentalogy of Cantrell")
  - Atrioventricular septal defects
  - Branch PS seen in up to 40%
  - Aortopulmonary collaterals
  - Persistent left superior vena cava
  - *D*-looped transposition of the great arteries
  - Ebstein's anomaly

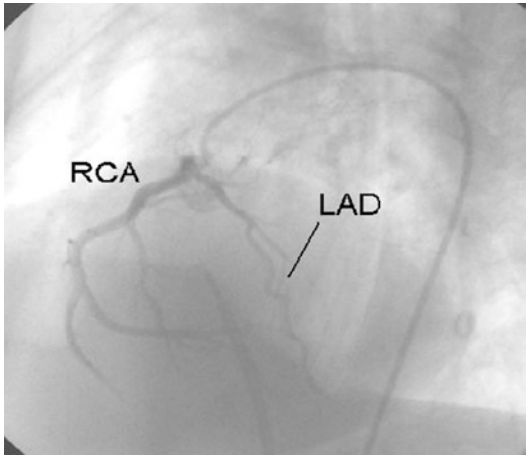

FIGURE. 23.2 Coronary angiogram showing an anomalous left anterior descending coronary artery arising from the right coronary artery and traversing the RVOT

- Genetics and maternal factors:
  - TOF may be a partially inherited syndrome and has been associated with genetic syndromes or chromosomal mutations in ~25% of cases, with over 15% of cases having the 22q11 deletion associated with the DiGeorge (velocardiofacial) syndrome. Genetic testing should be offered to all patients [13].

Childhood Repairs

Palliative Shunts (Aortopulmonary Shunts)

- Palliative shunts have historically been utilized to produce a compensatory left-to-right shunt and thus provide a complementary avenue for pulmonary arterial blood flow (Fig. 23.3). The vast majority of survivors who initially underwent these palliative procedures have since been converted to complete TOF repair.
  - The Blalock-Taussig-Thomas (BTT or BT shunt) shunt directs blood from the subclavian to the pulmonary artery.

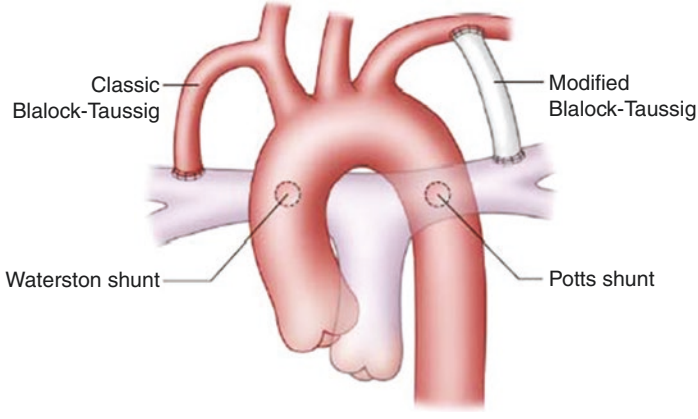

FIGURE 23.3 Schematic diagram showing the various locations of palliative systemic to pulmonary shunts [7]

    - Classic BTT shunt: subclavian is ligated and end-to-side anastomosed to the pulmonary artery (radial pulse and ipsilateral arm blood pressures are often reduced).
    - Modified BTT shunt: uses a prosthetic tube graft to connect the two arteries (the radial pulse and ipsilateral arm blood pressures are generally preserved).
  - Similar pulmonary blood flow augmentation was achieved through the Waterston (ascending aorta to pulmonary artery window) and Potts (descending aorta to left pulmonary artery window) shunts, which are rarely used today.
  - Pulmonary blood flow was difficult to control with these shunts, often resulting in progressive pulmonary hypertension (may be unilateral) and branch pulmonary artery stenosis.
  - Decreased diastolic blood pressure can cause decreased coronary artery perfusion and contribute to ischemia.

Complete Tetralogy of Fallot Repair

- Most patients born into the current era have undergone early complete TOF repair in infancy.
- Consists of patch closure of the VSD and a transannular incision and patch enlargement of the RV outflow tract (Fig. 23.4). In the modern era, if the annulus is of adequate size, it may not be incised to avoid the long-term risk of pulmonary insuficiency (PR).
  - Residual defects following this repair include free PR, which can lead to RV dilation/dysfunction over time, residual PS, and residual patch-related VSDs.

Rastelli Procedure

- The Rastelli procedure is used in patients who have concomitant *D*-looped transposition of the great arteries, or in patients who have severe PS or pulmonic valve aplasia for

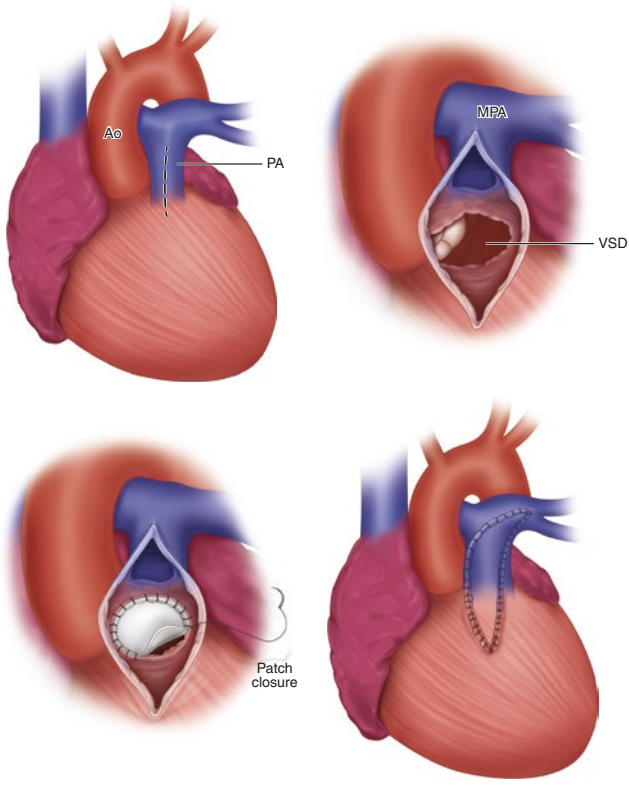

FIGURE 23.4 Surgical tetralogy of Fallot repair: (1) A trans-annular incision is made. (2) The VSD is exposed. (3) Patch-closure of the VSD is performed. (4) The infundibulum is resected and the RVOT is enlarged with a patch. *Ao* aorta, *MPA* main pulmonary artery, *PA* pulmonary artery, *VSD* ventricular septal defect

whom patch enlargement of the RVOT is not technically possible.

- A Rastelli conduit is a valved conduit from the RV to the main pulmonary artery (Fig. 23.5).
  - Long-term complications of this procedure include stenosis of the RV to PA conduit at the takeoff, touchdown, or at the level of the valve.

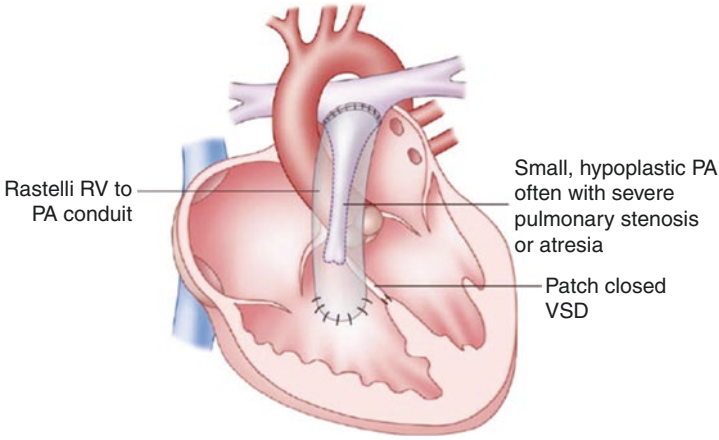

FIGURE 23.5 The Rastelli procedure [7]

– Stenoses have been addressed with transcatheter dilation in children and adolescents and with surgical upsizing of the conduit in older adolescents and adults. More recently transcatheter valve implantations using the Melody® valve have demonstrated success [14, 15].

Diagnostics

Clinical Presentation in Adults

- Young adult patients may present without prior interventions, particularly if they have very mild disease and have had little interface with medical care in childhood (often immigrants in the United States).
- Rarely patients may present status post only remote palliative procedures, but the vast majority present following complete repair.
- Patients post complete repair may be asymptomatic or may have late complications including PR and RV dilation/dysfunction resulting in exercise intolerance and volume overload, atrial arrhythmias, ventricular tachycardia (VT), and sudden cardiac death.

- Presentation with left heart failure symptoms is less common (see below)

Physical Exam

- Residual RVOT obstruction
  - Systolic crescendo-decrescendo murmur best over the pulmonic area
- Residual VSD
  - Harsh pansystolic murmur
- RV hypertrophy
  - RV heave
  - Right-sided gallop
- Pulmonic insufficiency
  - Low-pitched diastolic decrescendo murmur. Shorter murmurs generally signify more severe lesions, as there will be earlier equalization of pulmonary artery and RV pressures
  - A single A2 may be heard in the absence of functional pulmonic valve

Electrocardiogram [16] (Fig. 23.6)

- Right bundle branch block
  - Expected after repair and occurs due to surgical injury of the right bundle branch and remains long-standing
  - QRS duration may prolong over time due to right ventricular dilation
    - Annual QRS prolongation and absolute duration ≥180 ms are both markers of increased arrhythmic risk [17, 18].
- Right ventricular strain
  - RV hypertrophy

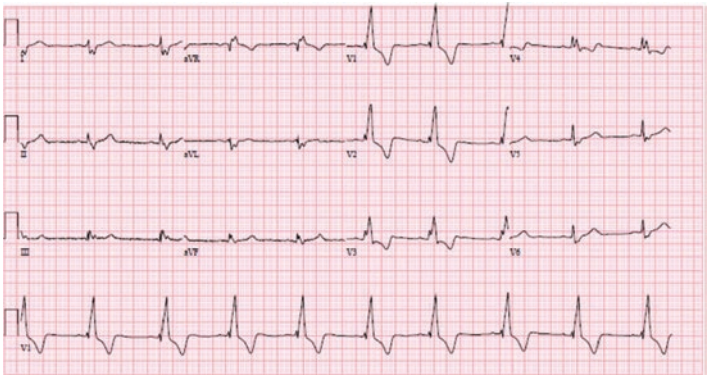

FIGURE 23.6 Representative electrocardiogram of an adult patient with surgically repaired tetralogy of Fallot

    - In a patient with right bundle branch block, this is defined by R' in $V1 \geq 1.5$ mV with right axis deviation.

- Right atrial enlargement with peaked P-waves
- PR prolongation and complete heart block are rare but can occur. This is more common post-Rastelli procedure.

Chest Radiograph

- Right ventricular enlargement
  - Anterior-posterior view (Fig. 23.7)
    - Rounded left heart border
    - Uplifted cardiac apex
    - May demonstrate a classic "boot-shaped" heart
  - Lateral view
    - Filling of the retrosternal space
    - Rotation of the heart posteriorly
  - Right-sided aortic arch may be visualized.

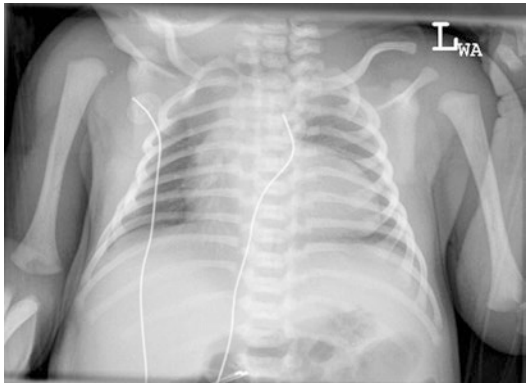

FIGURE 23.7 Chest radiograph of a child with uncorrected tetralogy of Fallot. Note the rounded left heart border and uplifted cardiac apex, giving the appearance of a "boot shaped" heart

Echocardiography

- Annual echocardiography is useful for surveillance of PR and aortic root dilation. Among patients who did not have a transannular resection and do not have significant PS or PR, frequent echocardiograms may not be necessary.
- Echocardiography is used to assess degree of PR but is limited in precise quantification of RV size and function when compared to MRI. However importantly, 3D imaging and quantitative RV echocardiographic parameters correlate with cardiac MRI volumes and ejection fraction and should be followed in all TOF patients [19].
- Table 23.2 highlights the essentials of echocardiographic assessment of patients with tetralogy of Fallot, both pre- and post-complete repair.

Table 23.2 Echocardiographic essentials for assessment [12]

Unoperated patient with TOF:	Postoperative patient with TOF:
1. VSD location, size, and shunt direction; additional VSDs	1. Residual VSD
2. Degree and nature of RV outflow tract obstruction	2. Residual infundibular, valvular, or branch PS; double chamber right ventricle
3. RV outflow tract and branch pulmonary artery gradients	3. Degree of PR
4. Pulmonary annulus, main and branch pulmonary artery dimensions	4. Residual atrial shunting
5. RV size, wall thickness, and quantitative assessment of function	5. RV volumes, quantitative systolic, and diastolic function
6. Coronary artery origins and course	6. Estimated RV pressure from Doppler peak tricuspid regurgitant jet velocity
7. Atrial septal anatomy	7. Aortic valve anatomy and function
8. Aortic arch situs	8. Aortic root dimensions
9. Aortopulmonary collaterals	9. LV size, global and segmental function
	10. Conduit location, size, and gradients, if present
	11. Prosthetic pulmonic valve stenosis or regurgitation, if present

Cardiac Catheterization

- Indications for catheterization [11]:
  - Coronary artery angiogram should be performed before any intervention for the RVOT, as ~5% of patients can have an anomalous LAD or LM coronary artery arising from the RCA, which may traverse the RVOT
  - Evaluation for and treatment of residual intracardiac (atrial or ventricular septal defects) or extracardiac (aortopulmonary collateral vessels, palliative systemic-pulmonary artery) shunts in patients who are persistently cyanotic

Advanced Imaging Techniques

- Patients with severe PR are at risk of progressive RV dilation and dysfunction and should undergo advanced imaging [20].
- Cardiac MRI is the gold standard for following RV dilation in patients with severe PR to assess PR quantification, as well as precise RV volumes and RV ejection fraction which may determine surgical timing [20, 21].
- Low-radiation cardiac CT angiography has also emerged as an important tool in defining coronary anatomy as well as precise measurement of the RVOT and is often used for Melody® valve planning (Fig. 23.8). RV size and function by cardiac CT also correlate well with MRI assessment and can be used as an alternative for patients who are unable to undergo MRI testing (pacer, claustrophobia) [21, 22].

Management of Complications in Adult Survivors

See Table 23.3 for summary of guidelines.

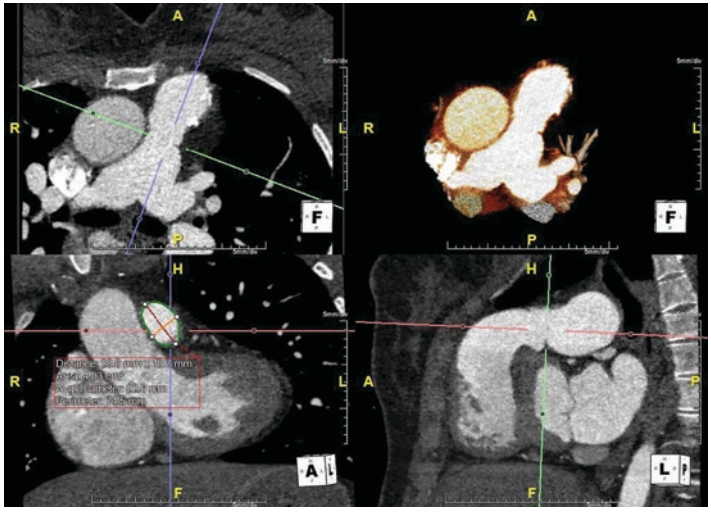

FIGURE 23.8 Cardiac CT angiography of an adult patient with tetralogy of Fallot demonstrating assessments and measures of the RV outflow tract

Arrhythmia

- Ventricular arrhythmias:
  - Sustained VT and sudden cardiac death are an important cause of mortality in this population
  - Risk factors include QRS prolongation (QRS duration ≥180 ms) [17], increased RV mass-to-volume ratio, ventricular dysfunction and history of atrial arrhythmia [23], as well as older age at complete repair
  - Management includes addressing ongoing hemodynamic insults (pulmonic insufficiency, pulmonary stenosis, persistent shunt), placement of implantable cardioverter defibrillator for secondary prevention, and targeted antiarrhythmics and/or ablation procedures
- Atrial arrhythmias [24]:
  - Atrial arrhythmias have been observed to occur in 20% of patients with TOF, with intra-atrial reentrant tachyarrhythmias (i.e. atrial flutter) predominating among

Table 23.3 ACC/AHA Guidelines 2008 [11]

Recommendations for evaluation and follow-up:

Class I

1. Patients with repaired tetralogy of Fallot should have at least annual follow-up with a cardiologist who has expertise in ACHD (*level of evidence: C*)
2. Patients with tetralogy of Fallot should have echocardiographic examinations and/or MRIs performed by staff with expertise in ACHD (*level of evidence: C*)
3. Screening for heritable causes of their condition (e.g., 22q11 deletion) should be offered to all patients with tetralogy of Fallot (*level of evidence: C*)
4. Before pregnancy or if a genetic syndrome is identified, consultation with a geneticist should be arranged for patients with tetralogy of Fallot (*level of evidence: B*)
5. Patients with unrepaired or palliated forms of tetralogy should have a formal evaluation at an ACHD center regarding suitability for repair (*level of evidence: B*)

Recommendations for imaging:

Class 1

1. Comprehensive echocardiographic imaging should be performed in a regional ACHD center to evaluate the anatomy and hemodynamics in patients with repaired tetralogy of Fallot (*level of evidence: B*)

Recommendations for diagnostic and interventional catheterization:

Class I

1. Catheterization of adults with tetralogy of Fallot should be performed in regional centers with expertise in ACHD (*level of evidence: C*)
2. Coronary artery delineation should be performed before any intervention for the RVOT (*level of evidence: C*)

Class IIb

1. In adults with repaired tetralogy of Fallot, catheterization may be considered to better define potentially treatable causes of otherwise unexplained LV or RV dysfunction, fluid retention, chest pain, or cyanosis. In these circumstances, transcatheter interventions may include:
   (a) Elimination of residual shunts or aortopulmonary collateral vessels (*level of evidence: C*)
   (b) Dilation (with or without stent implantation) of RVOT obstruction (*level of evidence: B*)
   (c) Elimination of additional muscular or patch margin VSD (*level of evidence: C*)
   (d) Elimination of residual ASD (*level of evidence: B*)

(continued)

Table 23.3 (continued)

Recommendations for surgery:

Class I

1. Surgeons with training and expertise in CHD should perform operations in adults with previous repair of tetralogy of Fallot (*level of evidence: C*)
2. Pulmonary valve replacement is indicated for severe pulmonary regurgitation and symptoms or decreased exercise tolerance (*level of evidence: B*)
3. Coronary artery anatomy, specifically the possibility of an anomalous anterior descending coronary artery across the RVOT, should be ascertained before operative intervention (*level of evidence: C*)

Class IIa

1. Pulmonary valve replacement is reasonable in adults with previous tetralogy of Fallot, severe pulmonary regurgitation, and any of the following:
   (a) Moderate to severe RV dysfunction (*level of evidence: B*)
   (b) Moderate to severe RV enlargement (*level of evidence: B*)
   (c) Development of symptomatic or sustained atrial and/or ventricular arrhythmias (*level of evidence: C*)
   (d) Moderate to severe TR (*level of evidence: C*)

Recommendation for interventional catheterization:

Class I

1. Interventional catheterization in an ACHD center is indicated for patients with previously repaired tetralogy of Fallot with the following indications:
   (a) To eliminate residual native or palliative systemic—pulmonary artery shunts (*level of evidence: B*)
   (b) To manage coronary artery disease (*level of evidence: B*)

Class IIa

1. Interventional catheterization in an ACHD center is reasonable in patients with repaired tetralogy of Fallot to eliminate a residual ASD or VSD with a left-to-right shunt greater than 1.5:1 if it is in an appropriate anatomic location (*level of evidence: C*)

Table 23.3 (continued)

2. Collaboration between ACHD surgeons and ACHD interventional cardiologists, which may include preoperative stenting, intraoperative stenting, or intraoperative patch angioplasty, is reasonable to determine the most feasible treatment for pulmonary artery stenosis (*level of evidence: C*)
3. Surgery is reasonable in adults with prior repair of tetralogy of Fallot and residual RVOT obstruction (valvular or subvalvular) and any of the following indications:
   (a) Residual RVOT obstruction (valvular or subvalvular) with peak instantaneous echocardiography gradient greater than 50 mmHg (*level of evidence: C*)
   (b) Residual RVOT obstruction (valvular or subvalvular) with RV/LV pressure ratio greater than 0.7 (*level of evidence: C*)
   (c) Residual RVOT obstruction (valvular or subvalvular) with progressive and/or severe dilatation of the right ventricle with dysfunction (*level of evidence: C*)
   (d) Residual VSD with a left-to-right shunt greater than 1.5:1 (*level of evidence: B*)
   (e) Severe aortic regurgitaiton with associated symptoms or more than mild LV dysfunction (*level of evidence: C*)
   (f) A combination of multiple residual lesions (e.g., VSD and RVOT obstruction) leading to RV enlargement or reduced RV function (*level of evidence: C*)

Recommendations for arrhythmias:

Class I

1. Annual surveillance with history, ECG, assessment of RV function, and periodic exercise testing is recommended for patients with pacemakers/automatic implantable cardioverter defibrillators (*level of evidence: C*)

Class IIa

1. Periodic Holter monitoring can be beneficial as part of routine follow-up. The frequency should be individualized depending on the hemodynamics and clinical suspicion of arrhythmia (*level of evidence: C*)

Class IIb

1. Electrophysiology testing in an ACHD center may be reasonable to define suspected arrhythmias in adults with tetralogy of Fallot (*level of evidence: C*)

patients <45 years and atrial fibrillation predominating among patients >55 years.
  - Risk factors include number and extent of cardiac surgeries, right atrial dilation for intra-atrial reentrant tachyarrhythmias, and left atrial dilation and LV systolic dysfunction for atrial fibrillation.

- Periodic Holter monitoring can be beneficial to assess for arrhythmia burden, with frequency individualized based on hemodynamics and clinical suspicion of arrhythmia.

Residual Pulmonic Stenosis

- Residual RVOT obstruction
  - Residual RVOT obstruction may rarely develop following complete TOF repair as the heart outgrows the enlargement initially afforded by the transannular patch.
  - ACC/AHA Guidelines state that consideration of surgical repair is reasonable in circumstances where the RVOT gradient is measured at >50 mmHg, where the RV to left ventricular (LV) pressure ratio is >0.7, or if there is evidence of progressive and/or severe dilation of the RV with dysfunction (class IIa) [11].

- Branch pulmonary stenosis
  - Branch PS may occur primarily or as a consequence of previous surgical intervention.
  - Surgical correction and transcatheter pulmonary artery dilation are options in cases of hemodynamically significant stenosis.

Pulmonary Insufficiency and Right Heart Failure

- Severity of PR is variable immediately post-TOF repair and depends on the integrity of the native pulmonary valve leaflets as well as the degree of leaflet coaptation

that remains following transannular patch placement. Pulmonary insufficiency may progress over several decades.

- The ACC/AHA Guidelines recommend pulmonic valve replacement for severe PR with any of the following [11]:
  - Symptoms of decreased exercise tolerance
  - Moderate to severe RV dysfunction or enlargement
  - Sustained atrial or ventricular arrhythmias
  - Less than moderate to severe tricuspid regurgitation (class IIa recommendation)
- Patients with severe PR should undergo cardiac MRI for assessment of RV volumes. Several studies utilizing cardiac MRI have reported BSA-indexed RV volumetric thresholds (RV end-diastolic volume $\geq$150 mL/m^2, RV end-systolic volume $\geq$85 mL/m^2) [25–32], at which point pulmonic valve relplacement resulted in normalization of RV size. In one of these studies, almost no patients with an RV end-diastolic volume >170 mL/m^2 or RV end-systolic volume >85 mL/m^2 achieved normalization of RV volume [29], suggesting that there may be a volumetric "point of no return" at which the potential for reverse RV mechanical remodeling is limited.
  - The findings from these studies have driven practice to perform routine CMR in patients with severe PR, and refer for pulmonic valve replacement in patients with who have met above thresholds.

- While there are rare case reports of use of the Melody® valve in the native pulmonic valve, transcatheter devices designed for deployment into native RVOT are being utilized at experienced centers.

Left Heart Failure

- Left heart failure in TOF is associated with poor outcomes and can occur as a result of several etiologies.

- Residual VSD and left ventricular volume overload
- Aortic regurgitation due to aortic root dilation (see below)
- LV dysfunction due to severe RV dilation and the reverse Bernheim phenomenon (leftward shift of the interventricular septum with subsequent left ventricular systolic and diastolic dysfunction)
- Pacemaker-associated cardiomyopathy
- Tachycardia-mediated cardiomyopathy (atrial arrhythmias are common)
- Always consider evaluation of coronary atherosclerotic disease when age appropriate

Thoracic Aortic Dilation [8]

- Etiology:
  - Aortic dilation has been associated with late corrective surgery, larger LV volumes, and severity of pulmonary stenosis, suggesting that volume overload to the aorta is likely a contributing factor.
  - Patients with TOF and aortic dilation have been noted to have advanced histologic degeneration of the aortic wall media, suggesting that underlying aortopathy may predispose to aneurysm in some patients.
- Complications:
  - Moderate to severe aortic regurgitation in up to 15% of patients potentially requiring valve replacement
- Severely dilated aorta that leads to dissection or rupture is exceedingly rare, with only four cases reported in the literature [33–36]. Three cases of dissection occurred at aortic diameter of >7 cm, while one occurred at a diameter of 5.3 cm [32]. There is little data to guide threshold for aortic repair, but we generally consider aortic repair at a threshold of greater than 5.5 cm.

Management of Pregnancy

- All patients with TOF, who are or who plan to become pregnant, should be seen by both ACHD specialists and high-risk obstetricians.
- Genetic counseling should be offered to all women with TOF who plan to become pregnant to assess for potentially heritable mutations or chromosomal anomalies.
- Patients with well-repaired TOF without RV dysfunction/failure or significant arrhythmic history generally tolerate pregnancy very well (World Health Organization pregnancy risk category II) [37, 38].
- Pregnancy may worsen PR and accelerate RV dilation [7], as intravascular volumes expand by about 40% during the second and third trimesters.
  - If right heart failure develops in the third trimester or peri-partum, treatment with diuretics is safe

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Chapter 24
Truncus Arteriosus

Christopher Valle and Michelle Hadley

Abbreviations

ASD	Atrial septal defect
CHD	Congenital heart disease
LV	Left ventricle
PA	Pulmonary arteries
PAH	Pulmonary arterial hypertension
PDA	Patent ductus arteriosus
PVR	Pulmonary vascular resistance
RV	Right ventricle
VSD	Ventricular septal defect

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Table 24.1 Historical background [1–4]

1798—First case documented by Wilson
1942—Lev and Safir define basic morphologic criteria
1949—Collet and Edwards classification
1962—First non-valved conduit
1965—Van Praagh's classification
1967—First successful surgical correction of truncus arteriosus performed by McGoon, Rastelli, and Ongley, who used an ascending aortic homograft as a valved conduit from the RV to the PA
1971—First conduit repair during infancy by Barratt-Boyes

Epidemiology

- Truncus arteriosus is rare, accounting for approximately 1.1% of all congenital heart disease (CHD) [1].
- There have been an estimated 30,000 children born with truncus in the United States since 1940 [2].
- For historical background, see Table 24.1.

Anatomic Definition and Pathophysiology

- Anatomy: [1]
  - Characterized by failure of the embryological truncus arteriosus to divide into the aorta and pulmonary arteries, leading to a single ascending vessel that gives rise to the aorta and pulmonary artery in varying configurations (Fig. 24.1):

  Believed to arise from derangements in neural crest cells and neural tube formation (Fig. 24.2)

  - It is hypothesized that the increased, combined ventricular output into the truncus leads to an enlarged truncus relative to a normal aorta at any given age.

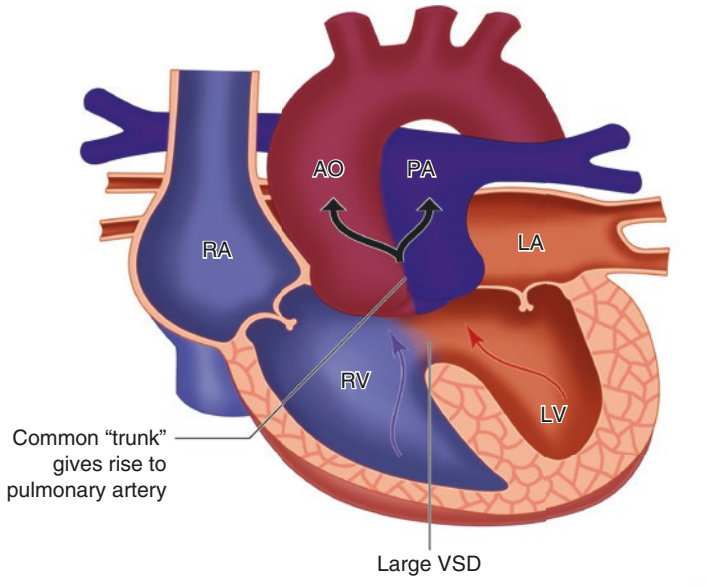

FIGURE 24.1 Truncus arteriosus

- The truncus overrides both ventricles in ~40%, the right ventricle (RV) in ~40% and the left ventricle (LV) in the remainder of cases.
- The truncal valve may have anywhere from one to six cusps, with three being most common (reported 42–64%), followed by four leaflets (25%), and two leaflets (8–15%).
- Valve cusps are often thickened and dysplastic, predisposing to mild-moderate degrees of valvular stenosis and/or regurgitation.
- Aortic arch abnormalities are common:

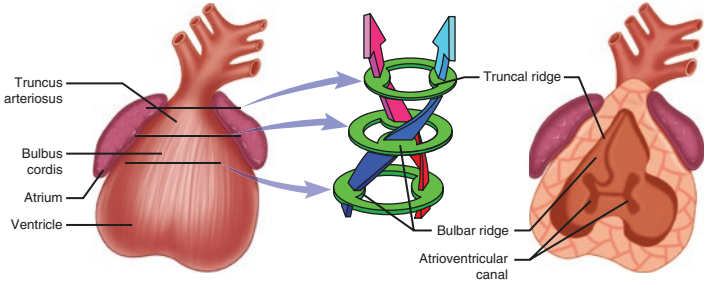

FIGURE 24.2 Embryologic division of the truncus arteriosus

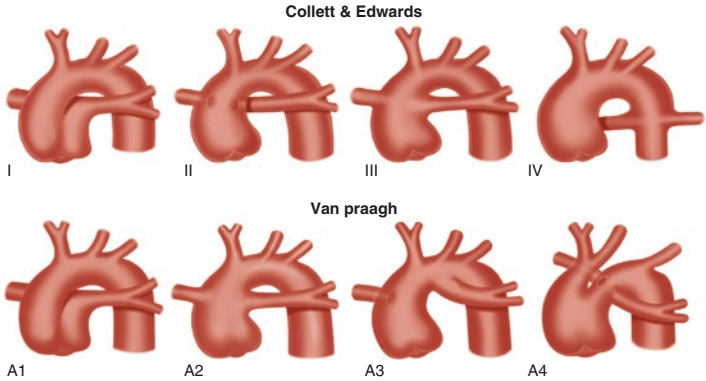

FIGURE 24.3 Truncus classifications [5]

20–30% of patients will have a right aortic arch.
10–20% of patients will have an interrupted aortic arch, typically between the left subclavian and carotid arteries:

Those with an interrupted arch always have a large patent ductus arteriosus (PDA).

- The Collett and Edwards classification describes the origin of the pulmonary arteries (PA) [5] (Fig. 24.3):

Type 1: a main PA arises from the left side of truncus and then divides into the right and left PAs.
Type 2: the right and left PAs arise side-by-side from posterior aspect of truncus.

Type 3: rare; the right and left PAs arise from lateral walls of truncus and are widely separated.

Type 4: no PAs, lungs supplied by aortopulmonary collaterals, often considered a subtype of pulmonary atresia.

– The vast majority of patients will have a ventricular septal defect (VSD), typically large and anterior:

In the absence of a VSD, the truncus will arise from a single ventricle, and the ventricle not giving rise to the truncus will become hypoplastic.

– Roughly 2/3 of patients will have normal origins of coronary arteries:

Approximately 30% have two arteries originating from the same sinus or single artery.

Approximately 25% have ostia above the sinotubular ridge.

- Physiology:
  - In patients with truncus arteriosus, there is mixing of the systemic and pulmonary venous blood flow in the shared single output trunk as well as through a VSD.
  - The subsequent clinical manifestations are determined by the volume of pulmonary blood flow as determined by (1) pulmonary vascular resistance (PVR), (2) the degree of truncal valve insufficiency, and (3) any comorbid aortic abnormalities.
  - PVR:

In the period immediately following birth, PVR is relatively high, restricting pulmonary blood flow and allowing for mixing in the intra- and extra-cardiac levels leading to mild-to-moderate cyanosis.

In the first several weeks of life, as the PVR declines, left-to-right shunting will occur as blood preferentially flows to the lower-resistance pulmonary vascular system.

Increased pulmonary flow leads to overcirculation and heart failure, which may rapidly progress to pulmonary arterial hypertension (PAH).

  - Truncal valve insufficiency:

Significant regurgitation leads to lower diastolic blood pressures and increased ventricular myocardial oxygen demand from increased volume load, predisposing to myocardial ischemia and ventricular dysfunction.

  - Comorbid aortic abnormalities:

Infants with an interrupted aortic arch or critical coarctation are ductal-dependent and develop pressure overload as the ductus closes.

- Spectrum of disease:
  - Truncus classically results in severe, cyanotic CHD necessitating surgical intervention within the first weeks to months of life after infants present with cyanosis, respiratory distress, and/or a murmur.
  - Uncorrected patients who survive beyond the first year of life (<15% of all uncorrected patients) subsequently developed Eisenmenger syndrome with profound cyanosis and functional impairment [8].
- Associated defects:
  - Secundum atrial septal defect (ASD), (9–20%)
  - Mild tricuspid stenosis (6%)
  - Aberrant subclavian arteries (4–10%)
  - Persistent superior vena cava draining into the coronary sinus (4–9%) [2, 6]
  - PDA (approximately 50%)
- Genetics and maternal factors:
  - Strong association with DiGeorge syndrome and 22q11 deletion [7, 8]

Diagnostics

Clinical Presentation in Adults

- Adults with truncus arteriosus fall into one of two categories:

– The majority have undergone surgical repair which in some variation involves the creation of an RV-to-PA conduit, closure of VSD, and creation of neoaortic valve from the truncal valve:

There is extremely limited data on the long-term outcomes and sequelae of patients with repaired truncus arteriosus.
From data on other patients with ACHD, long-term complications can be extrapolated:

RV-to-PA conduits are at risk for both stenosis and insufficiency and may need to be replaced either surgically or intervened upon percutaneously over time.
Aortic size may increase with time.
Residual VSD may result in LV volume load.
Truncal valve dysfunction and sclerosis, usually insufficiency.
Branch PA stenosis.
Arrhythmias.
Ventricular dysfunction.
Endocarditis.

– Rarely, unoperated patients with balanced physiology that spares the pulmonary vasculature from high flow will survive into adulthood [9], and these patients almost uniformly develop Eisenmenger syndrome (see Chap. 9).

Physical Exam

- If unrepaired:
  - Cyanosis and clubbing
  - Prominent single second heart sound
  - Systolic ejection murmur at the left sternal border (of truncal outflow)
  - Continuous bruits on the anterior or the posterior thorax from collateral vessels if present
- If repaired:
  - Signs of right heart failure if RVH or RV-to-PA conduit stenosis/regurgitation:

Elevated jugular venous pressure, prominent *a* wave, RV gallop
Lower extremity edema
Hepatomegaly or ascites

- Signs of left heart failure with pulmonary congestion if severe truncal regurgitation or residual VSD:

Harsh holosystolic murmur if residual VSD present (pending size and restriction)
Diastolic murmur of various length of truncal regurgitation with widened pulse pressure

Electrocardiography [3]

- If unrepaired:
  - Right bundle branch block, right axis deviation
  - Biventricular hypertrophy
- If repaired:
  - Normal axis
  - Biventricular hypertrophy

Chest X-Ray [3]

- Cardiomegaly
- Pulmonary plethora
- High position of pulmonary arteries
- 30%—Right aortic arch

Echocardiography

- Table 24.2 highlights the essentials of echocardiographic assessment.

Table 24.2 Echocardiographic essentials for assessment [3, 10, 11]

1. Single great artery with semilunar valve that overrides the ventricular septum and demonstrates continuity with the mitral valve
2. Enlarged left atrium
3. Abnormal origin of PAs
4. Conotruncal VSD
5. Truncal valve insufficiency and/or stenosis
6. Dilated aorta
7. Coronary artery anatomy
8. Aortic arch anatomy
9. Biventricular hypertrophy
10. Assess for residual VSD

Cardiac Catheterization [3]

- Assess RV-to-PA conduit stenosis or regurgitation, PVR and cardiac chamber pressures.
- Assess saturations and determine if evidence of residual shunting if not evident echocardiographically.
- Define complex anatomy if intervention is needed.

Advanced Imaging Techniques [3]

- Cardiac magnetic resonance imaging and computed tomography scans:
  - Quantify chamber sizes and function.
  - Conduit caliber quantification.
  - Branch pulmonary artery quantification.
  - Assess for residual shunting.

Table 24.3 ACC/AHA Guidelines 2008 [15]—not mentioned as discrete lesion

Recommendations
1. An individual primary caregiver or cardiologist without specific training and expertise in ACHD should manage the care of adults with complex and moderate CHD only in collaboration with level 2 or level 3 ACHD specialists
2. Frequent follow-up (generally every 12–24 months) at a regional ACHD center is recommended for adults with complex and moderate CHD
3. Adults with very complex CHD will require follow-up at a regional ACHD center at a minimum of every 6–12 months

Management of Adult Survivors [3, 10–12]

See Table 24.3 for summary of guidelines.

- Biannual visits to an ACHD center:
  - Annual echocardiogram by a CHD sonographer or sooner if history or physical changes.
  - Advanced imaging every 3–5 years.
  - Infective endocarditis prevention should be reviewed with all patients.
  - Patients with heart failure should be evaluated and managed in tertiary care centers experienced in the management of CHD and heart transplantation.
  - Patients with heart or respiratory failure should be evaluated and managed in tertiary care centers experienced in the management of CHD and lung or heart/lung transplantation.
- If unrepaired:
  - Cyanotic patients should remain well hydrated on long-distance flights.
  - Therapeutic phlebotomy may be considered only if symptomatic hyperviscosity syndrome and hemoglobin greater than 20 g/dL, hematocrit greater than 65%, and iron deficiency and dehydration have been excluded.

- If repaired:
  - Surgical or percutaneous intervention for patients with conduit dysfunction or branch PA stenosis.
  - Percutaneous PVR may be an option for some patients with RV-to-PA conduit dysfunction.

Management of Pregnancy

There are only two cases reported of pregnancy among mothers with truncus arteriosus, one in 1951 by Simon and Lustberg describing a full-term pregnancy in a woman with unrepaired truncus arteriosus who died suddenly 3 days following delivery, and the other reported in 1990 by Perry describing an uneventful delivery in a woman with repaired type I truncus arteriosus [13, 17]. The majority of women with repaired and unrepaired truncus arteriosus would categorize into World Health Organization (WHO) pregnancy risk class III, placing them at significantly increased maternal mortality or severe morbidity risk. RV-to-PA conduit stenosis or regurgitation, truncal valve insufficiency, aortic size, and ventricular function should all be carefully assessed ideally prior to pregnancy. In the event of a pregnancy, intensive cardiac and obstetric monitoring is recommended throughout pregnancy, childbirth, and puerperium [6]. Additionally, generally women with a history of conotruncal abnormalities should be offered genetic testing given the known association with chromosomal abnormalities (22q11.2 deletion syndrome).

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Chapter 25
D-Looped Transposition of the Great Arteries

Ada C. Stefanescu Schmidt

Epidemiology

- Dextro- or D-looped-transposition of the great arteries (D-TGA) has a reported birth incidence of 0.3/1000 patients.
- D-TGA is the most common cardiac cause of cyanosis in newborns [1, 2].
- No specific environmental triggers are associated with TGA.
- The overall survival of patients with atrial switch procedure is 75% at 25 years.
- As more infants are currently undergoing arterial switch procedures, long-term survival has improved, and the population of adults with repaired D-TGA is steadily increasing; the proportion of young adults with atrial switch procedures is decreasing.

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Anatomy

- TGA arises from an anomaly in the looping of the cardiac bulb and aortopulmonary trunk septation, giving rise to an abnormal connection between the ventricles and the great vessels resulting in ventriculo-arterial discordance.
  - The right ventricle (RV) gives rise to the aorta, while the left ventricle (LV) gives rise to the pulmonary artery (PA) (Fig. 25.1a).
  - Importantly, venous return and atrial and ventricular positioning are normal, and there is atrioventricular concordance:

    Inferior and superior vena cava → right atrium → RV → aorta
    Pulmonary veins → left atrium → LV → PA

  - In addition to the discordant ventricular to arterial connection, the anterior-posterior relationship of the great vessels is abnormal, with the origin of the PA being usually positioned posterior and leftward and the aorta positioned anterior and rightward. Less commonly, the aorta and pulmonary artery may be side by side.

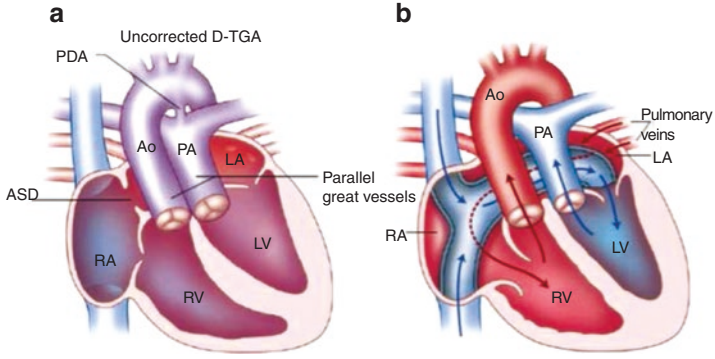

FIGURE. 25.1 Anatomy [1]. (**a**) Unrepaired. (**b**) After atrial switch repair

  - The proximal portions of the great vessels are in parallel (rather than orthogonal as with normal anatomy).
  - The heart may be shifted toward the middle or right (dextroposition) of the chest.

Physiology

- Since the systemic circuit (vena cava → right atrium → RV → aorta) and pulmonary circuit (pulmonary veins → left atrium → LV → PA) are in parallel and do not communicate, newborns with this lesion who survive the early hours after birth are dependent on a veno-systemic shunt, such as an atrial septal defect (ASD), ventricular septal defect (VSD), or patent ductus arteriosus (PDA), to promote mixing of deoxygenated and oxygenated blood.
- The presence and size of ASD or VSDs modify the presentation and severity of D-TGA.

Associated Defects

- Atrial or ventricular shunts are often associated with D-TGA, with up to 45% of patients having a VSD [3].
- Coronary anomalies (up to 40% of patients [4]), left ventricular outflow tract obstruction (25% of patients), and coarctation of the aorta (5% of patients) are also seen [3].
- Noncardiac defects are rare.

Operative Repair

- There are two main approaches for repair of D-TGA, both aiming at restoring the sequence of pulmonary and then systemic circulation: atrial switch procedure (Mustard and Senning) and the arterial switch (Jatene). The Rastelli procedure is less commonly utilized.

- Atrial septostomy/septectomy:

  Newborns without an ASD or VSD are dependent on the PDA for oxygenation, and as such treatment with prostaglandin after birth, followed by an atrial septostomy (percutaneously, Rashkind balloon septostomy or, surgically, Blalock-Hanlon septectomy), is needed in the first days of life to promote mixing and allow for growth.

- Atrial switch procedure (Senning or Mustard procedure, Fig. 25.1b):

  Pioneered by Dr. Ake Senning in 1957, 7 years after the Blalock-Hanlon atrial septostomy was first performed.

  Right atrial tissue is used after an atrial septostomy, to redirect the venous systemic inflow toward the mitral valve and LV thus to the pulmonary circulation [5].

  The pulmonary venous drainage then was redirected around the baffle toward the tricuspid valve, into the systemic RV.

  Though successful, the technical complexity of this method made it less popular than the Mustard atrial switch procedure, performed in 1963 by Dr. William Mustard, which used a pericardial or artificial patch to create the same baffle [6]

  Complications related to systemic RV dysfunction are outlined below.

- Arterial switch procedure (Jatene procedure, Fig. 25.2):

  First performed in the late 1970s and popularized in the early 1980s, the Jatene arterial switch is an anatomic correction of D-TGA by disconnecting the great arteries above the sinotubular junction and then reanastomozing them to the appropriate ventricle.

  The native valves and sinuses are left in place, and the native pulmonary valve is termed the neo-aortic valve as it is connected to the ascending aorta, and

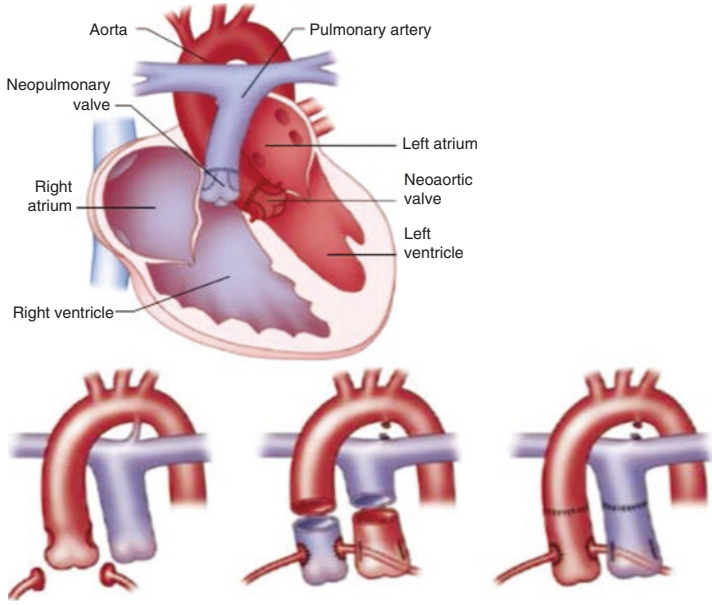

FIGURE. 25.2 Anatomy of D-TGA after arterial switch (Jatene) operation [1]

the native aortic valve is termed the neo-pulmonic valve as it is connected to the main PA.

Coronary arteries must be removed as buttons and reimplanted to the neo-aortic root.

In addition, the PA is generally placed anterior to the aorta, termed the "Lecompte maneuver" (Fig. 25.3).

In the modern era, the arterial switch procedure is the preferred method of surgical repair as it restores the RV to the subpulmonary position.

– Rastelli procedure:

Conduit from the subpulmonary LV to the PA

The operation of choice for patients who also have pulmonic stenosis and a VSD, usually a variation of a double outlet right ventricle (Chaps. 22 and 28).

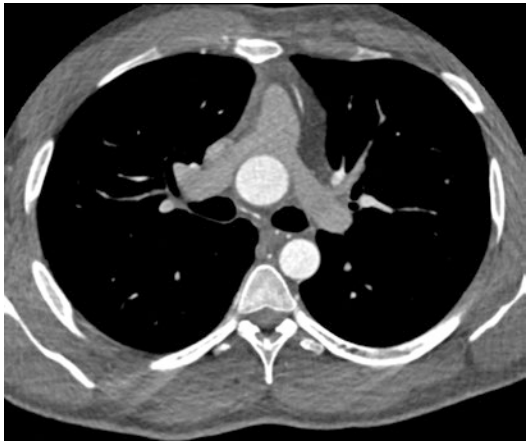

FIGURE. 25.3 Lecompte maneuver performed during arterial switch procedures. CT demonstrating the pulmonary artery draped over the ascending aorta. Proximal obstruction of the branch PAs may occur

Diagnosis

Clinical Presentation in Adults

- Adults with D-TGA almost all had surgical palliation in childhood, usually via a median sternotomy.
- Atrial switch procedure (either Mustard, most commonly, or Senning):
  - Usually presents with:

    Atrial arrhythmias (intra-atrial reentrant tachycardia is the most common, with cavotricuspid isthmus reentry being the most common location) occur in 20% of patients by age 20 years.

    Sinus node dysfunction (secondary to both extensive atrial surgical scar formation and associated hemodynamic abnormalities) and junctional bradycardia (50% of patients by age 20 years).

Signs of systemic RV failure (pulmonary edema, low cardiac output).
Systemic tricuspid regurgitation.
Ventricular arrhythmias.

– May present with:

Cyanosis (due to systemic venous atrium to pulmonary venous atrium shunt if they developed a leak through the atrial baffle).
Stroke (from a paradoxical embolus from the venous system through a right-to-left shunt in the baffle or from atrial thrombus due to atrial fibrillation).
Venous hypertension from a stenosis in the baffle (presenting with elevated jugular venous pressure and facial swelling as in SVC syndrome, congestion of the liver and cardiac cirrhosis from inferior vena cava stenosis, or pulmonary hypertension from pulmonary vein outflow stenosis). Systemic venous pathway obstruction occurs in up to 15% of patients with an atrial switch repair of D-TGA, with superior limb stenosis occurring more often than inferior limb stenosis.

• Arterial switch procedure (Jatene procedure):

– Less likely to be symptomatic later in life
– May present with:

Harsh systolic murmur due to supra-pulmonary and supra-aortic stenosis.
Coronary ischemia if there is stenosis at the surgical anastomosis sites.
Murmur of neo-aortic valve regurgitation
Left ventricular dilation
Arrhythmia and sudden cardiac death rates are not yet well defined in this young adult population.

– May have an ASD or more commonly a VSD that was not repaired (or perhaps not recognized) during their neonatal surgery

Physical Exam

- The exam will depend on the type of corrective surgery.
- Atrial switch procedure (Mustard or Senning):
  - Median sternotomy and prominent aortic (almost single) second heart sound (from the anteriorly placed aortic valve). If there is a clear two-component S2, pulmonary hypertension should be considered.
  - Holosystolic murmur of systemic TR and diffuse point of maximum impulse of dilated RV.
  - A systolic ejection murmur can be present if there is dynamic LVOT (subpulmonic) obstruction.
  - Sometimes elevated JVP, facial puffiness, swelling of the arms, and dilation of the veins over the upper thorax if there is superior vena cava or superior baffle limb obstruction, hepatic congestion if inferior baffle limb obstruction, pulmonary edema if pulmonary venous baffle obstruction or systemic RV failure is present.
- Arterial switch procedure (Jatene procedure):
  - Median sternotomy, normal PMI
  - Sometimes harsh systolic ejection murmur if there is supravalvular PS or AS, and diastolic murmur if there is neo-aortic valve regurgitation

Electrocardiogram

- Atrial switch procedure (Mustard or Senning):
  - Due to the systemic right ventricle, ECG will demonstrate right bundle branch block, voltage criteria for right ventricular hypertrophy often with repolarization abnormalities, and marked right axis deviation (Fig. 25.4a).
  - With the high frequency of atrial arrhythmias, there may be atrial flutter present.

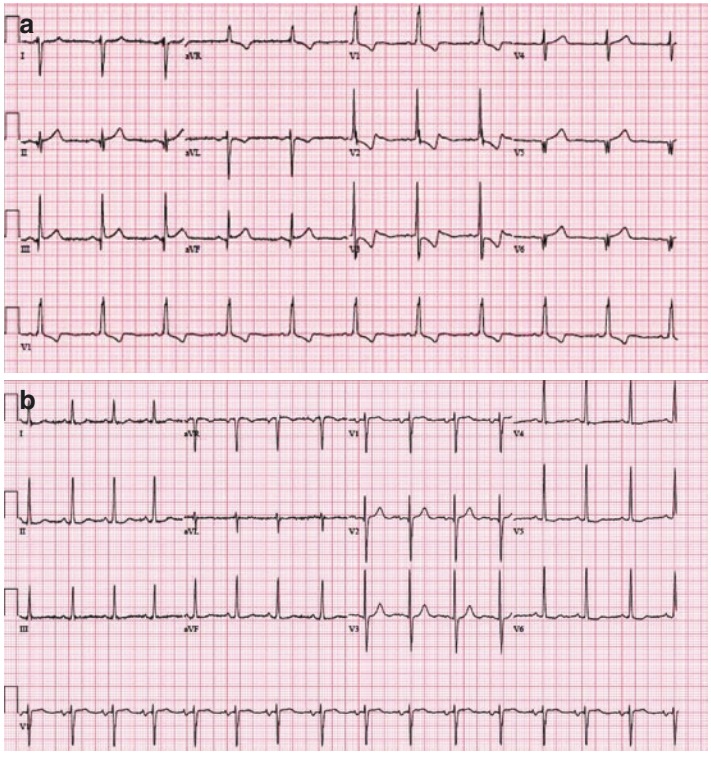

FIGURE. 25.4 Electrocardiogram of (**a**) patient with atrial switch procedure and (**b**) patient with atrial switch procedure

- Arterial switch procedure (Jatene procedure):
  - The ECG of patients with an arterial switch repair will usually be normal (Fig. 25.4b).

Chest X-Ray

- May reveal meso- or dextroposition of the heart, as well as a right- or left-sided aortic arch. The vascular pedicle is narrow with an oblong silhouette. Cardiomegaly may be apparent if there is overt heart failure.

Echocardiography (Table 25.1)

- Atrial switch procedure (Mustard or Senning):
  - Recall that the aortic valve and pulmonic valve in the parasternal long axis view will appear in parallel (aorta anterior).
  - Atrial size will not be able to be gauged in the setting of the atrial baffles for venous redirection.
  - Careful echocardiographic assessment of the baffle anatomy and flow, evaluating for stenosis and potential leaks, and ventricular and systemic atrioventricular valve function (see Fig. 25.5a–c). The LVOT should be evaluated for static or dynamic obstruction.
  - Small baffle leaks can be difficult to identify. The use of saline for contrast may increase the sensitivity of the

Table 25.1 Echocardiographic essentials for assessment [7]

After atrial switch (Mustard or Senning) procedure	After arterial switch (Jatene) procedure
1. Systemic RV size and function	1. Aortic root, supravalvar aortic dimensions, and gradient
2. Subaortic and aortic stenosis	2. Neo-aortic valve regurgitation
3. Subpulmonary LVOT obstruction	3. Neo-pulmonic valve function
4. Estimated subpulmonary ventricular pressure from mitral valve regurgitant velocity	4. Supra-pulmonary stenosis in MPA or branches
5. Tricuspid valve (systemic AV valve) regurgitation	5. LV size, mass, global and segmental function
6. Baffle pathway obstruction	6. RV size, wall thickness, and function
7. Baffle leak (consider agitated saline study if leak not obviously present by Doppler)	7. Proximal coronary artery patency
8. Associated lesions—VSD, valvar or branch PS, PDA, coarctation	8. Associated lesions—VSD, coarctation

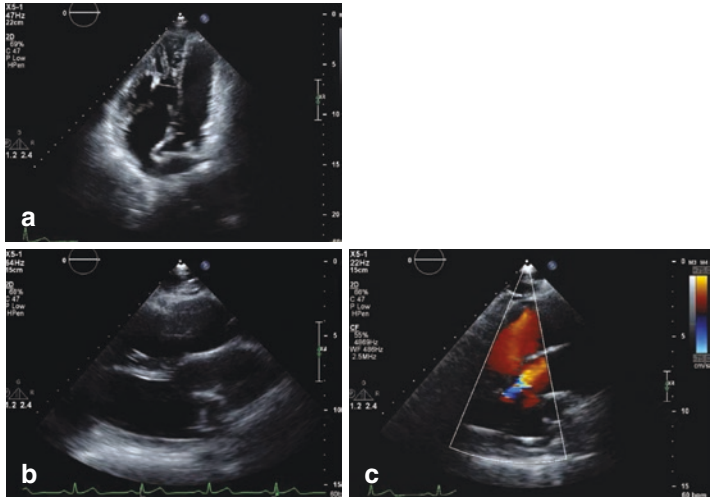

FIGURE. 25.5 (**a**) Apical four-chamber view of patient with a Senning atrial switch after D-TGA, with large, hypertrophied RV, small subpulmonic LV, atrial baffle (**b**) parasternal long view of the aorta originating from the RV, superior and parallel to the pulmonary artery, which originates from the LV, and (**c**) with color Doppler

echocardiogram if there is high clinical suspicion. Large baffle leaks can be suspected if there is subpulmonary ventricular dilation.

- Arterial switch procedure (Jatene procedure):
  - Assessment of the coronary ostia, valves, and great vessel size is necessary; neo-aortic root dimensions, in addition to screening for pulmonary artery stenoses in patients who have had the Lecompte maneuver (the right PA, in particular, lies in between the sternum and the aorta and may become compressed).

Cardiac Catheterization

- Atrial switch procedure (Mustard or Senning):
  - Right heart catheterization in patients with atrial baffles should only be performed by an experienced operator, as the risk of perforation is increased.
  - Baffle leaks can be closed percutaneously, and baffle stenosis can be successfully dilated by balloon enlargement and stenting in the hands of experienced operators.
- Arterial switch procedure (Jatene procedure):
  - Supravalvular pulmonary stenosis may require stenting.
  - Among patients with symptoms concerning for angina, coronary angiography may be performed to evaluate for coronary ostial stenosis; as the location of coronary reimplantation may vary, a nonselective neo-aortic root angiogram may be helpful to facilitate coronary engagement.

Advanced Imaging Techniques

- Cardiac CT and MRI are very useful in evaluating ventricular volume and function and baffle anatomy (see Fig. 25.6) and function including identification of baffle limb stenosis or leak and aortic and pulmonary artery dimensions. Baffle stenosis may be accompanied by azygous runoff which can sometimes be seen on advanced imaging.

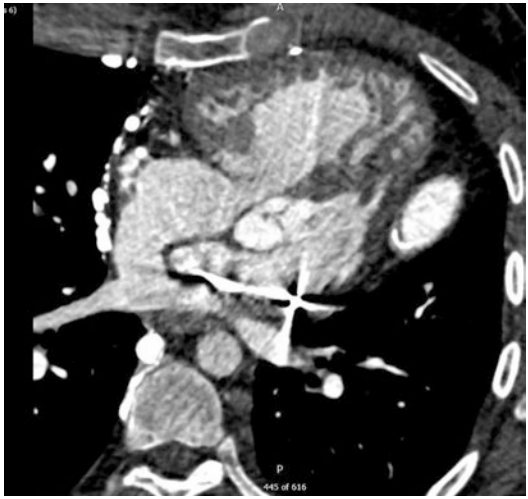

FIGURE. 25.6 CT of patient with Senning atrial switch procedure, showing pulmonary venous return going into atrial baffle and draining in systemic RV. Pacemaker lead seen in LA going into subpulmonic LV. Conduit from the LV apex to the PA seen adjacent to the LV (posterior ventricle)

- Cardiac CT can be used in conjunction with atrial mapping for ablation procedures, and coronary CTA is particularly helpful in the assessment of ostial coronary anatomy/narrowing.
- MRI may be more sensitive than echocardiography for baffle stenosis in the Mustard patient. Delayed gadolinium enhancement in cardiac MRI may help identify areas of scar susceptible to ventricular arrhythmia in at-risk patients.

Management in Adult Survivors

See Table 25.2 for summary of guidelines.

Table 25.2 ACC/AHA guidelines 2008 [3]

All

Class I

1. Patients with repaired D-TGA should have annual follow-up with a cardiologist who has expertise in the management of ACHD patients (*Level of Evidence: C*)

Class IIa

1. A concomitant maze procedure can be effective for the treatment of intermittent or chronic atrial tachyarrhythmias in adults with D-TGA requiring reoperation for any reason (*Level of Evidence: C*)

Class IIa

1. Routine surveillance with history, ECG, assessment of RV function, and periodic Holter monitoring can be beneficial as part of routine follow-up (*Level of Evidence: B*)

Class IIa

1. Antibiotic prophylaxis before dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa is reasonable in those with the following indications:
   (a) Prosthetic cardiac valve (*Level of Evidence: B*)
   (b) Previous IE (*Level of Evidence: B*)
   (c) Unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits (*Level of Evidence: B*)
   (d) Completely repaired CHD with prosthetic materials, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure (*Level of Evidence: B*)
   (e) Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device that inhibit endothelialization (*Level of Evidence: B*)
2. It is reasonable to consider antibiotic prophylaxis against IE before vaginal delivery at the time of membrane rupture in select patients with the highest risk of adverse outcomes. This includes patients with the following indications:
   (a) Prosthetic cardiac valve or prosthetic material used for cardiac valve repair (*Level of Evidence: C*)
   (b) Unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits (*Level of Evidence: C*)

Class III

1. Prophylaxis against IE is not recommended for non-dental procedures (such as esophagogastroduodenoscopy or colonoscopy) in the absence of active infection (*Level of Evidence: C*)

Recommendation for reproduction

Class I

1. Before women with D-TGA contemplate pregnancy, a comprehensive clinical, functional, and echocardiographic evaluation should be performed at a center with expertise in ACHD (*Level of Evidence: C*)

After atrial switch (Mustard or Senning) procedure

Class I

1. In patients with D-TGA repaired by atrial baffle procedure, comprehensive echocardiographic imaging should be performed in a regional ACHD center to evaluate the anatomy and hemodynamics (*Level of Evidence: B*)
2. Additional imaging with TEE, CT, or MRI, as appropriate, should be performed in a regional ACHD center to evaluate the great arteries and veins, as well as ventricular function, in patients with prior atrial baffle repair of D-TGA (*Level of Evidence: B*)

Class IIa

1. Echocardiography contrast injection with agitated saline can be useful to evaluate baffle anatomy and shunting in patients with previously repaired D-TGA after atrial baffle (*Level of Evidence: B*)
2. TEE can be effective for more detailed baffle evaluation for patients with D-TGA (*Level of Evidence: B*)

Class I

1. Diagnostic catheterization of the adult with D-TGA should be performed in centers with expertise in the catheterization and management of ACHD patients (*Level of Evidence: C*)

Class IIa

1. Interventional catheterization of the adult with D-TGA can be performed in centers with expertise in the catheterization and management of ACHD patients (*Level of Evidence: C*)

After arterial switch (Jatene) procedure

Class I

1. Adult survivors with Dextro-TGA (D-TGA) after ASO should have noninvasive ischemia testing every 3–5 years (*Level of Evidence: C*)

Class IIa

1. Coronary angiography is reasonable in all adults with D-TGA after ASO to rule out significant coronary artery obstruction (*Level of Evidence: C*)

Class I

1. Comprehensive echocardiographic imaging to evaluate the anatomy and hemodynamics in patients with D-TGA and prior ASO repair should be performed at least every 2 years at a center with expertise in ACHD (*Level of Evidence: C*)
2. After prior ASO repair for D-TGA, all adults should have at least one evaluation of coronary artery patency. Coronary angiography should be performed if this cannot be established noninvasively (*Level of Evidence: C*)

Class IIa

3. Periodic MRI or CT can be considered appropriate to evaluate the anatomy and hemodynamics in more detail (*Level of Evidence: C*)

Class I

1. It is recommended that surgery be performed in patients after the ASO with the following indications:
   (a) RVOT obstruction peak-to-peak gradient greater than 50 mmHg or right ventricle/left ventricle pressure ratio greater than 0.7, not amenable or responsive to percutaneous treatment; lesser degrees of obstruction if pregnancy is planned, greater degrees of exercise are desired, or concomitant severe pulmonary regurgitation is present (*Level of Evidence: C*)

(continued)

Table 25.2 (continued)

2. For adults with d-TGA after atrial baffle procedure (Mustard or Senning), interventional catheterization can be beneficial to assist in the following:
   (a) Occlusion of baffle leak (*Level of Evidence: B*)
   (b) Dilation or stenting of superior vena cava or inferior vena cava pathway obstruction (*Level of Evidence: B*)
   (c) Dilation or stenting of pulmonary venous pathway
3. Obstruction (*Level of Evidence: B*)
4. For adults with D-TGA after ASO, interventional catheterization can be beneficial to assist in dilation or stenting of supravalvular and branch pulmonary artery stenosis (*Level of Evidence: B*)
5. For adults with D-TGA, VSD, and PS, after Rastelli-type repair, interventional catheterization can be beneficial to assist in the following:
   (a) Dilation with or without stent implantation of conduit obstruction (RV pressure greater than 50% of systemic levels or peak-to-peak gradient greater than 30 mmHg; these indications may be lessened in the setting of RV dysfunction) (*Level of Evidence: C*)

Class I

1. Surgeons with training and expertise in CHD should perform operations in patients with D-TGA with the following indications:
   (a) Moderate-to-severe systemic (morphological tricuspid) AV valve regurgitation without significant ventricular dysfunction (*Level of Evidence: B*)
   (b) Baffle leak with left-to-right shunt greater than 1.5:1, right-to-left shunt with arterial desaturation at rest or with exercise, symptoms, and progressive ventricular enlargement that is not amenable to
2. Coronary artery abnormality with myocardial ischemia not amenable to percutaneous intervention (*Level of Evidence: C*)
3. Severe neo-aortic valve regurgitation (*Level of Evidence: C*)
4. Severe neo-aortic root dilatation (greater than 55 mm) after ASO.[575] (This recommendation is based on the data for other forms of degenerative aortic root aneurysms) (*Level of Evidence: C*)

Table 25.2 (continued)

2. Device intervention. (*Level of Evidence: B*)
   (a) Superior vena cava or inferior vena cava obstruction not amenable to percutaneous treatment (*Level of Evidence: B*)
   (b) Pulmonary venous pathway obstruction not amenable to percutaneous intervention (*Level of Evidence: B*)
   (c) Symptomatic severe subpulmonary stenosis (*Level of Evidence: B*)

Class I

1. Clinicians should be mindful of the risk of sudden arrhythmic death among adults after atrial baffle repair of D-TGA. These events usually relate to VT but may be caused in some cases by rapidly conducted IART or progressive AV block (*Level of Evidence: B*)
2. Consultation with an electrophysiologist who is experienced with CHD is recommended to assist with treatment decisions (*Level of Evidence: B*)
3. Pacemaker implantation is recommended for patients with D-TGA with either symptomatic sinus bradycardia or sick sinus syndrome (*Level of Evidence: B*)

Arrhythmia

- Atrial switch procedure (Mustard or Senning):
  - Periodic screening for brady- (heart block or sinus node dysfunction) or tachyarrhythmias (atrial or ventricular) is recommended.
  - Beta-blockers are recommended for control of atrial tachyarrhythmias, which occur in around 30% of patients. Prompt restoration of sinus rhythm, when possible, is preferred in patients with a systemic RV to optimize filling and ventricular function.
  - Predictors of sudden cardiac death include systemic ventricular dysfunction, severe tricuspid regurgitation, prolonged QRS duration, symptomatic heart failure or atrial arrhythmias, and RV fibrosis on MRI [8, 9].
  - Pacemaker implantation, lead extraction, and ablation of atrial arrhythmia circuits are feasible in patients with atrial baffles but should only be done by experienced

operators with detailed knowledge of the patients' surgical anatomy.
  - If a transvenous pacing system is planned, any baffle leak needs to be closed, regardless of size, in order to avoid paradoxical emboli which may arise from thrombus on the pacing leads. Active lead fixation is recommended.
  - Epicardial pacing is a favored approach in the setting of challenging venous access or baffle concerns.
  - Atrial pacing is appropriate for those without any AV nodal disease. Rate responsiveness is helpful in this young population with sinus node disease.
  - Devices with antitachycardia pacing mode can provide overdrive pacing of atrial arrhythmias (excluding atrial fibrillation) to address individuals with tachy-brady syndrome.

- Arterial switch procedure (Jatene procedure):
  - Atrial arrhythmias may occur but less frequent compared to patients with atrial switch procedure.
  - The rate of ventricular arrhythmias or sudden cardiac death is not yet well defined.

Heart Failure

- Atrial switch procedure (Mustard or Senning):
  - Reduction of the afterload of the systemic RV is critically important.
  - Development of systemic tricuspid regurgitation often accelerates progression of heart failure.
  - Angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) are often used for this purpose, as their effects, preventing LV adverse remodeling and decreasing adverse events in patients with acquired LV heart failure, may be extrapolated to failing RVs. Small trials in D-TGA patients with a spectrum of heart failure presentations have not been con-

clusive [10–15]; no differences in RV ejection fraction or symptoms were found in patients with systemic RV randomized to valsartan vs. placebo, though they did more often have preserved RV volumes, in the largest randomized trial to date ($n = 88$) [16].
  - Beta-blockers are associated with improvements in NYHA class and RV volumes by MRI [17].
  - Among patients with depressed systemic RV function, calcium channel blockers with negative ionotropic effects (such as diltiazem) should be avoided.
  - For patients with severe systemic RV failure, resynchronization therapy [18, 19] (with epicardial leads) and transplantation may be considered.

- Arterial switch procedure (Jatene procedure):
  - As the morphologic LV has resumed the systemic position, clinical heart failure is rare unless there is severe neo-aortic regurgitation.
  - Longer-term complications with the coronary arteries should be surveyed for actively as they could affect LV function over time; late coronary complications thus far appear rare.

Indications for Surgery in Adulthood

- Atrial switch procedure (Mustard or Senning):
  - Surgical intervention may be necessary if baffle stenosis or leaks cannot be addressed percutaneously.
- Arterial switch procedure (Jatene procedure):
  - Severe RV outflow tract stenosis (with peak-peak gradient ≥50 mmHg, RV/LV pressure ratio >0.7 or if dynamic and prior to pregnancy or symptomatic) is an indication for percutaneous or open repair.
  - Severe regurgitation of the pulmonic or aortic valves (if concomitant ventricular dilatation or dysfunction or aortic aneurysm >55 mm).

Pregnancy

- Guidance in pregnancy depends on the systemic ventricular function and associated defects. As the incidence of atrial arrhythmias and heart failure rises in pregnancy, the arrhythmic burden and potential for heart failure should be assessed and discussed, ideally prior to conception. When atrial arrhythmias are present, achieving sinus rhythm before conception if possible is advised; otherwise, beta-blockers tend to be well tolerated. Anticoagulation can be continued. Please see Chap. 37 for details on management.
- These complications arise in over a third of women with an atrial switch procedure [20].
- Pregnancy is not recommended in women with NYHA class III or IV heart failure [21] or with reduced systemic RV function.
- Preconception consultation with a multidisciplinary adult congenital heart disease team regarding pregnancy management and genetic counseling is essential.
- Cardiopulmonary exercise testing can inform risk and pregnancy course, while assessment of valvular disease, ventricular function, and arrhythmia risk should be included in the shared decision-making before embarking on pregnancy.

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Chapter 26
L-Loop or Congenitally Corrected Transposition of the Great Arteries (L-TGA or CCTGA)

Yamini Krishnamurthy

Abbreviations

ACHD	Adult congenital heart disease
AR	Aortic regurgitation
AV	Atrioventricular
CCTGA	Congenitally corrected transposition of the great arteries
CHD	Congenital heart disease
IE	Infective endocarditis
LA	Left atrium
L-TGA	L-loop transposition of the great arteries
LV	Left ventricle
MRI	Magnetic resonance imaging
PA	Pulmonary artery
PS	Pulmonary stenosis

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SV	Systemic ventricle
VSD	Ventricular septal defect

Epidemiology

- L-loop transposition of the great arteries (L-TGA) is a rare congenital heart disease with an incidence of 1 in 33,000 live births. L-TGA accounts for 0.4–0.6% of all congenital heart disease with a slight male predominance [1].
- Of note the term congenitally corrected TGA (CCTGA) is synonymous with L-TGA.
- For historical perspective, see Table 26.1.

Anatomic Definition and Pathophysiology

- Anatomy:
  - Desaturated blood from the right atrium empties into the morphologic left ventricle (LV) via a mitral valve, which gives rise to the pulmonary artery (PA). Fully saturated blood from the left atrium (LA) empties into the morphological right ventricle (RV) via a tricuspid valve, which gives rise to the aorta. The morphologic LV functions in the subpulmonary position, and the morphologic RV functions as the systemic ventricle. The tricuspid valve functions as the systemic atrioventricular (AV) valve. Double anatomic discordance at the AV and ventriculoarterial level allows for the physiologically normal direction of blood flow (Fig. 26.1).

Table 26.1 Historical background

In 1875, L-TGA was first described by the Bohemian pathologist Carl von Rokitansky from an autopsy of the heart of a 4-month-old female and 11-month-old male [2].
Early surgical intervention focused on repair of associated cardiac abnormalities. In 1990, Michel Ilbawi and colleagues introduced the “double switch” concept in which the morphologic left ventricle serves as the systemic ventricle [3].

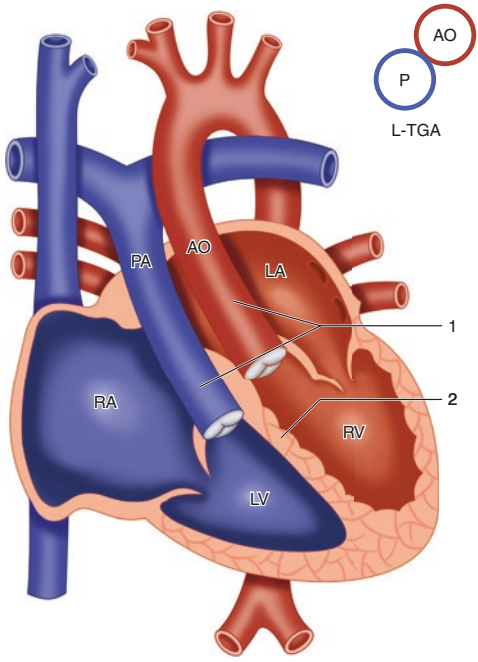

FIGURE 26.1 Diagram of congenitally corrected transposition of the great arteries demonstrating atrioventricular and ventriculoarterial discordance

  - The coronary arteries are inverted and supply their anatomic ventricle. The left coronary artery arises from the right facing aortic sinus, and the right coronary artery arises from the left facing aortic sinus.
  - The electoral bundles are also inverted (the left bundle is rightward and septal activation is also inverted).
  - The aorta is usually, though not always, anterior and to the left, and the aorta and PA may be side by side.
  - The heart's position in the chest is normal or midline in 80% of cases; dextrocardia is present in 20% of cases.

- Physiology and spectrum of disease:
  - Patients with L-TGA with associated anomalies usually come to medical attention in infancy or childhood

(detection of murmur, abnormal ECG, desaturation if PS and VSD, or clinical heart failure).

- Patients with L-TGA without associated anomalies may survive well into older age with essentially normal functionality [4]; thus diagnosis may be delayed until later adulthood and be made if a screening ECG or echocardiogram is obtained, or the patient presents with syncope due to heart block or clinical heart failure.
- In unrepaired L-TGA, regardless of time course, progressive deterioration with the onset of "left-sided" heart failure is likely and requires aggressive medical management and possible surgical intervention. This deterioration results from several factors including systemic RV function and systemic AV regurgitation:

  The morphologic RV will decline in its function as the systemic ventricle over time as it was not designed to handle chronic pressure load. High systolic pressures lead to hypertrophy of its free wall—shift of the interventricular septum toward the subpulmonary LV. This increases ventricular wall stress and leads to dysfunction [5]. Systemic RV hypertrophy is followed by dilation, which causes the annulus to dilate.

  Steady increase in systemic AV valve regurgitation occurs over time in L-TGA patients. Of note, it is difficult to determine if systemic AV valve regurgitation is causative or secondary to systemic RV dysfunction [6].

  Another possible explanation for the decreasing systemic RV function with increasing age has been the possibility of reduced coronary perfusion due to abnormal coronary anatomy [7].

- Because of the displacement of the AV bundle and abnormal course of conduction tissue, there is an increased risk of spontaneous heart block. Patients with L-TGA have a progressive risk of spontaneous complete AV block throughout life (2% per year) [8]. Atrial tachyarrhythmias, such as atrial fibrillation and flutter, often occur with increasing age and atrial enlargement.

- Associated defects:
  - Only 1% of cases are uncomplicated or do not have associated anomalies. Presence or absence of associated anomalies greatly affects the spectrum of disease.
  - Frequent associated anomalies include:

    Ventricular septal defects (VSDs) occur in 70% of patients and are usually perimembranous.
    Pulmonary stenosis (PS) occurs in 40% of patients and is usually subvalvular.
    Abnormalities of the systemic AV occur in up to 50–90% of patients (occasionally Ebstein-like malformations occur in which the valve is displaced inferiorly toward the cardiac apex) [4].

  - In CCTGA, the AV node is positioned anteriorly, and the His bundle runs anteriorly as well and across. An accessory AV node can also be present. There is a 2% rate of complete heart block per year in this population.
  - Two to four percent of patients have ventricular preexcitation syndrome (Wolff-Parkinson-White).
  - Other less common anomalies include atrial septal defect, patent ductus arteriosus, pulmonary atresia, double outlet right ventricle, aortic regurgitation, mitral valve abnormalities, supravalvular stenosis in the left atrium, and subaortic stenosis.
- Genetics and maternal factors:
  - No specific genetic defect has been defined for L-TGA; however, the recurrence risk of siblings of L-TGA is 2.6% with an overall recurrence risk of 5.2% for L-TGA patients to have some type of cardiac defects [1].

Diagnostics

Clinical Presentation in Adults

- Clinical symptoms in infancy and early childhood depend on the presence and severity of associated cardiac

anomalies. L-TGA without associated anomalies may go undiagnosed until adolescence or adulthood.
- Common presentations in adults include symptoms of left-sided heart failure (orthopnea, dyspnea on exertion, PND, etc.), abnormal ECG findings (noted below), cardiomegaly or mesocardia on chest radiographs, syncope, and unexplained heart block and murmurs that warranted referral to a cardiologist for further evaluation.

Physical Exam

- Loud second heart (A2) sound from the anteriorly placed aorta.
- Systemic AV valve insufficiency murmur if the tricuspid valve is abnormal or the systemic RV annulus is dilated.
- If systemic RV dysfunction is present, physical exam signs of typical "left heart" congestive heart failure may be notable (pulmonary edema, apical S3 gallop).
- If additional anomalies are present, physical exam signs relevant to those abnormalities may be present:
  - See Chaps. 5 and 18 for physical exam signs for VSD and PS.

Electrocardiography

- Due to ventricular inversion, the right and left bundles of His are also inverted; this causes septal depolarization to occur from right to left. Thus, classic ECG findings include Q waves in the right precordial leads and absent Q waves in the left precordial leads (Fig. 26.2a).
- Varying degrees of AV block can commonly be seen as well (first-degree AV block in up to 50% of patients and complete heart block in up to 50% of patients).
- Preexcitation may be observed in patients with L-TGA and Wolff-Parkinson-White.

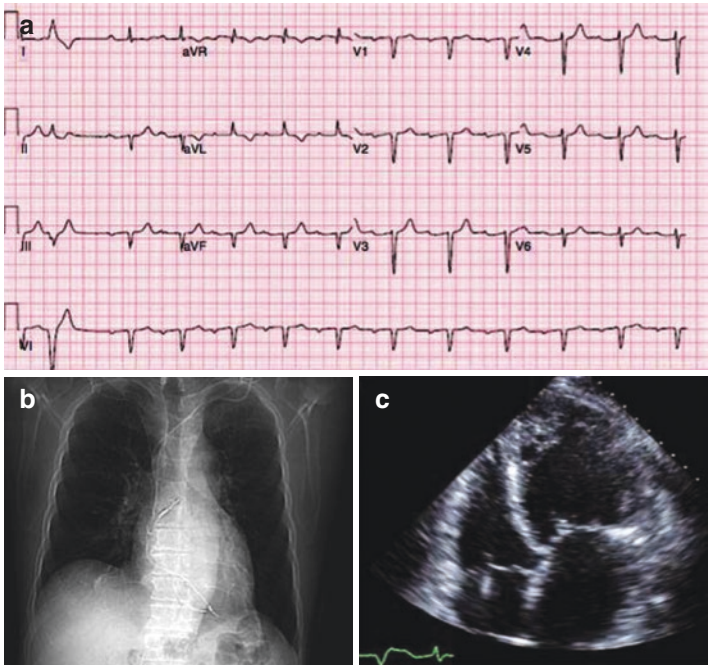

FIGURE 26.2 L-loop transposition of the great arteries. (**a**) ECG with first-degree AV block; Q waves in II, III, and aVF; and absence in V5 and V6 due to inversion of the right and left bundle branches causing septal activation to occur from right to left. (**b**) Chest radiography of patient with L-TGA and dual chamber pacemaker. (**c**) Four-chamber view demonstrating apical displacement of the systemic AV valve indicating this is a tricuspid valve and systemic right ventricle, pacer lead also noted in the morphologic (subpulmonary) LV (with permission from MGH Board Review. Gaggin and Januzzi. 2014)

- Patterns of left- or right-sided chamber enlargement may be notable as well.

Chest Radiography

- The diagnosis of L-TGA may be suspected from chest radiography. Common findings include (Fig. 26.2b):

  - Cardiac mass may be more midline.
  - As the normal relationship between the aorta and pulmonary artery is lost, the vascular pedicle appears abnormally straight. There may be a prominent upper left heart border due to the side-by-side configuration of the aorta and pulmonary artery, especially notable if there is aortic or pulmonary arterial dilation [4].
  - The ventricular border may also appear more vertical on the left side.

- L-TGA can be associated with dextrocardia and should be suspected with the presence of abdominal situs solitus and dextrocardia on chest radiography.

Echocardiography

- Standard 2D transthoracic echocardiography with color Doppler will generally make the diagnosis of L-TGA as well as diagnosis and detection of associated lesions. The apical four-chamber view best demonstrates the "inverted" ventricles (Fig. 26.2c). The more apically displaced AV valve will always be the tricuspid valve, and this will track with the morphologic RV.
- Table 26.2 highlights the essentials of echocardiographic assessment of patients with L-TGA.

Cardiac Catheterization

- Cardiac catheterization plays an important role in the diagnostic evaluation and management of unoperated L-TGA as well as postoperatively.
- Indications for cardiac catheterization include assessing hemodynamic status in the setting of arrhythmias (Class IIa), unexplained systemic RV dysfunction to define the degree of intracardiac shunting and coronary artery anatomy (Class IIa), and unexplained volume retention or cyanosis (Class IIa) [10].

Table 26.2 Echocardiographic essentials for assessment [9]

Native L-TGA	Postoperative patient with L-TGA
1. Identification of visceroatrial situs	1. Biventricular size and function
2. Establishment of cardiac position—levo-, meso-, or dextrocardia	2. Residual VSD
3. Demonstration of atrioventricular and ventriculoarterial discordance (RA-LV-PA; LA-RV-aorta)	3. Residual RV or LV outflow obstruction
4. Location, size, and direction of VSD if present	4. Degree of tricuspid regurgitation
5. Nature and degree of PS or subpulmonary outflow obstruction	5. Atrial baffles, if present
6. Anatomy and function of tricuspid valve (systemic AV valve)	6. Great artery anastomoses, if present
7. Size and function of the RV (systemic ventricle)	7. Conduit function, if present
8. Coronary artery anatomy	8. Neo-aortic size and insufficiency
	9. Coronary artery patency, if translocated

- Cardiac catheterization can provide hemodynamic assessment of associated abnormalities.
- A coronary evaluation is reasonable in patients with planned operative management who have risk of coronary disease because of age or other risk factors.

Advanced Imaging Techniques

- Cardiac magnetic resonance imaging (MRI) can help to define anatomy, systemic ventricular function, and volume assessment. For initial diagnosis, cardiac MRI may be useful for patients whose anatomy is not well-characterized by echocardiography. Additionally, echocardiography may be limited in assessment of systemic RV function; thus

cardiac MRI may be utilized for initial assessment and serial follow-up for SV and volume status [4]. Systemic AV morphology as well as degree of regurgitation can be determined through cardiac MRI.

- In patients with MRI-incompatible pacemakers, cardiac computed tomography can be performed to elucidate anatomy.

Management of Adult Survivors

See Table 26.3 for summary of guidelines.

Systemic Ventricular Failure and AV Valve Regurgitation

1. Medical management:
   (a) Medical management focuses on the prevention of progression of systemic RV dysfunction; thus reduction of preload and afterload is the primary goal. Sodium restriction, angiotensin-converting enzyme inhibitors, and diuretics are typically utilized.
   (b) Beta-blockers and cardiac glycosides may also be beneficial, but close monitoring is required as these treatments increase the risk for atrioventricular block.
   (c) If heart failure symptoms are present, the use of diuretic afterload reduction, beta-blockers, and angiotensin-converting enzyme inhibitors may be beneficial.
   (d) Of note, angiotensin receptor blockers are often utilized, as study of 88 systemic RVs showed small, though significant, improvement in RV mass and size parameters when treated with angiotensin receptor blocker (valsartan in this study) vs placebo. However, there was no significant effect on RV ejection fraction, exercise capacity, or quality of life [11].

Table 26.3 ACC/AHA guidelines 2008 [10]

Recommendations for evaluation and follow-up

Class I

1. All patients with CCTGA should have a regular follow-up with a cardiologist who has expertise in ACHD (*Level of Evidence: C*)
2. Echocardiography-Doppler study and/or MRI should be performed yearly or at least every other year by staff trained in imaging complex congenital heart disease (CHD) (*Level of evidence: C*)
3. The following diagnostic evaluations are recommended for patients with CCTGA:
   (a) ECG (*Level of Evidence: C*)
   (b) Chest radiography (*Level of Evidence: C*)
   (c) Echocardiography-Doppler study (*Level of Evidence: C*)
   (d) MRI (*Level of Evidence: C*)
   (e) Exercise testing (*Level of Evidence: C*)

Recommendation for catheter interventions

Class IIa

1. For patients with unrepaired CCTGA, cardiac catheterization can be effective to assess the following:
   (a) Hemodynamic status in the setting of arrhythmia (*Level of Evidence: C*)
   (b) Unexplained SV dysfunction, to define the degree of systemic AV valve regurgitation, degree of intracardiac shunting, and coronary artery anatomy (*Level of Evidence: C*)
   (c) Unexplained volume retention or cyanosis, especially when noninvasive assessment of pulmonary outflow obstruction is limited (*Level of Evidence: C*)

Recommendation for surgical interventions

Class I

1. Surgeons with training and expertise in CHD should perform operations for patients with CCTGA for the following indications:
   (a) Unrepaired CCTGA and severe AV valve regurgitation (*Level of Evidence: B*)
   (b) Anatomic repair with atrial and arterial level switch/Rastelli repair in cases in which the left ventricle is functioning at systemic pressures (*Level of Evidence: B*)
   (c) Simple VSD closure when the VSD is not favorable for left ventricle-to-aorta baffling or is restrictive (*Level of Evidence: B*)
   (d) LV-to-pulmonary artery conduit in rare cases with LV dysfunction and severe LV outflow obstruction (*Level of Evidence: B*)
   (e) Evidence of moderate or progressive systemic AV regurgitation (*Level of Evidence: B*)
   (f) Conduit obstruction with systemic or nearly systemic RV pressures and/or RV dysfunction after anatomic repair (*Level of Evidence: B*)
   (g) Conduit obstruction and systemic or suprasystemic LV pressures in a patient with nonanatomic correction (*Level of Evidence: B*)
   (h) Moderate or severe aortic regurgitation (AR)/neo-AR and onset of ventricular dysfunction or progressive ventricular dilation (*Level of Evidence: B*)

Recommendations for postoperative care

Class I

1. Patients with prior repair of CCTGA should have regular follow-up with a cardiologist with expertise in ACHD (*Level of Evidence: C*)
2. Echocardiography-Doppler study and/or MRI should be performed yearly or at least every other year by staff trained in imaging complex CHD (*Level of Evidence: C*)

Recommendation for infective endocarditis (IE) prophylaxis

Class IIa

1. Antibiotic prophylaxis before dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa is reasonable in those with the following indications:
   (a) Prosthetic cardiac valve (*Level of Evidence: B*)
   (b) Previous IE (*Level of Evidence: B*)
   (c) Unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits (*Level of Evidence: B*)
   (d) Completely repaired CHD with prosthetic materials, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure (*Level of Evidence: B*)
   (e) Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device that inhibit endothelialization (*Level of Evidence: B*)
2. It is reasonable to consider antibiotic prophylaxis against IE before vaginal delivery at the time of membrane rupture in select patients with the highest risk of adverse outcomes. This includes patients with the following indications:
   (a) Prosthetic cardiac valve or prosthetic material used for cardiac valve repair (*Level of Evidence: C*)
   (b) Unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits (*Level of Evidence: C*)

Class III

1. Prophylaxis against IE is not recommended for non-dental procedures (such as esophagogastroduodenoscopy or colonoscopy) in the absence of active infection (*Level of Evidence: C*)

Recommendation for reproduction

Class I

1. All women with CCTGA (whether repaired or not) should seek counseling from a cardiologist with expertise in ACHD before proceeding with a pregnancy (*Level of evidence: C*)

2. Surgical management:

   (a) Indications for surgical management include valvular abnormalities including moderate/severe or progressive systemic AV valve regurgitation in unrepaired or nonanatomic repaired patients, as well as moderate/severe aortic or mitral regurgitations in anatomically repaired patients. Additionally, conduit obstruction with elevated ventricular pressures and/or dysfunction and need for surgical correction of associated anomalies are indications for intervention (Table 26.3) [10].

   (b) Surgical options:

- Anatomic repair through a double switch procedure or Rastelli procedure is possible during infancy prior to the LV deconditioning. The use of this technique requires the LV to be functioning at systemic pressure or prepared for pressure loading with a pulmonary artery band. Mortality and morbidity are significantly higher for an anatomic approach in adult patients [12].
- Physiologic repair:
  - Tricuspid valve replacement (less often repair) for significant systemic AV regurgitation if systemic ventricular function is not severely compromised may help preserve systemic ventricular function [13].
  - Correction of associated anomalies. Of note, among patients with L-TGA, PS, and VSD, occasionally VSD patch and a subpulmonary LV to PA conduit may be considered; however complete relief of PS may result in septal shift toward the LV and worsening of systemic TR and systemic RV function. Some degree of PS may need to be preserved to maintain septal position and minimize increase in systemic TR.
- Cardiac transplantation may be the only surgical option in some patients with L-TGA and severe systemic RV dysfunction. VAD placement in systemic RVs can be anatomically challenging due to hypertrophied moderator band [14].

Arrhythmias

- If second- or third-degree atrioventricular heart block is present, pacemaker implantation (paced in the subpulmonary LV) is likely necessary.
- In patients with systemic RVs and ventricular dyssynchrony (which is not uncommon in patients with L-TGA given their increase risk for complete heart block), cardiac resynchronization has been shown to be an effective treatment in systemic RV dysfunction [15].

Follow-Up

- Patients with L-TGA should have regular follow-up with a cardiologist who has expertise in adult congenital heart disease (ACHD).
- The frequency of follow-up visits is determined by the presence of associated anomalies, as well as ventricular function and systemic AV valve function, and risk for arrhythmia and heart failure.
- Follow-up evaluation will generally include clinical examination, ECG, echocardiography and/or cardiac MRI, as well as cardiopulmonary exercise testing [10].

Infective Endocarditis Prophylaxis

- Infective endocarditis prophylaxis is indicated in many patients with L-TGA. Please see Chap. 20 for further details.

Management of Pregnancy

- Pregnancy is generally well-tolerated in patients with L-TGA, though prepregnancy cardiovascular assessment and counseling from a cardiologist with expertise in ACHD should be performed.

- Preconception evaluation should include oxygenation, ventricular and valvular function, as well as the presence of arrhythmias. This will include echocardiography, MRI, cardiopulmonary exercise testing, and Holter monitoring [16].
- Contraindications to pregnancy in this population include women with a depressed systemic RV function or those with significant systemic AV valve regurgitation, and history of clinical heart failure as the increased intravascular volume associated with pregnancy will not be well-tolerated.

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Part VI
Other Complex Lesions

Chapter 27
Ebstein's Anomaly of the Tricuspid Valve

Jonathan Kochav

Epidemiology

- Ebstein's anomaly of the tricuspid valve (TV) accounts for <1% of all cases of congenital heart disease, occurring in around 0.5 per 10,000 live births [1, 2]. The age at diagnosis can vary widely, from infancy to elder age, based on the wide spectrum of disease severity that exists.
- See Table 27.1 for historical perspective.

Anatomic Definition and Pathophysiology

1. Anatomy: (Fig. 27.1):

   (a) The fundamental lesion in Ebstein's anomaly is failure of delamination of the tricuspid leaflets from the right ventricular (RV) myocardium [8] (Fig. 27.2). This defect affects the septal and posterior leaflets more often than the anterior leaflet, resulting in a tethered "sail-like" anterior TV leaflet and apically displaced septal and posterior leaflets. The anterior leaflet is

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Table 27.1 Historical background

In 1864 a 19-year-old laborer was admitted to a German hospital with shortness of breath, palpitations, central cyanosis, and lower extremity edema. Upon his death, German pathologist Wilhelm Ebstein performed an autopsy and described in great detail and with immaculate sketches the anatomic abnormalities of what would be called Ebstein's anomaly of the tricuspid valve [3].
Despite this remarkable description and the relatively significant prevalence of this anomaly among patients with congenital heart disease, the first case of Ebstein's anomaly in a living patient was not reported until 1951 [4].
Ebstein's anomaly was treated with various surgical techniques starting in 1958 [5]. Valvular replacement was the treatment of choice until the 1970s when improved valvuloplasty repair techniques were developed, with the Danielson method predominating [6], followed by the Carpentier method [7], and most recently the cone repair.

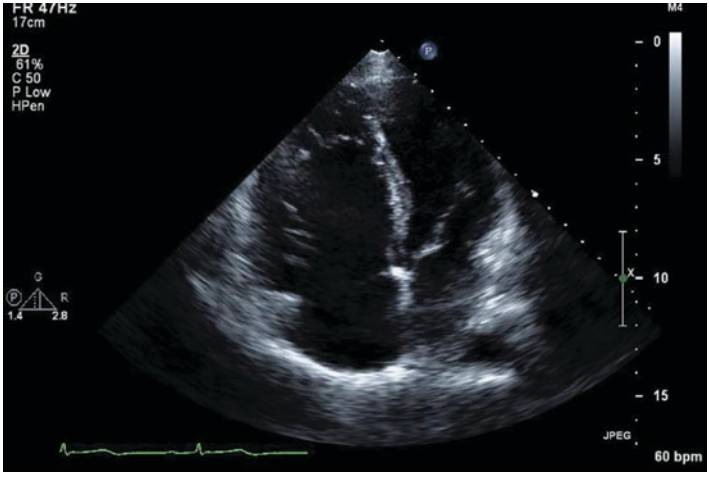

Figure 27.1 Transthoracic apical four-chamber view of a patient with Ebstein's anomaly showing apical displacement of the septal leaflet of the tricuspid valve and a small-sized functional right ventricle

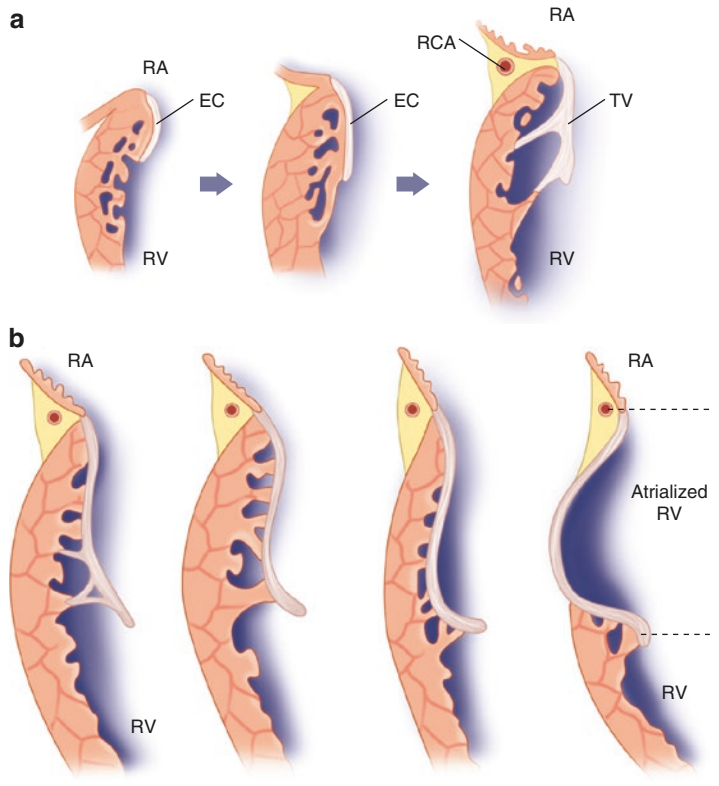

FIGURE 27.2 Schematic of (**a**) normal and (**b**) pathologic delamination of the tricuspid valve in Ebstein's anomaly. In the normal process of tricuspid valve delamination, the tricuspid valve tissue separates from the myocardium first apically and progresses to the base/annulus. In Ebstein's anomaly, the tricuspid valve is variably adherent throughout its length to the right ventricular myocardium, with four examples of progressive severity displayed from left to right. *RA* right atrium, *RV* right ventricle, *EC* endocardial cushion, *RCA* right coronary artery (Adapted from The Clinical Management of Congenital Heart Disease from Infancy to Adulthood by Douglas Moodie)

often redundant and elongated with short chordae tendineae and may be fenestrated.

(b) The apical displacement of the TV leaflets results in reduction of the functional RV size. The "atrialized"

portion of the true RV will have varying degree of wall thinning.

2. Physiology:
   (a) The resulting physiology is that of progressive tricuspid regurgitation and RV failure.
   (b) The functional RV can be quite small, myopathic, and RV contractility and compliance can be impaired, contributing to RV failure.
   (c) Free tricuspid regurgitation (TR) can contribute to significant right-sided volume overload with both right atrial (RA) and RV dilatation.
   (d) Associated atrial septal defects (ASD) or patent foramen ovale (PFO) are quite common, and in advanced cases, right-to-left shunting can lead to systemic cyanosis and increased risk of paradoxical embolism. Pulmonary arterial hypertension is rare in patients with Ebstein's anomaly.
3. Spectrum of disease:
   (a) Depending on the degree of adherence of the endocardial cushion to the RV, a wide spectrum of disease can exist. On the least severe end of the spectrum are patients with minimal TV deformity who have mild TV insufficiency, effectively normal right atrial and ventricular chamber sizes, and no associated congenital abnormalities. These patients may go undetected until adulthood and be diagnosed incidentally. On the other end of the spectrum are patients with severe TV distortion, significant valvular insufficiency, and small functional RVs that are poorly compliant and are usually identified in the neonatal period.
4. Associated defects:
   (a) Septal defects:

- The majority of patients (60–80%) have either an ASD or a PFO [9].
- Ventricular septal defects occur in only 8% of patients [10].

(b) Atrioventricular bypass tracts:

- Wolff-Parkinson-White syndrome is present in ~25% of patients, and multiple bypass tracts are common [11], sometimes resulting in recurrent SVT post-procedure.

(c) Right ventricular outflow tract obstruction:

- Pulmonic stenosis or pulmonary atresia

(d) Left-sided lesions (observed in up to 40% of patients) [10]:

- Left ventricular (LV) non-compaction (~18%)
- Bicuspid aortic valve (~8%)
- Mitral valve prolapse (4%)
  - Mitral valvular tissue may become "redundant" due to mitral annular compression from severe dilation of the right heart [12].

(e) Genetics and maternal factors:

- Associated with maternal lithium use [13], although this relationship has recently been brought into question [14].
- Myosin heavy chain gene MYH7 [15] and homeobox transcription factor gene NKX2.5 [16] mutations have been implicated.

Diagnostics

Clinical Presentation

- Neonates with Ebstein's anomaly can present with congestive heart failure, systemic cyanosis from right-to-left shunting, and clinically significant supraventricular arrhythmia (SVT):
  - Fewer than 50% of clinically symptomatic neonates with Ebstein's anomaly will survive to 5 years of age [17, 18].
  - On the other hand, the majority of children who develop symptoms from Ebstein's anomaly outside of the neonatal period will live to adolescence and adulthood.
- Ebstein patients with less severe pathology may be diagnosed incidentally in adulthood by cardiac imaging, when presenting with electrophysiologic complaints such as SVT secondary to bypass tracts, or late in adulthood due to late development of RV failure, paradoxical emboli, or desaturation.

Physical Exam

- Split heart sounds:
  - The first heart sound is split due to delayed RV conduction causing delayed TV closure.
  - The second heart sound may be split due to presence of an ASD or a right bundle branch block.
- Tricuspid insufficiency:
  - Tricuspid holosystolic murmur is best heard at the left lower sternal border and augments with inspiration.
  - This murmur can be difficult to appreciate in patients with either mild disease or very severe TR when flow across the valve is laminar and not turbulent.

- The "sail sound" refers to a loud snapping sound occurring in systole created by the large anterior leaflet. There may be multiple clicks during systole.
- Elevated jugular venous pressure may be absent due to a large RA.

Electrocardiogram [11] (Fig. 27.3)

- P-waves are often tall and broad ("Himalayan P-waves") because of prolonged conduction in the enlarged RA:
  - First-degree atrioventricular block can occur due to intra-atrial conduction delay.
  - Alternatively, PR interval shortening can occur in the context of an accessory pathway.
- Accessory pathways resulting in a Wolf-Parkinson-White pattern may be seen in 25% of patients:
  - The pathway is often right-sided and results in a negative delta wave in leads V1 and V2 [19].
  - Multiple accessory pathways are found in nearly 50% of these patients [20].
- Right bundle branch block with wide splintering of the QRS complex.

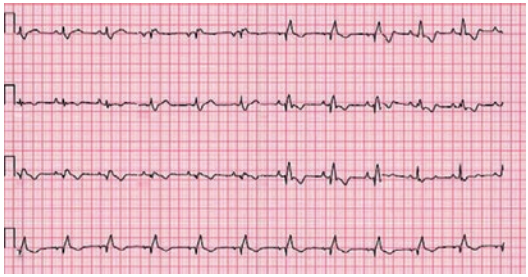

FIGURE 27.3 Representative electrocardiogram of an adult patient with Ebstein's anomaly. The electrocardiogram demonstrates right axis deviation, first-degree AV block, and complete right bundle branch block with marked splintering of the R' deflection

- Inverted T waves in the anterior precordial leads
- SVT secondary to atrioventricular reentrant tachycardia (AVRT), atrial tachycardia, atrial fibrillation, or atrial flutter is common and occurs in 30–40% of patients.

Chest Radiograph (Fig. 27.4)

- Right atrial and RV enlargement.
- Cardiac silhouette can be massive, with a "globular" shape similar to that seen in pericardial effusion.
- A cardiothoracic ration of >0.65 is associated with a worse prognosis [2].

Echocardiography

- Transthoracic echocardiography is the gold standard for diagnosis of Ebstein's anomaly and is useful for defining the TV anatomy, severity of tricuspid regurgitation, RV size, and associated abnormalities:

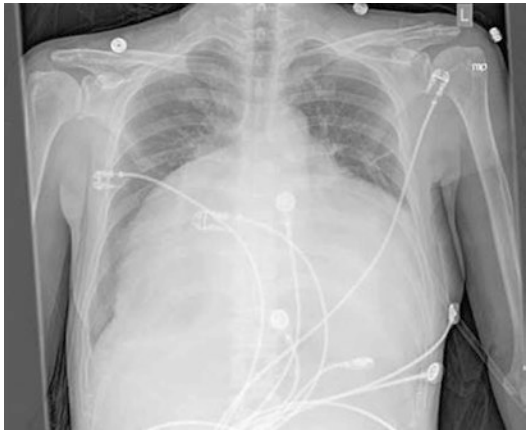

FIGURE 27.4 Representative chest radiograph of a patient with Ebstein's anomaly [36]

  - Characterized by apical displacement of the septal tricuspid leaflet of more than 8 mm in the apical four-chamber view [21, 22].
  - Identifies the redundant, elongated anterior tricuspid leaflet and evaluates the functional RV's size and function

- Transesophageal echocardiogram may be needed to fully evaluate associated lesions.
- Table 27.2 highlights the essentials of echocardiographic assessment of patients with Ebstein's anomaly of the tricuspid valve, both pre- and post-complete repair.

Cardiac Catheterization

- Cardiac catheterization has limited role in defining the physiology of Ebstein's anomaly outside of the use of right heart catheterization for defining filling pressures and cardiac output in cases of severe RV failure.

Table 27.2 Echocardiographic essentials for assessment [23]

Unoperated patient with Ebstein's anomaly	**Postoperative Ebstein's anomaly**
1. Tricuspid leaflet origin, position, size, and tethering	1. Anatomic assessment of tricuspid valve repair or replacement
2. Degree of tricuspid regurgitation	2. Degree of TR, presence of paravalvular leak
3. Right atrial and atrialized RV size and function	3. RA size
4. Functional RV size and function	4. RV size and function
5. Pulmonary valve stenosis	5. LV size and function
6. Main and branch pulmonary artery dimensions	6. Patency of Glenn shunt if present
7. Presence of atrial septal communication ± shunt direction	7. Patency of Fontan pathway if present
8. LV size and function	8. ASD device/patch position and residual shunt if present

- Placement of Swan-Ganz catheters to invasively measure pulmonary artery pressures may be difficult due to tricuspid regurgitation and abnormal right heart anatomy:
  - Injury to the TV with catheterization may occur, thereby worsening TR and precipitating clinical right heart failure.
  - Catheterization can also precipitate arrhythmias and may result in poor outcomes [24].
- The ACC/AHA guidelines recommend that coronary angiography should be performed prior to surgical repair for the assessment of coronary atherosclerosis for [21]:
  - (1) Men aged >35 years
  - (2) Premenopausal women aged >35 years with cardiac risk factors
  - (3) Postmenopausal women
  - (4) Younger patients for whom there is suspicion for coronary artery disease

Exercise Testing

- Exercise testing is recommended for the majority of patients with this disease. Importantly, as these patients have lived with cardiac disease for the entirely of their lives, they may not be aware of limitations or of slowly progressive changes in exercise capacity. Quantification of exercise capacity with cardiopulmonary exercise testing is critically important in managing these patients:
  - Exercise may unmask functional limitation and/or systemic hypoxemia and push toward surgical intervention in patients with unrepaired disease.
  - Mean peak VO_2 max of approximately 20 cc/kg/min has been reported among Ebstein populations with mean age of 39 years [25].
- Exercise testing may also be used to assess the clinical significance of ECG-evidenced bypass tracts:

  - Delta waves that disappear at higher heart rates are low risk of inducing SVT, as this indicates a long refractory period for the bypass tract.
  - However, it should be noted that multiple bypass tracts can be present, and some may be electrocardiographically silent concealed pathways.

Electrophysiology Studies

- Because of the high prevalence of atrioventricular bypass tracts, it is reasonable to perform Holter testing as part of a comprehensive evaluation for new diagnoses of Ebstein's anomaly, even if the ECG does not suggest preexcitation.
- Electrophysiology studies are indicated in patients in whom supraventricular arrhythmia is documented or suspected and may be considered in patients who have ECG-evidenced accessory pathways.
- Electrophysiology studies may also be employed in patients who develop ventricular tachycardia or fibrillation as a consequence of right heart failure.

Management of Complications in Adult Survivors

See Table 27.3 for summary of guidelines.

Tricuspid Regurgitation

1. Indications for intervention:
   (a) Each patient with Ebstein's anomaly is unique, and the decision to consider surgical intervention must be individualized for each patient.
   (b) In general, indications for consideration of surgical TV intervention may include (Class I recommendation) [21]:

Table 27.3 ACC/AHA guidelines 2008 [21]

Recommendations for evaluation and follow-up

Class I

1. All patients with Ebstein's anomaly should have periodic evaluation in a center with expertise in ACHD (*Level of Evidence: C*)
2. ECG, chest X-ray, and echocardiography-Doppler are recommended for the diagnostic evaluation of Ebstein's anomaly in adult patients (*Level of Evidence: C*)

Class IIa

1. Pulse oximetry at rest and/or during exercise can be useful in the diagnostic evaluation of Ebstein's anomaly in adult patients (*Level of Evidence: C*)
2. An electrophysiological study can be useful in the diagnostic evaluation of Ebstein's anomaly in adult patients if a supraventricular arrhythmia is documented or suspected (subsequent radiofrequency catheter ablation should be considered if clinically feasible) (*Level of Evidence: C*)
3. The following additional diagnostic tests can be useful for the comprehensive evaluation of Ebstein's anomaly in adult patients:
   (a) Doppler TEE examination if the anatomic information is not provided by transthoracic imaging (*Level of Evidence: B*)
   (b) Holter monitoring (*Level of Evidence: B*)
   (c) Electrophysiological study for history or ECG evidence of accessory pathway(s) (*Level of Evidence: B*)
   (d) Coronary angiography when surgical repair is planned, if there is a suspicion of coronary artery disease, and in men 35 years or older, premenopausal women 35 years or older who have coronary risk factors, and postmenopausal women (*Level of Evidence: B*)

Recommendation for reproduction

Class I

1. Women with Ebstein's anomaly should undertake prepregnancy counseling with a physician with expertise in ACHD (*Level of Evidence: C*)

Recommendation for endocarditis prophylaxis

Class IIa

1. Antibiotic prophylaxis before dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa is reasonable in cyanotic patients with Ebstein's anomaly and postoperative patients with a prosthetic cardiac valve (*Level of Evidence: C*)

Recommendations for medical therapy

Class I

1. Anticoagulation with warfarin is recommended for patients with Ebstein's anomaly with a history of paradoxical embolus or atrial fibrillation (*Level of Evidence: C*)

Recommendations for catheter interventions

Class I

1. Adults with Ebstein's anomaly should have catheterization performed at centers with expertise in catheterization and management of such patients (*Level of Evidence: C*)

Recommendations for electrophysiology management

Class IIa

1. Catheter ablation can be beneficial for the treatment of recurrent supraventricular tachycardia in some patients with Ebstein's anomaly (*Level of Evidence: B*)

Recommendations for surgical interventions

Class I

1. Surgeons with training and expertise in CHD should perform tricuspid valve repair or replacement, with concomitant closure of an ASD, when present, for patients with Ebstein's anomaly with the following indications:
   (a) Symptoms or deteriorating exercise capacity (*Level of Evidence: B*)
   (b) Cyanosis (oxygen saturation less than 90%) (*Level of Evidence: B*)
   (c) Paradoxical embolism (*Level of Evidence: B*)
   (d) Progressive cardiomegaly on chest X-ray (*Level of Evidence: B*)
   (e) Progressive RV dilation or reduction of RV systolic function (*Level of Evidence: B*)
2. Surgeons with training and expertise in CHD should perform concomitant arrhythmia surgery in patients with Ebstein's anomaly and the following indications:
   (a) Appearance/progression of atrial and/or ventricular arrhythmias not amenable to percutaneous treatment (*Level of Evidence: B*)
   (b) Ventricular preexcitation not successfully treated in the electrophysiology laboratory (*Level of Evidence: B*)
3. Surgical re-repair or replacement of the tricuspid valve is recommended in adults with Ebstein's anomaly with the following indications:
   (a) Symptoms, deteriorating exercise capacity, or New York Heart Association functional class III or IV (*Level of Evidence: B*)
   (b) Severe TR after repair with progressive RV dilation, reduction of RV systolic function, or appearance/progression of atrial and/or ventricular arrhythmias (*Level of Evidence: B*)
   (c) Bioprosthetic tricuspid valve dysfunction with significant mixed regurgitation and stenosis (*Level of Evidence: B*)
   (d) Predominant bioprosthetic valve stenosis (mean gradient greater than 12 to 15 mm Hg) (*Level of Evidence: B*)
   (e) Operation can be considered earlier with lesser degrees of bioprosthetic stenosis with symptoms or decreased exercise tolerance (*Level of Evidence: B*)

- Symptoms or deteriorating exercise capacity
- Cyanosis (oxygen saturation less than 90%)
- Paradoxical embolism
- Progressive cardiomegaly on chest radiography
- Progressive RV dilation or systolic dysfunction

(c) Indications for surgical re-repair or replacement of the tricuspid valve (Class I recommendation) [21]:

- New York Heart Association (NYHA) functional Class III or IV
- Severe TR after repair with progressive RV dilation, reduction of RV systolic function, or appearance/progression of atrial and/or ventricular arrhythmias
- Bioprosthetic valve failure

(d) While not specifically recommended by guidelines, medically refractory SVT may be considered as an indication for valvular intervention if it is felt that hemodynamic abnormalities are contributing to electrical instability.

(e) Asymptomatic adult patients without evidence of heart failure can be followed clinically for the development of symptoms.

2. Options for tricuspid valve intervention:

(a) Surgical creation of a monocusp valve:

- The most contemporary repair technique is called the "cone" procedure:
  - The anterior and posterior tricuspid valve leaflets are mobilized in their entirety from their anomalous attachments in the RV.
  - The free edge of this complex is rotated clockwise to be sutured to the septal border of the anterior leaflet, creating a "cone," the vertex of which remains fixed at the right ventricular apex and the base of which is sutured to the true tricuspid valve annulus level.
  - The atrialized RV is vertically plicated.

  - The septal leaflet is incorporated into the cone wall whenever possible, and the atrial septal defect is closed in a valved fashion to allow for venting of the pressure overloaded and dysfunctional right heart.

- This procedure has been quite successful, with relatively low in-hospital mortality (3–6%), late mortality (5–10%), or need for reoperation (3–10%) [6, 26].
- Decreases in severity of tricuspid regurgitation and improvement of NYHA functional class are seen postoperatively [27].
- Reoperation usually requires tricuspid valve replacement as re-repair is rarely successful.

(b) Tricuspid valve bioprosthesis:

- Tricuspid valve replacement is an option in patients for whom a "cone" procedure is not feasible, with similar rates of in-hospital mortality (6%) but a slightly increased re-operative rate (20% at 15 years) [28]. Other studies have shown nonsignificant freedom from reoperation at 12 years in tricuspid valve repair to replacement [28].
- This procedure can frequently be complicated by complete heart block.
- Bioprosthetic valves are preferred over mechanical valves because of the high risk of thrombosis with mechanical valves in the tricuspid position [28].
- Percutaneous tricuspid valve replacement with the Melody valve has also been described in a small cohort of patients with failure of a bioprosthesis in the tricuspid position [29].

(c) Bidirectional Glenn procedure (or bidirectional cavopulmonary connection):

- Consists of the creation of a shunt between the superior vena cava (SVC) and right pulmonary artery, thereby bypassing the RV.

- This procedure is often referred to as the "1.5 ventricle repair," and it can be used in patients with severely impaired RV function who are high risk for surgical treatment, or as an intraoperative salvage maneuver [30].
  - High-risk patients may include those with massive tricuspid valve dysfunction, extended atrialized right ventricle, poor ventricular contractility, or long-standing atrial fibrillation.
- Patients with very severe RV dysfunction may be functionally univentricular, and complete unloading with a subsequent Fontan procedure may be required (See Chap. 28), though this pathway is generally reserved for those presenting in the neonatal or infancy period.

Arrhythmia

- Atrioventricular reentrant tachycardia (AVRT):
  - Catheter ablation is indicated for patients with symptomatic or documented SVT.
  - SVT and accessory pathway management can be challenging secondary to multiple bypass tracts and significant variation in right atrial anatomy [31].
  - If catheter ablation fails or is not feasible, surgical ablation or interruption can be attempted.
- Atrial flutter/atrial fibrillation:
  - Atrial flutter and/or atrial fibrillation can be particularly devastating in cases of Ebstein's anomaly due to multiple bypass tracts and the risk for 1:1 conduction and can lead to sudden cardiac death.
  - Attempts can be made at percutaneous catheter-based treatment directed both at bypass tracts and atrial fibrillation, but if these fail, or if surgery is already planned, uni-atrial or bi-atrial maze procedures are indicated.

- Ventricular tachycardia/ventricular fibrillation:
  - Although rare, the right heart in Ebstein's anomaly may serve as a substrate for ventricular tachycardia or ventricular fibrillation [32].
- It should be noted that in patients with unrepaired ASD, percutaneous catheter-based treatments are associated with an increased risk of paradoxical embolism due to development of microemboli on ablation catheters, or at the groin access sites. The thin atrialized RV wall may also limit aggressive ablation.

Atrial Septal Defects

- During tricuspid valve repair or replacement surgery, ASD or PFO closure is often performed if the RV can support closure of this defect.
- Transcatheter device closure of the ASD or PFO may be indicated in some patients with sizable shunt fraction or paradoxical embolus if the degree of TR is mild to moderate (i.e., no surgical management otherwise indicated) and intra-procedural test occlusion indicates that the right heart will tolerate an intact atrial septum [33].
- Importantly, ASD or PFO closure among adult patients with poor RV compliance and right-to-left shunting may precipitate further right heart failure by eliminating the "pop-off."

Paradoxical Embolism

- Once paradoxical embolism occurs, patients should be anticoagulated indefinitely.
- The ASD can be closed if the hemodynamics allow (see section above).
- Treatment for atrial fibrillation should be addressed.

Left Heart Failure

- Left heart failure in Ebstein's anomaly can occur as a result of several etiologies:
  - LV dysfunction due to severe RV dilation and the reverse Bernheim phenomenon (leftward shift of the interventricular septum with subsequent left ventricular systolic and diastolic dysfunction)
  - Associated left ventricular non-compaction
  - Pacemaker-associated cardiomyopathy
  - Atherosclerotic cardiovascular disease

Management of Pregnancy

- All patients with Ebstein's anomaly who are, or plan to become pregnant, should be seen by both congenital heart specialists and high-risk obstetricians.
- Pregnancy is generally well tolerated [34], but patients with right heart failure, symptomatic TR, or right-to-left shunt with cyanosis should be discouraged from pregnancy, as the right heart may not be able to support the hemodynamic demands of pregnancy and cyanosis itself carries a risk to the fetus.
- Additional risks of pregnancy include increased risk of fetal loss (25% risk) and congenital anomalies in offspring (~5% risk) [34, 35].
- Patients with ASDs and PFOs may be at increased risk of right-to-left shunting and paradoxical embolization with the physiologic decline in systemic vascular resistance during second trimester.

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Chapter 28
Anatomic Variants of Univentricular Physiology and Fontan Palliation

Ada C. Stefanescu Schmidt

Epidemiology

- There are several congenital diagnoses, most with a wide spectrum of defects, that lead to univentricular physiology (Table 28.1). They can be broadly defined into three categories based on the morphology (right, left, or indeterminate) of the predominant ventricle.
- The defects most likely to lead to single ventricle repair include hypoplastic left heart syndrome (HLHS), tricuspid atresia, double inlet left ventricle, and defects with a straddling atrioventricular valve (such as an unbalanced atrioventricular canal defect). Less often, pulmonary atresia with intact ventricular septum (with a small RV or RV-dependent coronary circulation), double outlet right ventricle, and Ebstein anomaly may require single ventricle repair.

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Table 28.1 Diagnoses leading to univentricular physiology

Right ventricle dominant	Left ventricle dominant
1. Hypoplastic left heart syndrome (HLHS)	1. Tricuspid atresia (TA)
2. Double outlet right ventricle (DORV)	2. Double inlet left ventricle (DILV)
3. Double inlet right ventricle (DIRV)	3. Pulmonary atresia with intact ventricular septum (PAIVS)
4. Unbalanced AV canal defect (AVCD)	4. Unbalanced AV canal defect (AVCD)

- The most common type of univentricular heart at birth is HLHS, with an estimated incidence of 0.2–0.4 per 1000 live births [1, 2] followed by tricuspid atresia (TA) (0.06–0.08 per 1000 live births).
  - In adults, TA is more common than HLHS, as the latter carries a higher pediatric mortality.
- Incidence is likely to increase, especially in developed countries, as in utero and neonatal interventional options become more available.
- The incidence of some univentricular subtypes (HLHS in particular) is higher in siblings than in the general population and is thus thought to have a strong genetic component.

Hypoplastic Left Heart Syndrome (HLHS)

Anatomy (Fig. 28.1)

- Reduced blood flow during development, either due to lack of inflow (mitral atresia) or outflow (aortic atresia), is the most common cause of HLHS.
- An unbalanced atrioventricular canal defect (AVCD) can also lead to an underdeveloped left ventricle that cannot support the systemic circulation.
- The ascending aorta is often small and underdeveloped; flow is dependent on a patent ductus arteriosus.

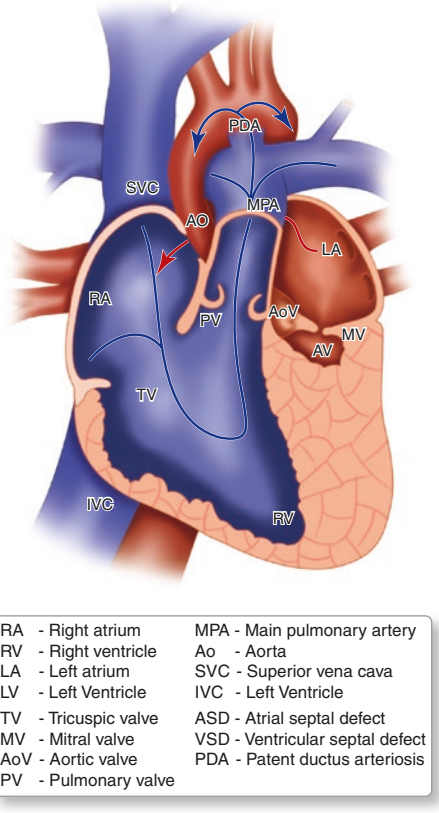

FIGURE 28.1 Hypoplastic left heart syndrome. Oxygenated pulmonary venous return into the left atrium return to the right atrium through an atrial septal defect. Flow into the aorta comes through the patent ductus arteriosus

Physiology

- Patients with HLHS have a systemic right ventricle, responsible for both pulmonary and systemic circulation.
- Progressive right heart failure is common with older age, especially in the setting of atrioventricular valve regurgitation and added volume load.

Spectrum of Disease

- Principal determinants of the severity of HLHS are the presence of a VSD (which generally is associated with a more well-developed left ventricle secondary to flow) and aortic valve defects (if atretic, systemic circulation is dependent on the size of the ductus arteriosus).

Associated Defects

- VSD occurs in a minority of patients.
- Turner syndrome (45, XO).
- Bicuspid aortic valve, subaortic stenosis, and aortic coarctation.

Tricuspid Atresia

Anatomy and Spectrum of Disease (Fig. 28.2)

- Following the same principle as mitral valve atresia and HLHS, the atretic or imperforate tricuspid valve leads to hypoplasia of the right ventricle; systemic venous return is depending on an ASD to reach the left atrium.
- A VSD is much more common in association with TA, leading to some development of the right ventricle and pulmonary valves, though subpulmonic or pulmonary valve stenosis are common due to insufficient flow.
- ~30% of patients have transposition of the great arteries (with the aorta arising from the hypoplastic right ventricle and the pulmonary artery from the left).

Associated Defects

- Mutations and deletions in the 22q11 chromosome [3].

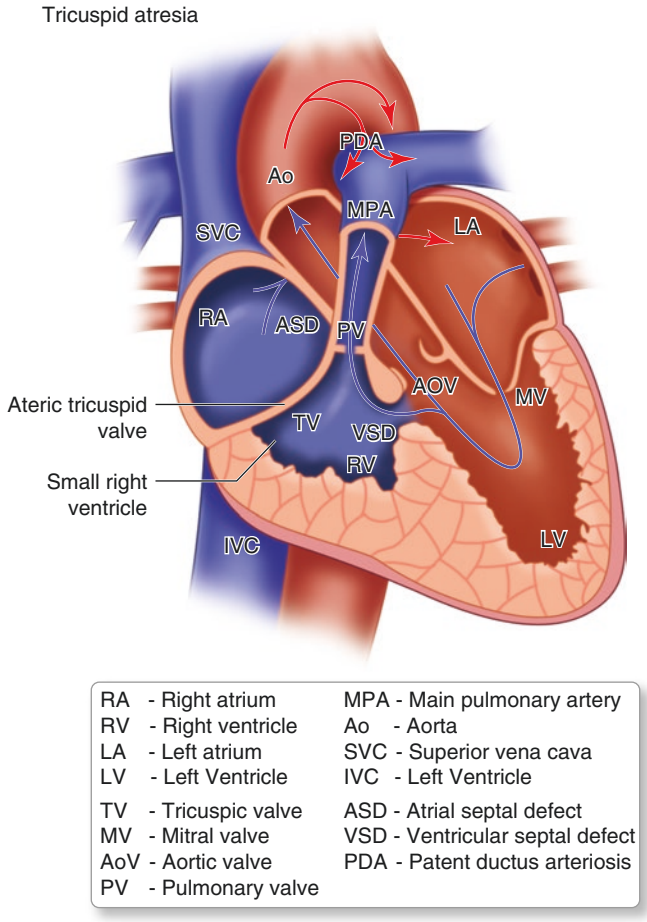

FIGURE 28.2 Tricuspid atresia

Double Outlet Right Ventricle (DORV)

- Spectrum of anatomic defects in which more than 50% of each great vessel (often the entire pulmonary artery and >50% of the aorta) originates from the right ventricle, through a VSD (Fig. 28.3).

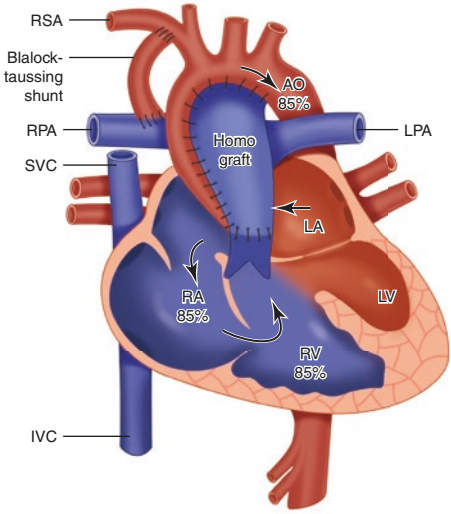

FIGURE 28.3 Double outlet right ventricle, after initial repair including a Blalock-Taussig shunt and Damus-Kaye-Stansel anastomosis of the ascending aorta and pulmonary trunk (indicated for patients with a hypoplastic aorta)

- Pathologic definition of DORV requires the presence of a conus beneath the pulmonic and aortic outflows.
- Location of the VSD (whether subaortic, subpulmonary, doubly committed, or remote from the great vessels) defines the subtype of DORV, as well as the operative repair strategy and in some cases may require a single ventricle physiology approach (see Chap. 22 for more details).

Double Inlet Ventricle (DIRV and DILV)

Anatomy

- More than 50% of each atrium is connected to one ventricular chamber, most commonly the left (DILV) (Fig. 28.4).

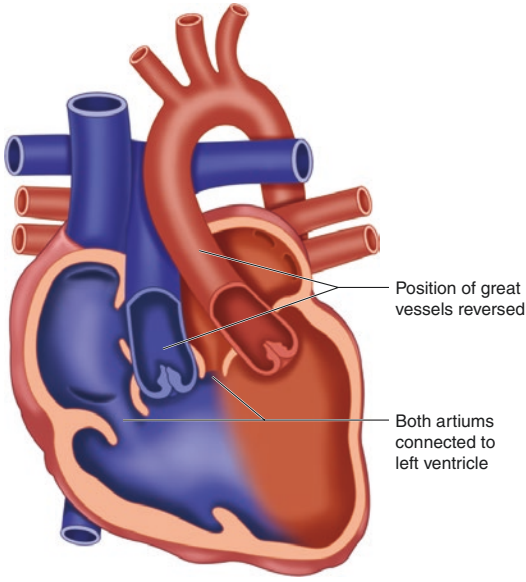

FIGURE 28.4 Double inlet left ventricle

- Usually both atrioventricular valves are near one another and have a morphology more similar to the mitral valve.
- Inlet septum is absent, giving rise to a large inlet VSD.

Physiology

- Cyanosis is common due to mixing of deoxygenated systemic venous return and pulmonary venous return in the ventricles through the large VSD.

Spectrum of Disease

- Size of the non-dominant chamber is dependent on the size of the VSD (a larger VSD allows greater flow in development to the non-dominant chamber resulting in a larger

chamber size and contribution to function). One of the atrioventricular valves may be atretic (if there is an ASD which allows mixing of venous return). If there is straddling of an AV valve that may also affect surgical repair strategy.

Associated Defects

- ASD is common.
- Levo-transposition of the great arteries (L-TGA) is common.

Pulmonary Atresia with Intact Ventricular Septum (PA-IVS)

Anatomy

- Imperforation of the pulmonary valve leads to lack of flow through the RV, leading to a small or hypoplastic RV.

Physiology

- Pulmonary circulation dependent on a patent ductus arteriosus (aortic to pulmonary shunt).
- Often multiple collaterals from the aorta to the pulmonary artery may be present and can be identified on exam as multiple continuous murmurs over the precordium and back.

Spectrum of Disease

- The function of the tricuspid valve (spectrum from tricuspid atresia to significant tricuspid regurgitation) has important implications for the possibility of a two-ventricle surgical repair.

Associated Defects

- When occurring in conjunction with PA-IVS, tricuspid atresia leads to a hypoplastic RV.
- RV to coronary artery connections can be seen and require coronary angiography for confirmation. If present, assessment of the coronary flow is important, as patients with RV-dependent coronaries (where flow depends on high RV pressures providing flow to the coronaries) will not tolerate interventions that decompress the RV and decrease RV pressure below systemic diastolic pressures (such as pulmonary valvuloplasty or insertion of RV-PA conduit) without addressing the coronary anatomy.

General Principles of Univentricular Repair

Operative Repair Options

- The choice of palliative surgery for univentricular heart depends on the underlying anatomy, size, and development of the non-dominant ventricle.
- Re-creating two ventricular chambers, by closing a VSD and redirecting venous return to the pulmonary artery, and pulmonary venous return toward the aorta, leads to the best long-term results, though is often challenging to realize and with serious short-term hemodynamic consequences.
- The more common procedure, termed "single ventricle repair," creates a baffle for deoxygenated systemic venous return to go to the pulmonary artery passively. Oxygenated blood from the pulmonary veins enters the univentricular chamber and is pumped to the systemic circulation (pulmonary outflow must be oversewn).
- If the non-dominant ventricle is developed well enough to provide some, but not all flow to the pulmonary circulation, a "1.5 ventricle repair" can be attempted. In this circulation, some of the systemic venous flow returns to the subpulmonary ventricle, while the rest is directed through

a baffle to the pulmonary artery (typically via a Glenn shunt).

- Staging of these palliative procedures is generally undertaken in order to accommodate the changing hemodynamics (in particular, the initially elevated pulmonary pressure) in the neonatal period.

Staged Procedures

1. Pulmonary artery (PA) band
   (a) Patients with univentricular physiology and without pulmonary stenosis are at risk for overcirculation of the pulmonary arteries. High flow results in increased pressures through the lungs in the first few months of life causing injury and progressive pulmonary endothelial dysfunction. The development of pulmonary hypertension precludes later Fontan palliation.
   (b) To prevent pulmonary overcirculation, a PA band made of synthetic material placed around the main PA (without the need for intracardiac surgery or cardiopulmonary bypass) creates a fixed stenosis that limits flow through the lungs and prevents the development of pulmonary hypertension.
   (c) The PA band is often removed during subsequent surgery; however, the area of the band may be scarred and present later in life as recurrent supra-pulmonary valve stenosis.
2. Blalock-Taussig shunt (BT shunt, also termed Blalock-Thomas-Taussig)
   (a) Patients who have insufficient pulmonary arterial flow (such as those with a dominant left ventricle and a small VSD or intact ventricular septum or with significant subpulmonic, pulmonary valve, or supra-pulmonic stenosis), a Blalock-Thomas-Taussig shunt can be performed to augment the flow to the lungs and allow normal development (see Fig. 28.5).

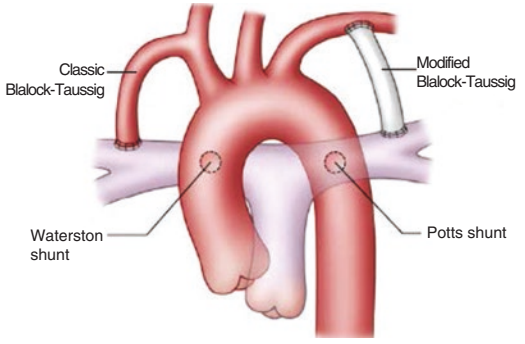

FIGURE 28.5 Palliative shunts (Figure from: DeFaria Yeh D, et al. Adult Congenital Heart Disease. In: H. K. Gaggin and J. L. Januzzi, eds. *Massachusetts General Hospital Cardiology Board Review*: Springer; 2014(1): 345–377)

(b) This procedure, developed by the surgeons Dr. Alfred Blalock and Dr. Vivien Thomas (a surgical technician at the time) and the cardiologist Dr. Helen Taussig, was first performed in 1944 in an infant with tetralogy of Fallot.

(c) The classic BTT shunt is an anastomosis of the subclavian artery (usually contralateral to the aortic arch), to the branch of the pulmonary artery. The arm therefore receives blood flow through collaterals, usually without symptoms, though with a markedly decreased brachial artery pulse which often makes a blood pressure measurement by sphygmomanometry unobtainable in that arm.

(d) A modified BTT shunt is created by the use of a synthetic graft between the subclavian and the pulmonary artery, retaining some flow to the arm.

(e) While the BTT shunt is often reversed with later stages of the procedure, the area of the pulmonary artery at the anastomosis site is often scarred and may develop stenosis leading to asymmetric pulmonary arterial flow (diagnosed by a lung perfusion scan, unexplained elevation in RVSP with branch PA gradient assessed by echocardiography, CT, or MRI). In the classic BTT

shunt patient, the decreased blood flow to the arm remains despite reversal of the BTT shunt (the subclavian artery is not reconnected).

(f) Central shunts, including the Waterston and Potts shunts (ascending or descending Ao to PA, respectively), may also have been employed in patients who are now older.

(g) Unintended consequences of any systemic to pulmonary arterial shunt include volume loading of the systemic ventricle, distortion of branch PAs, heterogeneous microscopic pulmonary vascular changes, and cyanosis.

3. Glenn shunt

(a) After the first few months of life, when pulmonary vascular resistance and pulmonary artery pressures have decreased to levels similar to the venous systemic pressures, the superior vena cava can be anastomosed directly to the pulmonary artery to allow gravity to provide passive flow of deoxygenated blood from the head and neck to the pulmonary arteries (typically done when infants are able to hold their head up).

(b) This can be the first palliative procedure in children with enough pulmonary blood flow in the neonatal procedure (or a large patent ductus arteriosus) or follow a BTT shunt in those infants who did not. It may also be the second step of a Norwood procedure.

4. Fontan procedure

(a) The Fontan procedure, named after Dr. Francois Marie Fontan who first performed it in 1971 [4], is a complete connection between systemic venous return and the pulmonary arteries (Fig. 28.6). The subtypes are:

- RA-to-PA: connection of the right atrial appendage to the pulmonary artery.
- The Bjork procedure was a Fontan modification which utilized a valved conduit between the RA and RV.
- Intracardiac: atrial tissue used to create a baffle from atrium to right pulmonary artery (lateral tunnel).

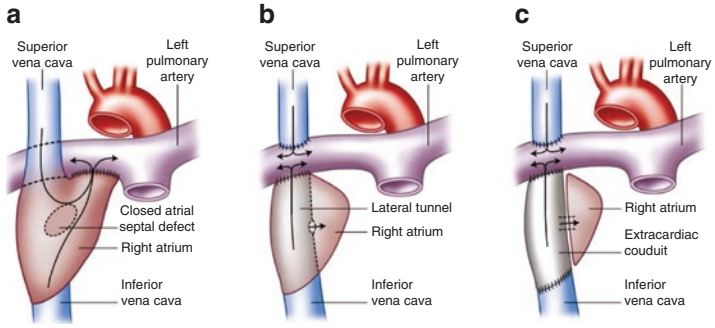

FIGURE 28.6 Fontan procedure (**a**) right atrial to pulmonary artery connection; (**b**) lateral tunnel Fontan, intracardiac; (**c**) extracardiac Fontan. (Figure from: DeFaria Yeh D, et al. Adult Congenital Heart Disease. In: H. K. Gaggin and J. L. Januzzi, eds. *Massachusetts General Hospital Cardiology Board Review*: Springer; 2014(1): 345–377)

- Extracardiac: synthetic material used to create a baffle from the IVC outside of the atrial chamber to the pulmonary artery.

(b) The baffle may initially be fenestrated (creation of a small hole within the baffle), in order to allow for pressure release (through creating a right-to-left shunt). This fenestration is then often closed in the postoperative period.

5. Norwood procedure (Fig. 28.7)

(a) The Norwood procedure refers to a sequence of three surgeries, specifically in infants with HLHS:

- Stage 1:
  - Atrial septectomy.
  - Main pulmonary artery is disconnected from the right and left pulmonary artery branches and is connected to the ascending aortic arch. The aorta is reconstructed and arises off the native pulmonic root.
  - Shunt from the aorta (often BTT shunt) is connected to the right and left pulmonary arteries to restore pulmonary blood flow.

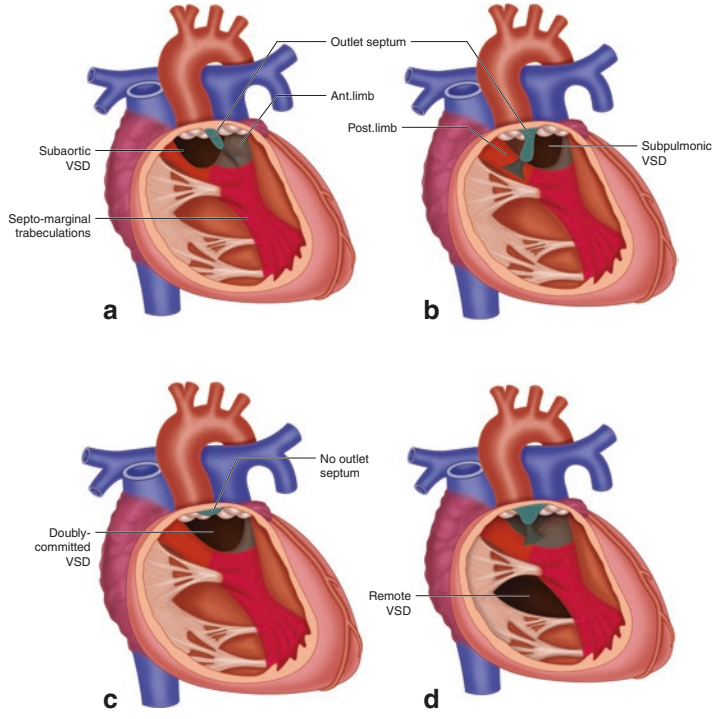

FIGURE 28.7 Norwood procedure

A Sano shunt or modification involves placement of a conduit between the RV and the PA branches (instead of a BTT shunt).

– Venous systemic return arrives to the right atrium → right (systemic) ventricle → pulmonic trunk → aorta → systemic circulation, a subset of which is shunted to the pulmonary arteries via BTT shunt → lungs → pulmonary veins → left atrium → right atrium (through septectomy) → back in systemic right ventricle.

- Stage 2:
  - About 6 months later, superior vena cava connected to the pulmonary arteries (usually through a Glenn procedure).

- Stage 3:
  - Two to three years later, a Fontan procedure is performed to direct all systemic venous return to the lungs as described above.

Diagnosis

Clinical Presentation in Adults

- Adults lost to follow-up after a childhood Fontan surgery generally present with hypoxia and cyanosis (due to right-to-left shunts, either through a Fontan fenestration or through systemic to pulmonary venovenous collaterals), atrial more often than ventricular arrhythmias, significant venous insufficiency, and cardiac cirrhosis.

Physical Exam

- Patients with a Fontan will have a single second heart sound (A2).
- An elevated JVP is concerning for elevated Fontan pathway pressures and should be investigated. Recall that the jugular venous pulsation will be challenging to assess as it is not classically pulsatile.
- Similarly, hypoxia is abnormal and should be worked up for possible baffle leaks or systemic to pulmonary venovenous collaterals.
- Chronic venous insufficiency in the lower extremities is common, with medial malleolar ulcers often being overlooked.
- Signs of hepatic dysfunction (jaundice, ascites, caput medusa, asterixis).

Electrocardiogram

- Variable depending on the primary anatomic defect.
- Atrial arrhythmias are common.

Chest X-Ray

- Assess atrial and ventricular size, the presence of pulmonary edema, or decreased pulmonic flow if branch PA stenosis is present, aortic dilation, especially in the conotruncal defects.

Echocardiography (see Table 28.2)

- Obtain an accurate surgical history in order to focus imaging on the baffles and vascular connections which were created.
- Assess the Fontan pathway for baffle leaks, obstruction, and intracardiac thrombus.
- Assess for systemic ventricular function as well as systemic AV valve regurgitation.

Cardiac Catheterization

- Catheterization may be performed to assess hemodynamics to aid in management and assess for Fontan pathway

Table 28.2 Echocardiographic Essentials for Assessment [5]

1.	Inferior vena cava (IVC) and SVC size and flow pattern
2.	Right atrial size
3.	Right atrial to PA anastomosis patency and flow patterns, if present
4.	Interatrial or extracardiac venous conduit flow patterns
5.	Branch PA size and flow pattern
6.	Thrombus within the systemic venous pathway
7.	Baffle fenestration flow and Doppler gradient
8.	Pulmonary venous inflow and left atrial size
9.	Atrioventricular valve function
10.	Systemic ventricular size and function
11.	Outflow tract obstruction
12.	Aortic valve stenosis or incompetence, size of the ascending aorta, and possible coarctation

leaks or stenoses, which can then be intervened on with device closure, balloon, or stenting.
- Cardiac catheterization can identify systemic to pulmonary venovenous collaterals as a recurrent source of hypoxia in these individuals. Coiling of the vessels or use of occluder devices to exclude the aberrant vessel can improve oxygen saturation and exercise tolerance and perceived quality of life.
- Procedures should only be performed by experienced congenital interventionalists at a tertiary center.
- At rest, the typical Fontan has systemic venous pressure which equals the PA pressure and ranges from 12 to 20 mmHg (different for each individual). The indexed pulmonary vascular resistance should be in the 1–3 Woods unit range. Although cardiac index in a Fontan may be low (1.5–3.5 L/min/m^2), it can augment up to two- to threefold with exercise.

Advanced Imaging Techniques

- CT and MRI are useful to assess for Fontan pathway fenestration/leaks or obstructions, ventricular size and function, late gadolinium enhancement, and the presence of and access to systemic to pulmonary venovenous collaterals.

Management in the Adult Survivor

The modified Choussat criteria for a favorable Fontan candidate, while useful to decide upon intervention in childhood, also serves as an excellent guide for potential complications in adulthood. The four tenets are:

[1] unobstructed ventricular inflow and outflow (including stenosis and regurgitation)
[2] good systolic and diastolic ventricular function
[3] good-sized proximal pulmonary arteries without obstruction and PVR <2.5 WU
[4] unobstructed pulmonary venous return.

See Table 28.3 for summary of guidelines.

Table 28.3 ACC/AHA guidelines 2008 for follow-up and treatment of patients after a Fontan procedure [6]

Class I

1. Lifelong follow-up is recommended for patients after a Fontan type of operation; this should include a yearly evaluation by a cardiologist with expertise in the care of ACHD patients (*Level of Evidence: C*)
2. Catheterization of adults with a Fontan type of repair of single ventricle physiology should be performed in regional centers with expertise in ACHD (*Level of Evidence: C*)

Class I

3. Management of patients with prior Fontan repair should be coordinated with a regional ACHD center. Local cardiologists, internists, and family care physicians should develop ongoing relationships with such a center with continuous availability of specialists (*Level of Evidence: C*)
4. At least yearly follow-up is recommended for patients after Fontan repair (*Level of Evidence: C*)
5. Arrhythmia management is frequently an issue, and consultation with an electrophysiologist is recommended as a vital part of care (Level of Evidence: C)
6. New-onset atrial tachyarrhythmia should prompt a comprehensive noninvasive imaging evaluation to identify associated atrial/baffle thrombus, anatomic abnormalities of the Fontan pathway, or ventricular dysfunction (Level of Evidence: C)
7. Warfarin should be given for patients who have a documented atrial shunt, atrial thrombus, atrial arrhythmias, or a thromboembolic event (Level of Evidence: C)
8. Reoperation after Fontan is indicated for the following:
   (a) Unintended residual ASD that results in right-to-left shunt with symptoms and/or cyanosis not amenable to transcatheter closure (*Level of Evidence: C*)
   (b) Hemodynamically significant residual systemic artery-to-pulmonary artery shunt, residual surgical shunt, or residual ventricle-to-pulmonary artery connection not amenable to transcatheter closure (*Level of Evidence: C*)
   (c) Moderate to severe systemic AV valve regurgitation (*Level of Evidence: C*)
   (d) Significant (greater than 30-mmHg peak-to-peak) subaortic obstruction (*Level of Evidence: C*)
   (e) Fontan pathway obstruction (*Level of Evidence: C*)
   (f) Development of venous collateral channels or pulmonary arteriovenous malformation not amenable to transcatheter management (*Level of Evidence: C*)

(g) Pulmonary venous obstruction (*Level of Evidence: C*)
(h) Rhythm abnormalities, such as complete AV block or sick sinus syndrome, that require epicardial pacemaker insertion (*Level of Evidence: C*)
(i) Creation or closure of a fenestration not amenable to transcatheter intervention (*Level of Evidence: C*)

Class IIa

1. Reoperation for Fontan conversion (i.e., revision of an atriopulmonary connection to an intracardiac lateral tunnel, intra-atrial conduit, or extracardiac conduit) can be useful for recurrent atrial fibrillation or flutter without hemodynamically significant anatomic abnormalities. A concomitant maze procedure should also be performed (*Level of Evidence: C*)

Class IIb

1. Heart transplantation may be beneficial for severe SV dysfunction or PLE (*Level of Evidence: C*)

Class IIa

1. It is reasonable to treat SV dysfunction with ACE inhibitors and diuretics (Level of Evidence: C)

Class I

1. Arrhythmia management is frequently an issue in patients after the Fontan procedure, and consultation with an electrophysiologist with expertise in CHD is recommended as a vital part of care (*Level of Evidence: C*)
2. New-onset atrial tachyarrhythmias should prompt a comprehensive noninvasive imaging evaluation to identify associated atrial/baffle thrombus, anatomic abnormalities of the Fontan pathway, or ventricular dysfunction (*Level of Evidence: C*)
3. Electrophysiological studies in adults with Fontan physiology should be performed at centers with expertise in the management of such patients (*Level of Evidence: C*)
4. Clinicians must be mindful of the high risk for symptomatic IART in adult patients who have undergone the Fontan operation. This arrhythmia can cause serious hemodynamic compromise and contribute to atrial thrombus formation. Treatment is often difficult, and consultation with an electrophysiologist who is experienced with CHD is recommended whenever recurrent IART is detected (*Level of Evidence: C*)

Class III

1. The estrogen-containing oral contraceptive pill is not recommended for ACHD patients at risk of thromboembolism, such as those with cyanosis related to an intracardiac shunt, severe PAH, or Fontan repair (*Level of Evidence: C*)

Arrhythmia

- Patients with an intracardiac Fontan are at highest risk for a bradyarrhythmia (heart block or sinus node dysfunction) or atrial tachyarrhythmia.
  - In particular, intra-atrial reentrant tachycardia (distinct from atrial flutter in that the reentrant circuit is around suture lines, and the atrial rate is generally slower than typical flutter) is seen over half of patients in their lifetime after a Fontan procedure [6].
- Avoidance of nodal agents with negative ionotropic effects is important (e.g., diltiazem) to prevent systemic ventricular dysfunction.
- A high burden of atrial arrhythmias in patients with an RA-PA or an intracardiac Fontan may be an indication for a revision and extracardiac Fontan creation.
- Ablations should be performed by electrophysiologists with ACHD experience.
- If a pacemaker is needed, epicardial placement is ideal; placement of leads in the atrium and through the coronary sinus to the systemic left ventricle is occasionally utilized but carries a high risk of perforation, right-left shunting, and embolization.

Heart Failure

- Fontan conduit failure, manifesting as "right" heart failure (venous hypertension, ascites), is prevalent in adults after a Fontan repair, in particular if increased pulmonary vascular resistance or LV systolic or diastolic dysfunction develops.
- Addressing any pulmonary or systemic arterial stenosis such as branch PS at old shunt sites or aortic coarctation is important.
- Treatment includes diuretics and, in select cases, pulmonary vasodilators.

- Screening for cirrhosis and hepatocellular carcinoma is recommended. Our center has every Fontan patient follow with a hepatologist annually.
- Systemic ventricular failure may occur, especially with a systemic right ventricle; close control of blood pressure and afterload reduction is essential.
- Given atrial tachyarrhythmias are common, prolonged duration of tachycardia may contribute to systemic ventricular dysfunction. Prompt restoration of normal sinus rhythm, rather than a rate control strategy, is usually recommended.
- Single ventricle patients typically live with low or low normal cardiac output.
- Serial cardiopulmonary exercise testing can be useful in better understanding potential causes to address in the aging or failing Fontan.
- In the "failing Fontan," several factors should be investigated and addressed if found: pathway obstruction, pulmonary vein compression, intracardiac regurgitation or obstruction, giant right atrium, any thrombosis or thromboembolism, atrial (more often than ventricular) arrhythmias, ventricular dysfunction or decreased cardiac output, protein-losing enteropathy, hepatic disease, and abnormalities of the pulmonary vascular bed.

Protein-Losing Enteropathy

- Protein-losing enteropathy (PLE) is a debilitating consequence of a Fontan procedure, thought to be due to chronically elevated systemic venous and portal pressures.
- It is diagnosed in 4–14% of patients after a Fontan procedure, usually in the first two decades after initial surgery [7, 8].
- Median survival is 5 years after diagnosis.
- Low albumin, recurrent ascites, and diarrhea should prompt investigation with a stool alpha-1 antitrypsin.

- PLE is further stimulated by elevated venous pressures in conjunction with increased inflammation (circulating tumor necrosis factor and other inflammatory markers).

Thromboembolic Risk

- The low pressures and slow flow through the Fontan circulation increase the risk of thrombus formation.
- The presence of a baffle leak (either created as a fenestration or developing over time due to baffle dehiscence) can lead to right-to-left embolization and stroke.
- The risk is particularly high in patients with a right atrial appendage to pulmonary artery Fontan.
- Aspirin may be utilized for thromboembolic prophylaxis; anticoagulation with warfarin is indicated for high-risk patients (RA-to-PA Fontan, pulmonary arterial stump, atrial tachyarrhythmias, prior thromboembolic events, underlying coagulopathy, PLE, depressed systemic ventricular function).
- There is not yet data available on the use of direct oral anticoagulants.

Non-cardiac Surgery

- As pulmonary circulation is dependent on passive venous return, patients are preload-dependent after a Fontan procedure and particularly sensitive to dehydration, venodilators, and positive-pressure ventilation. Early extubation after procedures is important to encourage when possible.
- If intubation is required, blood pressure must be closely monitored.
- Non-cardiac surgery, unless an emergency, should be performed at a center with ACHD expertise (Class 1, LOE C) [6]. At our center, we also request cardiac anesthesia consultation.

Indications for Transplant

- For patients with defined anatomic issues with the Fontan pathway, or symptoms linked to a high burden of atrial arrhythmias, conversion to an extracardiac Fontan (termed "Fontan revision") is often the first step in surgical management.
- Operative repair options are limited for patients with rising pulmonary artery pressures and a failing Fontan pathway or those with declining systemic ventricular function.
- Fontan patients represent ~40% of transplant recipients with a history of CHD based on a recent analysis of US administrative data [9].
- Short-term posttransplantation outcomes in Fontan patients are worse than in other ACHD patients [9, 10], though improving in recent studies. In those who survive the postoperative period, medium- and long-term outcomes are similar to other CHD patients and better than transplants recipients without CHD [11].
- Low peak oxygen consumption and heart rate reserve are helpful in determining transplant eligibility; the morbidity and mortality associated with transplant must however be weighed against that of the current palliated anatomy or possible surgical procedures, especially as the techniques for the latter continue to improve [11].
- Mechanical circulatory support is under investigation in congenital heart disease, but univentricular hearts still present a unique challenge, and underlying coagulopathy and early and progressive liver disease often pose significant bleeding risks in addition to anatomic and physiologic challenges.

Pregnancy

- Pregnancy in women who have undergone Fontan palliation carries a high risk of complications, particularly if there is systemic ventricular dysfunction, uncontrolled

arrhythmias, pulmonary hypertension, severe cyanosis, or chronic heart failure.

- Atrial arrhythmias should be managed in a timely way with medical therapy (beta blockade, digoxin), and cardioversion is safe in pregnancy if medical therapy fails.
- Cardiopulmonary exercise testing can be useful in predicting potential complications and in shared decision-making regarding risk/benefit with the patient.
- All individuals with complex congenital heart disease should have updated anatomic assessment, genetic counseling, and multidisciplinary assessment with the high-risk obstetric team, ACHD team, and obstetric anesthesia prior to pregnancy.
- Ensuring adequate preload during vaginal delivery is important.
  - Leg elevation or left lateral decubitus positioned may augment preload.

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Chapter 29
Left Ventricular Non-compaction

Evin Yucel

Abbreviations

ACE inhibitors	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin receptor blockers
CHD	Congenital heart disease
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVNC	Left ventricular non-compaction
RV	Right ventricle
WHO	World Health Organization

Epidemiology

- Left ventricular non-compaction (LVNC) is a rare cardiomyopathy.
- LVNC is the third most common primary cardiomyopathy among children (5–9.2% of cases) [1].

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- Adult prevalence is 0.017–0.26% in observational echocardiographic studies, with a 3:1 male to female ratio [2, 3].
- See Table 29.1 for historical background.

Anatomic Definition and Pathophysiology

- Anatomy:
  - Intrauterine arrest of normal myocardial compaction resulting in prominent trabeculae, deep intertrabecular recesses, and thickening of the myocardium in two distinct layers: compacted and non-compacted.
  - Predominantly involves the apical and mid-inferior and mid-lateral walls of the left ventricle (LV). Rarely the septum can be involved.
  - May be isolated (mostly seen in adult onset) or associated with other congenital heart diseases (CHD).
- Physiology:
  - Etiology of systolic dysfunction is unclear but is thought to be due to subendocardial hypoperfusion and microcirculatory dysfunction [1, 6–8].

Table 29.1 Historical background

In 1975, histology of persistent spongy myocardium with embryonic blood supply was initially described in children and was associated with other congenital cardiac anomalies. Later, in 1984, Engberding and Bender described LVNC in an adult using transthoracic echocardiogram, which demonstrated "a spongy myocardium with prominent sinusoids" [4]. Later in 1990, Chin et al. reported on eight patients with LVNC without any congenital cardiac anomalies suggesting the disease entity of "isolated non-compaction of the LV myocardium." The postmortem specimens in three patients demonstrated deep intertrabecular recesses lined with endothelium and continuous with endocardial endothelium suggesting that the recesses were not sinusoids [5].

- Diastolic dysfunction may be due to abnormal relaxation and restrictive filling, which is caused by the numerous prominent trabeculae [2, 9].
- Systolic and diastolic dysfunction result in increased left atrial pressure, LV end-diastolic volume, and LV end-diastolic pressure, with a decrease in cardiac output.
- Involvement of the right ventricle (RV) leads to right-sided heart failure.

- Spectrum of disease:
  - Patients may present with heart failure symptoms during fetal life, infancy, childhood, and adult years.
  - Some patients may have non-compaction with normal LV function.
  - The LV is uniformly affected; however, involvement of the RV has been described in some studies [1, 10].
  - Although earlier studies reported very high mortality rates of up to 35%, the utilization of guideline-directed medical therapy for heart failure in those studies was not reported. More recent series report lower mortality rates ranging between 2 and 15% [4, 11].

- Associated defects:
  - Twelve percent of patients with LVNC have associated congenital cardiac defects [12].

    Ebstein's anomaly (most common)
    Left ventricular outflow tract abnormalities and/or obstruction (congenitally abnormal aortic valves, subaortic stenosis, aortic coarctation)
    Tetralogy of Fallot
    Pulmonary stenosis
    Atrial and ventricular septal defects

- Genetics and maternal factors:
  - Familial forms, both X-linked and dominant, are seen in 40% of cases. The remainder of the cases are sporadic [13].

- In isolated form, genetic mutations are seen in the G4.5 gene, DTNA (α-dystrobrevin), cipher/ZASP, lamin A/C, and myosin heavy chain (MYH7), some of which are also commonly seen in hypertrophic cardiomyopathy [1, 11].
- In cases associated with other CHD, genetic mutations are seen in the α-dystrobrevin gene and transcription factor NKX2.5 [1].
- There are no reports of maternal factors linked to LVNC.

Diagnostics

Clinical Presentation in Adults

- Some patients may be asymptomatic and identified incidentally on imaging.
- Symptomatic patients present with chest pain or dyspnea or palpitations due to ventricular tachycardia.
- Triad of heart failure, ventricular arrhythmias, and systemic embolization is a hallmark of LVNC.
- It can also present as sudden cardiac death with a reported prevalence of 2–9% [11, 14].

Physical Exam

- No specific signs on physical exam.
- Signs of heart failure (elevated jugular venous pressure, displaced point of maximal impact, a third heart sound) will be evident.

Electrocardiography

- ECG findings are non-specific and can be completely normal.
- Left ventricular hypertrophy, inverted T waves, ST segment changes, atrial fibrillation, supraventricular tachycar-

dia, non-sustained ventricular tachycardia, and bundle branch blocks are common.
- Wolff-Parkinson-White pattern might be seen in pediatric patients or in association with Ebstein's anomaly.

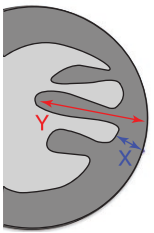
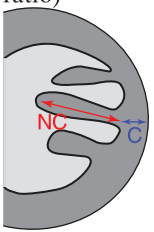
Chest X-Ray

- Patients with normal LV function may have a normal chest X-ray.
- An enlarged cardiac silhouette and/or pulmonary edema may be seen.

Echocardiography

- There are three different diagnostic criteria for LVNC, which are shown in Table 29.2. Out of the three, the criteria proposed by Jenni and colleagues are the most widely accepted and have been validated in at least one separate cohort, but sensitivity and specificity were not reported [15].
- All of the criteria described by various groups require the presence of thickened left ventricular wall consisting of two layers: a thin compacted epicardial layer and a markedly thickened endocardial layer with prominent trabeculations and deep recesses (Fig. 29.1).
- Contrast enhancement can improve visualization of the trabeculations.
- Myocardial strain imaging may be helpful:
  - Bellavia et al. demonstrated that LV strain values are decreased in isolated LVNC, with even those patients with normal LV systolic function demonstrating subclinical dysfunction [17].
  - Relative basal sparing with abnormal strain pattern in the apex has been shown to differentiate LVNC from dilated cardiomyopathy [18].

Table 29.2 Diagnostic criteria for LVNC

Criteria, year	Chin, 1990 [5]	Jenni, 2001 [15]	Stöllberger, 2002 [16]
Ratio	None suggested 	N:C >2 (maximal measured ratio) 	Not described
Timing	End-diastole	End-systole	End-systole
View	PLAX (at level of MV, pap muscles) and A4C (apex)	Parasternal SAX	Apical 4C
Location/ number	Not described	Mid-lateral, mid-inferior, apex	≥3 trabeculations located apical to the insertion of papillary muscles as visible in one image plane

Other	Progressive ↓ in the ratio of X:Y from the MV (0.92) → papillary muscle (0.59) → apex (0.20) Progressive ↑ in the LV free-wall thickness (Y) from the MV level to apex Mostly pediatric patients (age range 11 months to 22.5 years)	Color Doppler (Nyquist level to 20–30 cm/s) evidence of deep intertrabecular recesses filled with blood from the LV cavity LV systolic/diastolic dysfunction; LV thrombi	Perfused intertrabecular spaces by color Doppler Most patients had neuromuscular disorders

PLAX parasternal long axis, *MV* mitral valve, *A4C* apical 4 chamber, *LV* left ventricle, *NC* non-compacted, *C* compacted

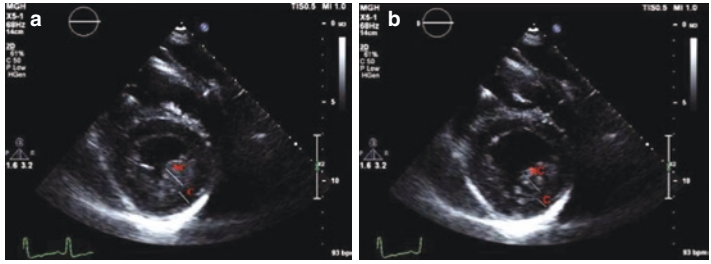


FIGURE 29.1 Short axis on a transthoracic echocardiogram of a patient with LV non-compaction in (**a**) systole and in (**b**) diastole. Two distinct layers of myocardium are seen. C is a compacted layer and NC is a non-compacted layer. A ratio of >2:1 in systole is required for the diagnosis of LV non-compaction by Jenni criteria

Cardiac Catheterization

- Normal coronary arteries.
- Left ventriculography shows excessive trabeculations and LV dysfunction.
- Right heart catheterization may demonstrate restrictive hemodynamics [19].

Advanced Imaging Techniques

- Cardiac magnetic resonance (CMR):
  - There are two different criteria for diagnosis of LVNC on CMR (Table 29.3).
  - Normal myocardium may contain hypertrabeculation in one or two segments [22].
  - Two-layered myocardium with non-compacted to compacted (NC/C) ratio >2.3 in **diastole** measured on **long-axis** views. See Fig. 29.2. (**Systolic** measurements on **short-axis** views are used in echocardiography according to the commonly used Jenni criteria.)
  - Myocardial fibrosis or scarring can be seen on late gadolinium enhancement imaging even in asymptomatic patients with normal LV function [23, 24].

Table 29.3 Studies of cardiac magnetic resonance imaging in LVNC

Peterson [20]	Jacquier [21]
NC/C >2.3 (maximal ratio used)	Trabeculated LV mass >20% of global ventricular mass
Diastole	End-diastole
Three long-axis views: horizontal, vertical long axis, and LV outflow tract	Long-axis 2-chamber, 4-chamber, and short-axis views
Apical non-compaction common in healthy	Percentage of trabeculated LV mass was 3× higher in patients with LVNC than in those with DCM or HCM

NC noncompacted, *C* compacted, *LV* left ventricle, *DM* dilated cardiomyopathy, *HCM* hypertrophic cardiomyopathy

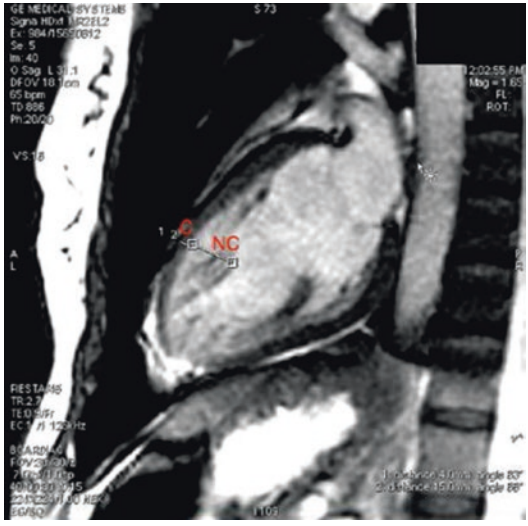


Figure 29.2 Sagittal section of the LV on MRI of a patient with LVNC. Prominent trabeculations are seen on the mid-anterior wall of the LV with two distinct layers. The ratio of non-compacted (NC) to compacted (C) ratio exceeded 2.3 in all apical segments and mid-anterior wall

- Cardiac computed tomography (CT):
  - The role of CT in diagnosis is less validated. In a small study, NC/C ratio >2.3 measured on long axis reliably distinguished LVNC patients from other cardiomyopathies [25]. In this study, LV apex was excluded from all measurements due to reports of thinner compacted myocardium in this region in normal patients.
- Positron-emission tomography and single-photon emission computerized tomography show diminished reserve of coronary blood flow in the compacted and non-compacted myocardium [1, 11].

Limitations of Current Diagnostic Criteria

- All of the echocardiographic criteria were generated retrospectively in a small number of patients, and there is poor correlation among them [26].
- In the presence of a high preload state (such as heart failure, sickle cell anemia, athletic heart, and pregnancy), the prevalence of increased LV trabeculations is unexpectedly high indicating that the current criteria may be too sensitive with a very low specificity.
- A substudy of the Multi-Ethnic Study of Atherosclerosis demonstrated that 43% of healthy patients without cardiac disease or hypertension has a N:C >2.3 on CMR in at least one region and 6% had N:C >2.3 in more than two regions.
- Among 1146 asymptomatic athletes, the prevalence of LV trabeculations was 18%, and 8% of the athletes fulfilled echocardiographic and CMR criteria for LVNC. ~1% of them had reduced systolic function (LVEF <50%) but had supranormal peak oxygen consumption and normal contractile reserve on cardiopulmonary exercise testing. There were no cardiac events in any of the athletes over a 2–3-year follow-up.
- Therefore, the current imaging criteria for LVNC appear to have low specificity when used in a population of low pretest probability of LVNC.

Management of Adult Survivors

- No guidelines are available for management of patients with LVNC.
- Asymptomatic patients with normal LV systolic function can be followed every 2–3 years with clinical assessment and echocardiography.
- Standard guideline-directed medical therapy for systolic and diastolic dysfunction with beta- blockers, ACE inhibitors, and ARBs should be utilized.
- Oral anticoagulation is recommended for left ventricular ejection fraction (LVEF) <40%, atrial fibrillation, previous history of embolic events, or known LV thrombi.
- Implantable cardioverter defibrillator should be considered for high-risk patients.
- Heart transplantation can be an option for refractory heart failure and end-stage cardiomyopathy.
- Clinical and echocardiographic screening of first-degree relatives is recommended.
- Presence of LVEF <50%, ECG abnormalities, arrhythmia, symptomatic presentation, or positive family history of cardiomyopathy poses a high risk, and these patients should be counseled to refrain from competitive sports or weightlifting.

Management of Pregnancy

- Pregnancy is associated with increased preload, which may result in an increased number of trabeculations in normal healthy patients:
  - In a prospective study, 102 healthy pregnant women were followed with TTE imaging during the first trimester, third trimester, and postpartum. Twenty-five percent of the women developed de novo trabeculations, which were more common in black, and 8% of the women fulfilled both criteria (Jenni and Chin) for diag-

nosis of LVNC. Interestingly about 75% of them should complete resolution in postpartum period and had no cardiac events over a 2-year follow-up [27].
  - Therefore, in the absence of symptoms and/or LV dysfunction, the diagnosis of LVNC during pregnancy should not be made unless resolution clearly does not occur post partum. This diagnosis should be made in conjunction with advanced imagers and cardiologists with longitudinal experience with this disease entity.

- There are no guidelines specific to patients with LVNC. However, patients with LVEF<30% and pulmonary hypertension of any cause are considered to be modified World Health Organization pregnancy risk class IV, which indicates an extremely high risk of maternal mortality or severe morbidity, and pregnancy is contraindicated [28].
- Preconception counseling should be performed in patients with LVNC regarding the genetic transmission and maternal risk of adverse cardiac events.
- Genetic evaluation for offspring may be offered.

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Chapter 30
Genetic Thoracic Aortic Diseases

Akl C. Fahed

Abbreviations

BAV	Bicuspid aortic valve
FTAAD	Familial thoracic aortic aneurysm or dissection

Epidemiology

- The prevalence of thoracic aortic aneurysms is uncertain. The diagnosis rate is ~16 cases per 100,000 men per year and ~9 cases per 100,000 women per year [1].
- The diagnosis rate is increasing due to the ageing population and the improvements and increased use of diagnostic imaging techniques.
- The epidemiology of specific genetic thoracic aortic syndromes is even less described:
  - *Marfan syndrome*: 2–3 per 10,000.
  - *Loeys-Dietz*: rare.

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  - *Vascular Ehlers-Danlos*: very rare.
  - *Bicuspid aortic valve*: BAV is the most common congenital anomaly affecting the aorta, occurring in 1–2% of the general population. Approximately 40% of patients with BAV exhibit thoracic aortic aneurysm.
  - *Turner*: Patients with Turner syndrome have increased rates of BAV, aortic coarctation, and aortic aneurysms. They often also have hypertension and other structural heart diseases.
  - *Familial thoracic aortic aneurysm dissection* (*FTAAD*): 11–19% of patients with thoracic aortic aneurysm or dissection have first-degree relatives suggesting a familial syndrome [2].
- See Table 30.1 for historical background.

Anatomic Definition and Pathophysiology

- Anatomy
  - A thoracic aortic aneurysm is a dilation of the aortic root (10%), ascending aorta (50%), aortic arch (10%), or descending aorta (40%).

Table 30.1 Historical Background

The first reported thoracic aortic disease was the case of King George II of Great Britain. He died in 1760 of pericardial tamponade due to acute ascending aortic dissection. The term "aortic dissection" however was not coined for another 40 years [13].
The French pediatrician Antoine-Bernard Marfan first described the skeletal features of the disorder in a 5.5-year-old girl named Gabrielle in 1896 [14]. Many experts do not believe Gabrielle had Marfan syndrome. He referred to the condition as dolichostenomelia (long, thin limbs) [15]. The association with ectopia lentis was not made until 1914 by Boerger [16]. Two historical figures have been suggested to possibly have Marfan syndrome, Abraham Lincoln and Niccolo Paganini.

- The normal diameter of the aorta increases with age and body surface area. Men have larger aortas than women. The normal diameter cutoffs are shown in Fig. 30.1 [2].

- Physiology
  - Thoracic aortic aneurysms occur primarily due to medial degeneration of the aortic wall.
  - Medial degeneration is characterized by loss of elastic fibers, apoptosis and dysfunction of smooth muscle fibers, increase in collagen production, and degradation of the extracellular matrix. As a result, the aortic wall becomes weak and dilates.
  - Aortic dissection occurs when the medial layer is disrupted with intramural hemorrhage that propagates and tracks within the media creating two lumens.
  - Although aortic rupture does occur, most clinical manifestations of aortic dissection are the consequence of arterial obstruction caused by false lumen propagation.

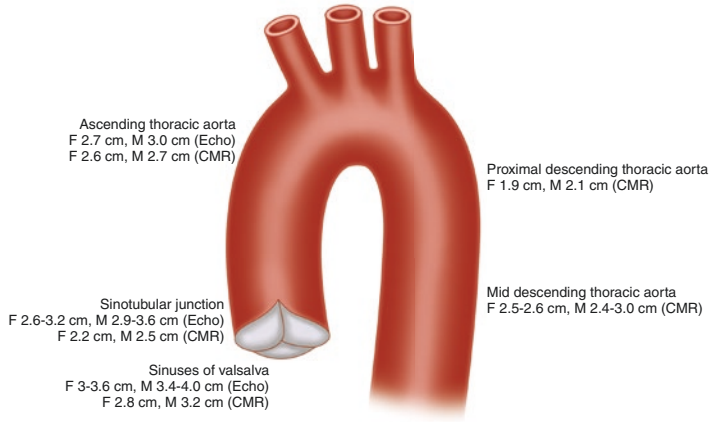

FIGURE 30.1 Normal aortic diameter. *Adopted from Goldfinger et al. JACC 2014*

- Spectrum of disease
  - While thoracic aortic disease occurs commonly in elderly due to atherosclerosis, hypertension, and inflammation, in young and middle age, it occurs due to genetic mutations that affect the connective tissue of the aortic wall resulting in the pathophysiology described above.
  - Thoracic aortic disease ranges from a small aneurysm detected incidentally or on screening and stable in size to rapidly enlarging aneurysms that require prophylactic surgery or aortic dissections which are associated with high morbidity and mortality.
  - Aortic dissections can manifest from asymptomatic to sudden cardiac death depending on anatomic location and associated malperfusion. They can be classified according to the DeBakey or Stanford systems.
  - DeBakey
    (I) Tear in the ascending aorta that propagates to the arch or beyond
    (II) Tear confined to the ascending aorta
    (III) Tear in the descending aorta distal to the left subclavian
  - Stanford
    (A) Tear in the ascending aorta with any amount of extension
    (B) Tear in the descending aorta distal to the left subclavian
- Associated defects
  - *Marfan*: ectopia lentis is highly specific to Marfan syndrome. Multiple common systemic correlates that are helpful in establishing a clinical diagnosis [3].
  - *Loeys-Dietz*: arterial tortuosity, orbital hypertelorism, bifid uvula or cleft palate, arachnodactyly, chest deformity, scoliosis, and dural ectasia [4].

  - *Vascular Ehlers-Danlos*: easy bruising, thin skin with visible veins, characteristic facial features, rupture of arteries, and gravid uterus or intestines [5].
  - *Bicuspid aortic valve*: valvular aortic stenosis or regurgitation and coarctation of the aorta.
  - *Turner*: short status, ovarian failure, and wide and short neck.
  - *Familial thoracic aortic aneurysm dissection* (*FTAAD*): bicuspid aortic valve.

- Genetics and maternal factors
  - *Marfan*: Autosomal dominant inheritance due to mutations in *FBN1* encoding fibrillin-1, a glycoprotein that inhibits transforming growth factor beta. TGF-β levels are elevated in Marfan patients leading to abnormal smooth muscle cell phenotype, increased matrix metalloproteinase (MMP) activity, and extracellular matrix breakdown in the medial layer of the ascending aorta [6].
  - *Loeys-Dietz*: Autosomal dominant inheritance due to mutations in *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, and *TGFB3* genes encoding members of the TGF-β signaling cascade [4].
  - *Vascular Ehlers-Danlos*: Mutations in *COL3A1* encoding type III procollagen [5].
  - *Bicuspid aortic valve*: Most BAV occurs sporadically, and there is substantial genetic heterogeneity. Several genetic syndromes include BAV such as Turner (monosomy X), Loeys-Dietz (*TGFBR1* and *TGFBR2*), DiGeorge (22q11.2 deletion), FTAAD (*ACTA2*), Andersen-Tawil (*KNJ2*), Larsen (*FLNB*), and Kabuki (*KMT2D* and *KDM6A*) [7].
  - *Turner*: Absence of one X chromosome in a phenotypic female (45X).
  - *Familial thoracic aortic aneurysm dissection* (*FTAAD*): Mutations in *TGFBR2*, *MYH11* (smooth muscle cell-specific myosin heavy chain), *ACTA2* (smooth muscle-specific alpha actin), *MYLK* (myosin light chain kinase), and *PRKG1* (protein kinase, cGMP-dependent, type I) [6].

Diagnostics

Clinical Presentation in Adults

- When aortic aneurysm is the only feature, the large majority are discovered incidentally on routine chest X-ray, CT, or echocardiogram because aortic symptoms are uncommon and physical exam findings are limited (e.g. aortic regurgitation murmur). Also many go undetected until they dissect or rupture.
- More commonly in syndromic/genetic cases such as Marfan, Loeys-Dietz, vascular Ehlers-Danlos, or Turner syndrome, it is the extra-aortic manifestations of the syndrome or the familial occurrence that prompt screening for aortic disease.

Physical Exam

- Diastolic murmur of aortic regurgitation may be present.
- External features of the disease are notable on physical exam as described in "associated defects" above.

Electrocardiography

- There are no specific ECG features in genetic thoracic aortic disease. However, there are reports of higher incidence of ventricular dysrhythmias, prolonged AV conduction, and QT prolongation in Marfan syndrome [8, 9].

Chest X-Ray

- Chest X-ray can show mediastinal widening or abnormal aortic contour but has a low sensitivity and is often insufficient to rule out the disease.

- In acute aortic dissection, mediastinal widening and abnormal aortic contour have a sensitivity of 64 and 71%, respectively [10].
- Bony skeletal manifestations such as *pectus carinatum* could be seen.

Echocardiography

- Transthoracic echocardiography (TTE) is used routinely to determine the size of the ascending aorta and evaluate for any associated malformation, especially aortic valve disease.
- Evaluation of aortic aneurysm size is of key importance since it determines management. Aortic size could be evaluated by echocardiography or advanced imaging techniques (CT or MRI).
- TTE is often limited in that it can visualize only the proximal several centimeters of the ascending aorta and as such miss aneurysms of the midportion of the ascending aorta.
- TTE may also underestimate the maximal diameter of the ascending aortic aneurysm if the aneurysm is larger in the section not captured on echocardiogram.

Cardiac Catheterization

- While ascending aortography can provide excellent assessment of the proximal aortic root, it is only rarely used in the evaluation of genetic thoracic aortic disease, since noninvasive testing (echo, CT, and MRI) is usually sufficient.
- Prior to surgical correction, coronary angiography might be necessary to rule out coronary artery disease.
- Prior knowledge of the aneurysm anatomy and careful manipulation of coronary catheters can help prevent iatrogenic dissection.

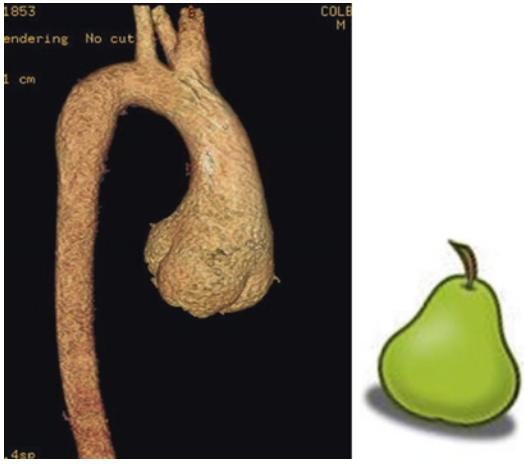

FIGURE 30.2 3D reconstructed computer tomography showing a typical ascending aortic aneurysm in a patient with Marfan Syndrome with effacement of the sinotubular junction. The appearance is similar to a pear in the aortic root

Advanced Imaging Techniques

- CT and MRI are should be used to evaluate and follow-up thoracic aortic aneurysm size (Fig. 30.2).
- MRI is longer and more time consuming but has the advantage of avoiding radiation especially in patients who require annual or biennial imaging for surveillance.
- Limitations of CT and MRI include motion artifacts which affect resolution as well as an inability to evaluate concomitant aortic valve disease.

Management of Adult Survivors

- Management requires a multidisciplinary team including primary care doctors, geneticists, cardiovascular specialists, imaging specialists, ophthalmologists, and orthopedic specialists.

- After making the diagnosis, the cornerstone of management is medical therapy and counseling and regular follow-up with imaging to prevent dissection and determine the optimal timing for surgical correction (see Table 30.2).
- All Marfan patients are treated with beta-blockers and/or angiotensin receptor blocker, usually losartan [11].
- Reduced hypertension and pulsatile wall flow may reduce aortic root growth and suppress TGF-β signaling which is responsible for complications in Marfan syndrome.
- In Loeys-Dietz syndrome, angiotensin receptor blockers ± beta-blocker.
- In Ehlers-Danlos syndrome, the benefit of medical therapy is unclear, although most experts endorse the use of beta-blockade for prevention of vascular events.
- Interval screening of aortic aneurysm size varies by disease, size, and rate of increase (Table 30.3).
- The recommendations for referral to surgery vary by disease and aortic root diameter (Table 30.2).

Table 30.2 Threshold for surgical referral

Patient	Aortic root diameter
Not genetic	≥5.5 cm ascending aorta or growth >0.5 cm/year
Marfan syndrome	≥5 cm ascending aorta, unless family history of dissection at <5 cm, or growth >0.5 cm/year or ≥4 cm and contemplating pregnancy
Loeys-Dietz syndrome	≥4.2 cm by transesophageal echocardiogram (internal diameter) or ≥4.4–4.6 cm by CT or CMR (external diameter)
Bicuspid aortic valve	≥5 cm
Patient undergoing aortic valve surgery	≥4.5 cm

Table 30.3 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines 2010 [17]

Recommendations for genetic thoracic aortic disease	
Class I	Class IIa
1. An echocardiogram is recommended at the time of diagnosis of Marfan syndrome to determine the aortic root and ascending aortic diameters and 6 months thereafter to determine the rate of enlargement of the aorta (*level of evidence: C*)	1. It is reasonable to consider surgical repair of the aorta in all adult patients with Loeys-Dietz syndrome or a confirmed *TGFBR1* or *TGFBR2* mutation and an aortic diameter of 4.2 cm or greater by transesophageal echocardiogram (internal diameter) or 4.4–4.6 cm or greater by computed tomographic imaging and/or magnetic resonance imaging (external diameter) (*level of evidence: C*)
2. Annual imaging is recommended for patients with Marfan syndrome if stability of the aortic diameter is documented. If the maximal aortic diameter is 4.5 cm or greater, or if the aortic diameter shows significant growth from baseline, more frequent imaging should be considered (*level of evidence: C*)	2. For women with Marfan syndrome contemplating pregnancy, it is reasonable to prophylactically replace the aortic root and ascending aorta if the diameter exceeds 4.0 cm (*level of evidence: C*)
3. Patients with Loeys-Dietz syndrome or a confirmed genetic mutation known to predispose to aortic aneurysms and aortic dissections (*TGFBR1*, *TGFBR2*, *FBN1*, *ACTA2*, or *MYH11*) should undergo complete aortic imaging at initial diagnosis and 6 months thereafter to establish if enlargement is occurring (*Level of Evidence: C*)	3. If the maximal cross-sectional area in square centimeters of the ascending aorta or root divided by the patient's height in meters exceeds a ratio of 10, surgical repair is reasonable because shorter patients have dissection at a smaller size, and 15% of patients with Marfan syndrome have dissection at a size less than 5.0 cm (*level of evidence: C*)
4. Patients with Loeys-Dietz syndrome should have yearly magnetic resonance imaging from the cerebrovascular circulation to the pelvis (*level of evidence: B*)	Class IIb
5. Patients with Turner syndrome should undergo imaging of the heart and aorta for evidence of bicuspid aortic valve, coarctation of the aorta, or dilatation of the ascending thoracic aorta. If initial imaging is normal and there are no risk factors for aortic dissection, repeat imaging should be performed every 5–10 years or if otherwise clinically indicated. If abnormalities exist, annual imaging or follow-up imaging should be done (*level of evidence: C*)	1. In patients with Turner syndrome with additional risk factors, including bicuspid aortic valve, coarctation of the aorta, and/or hypertension, and in patients who attempt to become pregnant or who become pregnant, it may be reasonable to perform imaging of the heart and aorta to help determine the risk of aortic dissection (*level of evidence: C*)

Recommendations for familial thoracic aortic aneurysms and dissections

Class I

1. Aortic imaging is recommended for first-degree relatives of patients with thoracic aortic aneurysm and/or dissection to identify those with asymptomatic disease (*level of evidence: B*)
2. If the mutant gene (*FBN1*, *TGFBR1*, *TGFBR2*, *COL3A1, ACTA2, MYH11*) associated with aortic aneurysm and/or dissection is identified in a patient, first-degree relatives should undergo counseling and testing. Then, only the relatives with the genetic mutation should undergo aortic imaging (*level of evidence: C*)

Class IIb

1. Sequencing of other genes known to cause familial thoracic aortic aneurysms and/or dissection (*TGFBR1*, *TGFBR2*, *MYH11*) may be considered in patients with a family history and clinical features associated with mutations in these genes (*level of evidence: B*)
2. If one or more first-degree relatives of a patient with known thoracic aortic aneurysm and/or dissection are found to have thoracic aortic dilatation, aneurysm, or dissection, then referral to a geneticist may be considered (*level of evidence: C*)

Class IIa

1. If one or more first-degree relatives of a patient with known thoracic aortic aneurysm and/or dissection are found to have thoracic aortic dilatation, aneurysm, or dissection, then imaging of second-degree relatives is reasonable (*level of evidence: B*)
2. Sequencing of the *ACTA2* gene is reasonable in patients with a family history of thoracic aortic aneurysms and/or dissections to determine if *ACTA2* mutations are responsible for the inherited predisposition (*level of evidence: B*)

- Patients should be counseled against competitive sports and isometric exercise which can increase the risk of dissection.
- Lipid levels should be optimized, and patients should be assisted with smoking cessation and avoidance of any stimulant drugs such as cocaine.
- Screening of first-degree relatives clinically and genetically is recommended depending on the condition and gene (Table 30.3).

Management of Pregnancy

- Pregnancy and the peripartum period impose a high risk of dissection.
- The highest incidence of dissection is in the third trimester (50%) followed by the peripartum period (33%).
- Women with known thoracic aortic disease who desire to be pregnant should be counseled regarding the risk of dissection and the heritable nature of the disease.
- During pregnancy, strict blood pressure control and echocardiogram monitoring to detect aortic expansion until birth are recommended.
- Prophylactic surgery during pregnancy may be considered if progressive aortic dilation and/or advancing aortic valve regurgitation are documented.
- Pregnant women with aortic aneurysms should be delivered in centers where cardiothoracic surgery is available.
- If there is significant aortic enlargement, dissection, or severe aortic valve regurgitation, delivery via cesarean section is recommended.
- Marfan syndrome with aortic dilation >4.0–4.5 cm is a contraindication to pregnancy.
- Type B dissections may still occur during pregnancy after surgical repair of ascending aneurysms [12].

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Part VII
Coronary Abnormalities

Chapter 31
Congenital Coronary Anomalies

Ada C. Stefanescu Schmidt

Epidemiology

- It is important to distinguish the four broad categories of congenital coronary anomalies:
  - Anomalous origin of the right (ARCAPA) or left coronary from the pulmonary artery (ALCAPA):

    As deoxygenated blood supplies the coronary circulation, these generally present in infancy.
    Rare, with a birth incidence of ALCAPA estimated at 0.02% in two European birth cohort studies [1, 2]; ARCAPA is even more rarely seen.
  - Coronary origin from the opposite sinus:

    Estimated prevalence ranges from 0.05% [2] to 0.2% in a population of children referred for an echocardiogram [3], to 0.5–1% in adults referred for coronary angiogram [4], and as high as 1.7% when including all benign coronary anomalies detected in adults referred for coronary CT [5].

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- Coronary fistulae.
- Normal variations originating in the same aortic cusp, including the separate ostia of the left anterior descending artery (LAD) and left circumflex artery (LCx), are common (not discussed below).

Anomalous Origin of the Right or Left Coronary from the Pulmonary Artery (ARCAPA and ALCAPA)

Anatomic Definition and Pathophysiology

- Anatomy:
  - Defects in septation of the great vessels lead to ARCAPA or ALCAPA
- Physiology:
  - The lower oxygen concentration in the venous blood of the pulmonary artery leads to demand ischemia during exertion in infancy (such as feeding).
  - As the pulmonary vascular resistance decreases in the first few months of age, coronary steal (blood flow from the coronary into the pulmonary artery) causes further ischemia and may cause myocardial infarction, resulting in early left ventricular dysfunction and mitral regurgitation.
  - The presentation of ALCAPA is most common in infancy, with irritability, poor feeding, and gradual presentation of heart failure; this was first described by Edward Bland, Paul Dudley White, and Joseph Garland in 1933 and termed the "Bland-White-Garland" syndrome. The symptoms can mimic infantile colic; presentation with sudden cardiac death is also unfortunately common.
- Spectrum of disease:
  - Coronary fistula may exist between the right coronary artery (RCA) and LAD or LCx, which may improve perfusion initially but lead to more severe ischemia if

there is coronary steal (as a larger myocardial territory is at risk).

- Associated defects:
  - Conotruncal defects such as transposition of the great arteries, Tetralogy of Fallot, or ventricular or atrial septal defects
- Treatment in infancy:
  - Surgical repair, by the creation of an aortopulmonary window and tunnel from the aorta to the left coronary ostium through the posterior PA, is termed the Takeuchi procedure; it has increased pediatric survival and has favorable long-term outcomes [6].
  - Direct coronary surgery is now preferred by either reimplantation of the left coronary button in the aorta or a bypass graft procedure.

Diagnostics

Clinical Presentation in Adults

- Presentation in adulthood is quite common [7]; adults may present with angina, heart failure, ventricular arrhythmias, or sudden cardiac death.
- Adults who had surgical repair in childhood, either with the Takeuchi procedure or coronary reimplantation, may present with ischemic symptoms from stenosis at the surgical suture site.
- Pulmonary valve regurgitation may be seen as a late complication of the Takeuchi repair [6].
- Adult patients who have undergone surgical intervention in childhood may have persistent left ventricular wall motion abnormalities or recurrent mitral regurgitation.

Physical Exam

- May include signs of heart failure, ischemic or functional mitral valve regurgitation, and pulmonary edema.

- A continuous flow bruit from large coronary collaterals may be heard anteriorly.

Electrocardiography

- Anterior Q waves indicating old anterior myocardial infarction (ALCAPA)
- Inferior Q waves (ARCAPA)

Chest X-Ray

- Cardiomegaly and pulmonary edema

Imaging

- Coronary origins are usually well visualized by echocardiography in children and adolescents; ventricular ejection fraction and mitral regurgitation should also be assessed. Cardiac catheterization and coronary CTA are useful to image the coronary anatomy and assess for collaterals and coronary fistulae. CTA Coronary CTA is particularly useful in patients who have had the Takeuchi procedure to visualize the complex anatomy.

Anomalous Coronary Artery Origin from the Opposite Sinus

Anatomic Definition and Pathophysiology

1. Anatomy (Fig. 31.1):
   (a) The most significant types of anomalous coronaries arising from the opposite sinus are left main or LAD arising from the right sinus and RCA arising from the left coronary sinus [8]. There are four anatomic variants that arise from the opposite sinus:

- *Prepulmonic course*: Course anterior to the RVOT. Rare and benign; typically associated with conotruncal defects (Fig. 31.1a).
- *Interarterial course*: Course between the aorta and the pulmonary artery, above the pulmonic annulus.
  - In addition to the abnormal course, these arteries often have a slit-like opening and proximal **intramural** course within the aortic wall (Fig. 31.1b); increased length of the intramural course correlates with worse outcomes.
- *Subpulmonic course*: Course within the conal septum which does not have an intramural course proximally (**also termed intraseptal** or **intraconal** course); these tend to have a more benign long-term prognosis (Fig. 31.1c).
- *Retroaortic course*: Course posterior to the aorta and thus away from the pulmonary artery. Typically anomalous LCx arising from the right coronary sinus, typically not clinically significant (Fig. 31.1d).

2. Physiology:

   (a) The main abnormalities linked with anomalous coronaries arising from the opposite sinus are due to the abnormal (slit-like, narrowed, angled) ostia, intramural aortic course, or interarterial course with compression between the aorta and pulmonary artery with great vessel torsion during systole.

3. Spectrum of disease:

   (a) High-risk features include [9]:

   - Interarterial course with intramural course and slit-like (oblique) or hypoplastic coronary ostium
   - Symptoms with presentation before age 50
   - Personal history of exertional syncope, ventricular tachycardia, or sudden cardiac death
   - Presence of ischemia in the territory of the anomalous coronary during stress testing

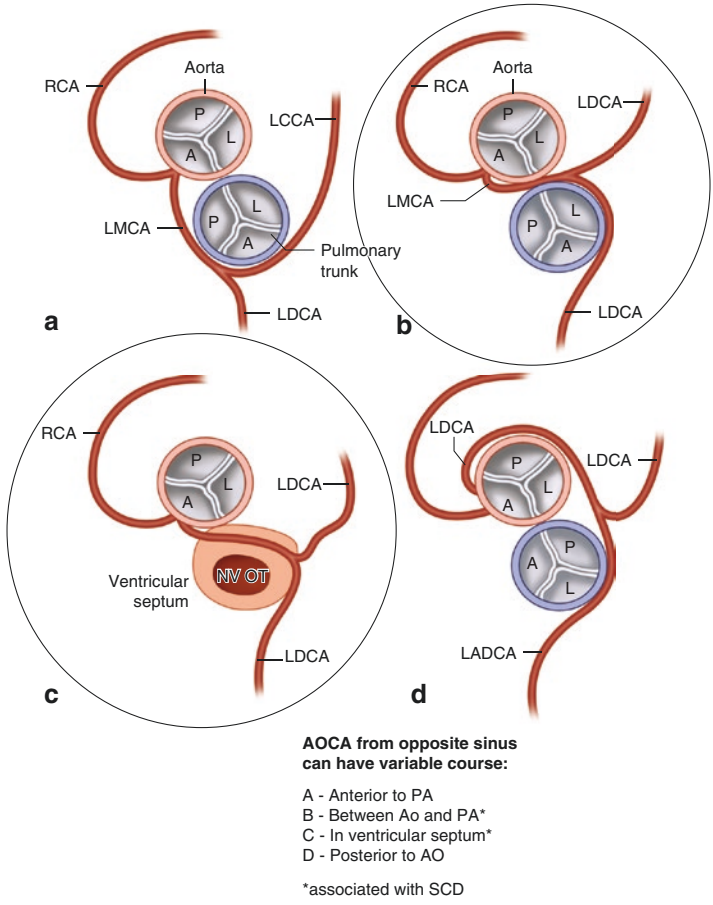

FIGURE 31.1

4. Associated defects:

   (a) May be seen in association with many congenital defects including bicuspid aortic valve disease [10, 11], rarely with hypertrophic cardiomyopathy [12].

(b) Anomalous origin of the LAD from the RCA with a course anterior to the pulmonary artery is seen in 3% of patients with Tetralogy of Fallot [13] and must be ruled out prior to surgery involving the right ventricular outflow tract, as it would be at risk of being transected during the initial right ventriculotomy for closure of a ventricular septal defect or resection of subpulmonic stenosis.
(c) Ostial obstruction or dysplasia is seen in patients with supravalvar aortic stenosis, who should be screened every 1–2 years for myocardial ischemia (Class I, LOE C) [14].

Diagnostics

Clinical Presentation in Adults

- While coronary anomalies are rare, they are a common cause of sudden cardiac death in adolescents and young athletes.
- Presentation with angina or myocardial infarction is overall less common than presentation with atypical chest pain or dyspnea [5, 15].
- Patients may have an initial negative ischemic workup including stress testing. Importantly young patients often have a higher exercise capacity than is tested on a standard Bruce treadmill test, and the symptoms they may have during amateur or professional sports may not be reproduced in the lab unless specifically sought. Cardiopulmonary exercise testing to maximal exertion may help elicit symptoms, ischemia, or arrhythmia.
- In addition, episodes of sudden cardiac death may have multiple contributing factors including chronic episodes of ischemia leading to myocardial scarring or fibrosis which may be arrhythmogenic, especially with adrenergic stimulus, electrolyte abnormalities during severe exercise, high blood pressure, or elevated afterload.

Physical Exam

- Often normal; look for signs of an associated congenital defect or other cardiac or non-cardiac causes of chest pain.

Electrocardiography

- Assess for Q waves indicating an old myocardial infarction or ST-T wave abnormalities indicating ischemia.

Chest X-Ray

- Usually normal.

Echocardiography

- A parasternal short-axis view can identify both the coronary ostia and is usually diagnostic, especially in adolescents and young, fit adults.
- Left ventricular function and aortic valve morphology should be assessed.

Cardiac Catheterization

- Anomalous coronary arteries are difficult to visualize and engage on coronary catheterization, thus requiring more IV dye and longer fluoroscopy time, making it a suboptimal first diagnostic test (though biplanar imaging may reduce needs to dye load and fluoroscopy time); if coronary origins are difficult to identify, initial engagements would move to cardiac CTA to define origins and course.
- Pulmonary artery catheter placement during coronary evaluation may be helpful to determine coronary course.

Advanced Imaging Techniques

- Coronary CTA is the test of choice for anatomic diagnosis as the origin, intramural course, interarterial course, and presence of calcification or atherosclerosis can all be delineated [14] (Fig. 31.2).
- Anomalous coronary ostial characteristics should be evaluated by a cardiac radiologist familiar with the various forms (determining intramural course vs. intraseptal course is a critical distinction and can be challenging).

Management

- If no high-risk features, lifestyle modification to prevent future atherosclerosis. Limited data for beta-blockers.
- If ≥1 high-risk feature, beta-blockade could be considered (limited data available in the literature); multidisciplinary discussion and consideration of surgical intervention in select cases with experienced surgeons.
- Current guidelines are nonspecific and extrapolated from limited outcomes data.[11] Our group recommends multidisciplinary review of each cases and surgical revascularization in the below scenarios:

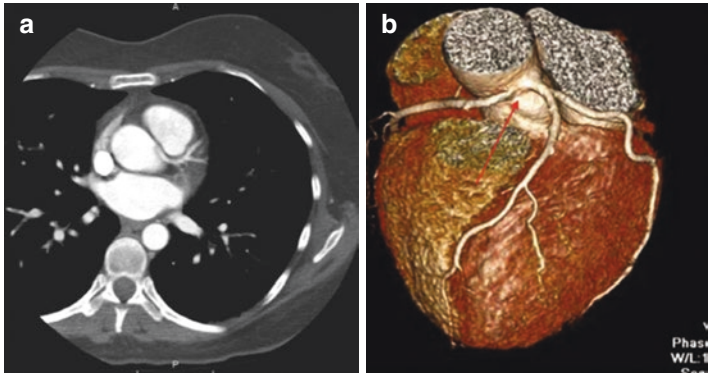

Figure 31.2

- Anomalous left main with interarterial course (between the aorta and PA) regardless of symptoms or age at presentation:

  Of note patients with anomalous left main coronary arteries with subpulmonic course without obstructive atherosclerosis may not need surgical revision and should be referred to an ACHD center for careful evaluation of imaging.

- Anomalous RCA with interarterial and intramural proximal course with history of VT or aborted SCD, syncope concerning for cardiac etiology, evidence of inferior ischemia (high-risk feature), without evidence of ischemia by stress testing but symptoms not otherwise explained, or young patients who cannot comply with exercise restriction (in certain well-repaired cases, exercise restriction may be lifted post intervention)

• Coronary artery unroofing (Fig. 31.3a) or creation of a neo-ostium (Fig. 31.3b), in experienced hands, has a very high success rate and very low rate of complications [15] and is preferred to coronary bypass graft (which carries a high rate of graft failure due to continued perfusion through the native ostium).

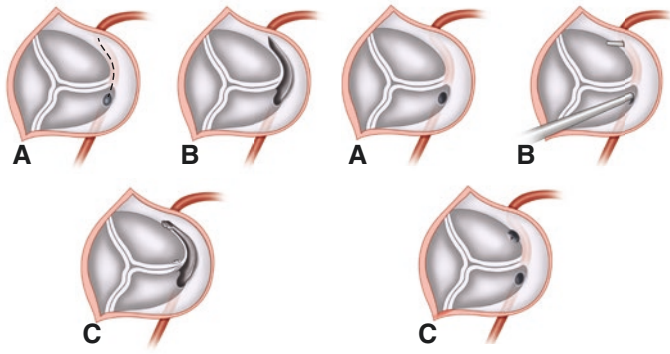

Figure 31.3

  - Unroofing carries small risk of aortic cusp prolapse and aortic insufficiency.

- There may be a residual risk of ventricular arrhythmia and sudden cardiac death despite anatomic repair of the anomalous coronary in patients with prior episodes of ischemia and myocardial scar formation or even unrecognized myocardial fibrosis.

Congenital Coronary Arteriovenous Fistula

Anatomic Definition and Pathophysiology

- Anatomy:
  - Fistula between the coronary arteries and coronary veins, pulmonary artery or veins, or endocardium (coronary-cameral fistula).

Diagnostics

Clinical Presentation in Adults

- Often asymptomatic and discovered incidentally during coronary angiogram, echocardiogram, or CTA performed for another indication.
- May present with thrombosis leading to myocardial infarction in downstream territory.
- If large, may lead to high-output heart failure and present with dyspnea, fatigue, cardiomegaly (particularly in coronary-cameral fistula entering the right heart).
- Rarely present with coronary ischemia due to steal phenomenon.
- Endarteritis is rare.

Physical Exam

- Usually asymptomatic; if large, continuous precordial bruit may be heard.

Electrocardiography

- May have signs of old myocardial infarction.

Cardiac Catheterization

- Modality of choice for diagnosis and treatment (Fig. 31.4).

Advanced Imaging Techniques

- May be well visualized on coronary CTA, especially if concerning for layering thrombus.
- Larger fistulae are generally very tortuous, and their confluence makes it difficult to ascertain size and path.

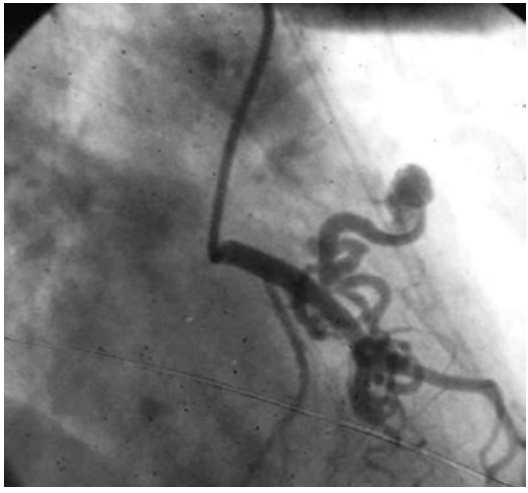

Figure 31.4

Management

- Small fistula does not require intervention and can be observed every 3–5 years.
- If large or symptomatic, or concerning for future thrombosis, percutaneous coiling is the preferred approach [14].

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Chapter 32
Kawasaki Disease

Yamini Krishnamurthy

Abbreviations

CMR	Cardiac magnetic resonance imaging
CTA	Computer tomography angiography
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease
LAD	Left anterior descending artery
LCX	Left circumflex artery
LMCA	Left main coronary artery
MRA	Magnetic resonance angiography
PDA	Posterior descending artery
RCA	Right coronary artery

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Epidemiology

- Kawasaki disease (KD) is more prevalent in Japan with an incidence of 264.8 per 100,000 children between 0 and 4 years old in 2012 [1]. In the United States, KD is much less common, with an incidence of 20.5 per 100,000 children <5 years of age in 2006 [2].
- KD is more common in Americans of Asian and Pacific Islander descent followed by non-Hispanic African American, Hispanic, and Caucasian children [2].
- KD is the most common cause of acquired heart disease in children.
- In the United States, KD is more common during the winter and early spring, with a male predominance of ~1.5× [3].
- For historical background, see Table 32.1.

Anatomic Definition and Pathophysiology

1. Anatomy:
   (a) KD may affect multiple regions of the heart, including the pericardium, myocardium, endocardium, valves, and coronary arteries.
   (b) Coronary arteries may become diffusely dilated or develop aneurysms.
   (c) Coronary artery aneurysms resulting from KD occur predominantly in the proximal segments and at bifurcations of coronary arteries and often involve multiple vessels. Common sites include the proximal left ante-

Table 32.1 Historical background

First described in Japan in 1967 by Tomisaku Kawasaki, though Kawasaki saw his first case in January 1961. In 1966, he reported definite cardiac involvement with patients who had abnormalities detected by electrocardiogram [4]. Kawasaki published the first English language report of patients in 1974.

rior descending artery (LAD), proximal right coronary artery (RCA), left main coronary artery (LMCA), left circumflex artery (LCX), distal RCA, and the junction between the RCA and posterior descending artery (PDA) [5].

2. Physiology and spectrum of disease:

   (a) KD is an acute, self-limited vasculitis of childhood with potential cardiac sequelae.
   (b) The cause of KD is unknown but suspected to be an immune response to an infectious etiology in conjunction with genetic susceptibilities. This is supported by incidence patterns related to geography, ethnicity, sex, age, and season [6].
   (c) Diagnostic criteria for complete KD include ≥5 days of fever and ≥4 of the 5 principal clinical features. Diagnostic criteria for incomplete KD include ≥5 days of fever and 2 of 3 of the principal clinical features [4]. The principal clinical features are:

      - Changes in extremities
        - Acute: erythema of the palms, soles; edema of the hands, feet
        - Subacute: periungual peeling of fingers, toes
      - Polymorphous exanthema
      - Bilateral bulbar conjunctival injection without exudate
      - Changes in the lips and oral cavity (erythema, cracked lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosae)
      - Cervical lymphadenopathy

   (d) In the absence of appropriate therapy (usually intravenous immunoglobulin [IVIG] and aspirin), symptoms may persist for 3–4 weeks. With IVIG, the fever usually resolves within 2 days.
   (e) Coronary artery aneurysms are thought to develop in ~15–25% of untreated cases. The incidence of aneurysms

is reduced (~5%) in patients who receive appropriate and timely treatment.

(f) Coronary artery lesions are marked by endothelial cell edema, proliferation, necrosis, and adhesion of polymorphonuclear leukocytes to endothelium. This is accompanied by increased levels of circulating cytokines, CD4 and CD8 cells, and circulating immunocomplexes. Enzymes upregulated during this inflammatory process, including matrix metalloproteinases, may affect arterial wall integrity and may be important for aneurysm formation as well as artery wall remodeling leading to stenosis [7].

(g) Approximately one-half to two-thirds of aneurysms resolve spontaneously. The likelihood of aneurysmal resolution appears higher in smaller lesions. The worst prognosis occurs with aneurysms with a diameter ≥8 mm, as they frequently develop stenotic lesions at the proximal or distal ends of the aneurysm. Thrombosis develops due to both the sluggish flow through the large aneurysm and stenosis at either ends of the aneurysm [8].

(h) Mortality related to KD results from cardiac sequelae including myocardial infarction due to thrombotic occlusion of aneurysm or stenosis and/or sudden cardiac death.

3. Associated defects:

(a) Aneurysms may form in other arteries, most often in the renal, iliac, or axillary.

(b) Myocarditis has been seen early in the KD course, though myocardial function typically improves after IVIG therapy.

(c) Valvular regurgitation such as mitral or aortic regurgitation may result from myocardial infarction or valvulitis.

4. Genetics and maternal factors:

(a) No specific gene is associated with KD.

(b) Positive family history is noted in ~1% patients affected with KD. The risk of occurrence in siblings is 2.1%, which is a relative risk of tenfold. The risk of occurrence in twins is ~13%. Higher rates in siblings and twins of affected patients suggest a possible role for genetic predisposition [9].

Diagnostics

Clinical Presentation in Adults

- The initial presentation of KD occurs predominantly in children and rarely in adults.
- For adults with missed KD, clinical presentation may be symptoms of coronary artery disease or myocardial infarction caused by thrombus formation in the aneurysmal segment of the coronary artery.

Physical Exam

- During the acute phase, if myocardial contractility is depressed, a gallop may be heard on auscultation. Additionally, a new murmur may be notable if valvular regurgitation is present.

Electrocardiography

- During the acute systemic vasculitis phase, electrocardiography may show arrhythmia, prolonged PR and/or QT intervals, or ST and T wave changes.
- If the initial clinical presentation includes myocardial ischemia, electrocardiographic signs of infarction may be present.

Echocardiography

- Because it is noninvasive and has a high sensitivity and specificity for the detection of abnormalities of the proximal LMCA and RCA in young children, echocardiography is the ideal imaging modality for screening (Fig. 32.1) [5].
- Echocardiography is performed to determine baseline coronary artery dimensions and anatomy, myocardial function, and valvular function.
- An echocardiogram is typically recommended at diagnosis, 2 weeks after disease onset, and 6 weeks after disease onset. Further follow-up studies are indicated as clinically needed.
- Definition of abnormalities:
  - Ectasia: Diffuse dilatation of a vessel without a segmental aneurysm. To classify as dilated, the coronary artery dimension indexed to body surface area should have a z-score > 2 (two standard deviations above the mean).

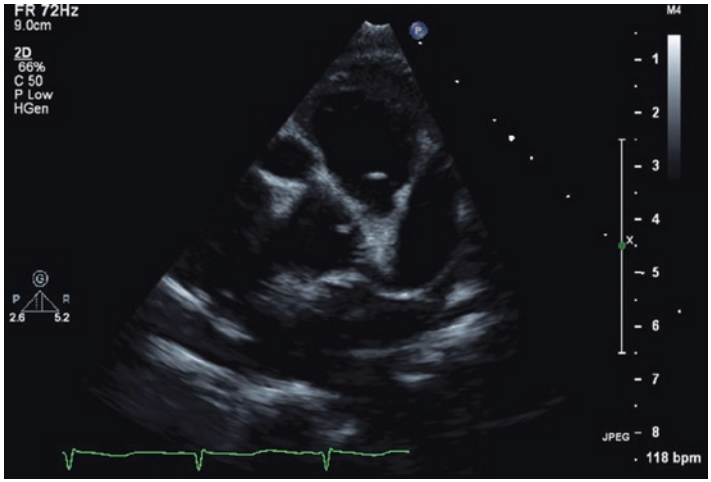

Figure 32.1 2-D echocardiogram of a 19-month-old male with Kawasaki disease demonstrating 0.91 cm (*z*-score 28.88, normal range: 0.1–0.2) dilation of left anterior descending artery as well as dilation of the proximal RCA

- Aneurysm: Coronary artery dilatation (dimension indexed to body surface area z-score > 2), involving <50% of the total length of the vessel. Aneurysms are considered saccular if their length and diameter are similar and fusiform if they exhibit symmetric dilatation with gradual proximal and distal tapering [5].

  Small aneurysm: <5 mm diameter
  Medium aneurysm: 5–8 mm diameter
  Giant aneurysm: >8 mm diameter

- 2-D imaging should be performed with the highest frequency transducer possible. Parasternal short- and long-axis views are most commonly used, though multiple imaging planes and transducer positions may be required for optimal visualization of all major coronary segments.

Cardiac Catheterization

- Coronary angiography is better able to delineate coronary artery anatomy compared to echocardiography, making it possible to detect stenosis or occlusion as well as the extent of collateral development (Fig. 32.2).
- In children with small lesions demonstrated by echocardiography, angiography unlikely provides additional information and is not recommended. Adults and patients with more complex lesions may benefit from coronary angiography 6–12 months after the onset of illness. Indications for angiography during follow-up intervals include [5]:
  - Changes to echocardiographic imaging of coronary arteries
  - Ventricular regional wall motion abnormalities
  - Clinical signs or noninvasive studies indicating myocardial ischemia
  - Failure to image distal coronary arteries in a patient in whom large proximal aneurysms have regressed
  - Previous surgical or catheter revascularization to determine efficacy of treatment

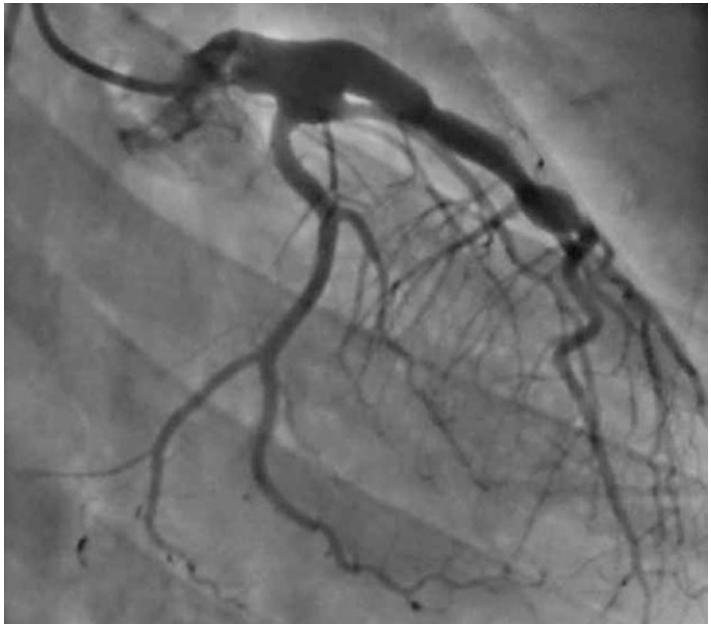

Figure 32.2 Coronary angiogram in a 25-year-old male with Kawasaki disease demonstrating aneurysmal dilation in the left main coronary artery as well as proximal and midportions of the left anterior descending artery that are aneurysmal

- Evaluation of aneurysms outside the coronary system with abdominal aortography and subclavian arteriography are recommended in patients with KD undergoing coronary arteriography for the first time [5].

Advanced Imaging Techniques

- Cardiac magnetic resonance imaging (CMR) and computed tomography angiography (CTA) can accurately delineate coronary artery aneurysms (Fig. 32.3) and peripheral aneurysms; thus these imaging modalities can play a role in diagnosis or, perhaps more importantly, non-invasive follow-up.

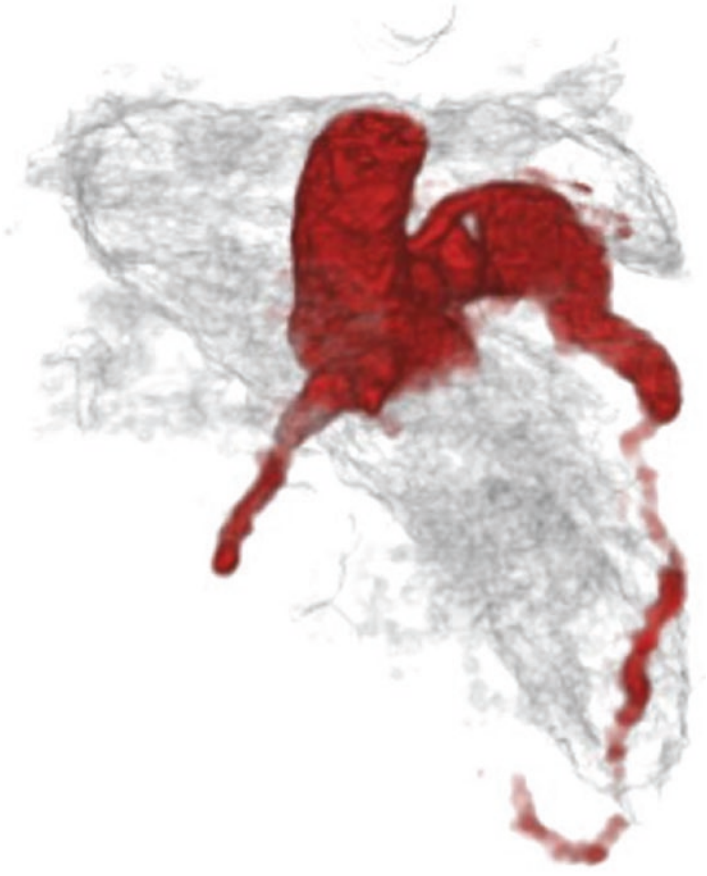

FIGURE 32.3 Cardiac CTA may noninvasively diagnose proximal coronary aneurysms

Management of Adult Survivors

Follow-Up and Management of Adult Survivors Based on Risk Stratification

- Follow-up and management of adult survivors are based on risk stratification. Risk level depends on the degree of

coronary artery involvement, which dictates frequency of follow-up, further imaging and testing, as well as indicated therapy [5] (Table 32.2).

- Antiplatelet therapy and anticoagulation are recommended for patients with large or giant aneurysms. Novel anticoagulants have not been studied in this setting but in some cases may be considered.

Catheter-Based or Surgical Intervention

- Catheter-based intervention:
  - Catheter interventions include balloon angioplasty and stent placement. For large or complex aneurysms, covered stents may be necessary.
  - Indications for catheter intervention [10]:

    Anginal symptoms with reversible ischemia on stress test

    Patients without ischemia but with >75% stenosis in LAD

  - Contraindications for catheter intervention:

    Patients who have vessels with multiple, ostial, or long-segment lesions

- Surgical interventions:
  - Excision or plication of coronary artery aneurysms has not been successful. Coronary artery bypass grafting is the primary surgical intervention of choice.
  - Indications for surgical revascularization:

    Severe occlusion of the main trunk of the LMCA
    Severe occlusion of >1 major coronary artery
    Severe occlusion in the proximal segment of the LD
    Collateral coronary arteries in jeopardy
- Cardiac transplantation:
  - Should be considered in patients with severe, irreversible myocardial dysfunction and coronary lesions for which interventional catheterization procedures or coronary artery bypass grafting is not feasible.

Management of Pregnancy

- Reproductive counseling is recommended in patients with risk level IV and V [5] (Table 32.2).

Table 32.2 ACC/AHA guidelines 2004 [5]

Risk level	Pharmacotherapy	Physical activity	Follow-up and diagnostic testing	Invasive testing
I (no coronary artery changes at any stage of illness)	None beyond 6–8 weeks	No restrictions beyond 6–8 weeks	Cardiovascular risk assessment and counseling at 5-year intervals	None
II (transient coronary artery ectasia, disappears within 1st 6–8 weeks)	None beyond 6–8 weeks	No restrictions beyond 6–8 weeks	Cardiovascular risk assessment and counseling at 3- to 5-year intervals	None
III (1 small-medium coronary artery aneurysm/ major coronary artery)	Aspirin at least until aneurysm regression is documented	<11 years old, no restriction beyond 1st 6–8 weeks; 11–20 years old, biennial stress test, evaluation with myocardial perfusion scan to guide physical activity; contact or high-impact sports discouraged for patients taking antiplatelet agents	Annual cardiology follow-up with echocardiogram and electrocardiography, combined with cardiovascular risk assessment, counseling; biennial stress test/evaluation of myocardial perfusion scan	Angiography, if noninvasive test suggests ischemia

IV (≥1 large or giant coronary artery aneurysm, or multiple complex aneurysms in same artery, without obstruction	Long-term antiplatelet therapy and warfarin (INR 2.0–2.5) or low-molecular weight heparin should be combined in giant aneurysms	Contact or high-impact sports should be avoided given the risk of bleeding; other physical activity guided by stress test/ myocardial perfusion imaging	Biannual follow-up with echocardiogram and electrocardiogram; annual stress test/ evaluation of myocardial perfusion scan	1st angiography at 6–12 months or sooner if clinically indicated; repeated angiography if noninvasive test, clinical or laboratory findings suggest ischemia
V (coronary artery obstruction	Long-term antiplatelet therapy and warfarin (INR 2.0–2.5) or low-molecular weight heparin should be combined in giant aneurysms; consider beta-blockers to reduce myocardial O_2 consumption	Contact or high-impact sports should be avoided given the risk of bleeding; other physical activities guided by stress test/ myocardial perfusion imaging	Biannual follow-up with echocardiogram and electrocardiogram; annual stress test/ evaluation of myocardial perfusion scan	Angiography recommended to address therapeutic options

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Part VIII
Principles in Adult Congenital Heart Disease

Chapter 33
Advanced Imaging in Adult Congenital Heart Disease

Sandeep Hedgire, Vinit Baliyan, and Brian Ghoshhajra

Introduction

- As the congenital heart disease (CHD) population enters adulthood, significant hemodynamic changes either due to physiologic changes or as a result of long-term complications from initial surgical repair often lead to imaging beyond the conventional echocardiography.
- The most recent societal appropriateness criteria and consensus statements consider both cardiac MRI (CMR) and cardiac CT more appropriate than invasive coronary angiography and scintigraphic evaluation in adult congenital heart disease (ACHD) also known as grown-up adult with congenital heart disease [1–3].
- Increased availability and technical advances in both ECG-cardiac gated CT and CMR can offer both a complementary and a problem-solving noninvasive assessment of complex anatomy and function [4].

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- Patient-centric and tailored image acquisition protocols are needed to fully characterize the complex anatomy and answer the diagnostic question while keeping the radiation dose in accordance with ALARA (as low as reasonably achievable) with CT and optimizing the scan time with CMR.
- This chapter will provide a concise overview of imaging protocols and highlight imaging appearances of commonly encountered complex CHD.

Imaging Techniques

Cardiac CT

- ECG-cardiac gated CT is a suitable modality that can offer precise delineation of complex anatomy, assess patency of vessels and baffles, and evaluate cardiac function [5–8].
- Image acquisition ideally should include an initial non-contrast scan which is helpful in avoiding erroneous interpretation of stigmata of prior surgeries, a common scenario in adults with CHD. This is followed by either a prospectively or retrospectively gated CTA acquisition and an optional delayed phase imaging. Suitable intravenous access by an 18G cannula is essential for optimal contrast opacification of smaller vessels like coronaries and collaterals.
- Advantages of the cardiac-gated CT include isotropic multiplanar reconstruction, excellent spatial resolution, and constantly improving temporal resolution as a result of advancement in scanner technology. Faster image acquisition times and an ability to scan patients with claustrophobia and metallic implants provide CT an edge in comparison with conventional echocardiography and CMR.
- Cardiac-gated CT is the modality of choice to noninvasively assess coronary arteries and congenital abnormalities of the coronary circulation [9].

- CT data provides the ability to use complementary post-processing and volume-rendering techniques such as maximal intensity projection (MIP), minimum intensity projection (MinIp), and volume-rendered and endoluminal views which often increase the conspicuity of imaging findings and provide supplemental information in addition to the conventional multiplanar images [10].
- CT offers these advantages at the expense of radiation exposure. Given concerns of radiation exposure, several dose reduction strategies and initiatives have evolved. It is now possible to maintain substantially lower radiation dose while imaging complex ACHD [11].

Cardiac MRI

- CMR provides excellent soft tissue resolution, precise assessment of complex anatomy, dynamic cine for assessment of cardiac function, and velocity-encoded phase contrast technique for shunt quantification without using ionizing radiation and iodinated contrast media [12–14].
- CMR is the modality of choice for estimation of ventricular volumes, ejection fraction, and myocardial mass [15]. Additionally with administration of the intravenous gadolinium-based contrast agent, a cardiac-gated magnetic resonance angiography (MRA) can be performed.
- Similar to CT/CTA technique, MRA data can be represented in various types of volume-rendering techniques.
- Presence of myocardial scar can also be assessed on the late gadolinium-enhanced (LGE) images. Identifying LGE implies poor prognostic factor in ACHD such as tetralogy of Fallot [16, 17].
- CMR is helpful not only for initial diagnosis but also for making management decisions that are often based on the precise estimation of ventricular volumes, shunt quantification, and assessment of postoperative shunts and baffles.
- Recent advances in faster gradients, image reconstruction techniques, and newer pulse sequences including 4D flow,

T1 and T2 mapping, arrhythmia rejection technique, free breathing acquisitions, and strain imaging have further strengthened utility of cardiac MRI in ACHD population [18]. The potential of these new advances is yet to be fully explored in the routine clinical studies. Limitations of CMR include claustrophobia, presence of metallic implants from prior complex cardiac surgeries, and prolonged scan duration which can be challenging in patients with heart failure given their limited breath hold capability and limited ability to lie flat for a prolonged time duration. Patients with limited renal function (glomerular filtration rate (GFR) < 30 mL min^{-1} m^{-2}) cannot receive intravenous gadolinium [1, 3, 19]; however acquisition of cine images for function, T2-weighted images for edema, and velocity-encoded phase contrast for shunt quantification or valvular assessment is not dependent on contrast media, and they can still be acquired in patients with poor renal function.

- Pacemaker-dependent patients were traditionally not subjected to CMR, but that practice is slowly evolving as our understanding of their safety in relation to magnetic field strength continues to improve [20–22].

Which Modality to Choose?

- Following a thorough assessment, the most important clinical questions should be in the center of the discussion when the choice of modality is made.
- For trainees, it may be helpful to reach out to colleagues in cardiac imaging who can help to make that decision in consideration of a benefit vs. risk tradeoff.
- A multidisciplinary approach including cardiologist with expertise in ACHD, electrophysiology, and interventional cardiology, radiologist, and cardiac surgeons is essential to make collective informed imaging and management decisions in these patients with complex CHD [23]. Although both CT and CMR can offer the assessment of complex anatomy, each one can be chosen over another depending on the individual patient scenario (Table 33.1).

Table 33.1 Choosing between CT and CMR in ACHD patients

Patient characteristics, clinical question	Choice of modality	Comment
Metallic implant/device [20, 21]	CT	CMR can be performed if the device is safe at available field strength
Claustrophobia, limited breath hold, or lying down supine capacity [24]	CT	CT offers quick image acquisition
Poor renal function (glomerular filtration rate (GFR) <30 mL min^{-1} m^{-2}) [19]	–	Both iodinated and gadolinium-based contrast agents cannot be used. Noncontrast MRI can provide more functional information than noncontrast CT
Concern for repeated radiation exposure for follow-up studies	CMR	CMR does not use ionizing radiation [25]
Anomalous coronary artery, preoperative assessment of coronary arteries	CT	CTA is the modality of choice for anomalous coronary assessment. Preoperative CTA can alleviate need for invasive coronary angiography [26, 27]
Redo sternotomy	CT	CT can offer important information about structures immediately posterior to sternal wires. MRI limited by susceptibility artifacts [28]

(continued)

Table 33.1 (continued)

Patient characteristics, clinical question	Choice of modality	Comment
Flow quantification	CMR	Velocity-encoded phase contrast cine can provide precise estimation of pulmonary-to-systemic flow ratio (Qp/Qs), valvular regurgitation velocity mapping, and estimation of stenosis gradient [19]
Myocardial perfusion imaging at rest and stress	CMR	CMR is current modality of choice for myocardial perfusion imaging at rest and stress [29]
Myocardial scar	CMR	LGE is a validated tool for assessment of myocardial scar [16, 17]

Segmental Approach

- The diagnosis of CHD is often made by clinical assessment and echocardiography.
- A cardiac imager relies on a segmental approach for identification of CHD [30]. The segmental approach involves the following steps: determining the situs, the orientation of ventricular loop, the origin and position of great vessels, and the atrioventricular and ventriculoarterial connections [31]. While the detailed discussion of each individual lesion is covered in the respective individual chapters, a schematic representation of segmental approach for diagnosis of ACHD is presented below (adapted from reference (Figs. 33.1, 33.2, and 33.3)) [32].

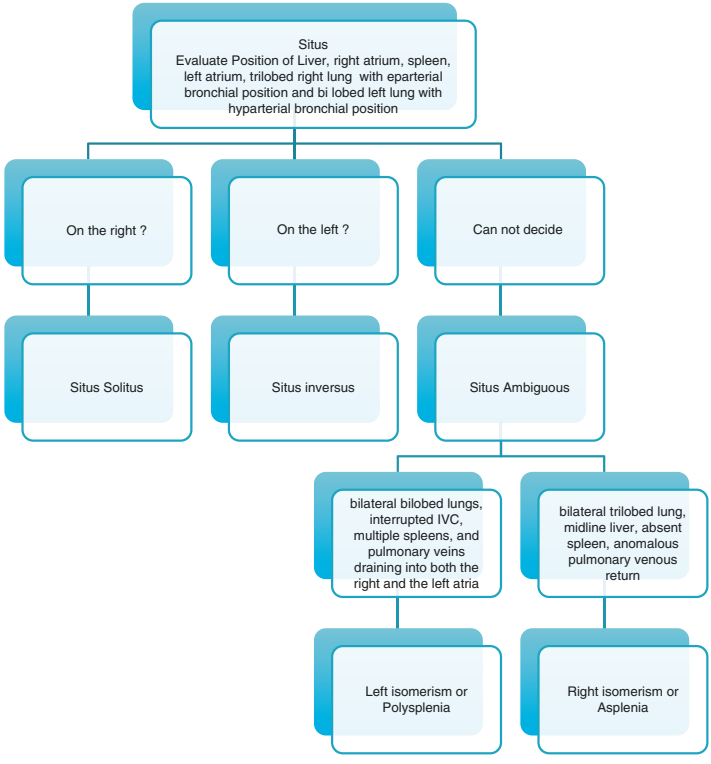

FIGURE 33.1 Determination of situs in ACHD patients

Role of Advanced Imaging in Specific Congenital Heart Disease Entities

Tetralogy of Fallot (TOF)

- After the introduction of surgical repair, there is a large population of repaired TOF patients requiring medical imaging [32].
- TOF is reviewed in Chap. 23; however to review the anomaly is due to the antero-cephalad deviation of the outlet septum during fetal development that results in the tetrad

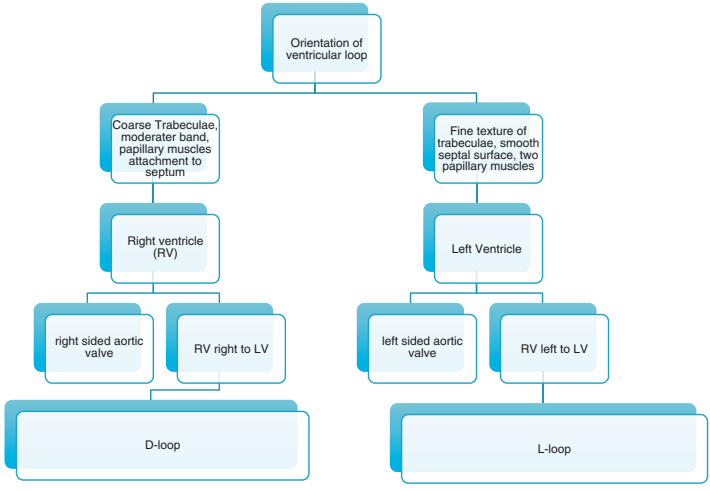

FIGURE 33.2 Identifying ventricles and assessment of ventricular looping

of right ventricular (RV) outflow tract (RVOT) obstruction, overriding aorta, ventricular septal defect (VSD), and RV hypertrophy. Primary surgical repair involves VSD closure and intervention to relieve the RVOT obstruction. In an older approach, transannular patching was used to target complete relief from RVOT obstruction. In current times, transannular patching is not a preferred approach, and some degree of residual obstruction at RVOT is tolerated [33, 34]. Transannular patching may leave behind a large area of akinesis in the RVOT and loss of the pulmonary valve integrity and function. In addition to pulmonary regurgitation and RV overload, arrhythmias, heart failure, and sudden cardiac death are other concerns in patients with TOF repair. Other issues may include concurrent left ventricular dysfunction, aortic root dilatation, and aortic regurgitation [33–35].

- CMR is the gold standard for the quantification of pulmonary regurgitation and assessment of multilevel right-sided obstruction. CMR can quantify ventricular volumes

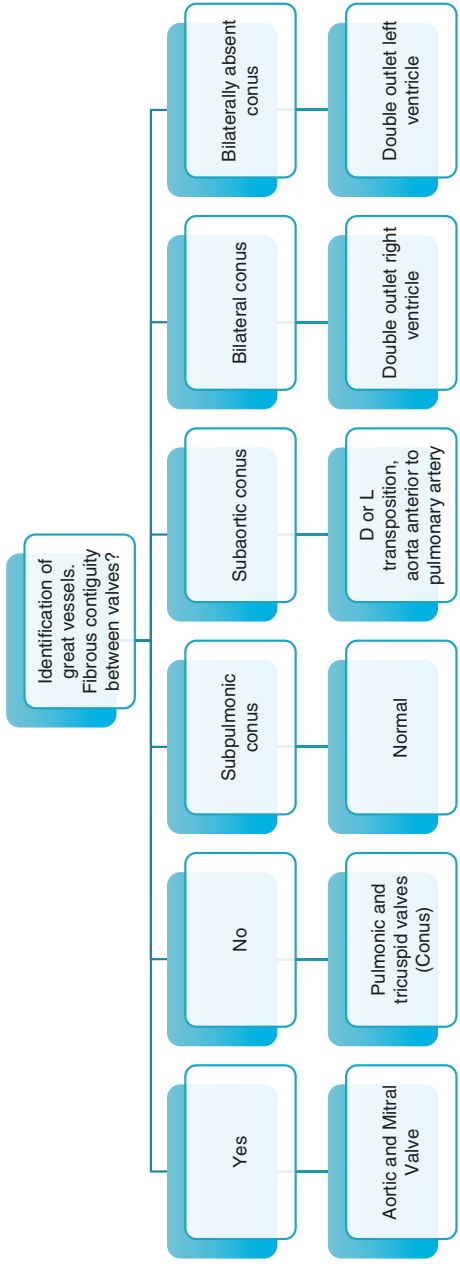

FIGURE 33.3 Classification of conotruncal abnormalities

and function as well as provide information for extracardiac structures including pulmonary arteries and aortopulmonary collaterals.

- CMR can be used for surveillance in patients with TOF without risk of ionizing radiation exposure [14]. Right ventricular volumes can be followed serially on CMR to look for progressive dilatation. It is important to note that the contours on both systolic and diastolic images should carefully include inner margins of the patch while estimating the volumes as it is often difficult to precisely exclude the patch altogether. It helps in patient selection for elective pulmonary valve replacement (RV end-diastolic volume index >150–160 mL m^{-2}) [36]. RV volumetric assessment can also be used to monitor the reverse remodeling of RV following percutaneous valve implantation. LGE in CMR is a marker of focal myocardial fibrosis, which correlates risk for ventricular arrhythmia and sudden death (Fig. 33.4) [37]. Akinetic area length at RVOT can also predict the onset of ventricular arrhythmia.

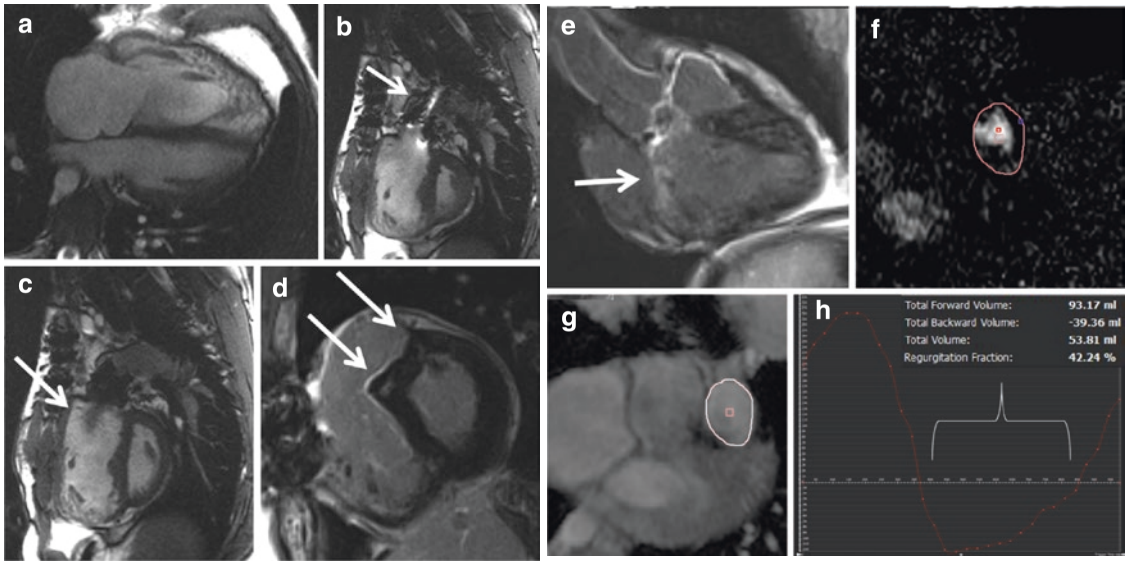

FIGURE 33.4 Surgically corrected TOF with pulmonary valve replacement. Axial Cine SSFP image (**a**) show dilated right heart chambers. Long axis cine SSFP images (**b**, **c**) at right ventricular outflow tract show a systolic jet across the valve extending into the pulmonary artery (**b**) with another diastolic jet along the RVOT (**c**) suggesting dysfunctional valve with stenosis and regurgitation (better seen on the cine images; gif). The delayed post-contrast images (**d**, **e**) show foci of abnormal late gadolinium enhancement along the interventricular septum and RVOT (post-surgical scar). Quantitative assessment with phase contrast imaging allows accurate quantification of regurgitant fraction (**f–h**)

- CT can play a complementary role, as an alternative in patients with contraindication to CMR. CT is the primary modality for preprocedure planning in percutaneous pulmonary valve insertion (specifically to quantify pulmonic annulus size and RVOT anatomy), and it can also be useful for preoperative coronary artery assessment in patients requiring valve repair (Fig. 33.5) [38, 39].

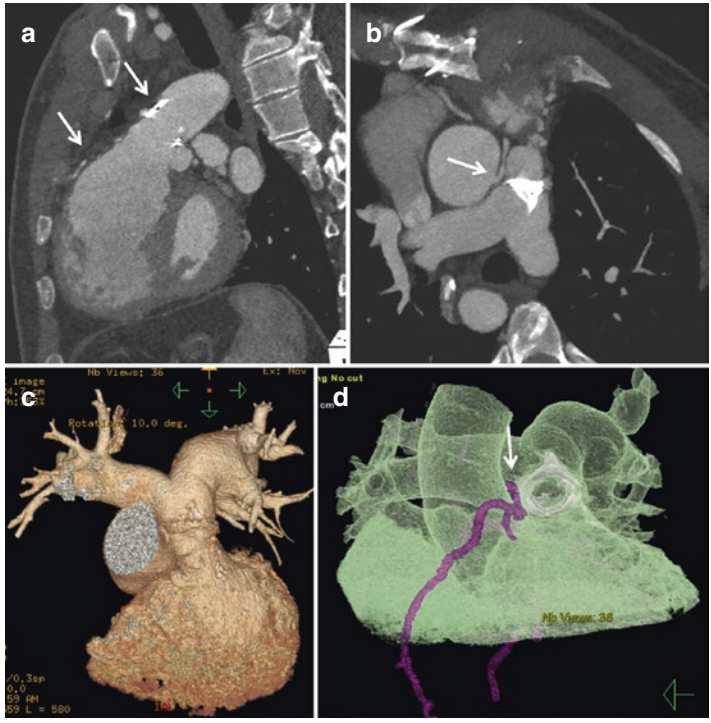

FIGURE 33.5 Preoperative coronary artery assessment prior to valve repair. Reformatted CT angiography along the RVOT shows aneurysmal dilation of the outflow tract with a bioprosthetic pulmonary valve. Oblique reformatted MIP image (**b**) shows an anomalous aortic origin of RCA in close proximity to the RVOT/Valve. Volume rendered images augment visualization of anatomy in three-dimensional space (**c**) with depiction of close relationship of RCA (purple shading) and valve (white shading) (**d**)

Aortic Coarctation

- Coarctation is defined as a narrowing in the proximal descending thoracic aorta adjacent to the aortic isthmus (between the ligamentum arteriosum and left subclavian artery). Significant aortic coarctation warrants early surgical correction [40]. Open surgical resection with primary anastomosis is the preferred treatment with other options being synthetic patch repair, graft interposition or subclavian flap repair, and balloon angioplasty and/or stent placement. Surgical techniques have significantly improved long-term survival, but these patients require monitoring with imaging due to a significant risk of late complications. Repaired coarctation requires screening for the complications such as recoarctation or aneurysm formation. Patients with synthetic patch repair have the highest risk to develop aneurysms. Patients with angioplasty alone have a high recurrence rate, and stenting mandates multiple reinterventions [41]. Aortic coarctation is often first detected by transthoracic echocardiogram. However the diagnosis may be missed if there is inadequate suprasternal imaging or the abdominal Doppler interrogation is omitted.
- MRA provides better anatomical definition, functional assessment, and visualization of collaterals.
- CMR can be useful to assess multilevel LVOT obstruction, aortic dimensions, aortic valve morphology, and collateral flow and is the current gold standard for assessing LV mass (Fig. 33.6).
- CTA is more useful for assessing stent lumen and fracture that can occur during redilatation (Fig. 33.7).

Left Ventricular Outflow Tract Obstruction

- Left ventricular outflow tract obstruction comprised of a heterogeneous group of disease entities that can be categorized into three types.
  - Valvular—usually due to bicuspid aortic valve
  - Subvalvular—due to discrete fibromuscular ridge/long fibromuscular narrowing beneath the base of the aortic valve

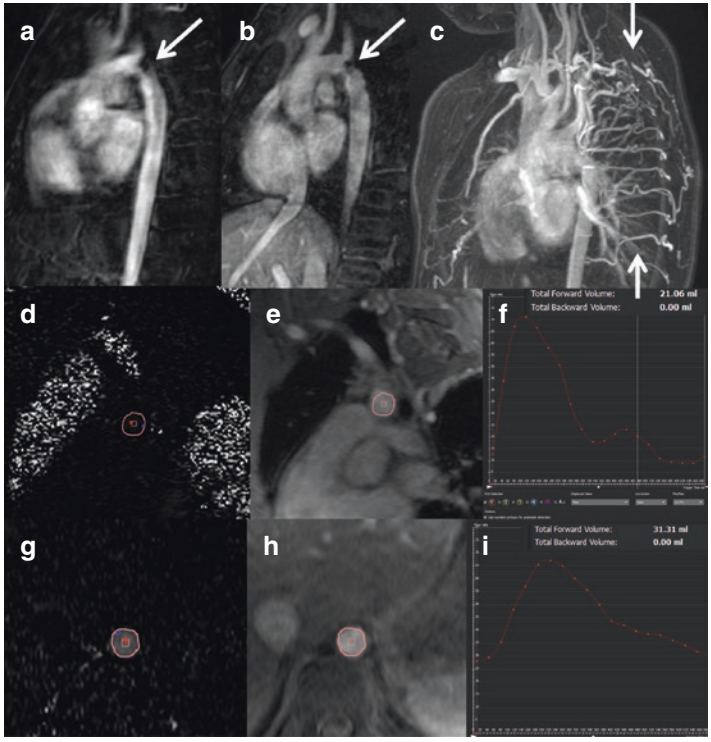

FIGURE 33.6 Aortic coarctation: quantitative assessment by MRI. Arterial (**a**) and equilibrium (**b**) enhancement phase images in the 'Candy Cane' view show an abrupt narrowing of the aorta just distal to the take-off of left subclavian artery (better depicted on the cine images; gif). Thick maximum intensity projection (MIP) image (**c**) is showing multiple dilated inter-costal collaterals. The contribution to the distal aortic flow via these collaterals can be quantified by phase contrast imaging (**d–i**). Measurements just proximal to the narrowing (**d–f**) show a forward flow of 21 cc, while distal descending thoracic aorta (**g–i**) shows a forward flow of 31 cc; suggesting approximately 32% [(31−21)/31] contribution from the collateral flow

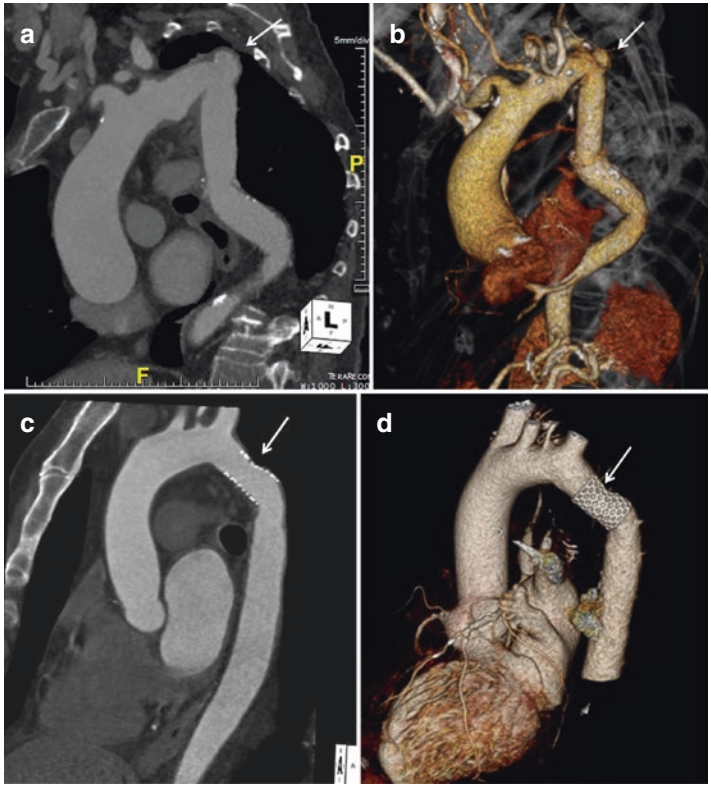

FIGURE 33.7 CTA for aortic coarctation. Oblique reformatted (**a**; candy cane view) and volume rendered (**b**) images show a sacular aneurysm arising from the proximal descending thoracic aorta at the site of coarctation repair. Similar CTA reconstructions a patient treated with angioplasty and stenting show a patent stent lumen without any evidence of stent fracture (**c**, **d**)

  - Supravalvular—may occur rarely if isolation begins at the superior margin of the sinuses of Valsalva as an hourglass deformity.

- Patients with BAV generally present with aortic stenosis or aortic regurgitation and can be associated with

dilatation of the ascending aorta and aortic coarctation. CT and CMR can be used in patients with incomplete assessment of morphology of the aortic root or ascending aorta [42].

- CT is better suited for post-stenting assessment as susceptibility artifacts limit evaluation by CMR.
- CMR and CT allow excellent characterization of morphology of the aortic valve and aortic valve stenosis severity, precise measurements of the aortic root/aorta and valve phenotypes (Fig. 33.8) [43, 44], and monitoring treatment response by detecting left ventricular mass regression (marker of favorable LV remodeling) [45].
- After a Ross procedure, RVOT obstruction and aortic regurgitation can be rarely noted, and CT/CMR may allow visualization of the RVOT obstruction in these cases.
- CT and CMR can be helpful to visualize the membrane of subvalvular left ventricular outflow tract obstruction (Fig. 33.9).

Atrial Septal Defects (ASDs)

ASDs can be of three major types including ostium secundum, ostium primum, and sinus venosus defects (not technically septal defects). Another less common type is unroofed coronary sinus (Fig. 33.10).

- Secundum ASD is the most common type usually seen in middle age [46], discovered incidentally on clinical examinations or imaging study.
  - CT and MRI can serve as guide prior to a planned percutaneous closure device placement by providing accurate estimate of the rim, which is the distance of the defect from other cardiac structures like tricuspid and aortic annulus, SVC, and IVC.

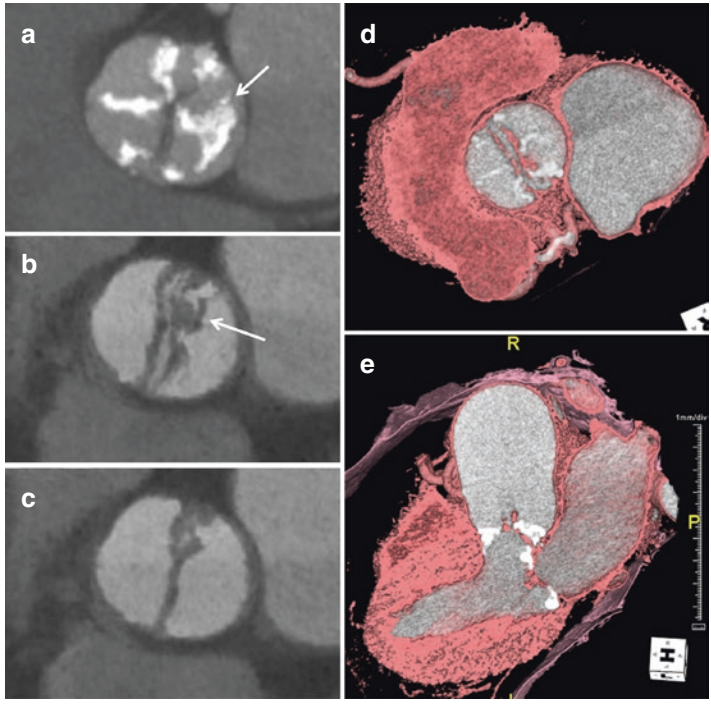

FIGURE 33.8 Bicuspid aortic valve. Axial MIP image (**a**) shows calcification within the leaflets of aortic valve. Minimum intensity projection (minIP) images in systole (**b**) and diastole (**c**) are demonstrate the stenotic thickened leaflets of a Sievers Classification type 0 bicuspid valve (no raphe is identified, and only two cusps are present). Volume rendered blood pool inversion images (**d**, **e**) allow 3D assessment of aortic root. The aortic valve function can be assessed by the cine reconstructed from minIP images at different cardiac phases (gif)

- Precise measurement of the rim is the key in these cases as rim <3 mm is contraindication for percutaneous device placement [46].
- Sinus venosus type is relatively uncommon (<15%) (and not a true atrial septal defect) and can be associated with

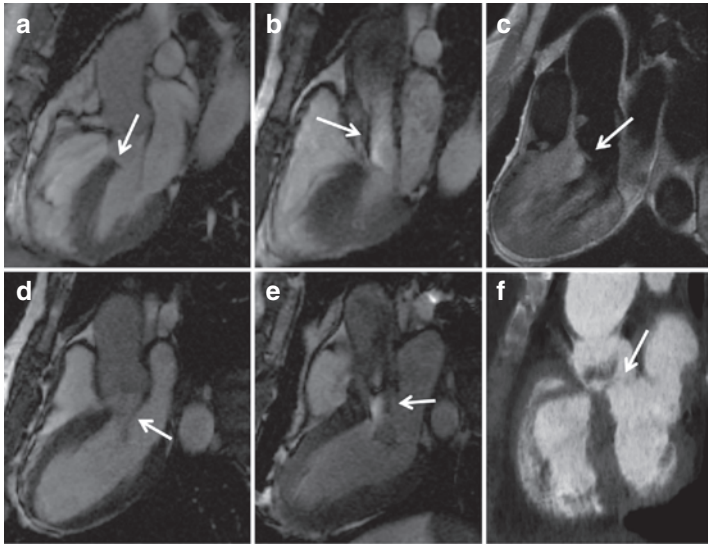

Figure 33.9 Subaortic membrane. SSFP images at the left ventricular outflow tract show evidence of a shelf like membrane in diastolic phases (**a**, **d**); better seen on spin echo T1 weighted image (**c**). There are systolic jets at the LVOT extending towards aortic valve and ascending aorta resulting from the subaortic stenosis (**b**, **e**; better seen on cine images; gif). Oblique reformated minIP image at the level of LVOT from a different patient also shows a subaortic membrane

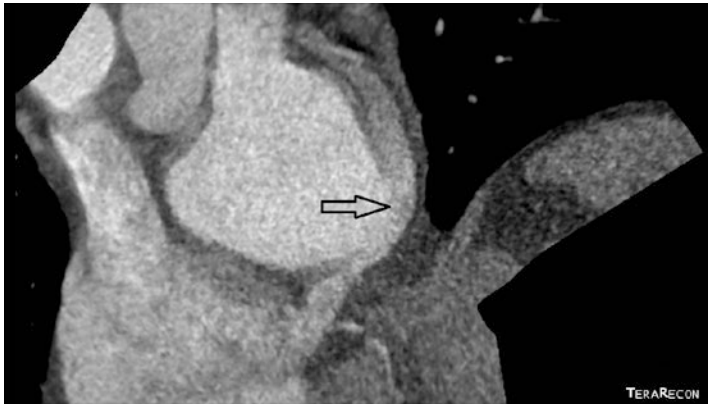

Figure 33.10 Unroofed coronary sinus draining into the left atrium (*hollow arrow*) incidentally detected in a 59 year old man

anomalous pulmonary venous return [47]. CMR and CT are better equipped to delineate associated anomalous pulmonary venous return, especially useful for detecting anomalous veins inserting above the level of azygous vein. The precise location of anomalous pulmonary venous drainage and its spatial relationship with the cavo-atrial junction are important for surgical planning [48].

- In the presence of anomalous pulmonary venous return without associated sinus venosus defect, CMR and CT both can identify the anomalous veins. Phase contrast MRI can provide estimate of the pulmonary-to-systemic flow (Qp/Qs) ratio. A ratio of 1:1.5 is required to surgically correct the anomalous veins as these patients are at risk of developing pulmonary hypertension and right ventricular dilatation and failure [49].

D-Looped Transposition of the Great Arteries

- TGA is an embryologic defect of conotruncal septal rotation, which results in ventriculoarterial discordance.
  - In adults with D-looped TGA (Fig. 33.11) who have undergone atrial switch surgery (Senning or Mustard procedure), systemic RV dysfunction is a determining factor for late morbidity and mortality in these patients. Baffle leaks and stenosis also increase morbidity.

    CT and CMR can better visualize baffle stenosis and quantify systemic RV function compared to echocardiography.

    CMR may also localize baffle leaks.
  - Arterial switch procedure with coronary reimplantation is the treatment of choice for D-looped TGA in the modern era. This procedure can be associated with neo-aortic root dilatation, supravalvular pulmonic stenosis, LV dysfunction, aortic regurgitation, and coronary occlusion.

    Cardiac gated CTA is especially suited for the evaluation of reimplanted coronary arteries.

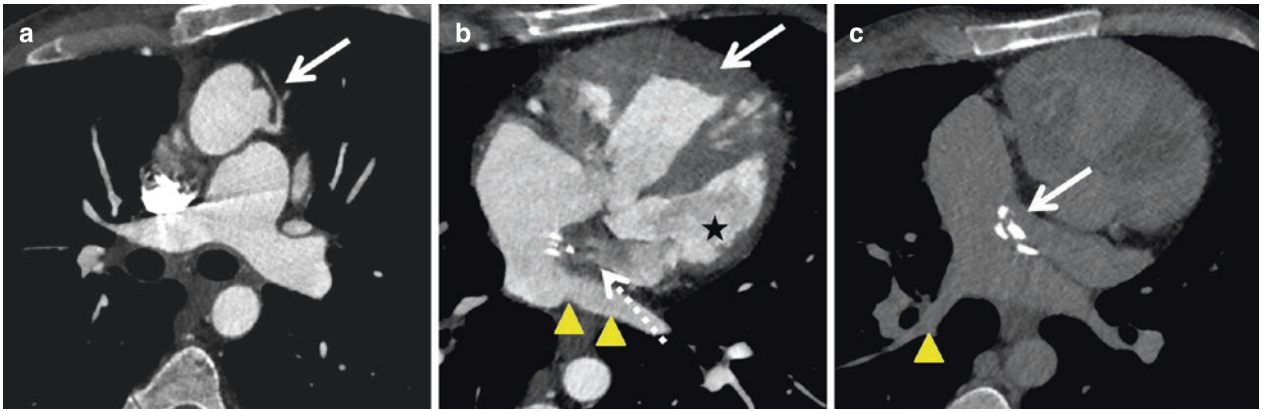

FIGURE 33.11 D-TGA. Axial CTA images show aorta (*arrow* in **a**) arising from morphologic right ventricle (*arrow* in **b**) and pulmonary artery arising from morphologic left ventricle (*asterisk* in **b**). The pulmonary veins (*arrowheads* in **b** and **c**) drain into the right atrium. The venous inflow is connected to left atrium via a baffle (*dotted arrow* in **b**, *arrow* in **c**) known as Mustard procedure. Delayed image were helpful in detecting baffle stenosis (*arrow* in **c**) in this case

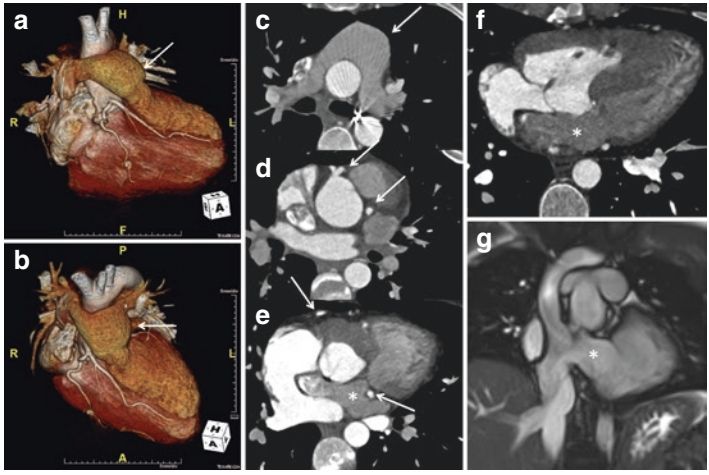

FIGURE 33.12 Repaired TGA with double switch and LeCompte maneuver. Volume rendered images (**a**, **b**) provide 3D assessment of the post-surgical anatomy; the pulmonary artery and its branches are seen in front of ascending aorta (**a–c**). CT is specially suited for the evaluation of reimplanted coronary arteries (**d**, **e**; *arrows*). Cardiovascular CT is helpful for the assessment of atrial inflow patency (**e**, **f**; *asterisks*). Oblique coronal SSFP image (**g**) also shows the patency of atrial baffle and vena cavae (better seen on cine; gif)

CMR may also provide adequate evaluation of proximal coronary segments, although inferior to CT in excluding stenoses.

Main pulmonary artery and branches are difficult to image by echocardiography. CMR can provide a detailed assessment of RVOT and the pulmonary artery and its branches (Fig. 33.12).

Congenitally Corrected Transposition of the Great Arteries

- Congenitally corrected TGA (ccTGA) is a result of co-occurrence of atrioventricular and ventriculoarterial discordance. ccTGA can be associated with tricuspid valve

abnormality (Ebstein type) and systemic tricuspid regurgitation. Echocardiography is the primary modality to assess RV dysfunction and tricuspid regurgitation.
- CMR allows quantification of systemic RV ejection fraction and enable decision-making for tricuspid valve replacement [48].
- CMR can also show areas of LGE in patients with focal RV fibrosis which correlates with disease progression and predicts outcomes [50]. It can help in identifying patients with severe ventricular dysfunction and RV fibrosis who are at risk of sudden cardiac death [48].
- Cardiac CT may be useful in the assessment of the coronary sinus anatomy for cardiac resynchronization planning.

Single-Ventricle Fontan Procedure

- Complex single-ventricle anatomy and Fontan palliation and surgical variants are discussed in Chap. 27.
- Patients with a single ventricle after Fontan palliation require frequent surveillance imaging.
- There is a risk for thrombus formation in the dilated right atrium after atriopulmonary Fontan due to sluggish flow and/or in the disconnected pulmonary trunk after TCPC.
- CMR and CT are important second-line techniques to quantify the ventricular volumes and function, to establish patency of the conduit and excluding thrombus (Figs. 33.13 and 33.14). Both CT and CMR can detect collateral vessel development. Smaller vessels are better detected with thin sub-millimeter CT slices as CMR often loses its signal-to-noise ratio at thinner slices. CT can also assess the presence of pulmonary embolism and associated lung parenchymal changes such as infarcts in ACHD patients with Fontan.
- CMR also has potential to detect focal areas of ventricular fibrosis that can cause ventricular tachycardia in these patients [51].

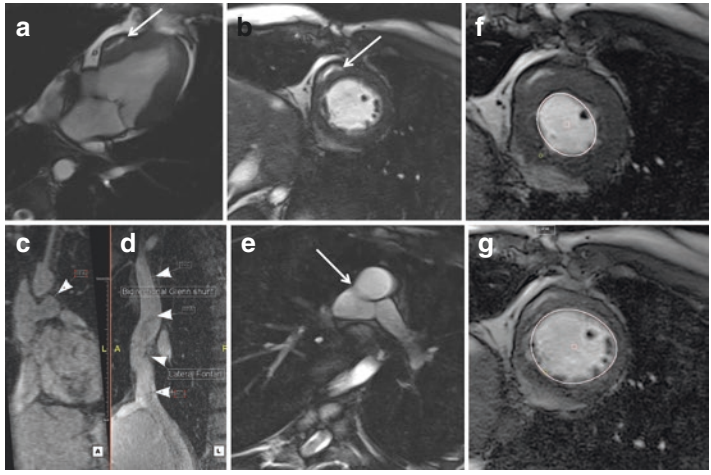

FIGURE 33.13 Single ventricle after Fontan palliation—MR assessment. Axial balanced SSFP images in four-chamber and short axis planes show a small rudimentary right ventricle (**a**, **b**). Post contrast (**c**, **d**) and axial SSFP (**e**) images demonstrate patency of the conduit without any evidence of thrombus. Cine SSFP images allow accurate assessment of ventricular volumes and function (**f**, **g**)

Coronary Anomalies

- Coronary anomalies are rare with a reported incidence of approximate 0.3% of patients in an autopsy study [52].
- Most of the coronary anomalies are considered benign (including those with retroaortic course and those with prepulmonic course) with approximately 20% having a potential for causing myocardial ischemia and sudden death [53] including:
  - Anomalous coronary ostium with an interarterial course
  - Anomalous coronary artery from the pulmonary artery (ALCAPA)

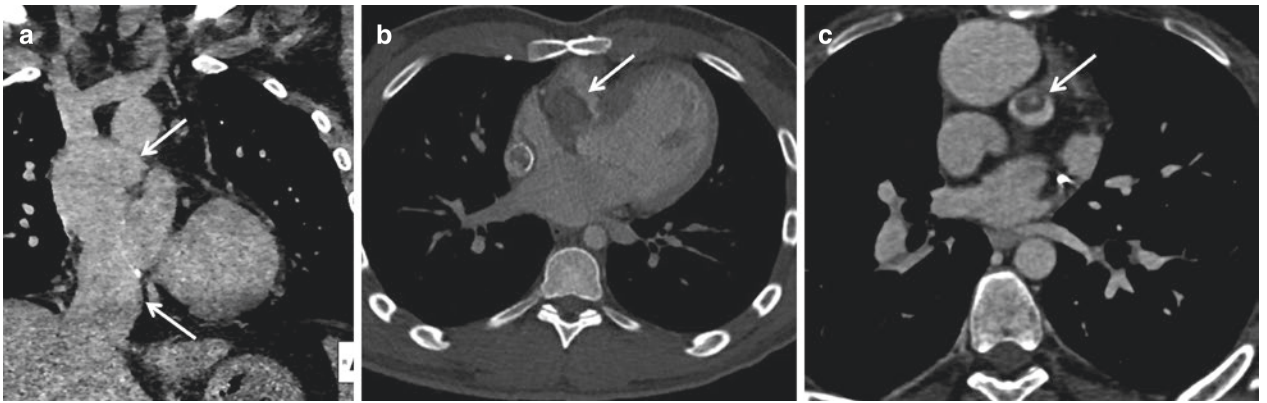

FIGURE 33.14 Single ventricle after Fontan palliation—CT assessment. Coronal reformatted image from a delayed phase CTA (**a**) depicts patency of the conduit and vena cavae without any evidence of thrombus. A patient with pulmonary atresia and Fontan palliation developed a large filling defect (indicating thrombus) in the hypoplastic right atrium (**b**). Axial CT angiography image (**c**) from a different patient with DORV status post palliation with a lateral tunnel Fontan shunt developed a thrombus in the blind-ending ligated pulmonary artery stump (filling defect in panel **c**)

- Coronary artery anomalies cannot be adequately characterized by echocardiography nor with invasive coronary angiography [54].
- Coronary CTA is noninvasive and suited for evaluation of coronary anomalies given three-dimensional capability.
- CTA can be used as a confirmatory test for patients with equivocal findings on catheter angiography [55, 56].
- CTA is the primary screening modality for evaluation of suspected coronary anomalies [2, 57].
- CTA is highly accurate for the detection of interarterial course and in addition can show characteristics such as "slit-like" ostial orifice (a sign of hemodynamic significance) (Figs. 33.15 and 33.16) [56, 58].
- Catheter angiography can detect ALCAPA, but diagnosis can be challenging due to the presence of high-flow shunting and numerous collaterals. The determination of interarterial course is also limited on catheter angiography as it requires extramural information that can only be provided by cross-sectional imaging (particularly by CTA).

Double-Outlet Right Ventricle

- Double-outlet right ventricle is an entity where both great vessels arise entirely (or >50%) from the right ventricle. Based on the surgical approach adopted for correction, it has been divided into four subtypes, including Fallot type, TGA type, VSD type, and non-committed VSD type [59].
- Postoperative issues include subaortic or subpulmonary obstruction, a residual VSD, and conduit stenosis/regurgitation. MRI or CT is excellent for evaluation of the morphology of ventricles and patency of both outflow tracts. These modalities are highly sensitive for detection of the common problems such as subaortic or subpulmonary obstruction, residual VSD, and conduit stenosis/regurgitation [60, 61].

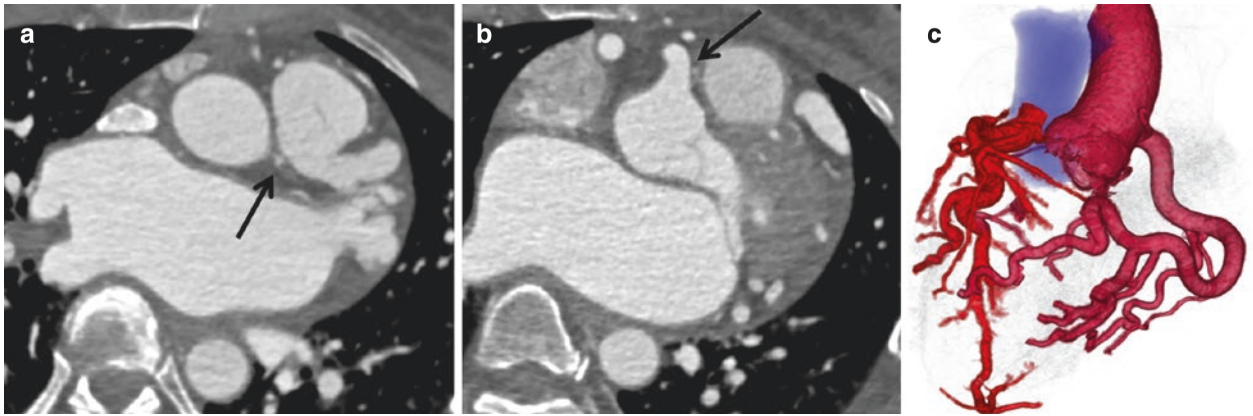

FIGURE 33.15 ALCAPA. Axial coronary CT angiography image (**a**) demonstrates the left coronary artery arising from the pulmonary trunk; the right coronary artery (RCA) arises normally from the aorta (**b**). Both coronary arteries are markedly dilated and tortuous, a global finding which is often well-demonstrated on volume rendered image reconstructions (**c**)

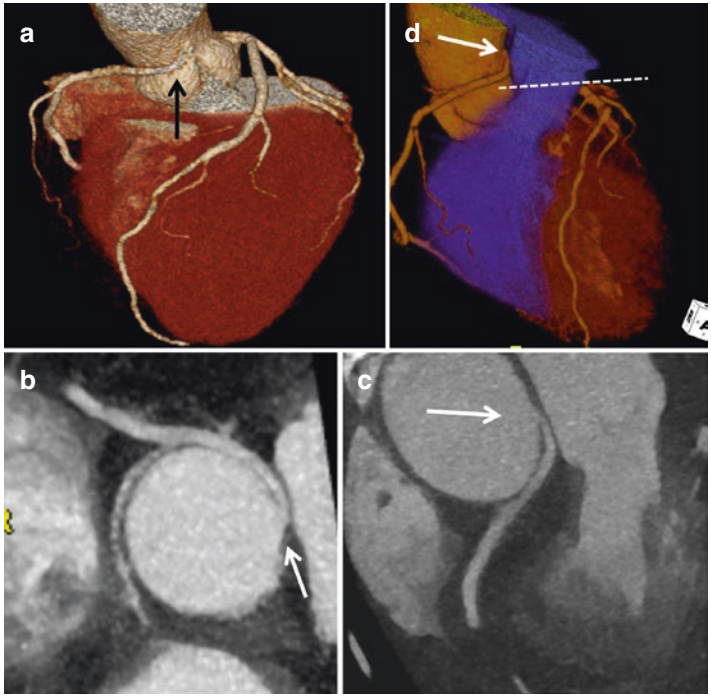

FIGURE 33.16 Anomalous aortic origin of the RCA with interarterial course. VRT images (**a**, **b**) show abnormal origin of right coronary artery from ascending aorta above the level of coronary sinus with an abnormal proximal intramural, interarterial course. The artery arises at an acute angle from the aortic lumen (as seen on oblique reformatted MIP images; **c**, **d**) with a slit like proximal stenotic segment [**e**; compared to (**f**) circular outline distal in course]. Artery arises at a level above the pulmonary annulus (*dashed line*; **d**). Confirming an interarterial course

Advanced CHD Imaging During Pregnancy and Lactation

- Imaging of CHD in pregnancy poses a multifaceted challenge to the care team and the cardiac radiologist due to concerns related to radiation exposure and use of both iodinated and gadolinium-based contrast media.

- Choice of imaging modality should always consider if the imaging is necessary to improve maternal and fetal outcome. When possible imaging study with non-ionizing radiation should be used. If CT is chosen over MRI, every attempt must be made to keep the radiation dose in as low as reasonably achievable, i.e., limiting the field of view and choosing lower radiation parameters and newer reconstruction techniques. It is prudent to be aware that the American College of Radiology does not recommend withholding use of iodination contrast media [62].
- With the CMR, several noncontrast techniques are available which can be used as alternatives. As previously stated, evaluation of myocardial edema, cine images for function, and ventricular volume estimation as well as shunt quantification is independent of contrast administration. As the effects of gadolinium-based contrast media on the fetus are largely unknown, both the American College of Radiology and the American College of Obstetricians and Gynecologists advise for cautious use [62, 63].
- Lastly, in lactating women, it is safe to continue breastfeeding after receiving iodinated or gadolinium-based contrast media according to the American College of Radiology recommendation. Every mother should, however, be given the choice of temporarily stopping breastfeeding for 12–24 h [64–66].

Summary

Cardiac CT and CMR are key imaging tools for ACHD patients and provide a comprehensive assessment of complex anatomy and function. Type of congenital lesion and individual patient characteristics can help in choosing the right imaging modality and allow protocol optimization. Attempts to lower radiation dose with CT and decreasing the scan time with CMR while maintaining diagnostic image quality are essential in the care of ACHD patients.

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Chapter 34
Cardiopulmonary Exercise Testing in ACHD

Ada C. Stefanescu Schmidt

Abnormal Exercise Capacity in ACHD

- Adults with congenital heart disease (CHD) very commonly have reduced aerobic capacity and exercise intolerance, often on par with patients with chronic acquired heart failure [1, 2].
- Self-estimated physical function is not a reliable predictor of actual exercise capacity in ACHD patients, in part due to a baseline of exercise limitation since childhood, sedentary lifestyle, and chronicity of symptoms [3].
- Underlying cardiac anatomy, lack of heart rate response to exercise, pulmonary arterial hypertension, and impaired pulmonary function are important correlates of impaired exercise capacity [2].
- A symptom-limited cardiopulmonary exercise test (CPET) has proven to be an essential tool to objectively evaluate the functional cardiovascular capacity in ACHD patients, identify the mechanisms of limitation, and importantly help individualize exercise prescription.

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Cardiopulmonary Exercise Testing

- CPET is a commonly used test to assess exercise capacity as well as cardiovascular and pulmonary limitations [4]:
  - CPET is particularly helpful in ACHD patients who have had a chronically limited and decreasing exercise capacity and adapt to worsening symptoms of heart failure by reducing their functional level [3].
  - CPET is reasonable to repeat "periodically" in patients with moderate to severe CHD [5, 6] or when symptoms change.
  - CPET can also be used to diagnose chronotropic incompetence and establish a training regimen for conditioning.
- The CPET is distinct from a standard cardiac stress test by the measurement of gas exchange (inhaled oxygen and exhaled carbon dioxide), to allow for estimation of oxygen consumption during exercise.
- A CPET is composed of an exercise test with measurement of several physiologic parameters, which range from simple electrocardiographic and finger plethysmography to invasive measurements of pulmonary and systemic arterial pressures
- The exercise modality is most commonly a bicycle, as it allows the upper body to be stationary to facilitate measurements, though a treadmill or rowing machine can also be used.
- The "level" of the CPET is commonly used to describe the number of physiologic parameters that are measured:
  - CPET level 1:

    Consists of exercise, continuous electrocardiographic monitoring, blood pressure measurements, and gas exchange measurements

  - CPET level 2:

    As above, with a radial arterial catheter to measure oxygen and carbon dioxide content and pH

  - CPET level 3:

    All of the above, with the addition of a Swan-Ganz catheter to continuously monitor pulmonary arterial and wedge pressures, as well as central venous blood oxygen saturation

- Radionuclide imaging:
  - Tagged red blood cell radionuclide imaging (with technetium-99m) can be performed during the test, to measure ventricular size, stroke volume, and thus biventricular ejection fraction at rest and with exercise.

Measured Parameters

- The peak oxygen consumption (peak VO_2 or VO_2 max) is one of the more informative results from a CPET and an estimate of the peak combined aerobic performance of the cardiac, pulmonary, and muscular systems. It is usually indexed to weight (units of milliliter per kilogram per minute):
  - It can be expressed as percentage of predicted peak VO_2 for a normal subject of the same age and sex [7]. While it is commonly reported, it is less useful in patients with moderate or severe CHD as they will never have normal values, and there is limited data to benchmark their % predicted peak VO_2 with long-term outcomes. Distribution of peak VO_2 for CHD patients from a large tertiary center cohort, in general and for specific diagnoses, is a very useful reference [8] (Fig. 34.1).

  - Poor exercise capacity, as assessed by peak VO_2, strongly correlates with risk of hospitalization or death [2].
  - A peak VO_2<20 mL/kg/min is associated with poor prognosis [9]; a peak VO_2 <14 mL/kg/min is one of the criteria used in the non-congenital patients for consideration of heart transplant [10].

- Ventilatory efficiency, calculated as the ratio of ventilation per unit of carbon dioxide production (VE/VCO_2), is a marker of pulmonary perfusion, ventilation/perfusion mismatch, and physiologic dead space. It is another commonly used predictor of morbidity and mortality [11], with higher values (more ventilation needed to clear each unit of carbon dioxide produced with exercise) being associated with worse outcomes.
- Peak O_2 pulse is a marker of stroke volume and oxygen extraction. It is obtained by dividing the peak VO_2 by the HR at peak exercise.
- Heart rate reserve is a marker of cardiac limitation; a lower heart rate reserve is associated with poor prognosis and higher incidence of death or progression to transplant in Fontan patients [12].
- Biventricular ejection fraction, both at rest and with exercise, can be assessed by radionuclide ventriculography:

  - The appropriate response of the right ventricle is an increase in the ejection fraction. Abnormal right ventricular reserve (unchanged or decreased right ventricular EF at peak exercise) has been shown to be associated with a higher risk of heart failure exacerbation, arrhythmias requiring treatment, and death in midterm follow-up [13].

- Exercise oscillatory ventilation is associated with more severe heart failure [14].

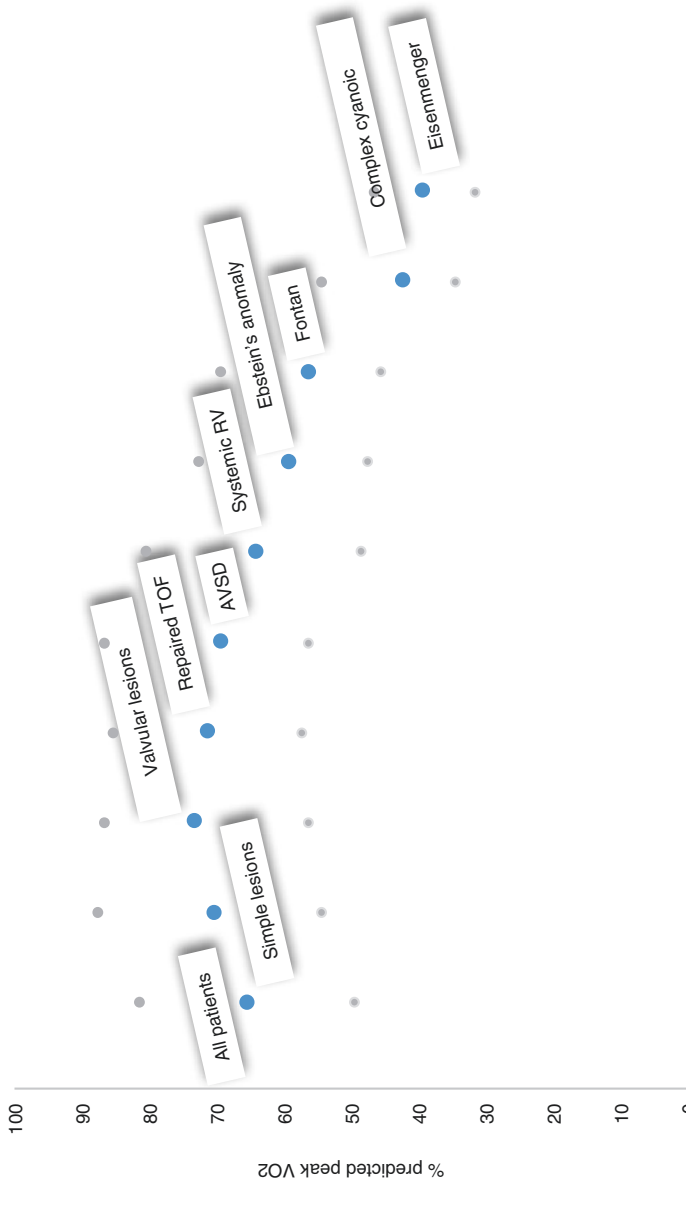

FIGURE. 34.1 Mean % predicted peak VO_2 (and interquartile range) in 1375 patients with ACHD. Adapted from Inuzuka et al. [8]

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Chapter 35
Obesity and Exercise Recommendations in Adult Congenital Heart Disease

Laura D. Flannery

- Background: Issues with obesity often begin in childhood for congenital heart disease (CHD) patients.
  - More than 25% of children with CHD are overweight [1–3].
  - There are risk factors unique to CHD population that likely contribute to obesity:
    - Children initially experience failure to thrive and malnutrition in infancy, and they are often prescribed interventions for weight gain prior to surgical interventions, which include high-calorie and high-fat supplements [1].
    - Children are often also put on physical activity restrictions prior to surgical intervention [1].
    - However, these habits often persist into adulthood despite resolution of need for diet supplementation and activity restriction after repair, which contributes to obesity. Activity restriction in children with CHD is the strongest predictor of obesity [4].

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  - Obesity in children with CHD is associated with traditional risk factors in childhood obesity as well, such as parental obesity and Hispanic ethnicity [3, 5].
  - More boys with CHD have obesity than girls, which is disparate with general population trends where there are no gender differences [2].
  - Poor self-esteem and perceived confidence in children with CHD may also limit a child's initiative to participate in physical activity [6].
  - Pediatric cardiologists may recommend activity limitation in excess of guideline recommendations, and parents may further impose unnecessary exercise restrictions [7]. Only slightly more than half of parents of children with CHD know the appropriate exercise restriction for their children [8].

- Rates of obesity in adults with congenital heart disease (ACHD):
  - Various studies have indicated that rates of obesity in adults with CHD are similar to or slightly less than overall rates of adult obesity [2, 9, 10] Approximately 25% of the ACHD population in the USA is overweight or obese [10].
  - The obesity rate in the overall population is obviously not an ideal standard. Furthermore, CHD patients are ideally in lifelong cardiac care and should benefit from optimal obesity prevention.

- Prevention:
  - As more children with CHD are surviving into adulthood, awareness of the risk of obesity and optimizing lifestyle modification to prevent obesity is of utmost importance to their overall health.
  - Providers must strive to include lifestyle counseling as part of all care visits with ACHD patients.
  - Cardiopulmonary exercise testing may guide safe exercise prescription in most patients.
  - In general, exercise recommendations are based on expert consensus rather than outcome-driven data.

Exercise recommendations should be made on an individualized patient-by-patient basis with an emphasis on risk/benefit analysis and with a team-based approach involving providers with expertise in congenital disease and sports cardiology.

- Exercise recommendations per phenotype:
  - Shunt patients (atrial and ventricular septal defects, patent ductus arteriosus) [11, 12]:
    - Asymptomatic patients with repaired shunts or unrepaired small shunts can participate in activities without restriction.
    - Symptomatic patients with shunts should limit competitive activities prior to repair if their pulmonary artery pressures are elevated.
    - Unrepaired shunt patients with Eisenmenger's physiology have a high risk of sudden cardiac death during intense activities, and competitive exercise and isometrics should be avoided. Individualized exercise programs should be created for patients who are asymptomatic, have an oxygen saturation greater than 80%, have no evidence of arrhythmia, and have no ventricular dysfunction.
  - Patients with obstructive lesions (coarctation of the aorta, aortic stenosis, pulmonary valve stenosis) [11, 12]:
    - Patients with obstructive lesions with moderate to severe pressure gradients should refrain from activity, especially static exercise, until repair.
    - Asymptomatic patients with low gradients can participate without restriction.
  - Cyanotic heart disease (tetralogy of Fallot, double-outlet right ventricle, transposition of the great arteries, univentricular circulation) [11, 12]:
    - Repaired tetralogy of Fallot, double-outlet right ventricle, and transposition of the great arteries can have liberal exercise recommendations. This is the

subgroup where unnecessary exercise limitations are most imposed.
    - Asymptomatic repaired Fontan (univentricular circulation) patients hav.e reduced exercise capacity due to single ventricular circulation but should be encouraged to do low-intensity exercise as they will benefit from it.

- Patients with Marfan syndrome can participate in low-moderate static and low-intensity dynamic exercise if they do not have aortic root dilation, moderate or severe mitral regurgitation, or a family history of dissection or sudden cardiac death [12].
- Patients with aortic root dilatation (Marfan, familiar aortic aneurysm) should participate in low-intensity activities. They should refrain from contact sports regardless of presence or absence of aortic root dilatation [11].
- Patients with hypertrophic cardiomyopathy should refrain from competitive sports except low-intensity activities, regardless of symptoms, LV outflow tract obstruction, or prior interventions [13].
- Patients with anomalous origins of the coronary arteries [12]:
    - Patients with anomalous left coronary that arises from the right sinus of Valsalva are advised to avoid strenuous exercise, especially when the course of the artery passes between the aorta and pulmonary artery.
    - Patients with anomalous right coronary that arises from the left sinus of Valsalva should receive a stress test prior to exercise. They should be advised to avoid strenuous exercise if they are symptomatic or have signs of ischemia or arrhythmia on the stress test.
    - Repair may be offered to remove exercise restriction. If repair is successful, patients may be able to participate in all sports if asymptomatic with negative stress test 3 months after repair.

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Chapter 36
Endocarditis Prophylaxis in ACHD

Evin Yucel

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
CHD	Congenital heart disease
IE	Infective endocarditis

Overview

- In the United States, there has been a change in the epidemiology of infective endocarditis (IE) due to [1]:
  - Decreased prevalence of rheumatic heart disease
  - An increase in invasive procedures and prosthetic device implantations
  - Increase in high-risk patient groups (intravenous drug users, patients with human immunodeficiency virus infections, and diabetes mellitus)
  - Increase in survival of IE-risk prone populations, such as adults with congenital heart disease (CHD)

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- There has been a steady increase in the incidence of IE over the past decade (15 per 100,000 population) [2].
- Patients with underlying CHD are at a higher risk of developing IE with an increased mortality [3]. Among the unoperated patients, those who have small ventricular septal defects are at highest risk of IE but are associated with low risk of mortality [4, 5].
- Common pathogens in adult patients with CHD are *Staphylococcus* and *Streptococcus*.
- Revised guidelines for antibiotic prophylaxis for prevention of IE were released in 2007 by the American Heart Association (AHA) and the American College of Cardiology (ACC), and a focused update was released in 2008 [6, 7]. European Society of Cardiology guidelines for endocarditis management were followed in 2009 and recently updated in 2015. Both the societies restricted the use of antibiotic prophylaxis to highest-risk patients [8].
- In 2008, the National Institute for Health and Care Excellence (NICE) guidelines in the UK published recommendations against *any* antibiotic prophylaxis for dental or non-dental procedures regardless of the patient's risk [9]. In a follow-up analysis of UK data collected from 2000 to 2013, there was a significant decrease in antibiotic prophylaxis prescriptions, whereas there was an increase in the incidence of IE in both high-risk and lower-risk patients starting in 2008 [10].

Rationale for Antibiotic Prophylaxis

- Development of IE is presumed to involve:
  - Formation of thrombus on a cardiac valve tissue at a site of endothelial damage
  - Secondary infection with bacteria
  - Proliferation of bacteria leading to formation of vegetations

- Eliminating the occurrence of bacteremia may decrease the risk for the development of IE; however, there is no robust evidence that antibiotic prophylaxis prevents IE.
- Maintenance of oral hygiene may play a more significant role in reducing the incidence of IE [6, 11, 12].

High-Risk Conditions That Require IE Prophylaxis by 2007 AHA/ACC Guidelines on Antibiotic Prophylaxis for Prevention of IE [6]

- Prosthetic heart valves or prosthetic material used for cardiac valve repair
- A prior history of IE
- Unrepaired cyanotic CHD, including palliative shunts and conduits
- Completely repaired CHD with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
- Repaired CHD with residual defects at the site or adjacent to the site of the prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

Procedures Requiring IE Prophylaxis

- Dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa, including routine dental cleaning
- Procedures of the respiratory tract that involve incision or biopsy of the respiratory mucosa
- Gastrointestinal or genitourinary procedures in patients with infections at these sites

- Procedures on infected skin, skin structure, or musculoskeletal tissue
- Surgery to place prosthetic heart valves or prosthetic intravascular or intracardiac materials

Conditions That Do Not Require IE Prophylaxis

- Patients with isolated secundum atrial septal defect
- Patients who are 6 or more months after successful surgical or percutaneous repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus with no residual shunt
- Patients with physiological, functional, or innocent heart murmurs

Recommended Antibiotic Regimens

- All antibiotics should be administered 60 min prior to the procedure except for Vancomycin which should be administered 120 min prior to the procedure.

	Agent	**Adult dosing**	**Children dosing**
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR		
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV

	Agent	Adult dosing	Children dosing
Allergic to penicillins—oral	Cephalexin	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Zithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins and unable to take oral medication	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
	OR		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV
	OR		
	Vancomycin	15–20 mg/kg, no to exceed 2 g per dose	15 mg/kg to a maximum dose of 1 g

Adapted from ACC/AHA 2008 Guideline Update on Valvular Heart Disease: Focused Update on Infective Endocarditis [7]

ACC/AHA guidelines 2008 [1]

Recommendations for infective endocarditis prophylaxis:

Class I

1. ACHD patients must be informed of their potential risk for IE and should be provided with the AHA information card with instructions for prophylaxis (*Level of Evidence: B*).

Class IIa

1. Antibiotic prophylaxis before dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa is reasonable in patients with CHD with the highest risk for adverse outcome from IE, including those with the following indications:

ACC/AHA guidelines 2008 [1]

(a) Prosthetic cardiac valve or prosthetic material used for cardiac valve repair (*Level of Evidence: B*)

(b) Previous IE (*Level of Evidence: B*)

(c) Unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits (*Level of Evidence: B*)

(d) Completely repaired CHD with prosthetic materials, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure (*Level of Evidence: B*)

(e) Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device that inhibits endothelialization (*Level of Evidence: B*)

2. It is reasonable to consider antibiotic prophylaxis against IE before vaginal delivery at the time of membrane rupture in select patients with the highest risk of adverse outcomes. This includes patients with the following indications:

(a) Prosthetic cardiac valve or prosthetic material used for cardiac valve repair (*Level of Evidence: C*)

(b) Unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits (*Level of Evidence: C*)

Class III

1. Prophylaxis against IE is not recommended for non-dental procedures (such as esophagogastroduodenoscopy or colonoscopy) in the absence of active infection (*Level of Evidence: C*)

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Chapter 37
Pregnancy in Adults with Congenital Heart Disease

Evin Yucel

Abbreviations

AHA	American Heart Association
CARPREG	Canadian Cardiac Disease in Pregnancy
CHD	Congenital heart disease
CO	Cardiac output
HR	Heart rate
WHO	World Health Organization
RBC	Red blood cell
SVR	Systemic vascular resistance
ZAHARA	Zwangerschap bij Aangeboren HARtAfwijkingen

Overview

- As a result of medical and surgical advances, there is an increasing number of women with congenital heart disease (CHD) surviving to childbearing age [1].

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- Maternal mortality is uncommon in patients with CHD, except in the setting of Eisenmenger syndrome, severe systemic cardiomyopathy, and Marfan syndrome with aortopathy.
- Maternal hypoxemia is associated with high incidence of fetal loss, even in the absence of Eisenmenger physiology. In a series of 90 patients, the rate of live births decreased to below 20% when maternal resting oxygen was <85% [2].
- A multidisciplinary approach to the pregnant woman with CHD is essential for favorable maternal and fetal outcomes.
- In general, for women with CHD, cesarean delivery is only recommended for obstetric reasons and for women who are on full anticoagulation during delivery, due to the risk of fetal intracranial hemorrhage [3].
- The recent American Heart Association (AHA) [4] and European Society of Cardiology [5] guidelines do not support the use of antibiotic prophylaxis during vaginal delivery, owing to the limited data. However, for those at highest risk of an adverse outcome, such as patients with Eisenmenger syndrome or cyanosis, it can be considered at the time of rupture of the membrane [2].

Hemodynamic Changes of a Normal Pregnancy and Delivery

- Numerous maternal physiological adaptations take place to supply the increased metabolic requirements by the mother and the fetus, which include (Fig. 37.1):
  - ↑ heart rate (HR) (~15–30%), which peaks during delivery
  - ↑ plasma volume, which reaches its peak around delivery
  - ↑ red blood cell (RBC) mass due to ↑ in erythropoietin
  - ↓ systemic vascular resistance (SVR) due to low flow resistance circuit in the placenta, increase in endo-

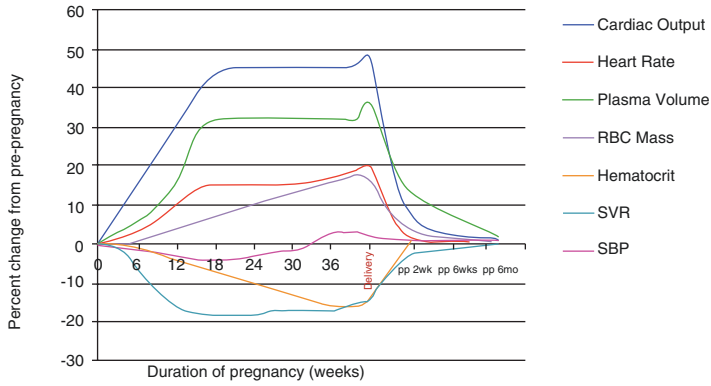

FIGURE. 37.1 Hemodynamic changes during pregnancy, delivery, and postpartum. *RBC* red blood cell, *SBP* systolic blood pressure, *SVR* systemic vascular resistance

thelial prostacyclins, enhanced nitric oxide production, and increased relaxin

- Increase in plasma volume (increased preload) combined with an increase in HR leads to increase in cardiac output (CO). CO normally rises approximately 30–50% (1.8–2.0 L).
- The increase in RBC mass is less than the rise in plasma volume, which creates a relative anemia and a decrease in hematocrit.
  - Relative anemia is beneficial in normal pregnancies, where there is a reduction in blood viscosity, which reduces resistance to flow and facilitates placental perfusion.
- The decrease in SVR maintains the systolic blood pressure at a normal value throughout pregnancy.
- Central venous pressure and pulmonary capillary wedge pressure remain normal throughout pregnancy [6].
- All of the major hemodynamic shifts occur early in the second trimester and begin to normalize within the first few days postpartum and return to baseline by 6 months [7].

- During delivery, there is an increase in CO, central venous pressure, and arterial pressure due to uterine contractions [8].
- However, Valsalva maneuver during the second stage of delivery elicits a transient fall in venous return and CO. Limiting the second stage of delivery by passive descent or assisting with forceps or vacuum extraction is beneficial in patients with critical left-sided obstruction (aortic stenosis, mitral stenosis), pulmonary arterial hypertension, or low stroke volume (i.e., Fontan circulation) [9].
- Post delivery, there is as much as 500 mL of blood sequestered to the mother (autotransfusion). Autotransfusion and increase in SVR may unmask myocardial dysfunction in women who have abnormal systemic ventricles.

Preconception Risk Prediction and Counseling

- Women with CHD may have multiple unique factors including abnormal anatomy and or abnormal cardiac physiology that may increase risk of pregnancy and require individualized care.
- Maternal risk can be assessed using various risk predictors:
  - Lesion complexity:
  - In a systemic literature review, Drenthen et al. demonstrated the occurrence of the most important cardiac event rates organized by lesion (Fig. 37.2) [10].
  - CARPREG (Canadian Cardiac Disease in Pregnancy) risk score
  - ZAHARA (Zwangerschap bij Aangeboren HARtAfwijkingen) risk score
  - Modified WHO (World Health Organization) classification
- Conditions with increased pregnancy risk include:
  - Prior adverse cardiac event (arrhythmia, stroke, transient ischemic attack, pulmonary edema)

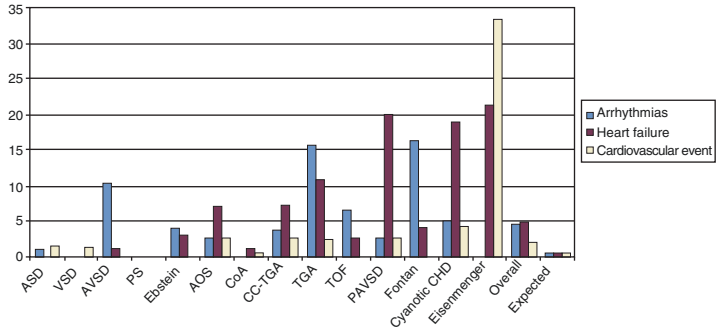

FIGURE. 37.2 Lesion-specific cardiac complications encountered during pregnancy in women with congenital heart disease. The last column named "expected" shows the expected rates in health women. *ASD* atrial septal defect, *VSD* ventricular septal defect, *AVSD* atrioventricular septal defect, *PS* pulmonic stenosis, *AOS* aortic stenosis, *CoA* coarctation of aorta, *CC-TGA* congenitally corrected transposition of the great arteries, *TGA* transposition of the great arteries, *TOF* Tetralogy of Fallot, *PAVSD* pulmonary atresia with ventricular septal defect, *CHD* congenital heart disease. Reproduced with permission from Drenthen et al. [10]

  - Poor functional capacity
  - Abnormal chronotropic response on cardiopulmonary exercise stress testingPulmonary hypertension
  - Aortic dilation
  - Anticoagulation
  - Mechanical prosthetic valves and anticoagulation
  - Cyanosis
  - Impaired systemic ventricular function
  - Subpulmonary ventricular dysfunction

- In 2001, CARPREG investigators introduced a risk stratification score based on a prospective cohort of pregnant women with heart disease and their outcomes of 599 pregnancies not ending in miscarriage [11].
  - Women with adult congenital heart disease consisted of 74% of the cohort.

  - Four major predictors for primary cardiac events were:
    Prior cardiac event (heart failure, transient ischemic attack, or stroke before pregnancy) or arrhythmia
    Baseline New York Heart Association class >II or cyanosis
    Left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, or peak left ventricular outflow tract gradient >30 mmHg by echocardiography)
    Reduced systemic ventricular systolic function (ejection fraction <40%)
  - A risk score was derived for each pregnancy based on the number of predictors. The estimated risk of a cardiac event in pregnancies with 0, 1, and >1 points was 5%, 27%, and 75%, respectively.

- More recently, in 2010, ZAHARA investigators proposed a modified risk score based on their cohort of 1802 pregnant women with congenital heart disease [12].

  Table 37.1 shows the major predictors of outcomes and the points given to each.
  Table 37.2 shows the modified risk score for cardiac complications during completed pregnancies in women with CHD.

Table 37.1 Predictors of cardiac outcomes and points given to each one of them

Predictors of cardiac outcomes	Points
History of arrhythmias	1.5
Cardiac medication before pregnancy	1.5
NYHA class >II prior to pregnancy	0.75
Left heart obstructions (peak left ventricular outflow gradient >50 mmHg or aortic valve area <1.0 cm^2)	2.5
Moderate or severe systemic atrioventricular (AV) valve regurgitation	0.75
Moderate or severe pulmonary AV valve regurgitation	0.75
Mechanical valve prosthesis	4.25
Corrected or uncorrected cyanotic heart disease	1

Adapted from Drenthen et al. [12]

Table 37.2 Modified ZAHARA risk score for cardiac complications during completed pregnancies in women with congenital heart disease

Points	Percentage of the total number of completed pregnancies (%)
0–0.50	2.9
0.51–1.50	7.5
1.51–2.50	17.5
2.51–3.50	43.1
>3.51	70

Adapted from Drenthen et al. [12]

- Modified World Health Organization (WHO) classification (Table 37.3) provides commonly used risk stratification and recommendations for management for pregnant women with cardiovascular disease.
- A prospective validation study showed that cardiac complications during pregnancy for women with CHD were best predicted by WHO classification followed by ZAHARA as compared to CARPREG [13], but did not reliably predict fetal outcomes [14].
- Among pregnant women with CHD who deliver successfully, one study suggested lower rate of mortality compared to women who have not had a pregnancy or men with CHD [15]. This requires further delineation but may be related to having enough cardiac reserve to tolerate the significant physiologic stressors of pregnancy.

Fetal Risks

- Fetal risks include risk of prematurity, small for gestation age, offspring mortality, and the risk of recurrence of CHD and are closely related to the complexity of the maternal heart disease (Fig. 37.3).

Table 37.3 Modified WHO risk classification and management recommendations

WHO pregnancy risk classification	Conditions
I No detectable increased risk of maternal mortality and no/mild increase in morbidity	• Uncomplicated, small, or mild – Pulmonary stenosis – Patent ductus arteriosus – Mitral valve prolapse • Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) • Isolated atrial or ventricular ectopic beats
II (If otherwise well and uncomplicated) Small increased risk of maternal mortality or moderate increase in morbidity	• Unoperated atrial or ventricular septal defect • Repaired tetralogy of Fallot • Most arrhythmias
II–III (Depending on individual)	• Mild left ventricular impairment • Hypertrophic cardiomyopathy • Native or tissue valvular heart disease not considered WHO I or IV • Marfan syndrome without aortic dilatation • Aorta <45 mm in aortic disease associated with bicuspid aortic valve • Repaired coarctation

Table 37.3 (continued)

WHO pregnancy risk classification	Conditions
III Significantly increased risk of maternal mortality or severe morbidity. Expert counseling required. If pregnancy decided upon, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth, and postpartum	• Mechanical valve • Systemic right ventricle • Fontan circulation • Cyanotic heart disease (unrepaired) • Other complex congenital heart disease • Aortic dilatation 40–45 mm in Marfan syndrome • Aortic dilatation 45–50 mm in aortic disease associated with bicuspid aortic valve
IV Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs termination should be discussed. If pregnancy continues, care as for class III	• Pulmonary arterial hypertension of any cause • Severe systemic ventricular dysfunction (EF<30%, NYHA III–IV) • Previous peripartum cardiomyopathy with any residual impairment of left ventricular function • Severe mitral stenosis, severe symptomatic aortic stenosis • Aortic dilatation >45 mm in Marfan syndrome • Aortic dilatation >50 mm in aortic disease associated with bicuspid aortic valve • Native severe coarctation

Adapted from Thorne [23]

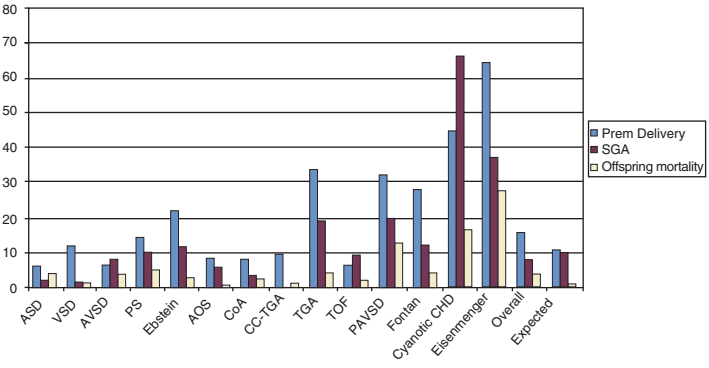

FIGURE. 37.3 Lesion-specific fetal complications encountered during pregnancy in women with congenital heart disease. The last column named "expected" shows the expected rates in health women. Abbreviations—same as Fig. 37.2. *SGA* small for gestational age. Reproduced with permission from Drenthen et al. [10]

- Fetal and perinatal mortality of 4% is observed in offspring of women with CHD, and these are related to a relatively high incidence of premature delivery and recurrence of CHD [10].
- Risk factors that are associated with adverse fetal outcomes are complexity of maternal CHD, maternal pre-pregnancy functional class>II or cyanosis, maternal left heart obstruction, smoking during pregnancy, multiple gestation, use of oral anticoagulants during pregnancy, and mechanical heart valve prosthesis [16].
- The risk of CHD in the general population is 0.8%. The risk is increased to 3–7% in the offspring of patients with CHD. Women with a CHD have a greater risk of CHD in their offspring than men with CHD [17]. Therefore, all men and women with CHD should be offered a fetal echocardiogram at 18–22 weeks gestation [3].
- Cyanotic CHD, patients with Fontan physiology, Eisenmenger syndrome, and pulmonary atresia with ventricular septal defect have the highest rate of maternal complication or adverse cardiac event, fetal complications

of premature delivery, intrauterine growth retardation, and mortality. For these women, counseling for contraception should begin at a young age.

Mechanical Valves and Anticoagulation

- Women on anticoagulation are at a higher risk of complications during pregnancy due to the risk of bleeding and mechanical valve thrombosis.
- All women with mechanical heart valves should undergo preconception counseling by a cardiologist with expertise in valvular heart disease and pregnancy.
- The risk of thromboembolism is greatest for small, single-leaflet tilting disk prostheses and least in large aortic-bileaflet tilting disk valves but still a significant concern.
- Warfarin crosses the placenta and can cause embryopathy during the first trimester; however, teratogenic effects have been shown to be less common (risk of embryopathy <1%) when daily doses ≤5 mg are used [18, 19].
- Conversely, low molecular weight heparin (LMWH) does not cross the placenta but is associated with higher rates of thromboembolic complications due to subtherapeutic serum levels and requires careful monitoring for adequate anticoagulation. The risk of valve thrombosis can be nearly 5% on heparin vs. <1% on warfarin during pregnancy.
- Therefore, the 2014 AHA and American College of Cardiology guidelines for the management of valvular heart disease recommend continuation of warfarin during pregnancy if the warfarin dose used to achieve a therapeutic international normalized ratio is ≤5 mg [20].
- Patients who require higher doses should instead be treated with dose-adjusted low molecular weight heparin, with a target peak anti-XA level of 0.8–1.2 U/mL for the first trimester, followed by a transition to warfarin for the remainder of the pregnancy [20]. In the future, trough measurements may prove to be useful as well.

- Unfractionated heparin is a less attractive alternative, owing to the requirement of continuous infusion and its association with osteoporosis, thrombocytopenia, and higher rates of thromboembolic complications. LMWH has an enhanced anti-XA:IIa ratio which also results in a reduced bleeding risk while also offering stable and predictable pharmacokinetics and a higher bioavailability and half-life.
- Warfarin should be replaced with continuous infusion of unfractionated heparin 10 days prior to the planned delivery to decrease the risk of fetal/neonatal intracranial hemorrhage.
- All women with mechanical valves should be on low-dose aspirin throughout pregnancy.
- There should be 24 h between the last dose of LMWH and an epidural to reduce complication risk.
- Heparin may be resumed 6–12 h after vaginal delivery and warfarin resumed 2–3 days postpartum (with LMWH bridge until therapeutic) if no contraindications.

Genetic Counseling

- Syndromic diseases usually are autosomal dominant conditions with a transmission risk of 50%. Therefore, AHA recommends genetic testing for all patients with clinical features of syndromic diseases, including Marfan, Holt-Oram, Noonan, Alagille, CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital abnormality, and ear abnormality), 22q11.2 microdeletion, and Williams syndromes.
- Patients with CHD lesions associated with 22q11 deletion syndrome and/or DiGeorge syndrome, including tetralogy of Fallot, interrupted aortic arch, truncus arteriosus, ventricular septal defect with aortic arch anomaly, isolated aortic arch anomaly, or discontinuous branch pulmonary arteries, should also be offered genetic testing.

- Additionally, Heart Rhythm Society recommends genetic evaluation in the setting of maternal channelopathies and cardiomyopathies [21].

Cardiac Surgery During Pregnancy

- Due to the high rate of fetal mortality, cardiac surgery should be limited to cases in which medical and interventional treatments fail [5, 22]. It should be delayed as much as possible to reduce the risk of fetal immaturity.
- Early delivery before cardiac surgery should be considered when gestational age is >28 weeks [5].

Anesthesia and Delivery

- Planning for the delivery in advance with a multidisciplinary team and circulation of the plan to the staff members is critical in obtaining favorable maternal and fetal outcomes.
- Vaginal delivery should be preferred unless there is an obstetric indication for cesarean delivery, maternal hemodynamic decompensation, therapeutic anticoagulation, or patient has Marfan syndrome with aortic root diameter >4 cm [4, 5].
- In patients with critical obstructive lesions, fragile aortas, and pulmonary hypertension, assisted second stage of vaginal delivery should be performed with vacuum extraction or forceps to avoid Valsalva maneuver during delivery.
- Pulmonary artery catheters are usually not indicated unless the mother develops severe heart failure and/or cardiogenic shock.
- Monitoring that may be required during labor:
  - Continuous pulse oximetry for patients with cyanotic CHD or right to left shunting

- Telemetry for patients with increased risk of developing serious arrhythmias, such as ventricular tachycardias
- 5-lead EKG monitoring for patients at risk for myocardial ischemia
- External defibrillator in patients with a history of poorly tolerated tachyarrhythmias
- Intra-arterial catheter for high-risk patients having cesarean delivery

Recommendations for Pregnancy and Contraception

Class I

1. Patients with CHD should have consultation with an ACHD expert before they plan to become pregnant to develop a plan for management of labor and the postpartum period that includes consideration of the appropriate response to potential complications. This care plan should be made available to all providers. (*Level of Evidence: C*)
2. Patients with intracardiac right-to-left shunting should have fastidious care of intravenous lines to avoid paradoxical air embolus. (*Level of Evidence: C*)
3. Prepregnancy counseling is recommended for women receiving chronic anticoagulation with warfarin to enable them to make an informed decision about maternal and fetal risks. (*Level of Evidence: B*)

Class II

1. Meticulous prophylaxis for deep vein thrombosis, including early ambulation and compression stockings, can be useful for all patients with intracardiac right-to-left shunt. Subcutaneous heparin or low molecular weight heparin is reasonable for prolonged bed rest. Full anticoagulation can be useful for the high-risk patient. (*Level of Evidence: C*)

Class III

1. The estrogen-containing oral contraceptive pill is not recommended for ACHD patients at risk of thromboembolism, such as those with cyanosis related to an intracardiac shunt, severe PAH, or Fontan repair. (*Level of Evidence: C*)

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Chapter 38
Heart Failure and Transplant in Adult Congenital Heart Disease

Laura D. Flannery

- Epidemiology of heart failure (HF) in adults with congenital heart disease (ACHD):
  - HF is one of the leading causes of morbidity and mortality in ACHD [1].
  - Hospitalizations for HF in the ACHD population have nearly doubled between 1998 and 2005 [2].
  - Prevalence of HF increases with age, and most patients with CHD will present with heart failure for the first time in adulthood [3, 4].
  - Prevalence of HF is highest in [3, 4]:
    - Transposition of the great arteries (TGA) with systemic right ventricles (i.e., D-TGA status post-atrial switch procedure or congenitally corrected TGA).
    - Tetralogy of Fallot.

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  - Single ventricle physiology.
  - Development of HF portends a poor prognosis for ACHD patients, with a 1-year mortality of 24% and a 3-year mortality of 35% for ACHD patients after a HF admission [5] (Fig. 38.1).
- Challenges in management of HF in ACHD [6, 7]:
  - Consistent definition and identification of ACHD patients in HF is difficult as the presentation and etiologies are diverse.
  - It can be difficult to recognize HF in ACHD as many patients feel asymptomatic and may not be aware of slowly progressive exercise limitations.
  - The major trials in HF excluded ACHD patients, so applicability of typical first-line interventions is uncertain.
- Various etiologies of HF in ACHD [3]:
  - Mechanisms of cardiomyopathy:

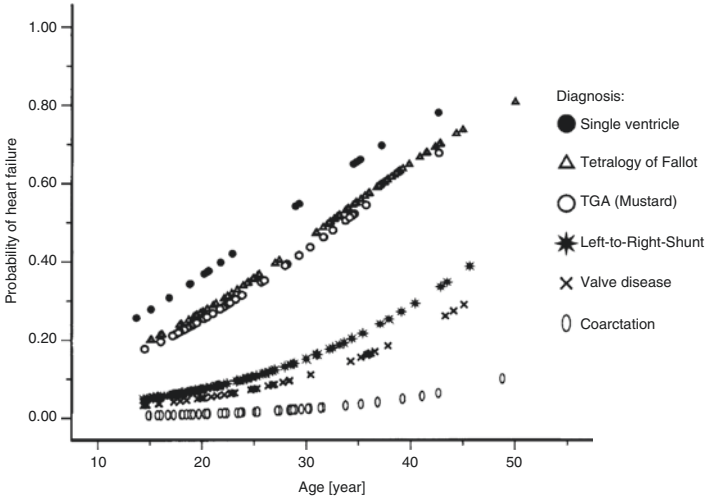

Figure 38.1 Incidence/prevalence of HF in ACHD. Reprinted from *The American Journal of Cardiology;* Norozi K, Wessel A, Alpers V, et al. Incidence and Risk Distribution of Heart Failure in Adolescents and Adults With Congenital Heart Disease After Cardiac Surgery. p1238–43 (2006) [4], with permission

    - Pressure-loading lesions (such as coarctation of the aorta) leading to hypertrophy and diastolic abnormalities
    - Volume-loading lesions causing ventricular remodeling (i.e., severe pulmonic regurgitation leading to RV dilation and dysfunction)
    - Intrinsic congenital myopathy such as in Ebstein's anomaly or left ventricular non-compaction
    - Right ventricle acting as systemic ventricle (D-TGA with atrial switch procedure or congenitally corrected TGA)
    - Tachyarrhythmia-mediated myopathy
    - Pacemaker-mediated myopathies
    - Dyssynchrony from abnormal development of bundle branch blocks
    - Myocardial injury from chronic hypoxia
    - Ischemia due to anomalous coronary origin or ostial restenosis among patients who have undergone coronary artery reimplantation
  - Pulmonary hypertension (may be shunt-related or secondary to left-sided obstructive disease).
  - Volume expansion during pregnancy [8].
  - Neurohormonal activation due to persistent abnormal cardiac pressure, compliance, volume, and flow.
  - Always consider superimposed acquired cardiac disease as ACHD patients are living longer (atherosclerotic coronary artery disease, atrial fibrillation, diabetes-mediated cardiomyopathy).

- Recognizing HF in ACHD:
  - Because of lifelong adaptation to an abnormal cardiovascular system, many patients feel asymptomatic despite progressive functional decline [9].
  - HF may often first manifest as arrhythmia [9]; therefore, any new onset arrhythmia in ACHD necessitates echocardiography to assess for new structural disease or ventricular dysfunction.

- Right heart failure is common and may be indolent and unrecognized [9].
- Fontan patients may first manifest Fontan failure with evidence of lymphatic dysfunction: chronic diarrhea due to protein-losing enteropathy or coughing of bronchial casts due to plastic bronchitis [9].
- Be vigilant for other common signs of progressing HF: hyponatremia, worsening renal function, and intolerance to medications (causing hypotension) [9].
- Interpretation of NT-proBNP in ACHD patients is difficult [8].
  - Complex ACHD lesions have higher baseline levels, and hypoxia is known to increase BNP which can therefore confound interpretation in cyanotic ACHD.
  - However, NT-proBNP has been shown to correlate with increasing ventricular size and decreasing ejection fraction, and trending NT-proBNP may offer insight into the presence of subclinical HF.
- Stratification of ACHD patients by the Seattle Heart Failure Model score identifies patients at high risk of HF admission and mortality [10].
- Cardiopulmonary exercise testing (CPET) is a quantitative and informative tool to guide prognosis and advance of therapies [8].

- Management of HF in ACHD (Fig. 38.2):
  - Optimization of HF with typical pharmacological management is standard, though research demonstrating benefits in ACHD is limited.
    - Decongestions with diuretics is the mainstay for management of volume expansion.
    - Beta-blockers are often prescribed to ACHD patients regardless of arrhythmia prevention, but the benefit of beta-blockers in HF has not yet been demonstrated in ACHD and is inferred from ischemic cardiomyopathy [8].
    - Similarly, no studies have addressed the benefit of angiotensin-converting enzyme inhibitors or angioten-

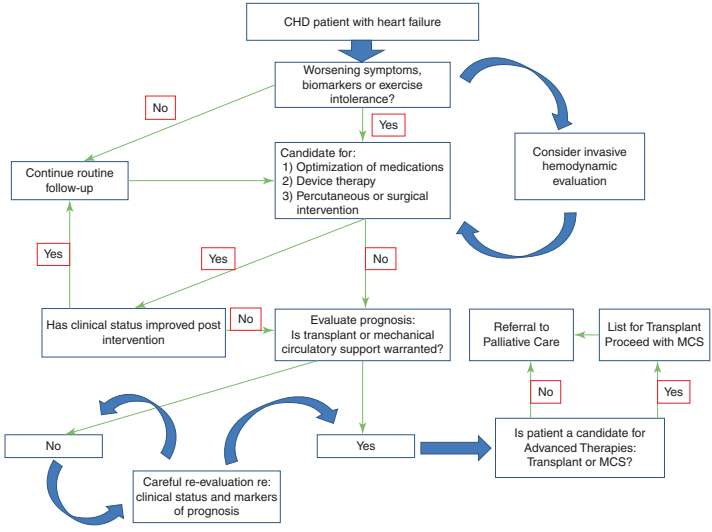

FIGURE 38.2 Approach to HF in ACHD. Reprinted from *Circulation*; Ross HJ, Law Y, Book WM, et al. American Heart Association Adults With Congenital Heart Disease Committee of the Council on Clinical Cardiology and Council on Cardiovascular Disease in the Young, the Council on Cardiovascular Radiology and Intervention, and the Council on Functional Genomics and Translational Biology. Transplantation and mechanical circulatory support in congenital heart disease: a scientific statement from the American Heart Association. 133:802–20 (2016) [15], with permission

sin II receptor blockers in ACHD patients. It is thought that these patients often have decreased renin-angiotensin-aldosterone system activation and therefore receive less benefit from these medications [8].

- Valsartan was studied in patients with systemic RVs (D-TGA with atrial switch or congenitally corrected TFA) in a randomized placebo-controlled trial (n = 88) which demonstrated some improvement in RV end diastolic volume and RV mass by MRI at 3 years but no improvement in RV ejection fraction, exercise capacity, or quality of life [11].

- Pulmonary vasodilators in patients with pulmonary hypertension have shown to be beneficial in ACHD. A significant improvement in survival was noted among Eisenmenger patients who received advanced pulmonary vasodilator therapy compared to those who did not [12]. Of note, the concern for reversal of shunt in patients with right-to-left shunt has not been demonstrated in these studies [13, 14].

  – Early consideration of invasive procedures, in the of setting shunts or obstruction, to reduce and limit HF is key and unique to ACHD patients (i.e., is there a shunt that can be closed, a stenotic baffle that can be stented, etc.) [15]
  – Indications for cardiac resynchronization therapy are currently extrapolated from acquired HF [8].

- Potential indications for heart transplantation in ACHD:

  – NYHA Class III, IV
  – Cardiogenic shock (requiring inotropes or mechanical circulatory support)
  – Decreased pVO_2 (will vary), <12–14 mL/kg/min or <50% predicted (recall that mean pVO_2 for the general population and for specific CHD lesions are not always similar)
  – Intractable malignant arrhythmias

- Heart transplantation in ACHD:

  – The prevalence of heart transplant among ACHD has increased by 41% from 1999 to 2008 [16].
  – ACHD patients who receive heart transplants have higher mortality rates immediately postoperatively than non-ACHD patients who receive transplants; however they benefit from better long-term survival [17].
  – ACHD patients are more frequently listed at lowest priority [6].
  – Wait-list mortality is similar for ACHD and non-ACHD patients on the transplant list, despite non-ACHD population receiving more transplants [6].

- Death or de-listing due to worsening clinical status from the heart transplant list is more likely for ACHD patients than non-ACHD patients [6].

- Transplant considerations:
  - The criteria to determine priority status for heart transplant may misclassify prognosis in the ACHD population [6].
    - ACHD patients are generally not candidates for mechanical circulatory support (MCS) due to anatomic difficulties, shunts, multiple prior operations, or other hemodynamic challenges. However, the presence of an LVAD or other MCS increases priority status listing for transplantation. Only 3% of ACHD patients who receive transplant had mechanical circulatory support versus 17% of non-ACHD patients [18].
    - Patients may not benefit from inotropic support or may not be candidates for hemodynamic monitoring with a PA line, which also leads to a higher priority status listing. Some patients may be exempted by regional committees and assigned status 1Ae if needed.
  - ACHD patients are often referred to transplant late, perhaps due to delayed recognition of symptoms, barriers in health-care delivery, or gaps in care 6.
  - ACHD patients often have more comorbidities, such as renal failure, liver failure, prior strokes, protein-losing enteropathy, compromised lung function, or hematological disorders 6. These complications may preclude single-organ transplantation; some patients may be considered for dual-organ transplantation (heart/lung, heart/liver, or heart/kidney). How these comorbidities affect prognosis posttransplant as compared to non-ACHD has yet to be studied.

- Pretransplant considerations in ACHD [15]:
  - Psychosocial: increased rates of depression, anxiety, post-traumatic stress disorder, obsessive-compulsive disorder in patients with ACHD.
  - Surgical risk given multiple past cardiac surgeries.
  - Assessment of collateral vessels within the chest wall, increase perioperative bleeding risks.
  - Cardiac and great vessel anatomy: may require extensive reconstruction; dextrocardia and complex anatomy may be particularly challenging.
  - HLA sensitization.
  - Thorough evaluation of pulmonary vascular resistance.
  - Assessment for other organ dysfunction, especially the liver and kidney.
- Important contraindications to heart transplant in ACHD:
  - Multi-organ failure
  - Active malignancy
  - Active hepatitis C
  - Other severe multiple congenital anomalies
- Relative contraindications to heart transplantation in ACHD may include:
  - Increased pulmonary vascular resistance (though may recover or may be a candidate for heart-lung evaluation)
  - Morbid obesity (weight loss surgery is increasingly being considered in the ACHD population)
  - Extensive collateral vessels increasing bleeding risk
  - Heterotaxy syndromes (may affect anatomic connections)

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Chapter 39
Atherosclerosis in Adult Congenital Heart Disease

Laura D. Flannery

- **Background**: Several studies have demonstrated an increasing burden of atherosclerotic cardiovascular disease (ASCVD) in individuals with adult congenital heart disease (ACHD).
  - The number of hospitalizations for ACHD has increased more for coronary artery disease than for any other disease process (by 119% from 1998 to 2005) [1].
  - Coronary artery disease is currently the second most common cause of hospital admission for ACHD in the United States (arrhythmia is the first) [1].
  - As of 1990, myocardial infarction has replaced arrhythmia as the leading cause of death for non-cyanotic lesions [2].
  - A Canadian population-based cohort study reported a 7% rate of myocardial infarction in ACHD as compared to an age-matched prevalence of 5% [3].
  - A single center in Canada performed a retrospective chart review which revealed that 14% of their ACHD

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population had angiographically confirmed coronary artery disease before the age of 40 [4].

- **Traditional risk factors for ASCVD in ACHD**:
  - An estimated 85% of children with CHD now survive into adult life [5]. As the ACHD population ages, age alone will drive an increasing risk of atherosclerosis.
  - 80% of individuals with ACHD have at least one ASCVD risk factor:
    - Notably, studies have indicated a higher prevalence of hypertension and diabetes mellitus (DM) than in the general population and age-matched controls but a lower prevalence of smoking and obesity [6–8].
    - Other studies, however, have indicated that children born with CHD, who traditionally experienced failure to thrive and low-weight issues, are now becoming overweight at rates similar to that of the general pediatric population, which portends similar rates of obesity in adulthood [9, 10].
    - The risk of diabetes is higher in patients with cyanotic ACHD than acyanotic ACHD. It is hypothesized that hypoxia negatively impacts glucose metabolism [11].
    - Coarctation of the aorta is often associated with systemic hypertension, even after repair [12].
- **Additional risk factors unique to ACHD**:
  - Certain congenital heart defects are associated with an increased risk of atherosclerotic coronary artery disease due to the pathophysiology of their defect, such as coarctation of the aorta [12, 13].
  - Other patients may be at risk because of coronary artery reimplantation that is required in reparative procedures, such as in the arterial switch operation for transposition of the great arteries [14].
  - Patients who undergo multiple palliative procedures may be exposed to repeated episodes of ischemia-reperfusion injury [15].

- Given the complexity of ACHD patients, it is possible that primary prevention is not prioritized (either by limited time for clinicians or lack of understanding by patients) in clinic visits. It has been demonstrated that in a tertiary care center, ACHD patients are less likely to receive statin prescriptions for guideline-based primary prevention than non-ACHD patients (Fig. 39.1) [16].

- **Diagnosis and management**:
  - ACHD patients should have the benefit of lifelong cardiovascular preventative care and theoretically, ideal risk factor modification.
  - Vigilance regarding risk factor modification, measuring of HbA1c and lipid panels, and primary prevention with aspirin and statin therapies must become a part of routine care of the ACHD patient.
  - Guidelines for HMG CoA reductase inhibitor (statin) use for adults ages 40–75 years should be followed unless significant contraindications exist. These include:
    - Moderate-intensity statin prescription for adults ages 40–75 years with DM.
    - High-intensity statin for adults ages 40–75 with DM and ASCVD risk >7.5% at 10 years.

Figure 39.1 Statin prescription rates in subjects with guideline-based indication

    - In patients without DM, moderate-intensity statin for ASCVD Risk 5–7.5%
    - In patients without DM, moderate- to high-intensity statin for ASCVD Risk >7.5%

- USPSTF guidelines recommend low-dose aspirin for primary prevention of cardiovascular disease and colorectal cancer in adults ages 50–59 years with ASCVD risk >10% at 10 years.

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Index

A
ACC/AHA guidelines 2008
  coarctation of the aorta, 126–129
  congenital mitral stenosis, 182
  double-chambered right ventricle, 277
  Ebstein's anomaly, 382
  L-loop transposition of the great arteries, 363
  subaortic stenosis, 193
  subpulmonic stenosis, 268
  supravalvular aortic stenosis, 215
  tetralogy of Fallot, 309–311
Adult congenital heart disease (ACHD)
  abnormal exercise capacity in, 511
  CT *vs*. CMR, selection of, 480–482
Alagille syndrome, 254
Ampltazer duct occluder, 102
Anesthesia and delivery, 545
Aneurysm, 467
Anomalous coronary artery origin from the opposite sinus
  anatomy, 450
  cardiac catheterization, 454
  chest X-ray, 454
  clinical presentation, 453
  coronary CTA, 455
  echocardiography, 454
  electrocardiography, 454
  high-risk features, 451
  interarterial course, 451
  management, 455–457
  physical exam, 454
  physiology, 451
  prepulmonic course, 451
  retroaortic course, 451
  subpulmonic course, 451
Anomalous origin of the left coronary from the pulmonary artery (ALCAPA)
  anatomic definition and pathophysiology, 448–449
  catheter angiography, 501
  chest X-ray, 450
  clinical presentation, 449
  coronary CTA, 450
  electrocardiography, 450
  epidemiology, 447
  physical exam, 449–450

D. DeFaria Yeh, A. Bhatt (eds.), *Adult Congenital Heart Disease in Clinical Practice*, In Clinical Practice,
https://doi.org/10.1007/978-3-319-67420-9

Anomalous origin of the right coronary from the pulmonary artery (ARCAPA)
anatomic definition and pathophysiology, 448–449
chest X-ray, 450
clinical presentation, 449
coronary CTA, 450
electrocardiography, 450
epidemiology, 447–448
physical exam, 449–450
physical exam, 450
Antibiotic prophylaxis, 526
infective endocarditis prevention, 527
rationale for, 526
Antibiotic regimens, 528
Anticoagulation, 470
pregnant women on, 543–544
Antiplatelet therapy, 470
Aorta, 6
Aortic coarctation
CTA, 491
MRI, 490
Aortopulmonary shunts, 299–300
Aortopulmonary window, 112–113
Arrhythmia, 51, 161, 385–386
L-TGA, 365
and sudden death, 136
Arteries, 6
Asplenia syndrome, 14
Atherosclerotic cardiovascular disease (ASCVD), 560
Atrial chambers, 3
Atrial septal defects (ASD)
advanced imaging techniques, 43–44
anatomy, 31
cardiac catheterization, 42
chest radiograph, 39
clinical presentation in adults, 37–38
complications, 49
and Ebstein's anomaly, 386
echocardiography, 41–42
electrocardiogram, 39
epidemiology, 31
genetic and maternal factors, 37
management
of adult survivors, 44–51
of pregnancy, 52
physical exam, 38–39
physiology, 34
septum primum defect, 32, 35
septum secundum defect, 33
sinus venosus defect, 33
spectrum of disease, 35
Atrioventricular (AV) valves, 8
Atrioventricular canal-type defect, 35
Atrioventricular septal defects (AVSD)
advanced imaging techniques, 83
anatomy, 71
atrial arrhythmia, 87
cardiac catheterization, 82
chest radiography, 82
clinical presentation in adults, 79
complete heart block, 87
echocardiography, 82
electrocardiogram, 81–82
epidemiology, 71
forms of, 72
in patients with trisomy 21, 78
infective endocarditis prophylaxis, 87
LV outflow tract obstruction, 86
management, 83–88
of pregnancy, 88
medical management, 87
physical exam, 80–81
physiology, 77
pulmonary artery banding, 79
spectrum of disease, 71
surgical management, 86
surgical repair of, 79
Atrium, 3

B
Balloon valvuloplasty, 244, 245
Bicuspid aortic valve (BAV), 219, 432, 435
Bidirectional cavopulmonary connection, 384
Bidirectional Glenn procedure, 384
Blalock-Thomas-Taussig shunt (BTT shunt), 299, 400, 402
Bland-White-Garland syndrome, 448
Bulboventricular loop, 8

C
Calcium channel blockers, 133
Canadian Cardiovascular Society, 183
Cardiac catheterization
  congenital coronary arteriovenous fistula, 458
  Ebstein's anomaly, 379
  Kawasaki disease, 467–468
  left ventricular non-compaction, 424
  supravalvular pulmonic stenosis, 256
  thoracic aortic disease, 437
  valvular pulmonic stenosis, 240
Cardiac chambers morphology, 3–9
Cardiac CT, left ventricular non-compaction, 426
Cardiac MRI
  features, 479
  left ventricular non-compaction, 424
  limitations, 480
  single-ventricle Fontan procedure, 498
  tetralogy of Fallot, 484–486
Cardiac position, 3, 4
Cardiac resynchronization therapy, 554
Cardiac surgery, during pregnancy, 545
Cardiac-gated CT, 478
  advantages, 478
Cardiopulmonary exercise test (CPET)
  biventricular ejection fraction, 514
  heart rate reserve, 514
  peak oxygen consumption, 513
  vs. standard cardiac stress test, 512
  tagged red blood cell radionuclide imaging, 513
  uses, 512
  ventilatory efficiency, 514
Catheter-based intervention, KD, 470
Catheter-based therapy, 130
Cesarean delivery, and anesthesia, 546
Chamber enlargement, 29
Chest X-ray
  ALCAPA and ARCAPA, 450
  anomalous coronary artery origin from the opposite sinus, 454
  Ebstein's anomaly, 378
  left ventricular non-compaction, 421
  supravalvular pulmonic stenosis, 256
  thoracic aortic disease, 436–437
  valvular pulmonic stenosis, 239
Circle of Willis (berry) aneurysms, 219
Clubbing of fingers, 122

Coarctation of the aorta
ACC/AHA guidelines 2008, 226–227
advanced imaging techniques, 224–225
anatomy, 218
Bicuspid aortic valve (BAV), 219
cardiac catheterization, 223
chest X-ray, 221–222
choice of intervention, 229
clinical presentation in adults, 220
echocardiography, 222–223
electrocardiography, 221
epidemiology, 217–218
genetics, 220
long-term follow-up, 229
management
of adult survivors, 225–230
of pregnancy, 230
physical exam, 220–221
physiology, 218
postductal, 219
preductal, 219
types of, 219
Coarctation, defined, 489
Collett and Edwards classification, 322
Common arterial trunk, 6
Computer tomography (CT)
double-outlet right ventricle, 501
single-ventricle Fontan procedure, 498
tetralogy of Fallot, 488
Congenital coronary anomalies. *See also* Anomalous origin of the left coronary from the pulmonary artery (ALCAPA); Anomalous origin of the right coronary from the pulmonary artery (ARCAPA)
Congenital coronary arteriovenous fistula, 457–459
Congenital heart disease (CHD)
advanced imaging, role of
aortic coarctation, 489
atrial septal defects, 492–495
ccTGA, 497–498
D-TGA, 495–497
left ventricular outflow tract obstruction, 489–492
tetralogy of Fallot, 483–488
segmental approach, 482
Congenital heart disease-pulmonary arterial hypertension (CHD-PAH), 117
Congenital mitral stenosis
ACC/AHA guideline, 182
anatomy, 176
associated defects, 179
diagnostics
advanced imaging techniques, 182
cardiac catheterization, 181
chest X-ray, 180
clinical presentation, 179
echocardiography, 180–181
electrocardiography, 180
physical exam, 180
epidemiology, 175
historical background, 176
management
of pregnancy, 183–184
management of patients with, 182–183
physiology, 178
spectrum of disease, 179
Congenital rubella syndrome, 254
Congenital valvular aortic stenosis
advanced imaging techniques, 202
anatomy, 196
cardiac catheterization, 200
chest X-ray, 199
clinical presentation, 198

echocardiography, 200–202
electrocardiography, 199
epidemiology, 195–196
genetics and maternal factors, 198
management
of adult survivors, 202–205
of pregnancy, 205–207
physical exam, 199
physiology, 197
spectrum of disease, 197
with aortopathies, 198
with subaortic stenosis, 198
Congenitally corrected TGA (CCTGA). *See* L-loop transposition of the great arteries (L-TGA)
Conotruncal abnormalities, 485
Cor triatriatum, 167–173
Coronary artery anomalies, incidence, 499
Coronary AV fistula to right atrium, 114
Coronary CTA
ALCAPA and ARCAPA, 450
anomalous coronary artery origin from the opposite sinus, 455
congenital coronary arteriovenous fistula, 458
coronary artery anomalies, 501
Coronary sinus defect, 36

D

DeBakey classification, 434
Dextrocardia, 3
advanced imaging techniques, 22
anatomy, 12
cardiac catheterization, 20
chest X-ray, 18–19
clinical presentation in adults, 16
dextroversion, 18
echocardiography, 19–20
electrocardiography, 17–18
epidemiology, 11–12
genetics and maternal factors, 16
Kartagener's syndrome, 16
management
of adult survivors, 22
of pregnancy, 22
physical exam, 17
physiology, 15
situs ambiguous, 14
situs inversus, 13
situs solitus, 12
spectrum of disease, 15
Direct coronary surgery, 449
Double inlet ventricle (DIRV and DILV), 396–398
Double outlet right ventricle (DORV), 395–396, 501
anatomy, 284
arrhythmias, 293
associated defects, 287
classification, 285
definition, 284
diagnostics
cardiac catheterization, 290
chest X-ray, 289
clinical presentation in adults, 288–290
echocardiography, 289–290
electrocardiography, 289
magnetic resonance imaging (MRI), 290
physical exam, 288–289
epidemiology, 283–284
follow-up, 290–292
infective endocarditis prophylaxis, 293
management
of adult survivors, 290–293
of pregnancy, 293
physiology, 284
repaired patients, 292
spectrum of disease, 286
sudden cardiac death, 293
unrepaired patients, 292

Double-chambered right ventricle (DCRV)
ACC/AHA guidelines 2008, 277
advanced imaging techniques, 276
anatomy, 272
associated defects, 274
cardiac catheterization, 276
chest X-ray, 275
diagnostics
clinical presentation in adults, 274–276
electrocardiography, 275
epidemiology, 272
genetics and maternal factors, 274
management
of adult survivors, 276–278
of pregnancy, 278–279
physical exam, 275
physiology, 272
transthoracic echocardiography (TTE), 275

E

Ebstein's anomaly
ACC/AHA guidelines, 382
anatomy, 371–374
atrioventricular bypass tracts, 375
cardiac catheterization, 379–380
chest radiograph, 378
clinical presentation, 376
complications, management of
arrhythmia, 385–386
atrial septal defects, 386
paradoxical embolism, 386
tricuspid regurgitation, 381–385
echocardiography, 378–379
electrocardiogram, 377–378
electrophysiology studies, 381
epidemiology, 371
exercise testing, 380
genetics and maternal factors, 375
historical background, 372
left heart failure, 387
left-sided lesions, 375
physical examination, 376–377
physiology, 374
pregnancy, 387
right ventricular outflow tract obstruction, 375
septal defects, 374
Echocardiography
anomalous coronary artery origin from the opposite sinus, 454
Ebstein's anomaly, 378–379
Kawasaki disease, 466–467
left ventricular non-compaction, 421–424
supravalvular pulmonic stenosis, 256
thoracic aortic disease, 437
valvular pulmonic stenosis, 239–240
Ectasia, 466
Eisenmenger exam, 39
Eisenmenger syndrome, 51, 118, 122, 125–134
Electrocardiography
ALCAPA and ARCAPA, 450
anomalous coronary artery origin from the opposite sinus, 454
congenital coronary arteriovenous fistula, 458
Ebstein's anomaly, 377–378
ECG-gated cardiac CT, 478
Kawasaki disease, 465
left ventricular non-compaction, 420–421
supravalvular pulmonic stenosis, 256

thoracic aortic disease, 436
valvular pulmonic stenosis, 239
Electrophysiology and Ebstein's anomaly, 381
Erythrocytosis, 134–135
Exercise recommendations
anomalous origins of coronary arteries, patients with, 522
for aortic root dilatation, 522
for cyanotic heart disease patients, 521, 522
for hypertrophic cardiomyopathy, patients with, 522
for Marfan syndrome patients, 522
for obstructive lesions, patients with, 521
for shunt patients, 521

F
Familial thoracic aortic aneurysm dissection (FTAAD), 432, 435
Fetal risks, 539
Fontan palliation and pregnancy, 413
Fontan procedure, 402, 403
consequences of
arrhythmia, 410
heart failure, 410–411
non-cardiac surgery, 412
protein-losing enteropathy, 411–412
thromboembolic risk, 412
transplant indications, 413

G
Genetic counseling, 544
Genetic thoracic aortic disease. *See* Thoracic aortic disease
Genetic transmission, 230
Gerbode defect, 110–112
Glenn shunt, 402
Great arteries, 9
Guanylate cyclase inhibitor, 132

H
Heart failure (HF)
epidemiology, 549
etiologies, 550
incidence/prevalence, 550
management challenges, 550
pharmacological management, 552–554
Heart transplantation
contraindications, 556
indications, 554
pretransplant considerations, 556
relative contraindications, 556
transplant considerations, 555–556
Hemodynamic changes, of normal pregnancy and delivery, 534
Hemoptysis, 136
HMG CoA reductase inhibitor, guidelines for, 561
Hypertension, 230
Hyperuricemia, 136–137
Hypoplastic left heart syndrome (HLHS), 392–394
Hypoxemia, 134

I
Infective endocarditis (IE), 525–527
prophylaxis, 68, 293, 365, 527–528
Infundibular stenosis, 267
Intracardiac shunting, 48–49
Intramitral ring, 177
IV epoprostenol/treprostinil, 133

K
Kartagener's syndrome, 16
Kawasaki disease (KD)
anatomy, 462
cardiac catheterization, 467–468
cardiac magnetic resonance imaging (CMR), 468
cardiac transplantation, 471
catheter-based intervention, 470
clinical features, 463
clinical presentation, 465
computed tomography angiography (CTA), 468
echocardiography, 466–467
electrocardiography, 465
epidemiology, 462
follow-up and patient management, 469–470
genetics and maternal factors, 464, 465
physical exam, 465
physiology, 463, 464
reproductive counseling, 471
surgical intervention, 471
Keutel syndrome, 254

L
Lactating women, CHD imaging, 504
Left heart failure, Ebstein's anomaly, 387
Left ventricular non-compaction (LVNC)
anatomy, 418
associated defects, 419
cardiac catheterization, 424
cardiac computed tomography, 426
cardiac magnetic resonance, 424
chest X-Ray, 421
clinical presentation, 420
diagnostic criteria, limitations of, 426
echocardiography, 421–424
electrocardiography, 420–421
epidemiology, 417
genetics and maternal factors, 419
patient management, 427
physical exam, 420
physiology, 418
positron-emission tomography, 426
pregnant women, 427–428
single-photon emission computerized tomography, 426
Left-to-right shunts, 117
Levocardia, 3
L-loop transposition of the great arteries (L-TGA), 359
ACC/AHA guidelines, 363
anatomy, 354–356
arrhythmias, 365
associated defects, 357
AV valve regurgitation, 362–364
cardiac catheterization, 360–361
cardiac CT, 362
cardiac MRI, 361
chest radiography, 359–360
clinical presentation, in adults, 357–358
echocardiographic essentials, 361
echocardiography, 360
electrocardiography, 358–359
epidemiology, 354
follow-up, 365
genetics and maternal factors, 357
historical background, 354
infective endocarditis prophylaxis, 365
physical exam, 358

physiology and spectrum, 355–357
pregnancy, 365
systemic ventricular failure, 362–364
Loeys-Dietz syndrome, 431, 434, 435

M
Magnetic resonance imaging (MRI)
aortic coarctation, 490
DORV, 290, 501
supravalvular pulmonic stenosis, 256–257
thoracic aortic disease, 438
See also Cardiac MRI
Marfan syndrome, 431, 434, 435
Maternal risk assessment, 536
Mechanical heart valves, pregnant women on, 543
Mesocardia, 3
Mitral ring, 177
Mitral valve, 4
modified Choussat criteria, 407
Murmur, 96

N
National Institute for Health and Care Excellence (NICE) guidelines, 526
Non-cardiac surgery, 412
Non-infundibular subvalvular pulmonic stenosis, 267
Norwood procedure, 403–405

O
Obesity, 520
prevention, 520
rates of, 520
risk factors contributing to, 519
Oral anticoagulants, 133
Oral endothelin antagonists, 132
Overriding, 5
Oxygen content, 28

P
Palliative shunts, 401
Paradoxical emboli, 51, 68, 135–136, 386
Partial anomalous pulmonary venous return (PAPVR)
anatomy, 153
clinical presentation, 156
echocardiography, 159
electrocardiogram, 157
incidence of, 151
management, 159–161
physical exam, 157
physiology, 154
Patent ductus arteriosus (PDA)
advanced imaging techniques, 99–100
anatomy, 93
cardiac catheterization, 98
chest radiography, 97
clinical presentation in adults, 95–96
echocardiography, 97–98
electrocardiogram, 97
embryology, 91
epidemiology, 91
genetic factors, 95
management
in adult survivors, 100–103
of pregnancy, 103
physical exam, 96–97
physiology, 94
spectrum of disease, 94
Persistent left superior vena cava (PLSVC), 143–149
Phosphodiesterase-5 (PDE-5) inhibitors, 132
Platypnea-orthodeoxia, 38
Polysplenia, 14

Preconception, risk prediction and counseling, 536–543
Preeclampsia, 230
Pregnancy, 137–138
  cardiac surgery during, 545
  CHD imaging during, 503
  Ebstein's anomaly, 387
  Fontan palliation, 413
  hemodynamic changes, of normal, 534
  Kawasaki disease, 471
  left ventricular non-compaction, 427–428
  L-TGA, 365
  modified WHO risk classification and management recommendations, 540–541
  and PAPVR, 162
  risk stratification and recommendations, 539
  supravalvular pulmonic stenosis, 261
  and TAPVR, 162
  thoracic aortic disease, 442
  valvular pulmonic stenosis, 248
Primitive cardiac tube, 8
Prostacyclin inhibitors, 132
Pulmonary arterial hypertension, 125–134
Pulmonary arterial vasodilators, 131
Pulmonary artery (PA)
  band, 400
  dilation, 247
Pulmonary Atresia with Intact Ventricular Septum (PAIVS), 398–399
Pulmonary hypertension
  advanced imaging techniques, 124
  anatomy, 117–120
  cardiac catheterization, 124
  chest radiography, 121–123
  diagnostics, 120–125
  echocardiography, 123
  electrocardiogram, 121
  epidemiology, 117
  exercise testing, 124–125
  physiology, 117–120
  and RV failure, 121
  workup, 125
Pulmonary trunk, 6
Pulmonary valve replacement, 245, 246
Pulmonary vascular resistance (PVR), 118
Pulmonary venous, embryology, 151

Q
Qp/Qs ratio, 27

R
Rastelli procedure, 300–302
Right-sided pressure overload, 29

S
Scimitar syndrome, 155, 158
Selexipag, 132
Septum secundum defect, 36
Shone's complex, 219
Shunt
  lesions features, 27–30
  size, 27
Single ventricle Fontan procedure, 499
Sinus of valsalva fistula (SVF), 107–109
Sinus venosus defect, 36
Situs, 7
Situs inversus, 15
Solitary arterial trunk, 6

Spinnaker syndrome, 267
Stanford classification, 434
Statin prescription, for ASCVD, 561, 562
Straddling, 5
Subaortic stenosis
  ACC/AHA guidelines 2008, 193
  advanced imaging techniques, 192
  anatomy, 188
  cardiac catheterization, 191
  chest X-ray, 190
  clinical presentation in adults, 189
  diffuse subvalvular stenosis, 189
  echocardiography, 190–191
  electrocardiography, 189
  management
    of adult survivors, 192
    of pregnancy, 192–193
  physical exam, 189
  physiology, 188
  prevalence of, 187
  spectrum of disease, 188
Subpulmonic stenosis
  ACC/AHA guidelines 2008, 268
  anatomy, 266
  embryology, 266
  epidemiology, 265–266
Subvalvular mitral stenosis, 177
Supravalvular aortic stenosis
  ACC/AHA guidelines 2008, 215
  anatomy, 210
  associated defects, 211
  cardiac catheterization, 214
  cardiac magnetic resonance (CMR) imaging, 214
  chest X-ray, 213
  clinical presentation in adults, 211
  echocardiography, 213–214
  electrocardiography, 213
  epidemiology, 209–210
  genetics and maternal factors, 211
  management
    of adult survivors, 214
    of pregnancy, 214–215
  physical exam, 212–213
  physiology, 210
  spectrum of disease, 211
Supravalvular mitral stenosis, 177
Supravalvular pulmonic stenosis
  Alagille syndrome, 254
  anatomy, 252
  associated defects, 253
  cardiac Catheterization, 256
  chest X-ray, 256
  clinical presentation, 255
  congenital rubella syndrome, 254
  during pregnancy, 261
  echocardiography, 256
  electrocardiography, 256
  epidemiology, 252
  Keutel syndrome, 254
  MRI and CT, 256–257
  physical exam, 255
  physiology, 253
  right ventricular angiographic characterization, 257
  surgical therapy, 260, 261
  transcatheter intervention, 258, 260
  Williams-Beuren syndrome, 254

T

Tagged red blood cell radionuclide imaging, 513
Takeuchi procedure, 449
Taussig-Bing variant, 286

Tetralogy of Fallot (TOF), 483–489
ACC/AHA guidelines 2008, 309–311
anatomy, 295
associated defects, 297
childhood repairs, 299–302
complete repair, 300
diagnostics, 302–307
palliative shunts, 299–300
Rastelli procedure, 300–302
definition, 265
diagnostics
advanced imaging techniques, 307
cardiac catheterization, 305–307
chest radiograph, 304–305
clinical presentation in adults, 302–303
echocardiography, 305
electrocardiogram, 303–304
physical exam, 303
epidemiology, 295
management
of complications, adult survivors
arrhythmia, 307–314
left heart failure, 313
pulmonary insufficiency, 312
residual pulmonic stenosis, 312
thoracic aortic dilation, 314
of pregnancy, 315
physiology, 297
spectrum of disease, 297
Thoracic aortic disease
anatomy, 432
associated defects, 434
cardiac catheterization, 437
chest X-ray, 436–437
clinical presentation, in adults, 436
CT, 438
DeBakey classification, 434
echocardiography, 437
electrocardiography, 436
epidemiology, 431–432
genetics and maternal factors, 435
management of
adult survivors, 438–442
pregnant women, 442
MRI, 438
physical exam, 436
physiology, 433
recommendations, 440–441
Stanford classification, 434
surgical referral, 439
Total anomalous pulmonary venous return (TAPVR)
anatomy, 152
cardiac catheterization, 159
chest radiography, 158
childhood repairs, 155–156
clinical presentation, 156
echocardiography, 158
electrocardiogram, 157
incidence of, 151
management, 161
imaging techniques, 159
physical exam, 157
physiology, 153
Transthoracic echocardiography (TTE), 437
Tricuspid atresia, 394, 395
Tricuspid regurgitation, 381–385
Tricuspid valve, 4
bioprosthesis, 384
Truncal valve insufficiency, 324
Truncus arteriosus
advanced imaging techniques, 327
anatomy, 320
associated defects, 324

cardiac catheterization, 327
chest X-ray, 326
classifications, 322
clinical presentation in adults, 324–325
diagnostics, 324–327
echocardiography, 326–327
electrocardiography, 326
embryologic division, 322
epidemiology, 320
genetics and maternal factors, 324
management
of adult survivors, 328–329
of pregnancy, 329–328
physical exam, 325–326
physiology, 323
recommendations, 328
spectrum of disease, 324
Turner syndrome, 219, 432, 435

U
Univentricular physiology
diagnosis, 391, 392
DIRV and DILV, 396–398
double outlet right ventricle, 395–396
hypoplastic left heart syndrome, 392–394
pulmonary atresia with intact ventricular septum, 398–399
tricuspid atresia, 394
Univentricular repair
cardiac catheterization, 406–407
Chest X-Ray, 406
clinical presentation, 405
echocardiography, 406
electrocardiogram, 405
operative options, 399–400
physical exam, 405
staged procedures, 400–405
Blalock-Thomas-Taussig shunt, 400–402
Fontan procedure, 402, 403
Glenn shunt, 402
Norwood procedure, 403–405
pulmonary artery (PA) band, 400

V
Vaginal delivery, and anesthesia, 545–546
Valvectomy, 246
Valvular intervention
balloon valvuloplasty, 244, 245
contraindications, 244
follow-up, 246
indications, 244
surgical therapy, 245, 246
Valvular pulmonic stenosis
anatomy, 235–236
associated defects, 237
cardiac catheterization, 240
chest radiograph, 239
clinical presentation, 238
congenital cardiovascular defect, 237
during pregnancy, 248
echocardiography, 239–240
electrocardiogram, 239
epidemiology, 235
imaging techniques, 240
management of, 241–247
pulmonary artery dilation, 247
valvular intervention, 244–247
Noonan syndrome, 237
physical exam, 238
physiology, 237
Valvular relationships, 4
Vascular Ehlers-Danlos syndrome, 432, 435
Ventricles, 6

Ventricular loop, 8
1.5 Ventricle repair, 385
Ventricular septal defects (VSD)
advanced imaging techniques, 63–64
cardiac catheterization, 63
chest X-ray, 62
clinical presentation in adults, 60–61
defects, 58
echocardiography, 62–63
electrocardiogram, 61–62
epidemiology, 55
management
of adult survivors, 64–68
of pregnancy, 68
physical exam, 61
physiology, 57
types of, 55
Vessels, 9
Visceroatrial situs, 7
Volume overload, 29

W
Williams syndrome, elfin facies of, 212
Williams-Beuren syndrome, 254