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Lana Tsao
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Clinical Cases in Right Heart Failure

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Clinical Cases in Cardiology

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Clinical Cases in Right Heart Failure

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Foreword

Historically, physicians have sought to separate the left ventricle and the right ventricle when discussing heart disease. Clinicians typically try to distinguish "left heart failure" from "right heart failure" and less frequently biventricular failure. Even experienced practitioners find the management of right heart failure daunting due to its associated morbidity and mortality. Hepatic and renal dysfunction is often present in parallel. Indeed, once the right heart is failing, patients are on a rapid decline and increasingly difficult to manage. The aims of this book edited by Afari and Tsao are to educate the reader about the multiple presentations of right heart failure and to recognize specific clinical scenarios that will lead to a "precision medicine" approach to treatment. Indeed, astute clinicians should make every effort to protect the right ventricle (prevention) when possible. They must realize the right ventricle may be quite resilient when dysfunctional, and has the capacity to recover to a significant degree when provided the right management [1].

Why has the right ventricle been ignored until recently? The right ventricle has a complex anatomic structure. Its geometry has rendered quantitative imaging techniques standard for the left ventricle very challenging when imaging the right ventricle. Understanding the techniques and limitations of imaging the right ventricle is paramount knowledge necessary for the clinician. Serial imaging also plays a key role in assessing right ventricular recovery and reserve. A most challenging, perplexing, complex clinical question is to determine if the right ventricle has the capacity to improve when dysfunctional if a primary treatment strategy is deployed upstream. The most poignant example would be predicting

recovery of right ventricular function in a patient being considered for a left ventricular assist device (LVAD) with evidence of right heart failure. As described in this book, new advanced imaging techniques and risk stratification applied in various clinical scenarios will provide the guidance needed for successful management. This book is timely as we are now immersed in a growing array of percutaneous techniques to treat valvular heart disease. These innovative techniques mandate the understanding of right ventricular function as well as the complex interaction between the right and left ventricle. Emerging data has informed clinicians that understanding the right ventricle might be the central discriminating factor to predict the success and outcomes for most patients being considered for a variety of heart failure treatments including LVAD, valve surgery, percutaneous mitral valve devices, cardiac resynchronization device, coronary artery bypass, lung transplant, and others.

The chapters in this book will provide an understanding of important clinical scenarios including cardiac transplantation, mechanical circulatory support, pulmonary hypertension, congenital heart disease, valvular heart disease, and unique conditions isolated to the right ventricle. Today, there is a greater appreciation of the central role of the right ventricle in the pathophysiology of heart failure and its impact on hepatic and renal function [2, 3]. The right ventricle should be thought of in parallel and not in isolation. The right ventricle is of central importance in cardiovascular pathophysiology; thus, general and heart failure cardiologists need to strive to master the right heart and understand its potential to fail. Longstanding dogma has dictated that treatment of right heart failure consists of cardiac glycosides, diuretics, and treating underlying left heart disease when right ventricular failure is present. Fortunately, as described in this book, a plethora of effective and emerging treatments and imaging modalities now enable the clinician to recognize, protect, and treat more effectively right heart failure.

The editors have a longstanding interest and appreciation for the importance of the right ventricle and are experienced and astute heart failure cardiologists. Treating right ventricu-

lar disease requires a consummate clinician to synthesize the composite clinical data and recommend the most appropriate management which is frequently a daunting task. This book provides the knowledge to provide a framework to recognize, understand, and manage right heart failure encompassing the diverse clinical scenarios.

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Contents

Chapter 1
Introduction to the Right Heart

Maxwell E. Afari and Lana Tsao

1.1 Historical Perspective

The right ventricle (RV) has been misunderstood since ancient times. The earliest description of the RV was by Hippocrates (460–375 BC), who is considered the father of medicine. He described the RV as the source of nutrient (air), which is brought to the lungs and subsequently transferred to the left ventricle (LV) [1]. This was corroborated by Galen, who suggested that venous blood from the RV could move to the left ventricle (LV) via invisible pores [1].

In a theological book published in 1553, the Spaniard Michael Serveto correctly described what is currently known as the modern day pulmonary circulation. He proposed that blood passes from the RV into the lungs through vessels before entering the LV. Unfortunately, he was burned alive for his writings as well as for proffering opinions which

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were contrary to orthodox doctrine. The Italian anatomist, Realdo Colombo (1516–1559), independently described the RV, as carrying nutrients to the LV [2]. Neither Serveto nor Colombo's work was able to overthrow Galenic doctrine.

Finally, in 1616, William Harvey revoked Greek Doctrine with his treatise *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, otherwise known as Anatomical Exercises on the Motion of the Heart and Blood in Animals. He described the body's circulation in detail as a closed system with a clear relationship between the right and left side of the heart [2].

Nonetheless, the RV remained largely ignored as most research focused on the LV. In 1941, despite extensive damage to the RV of an experimental canine model through electrocautery ablation of the free wall of the RV, only minimal changes were seen in the venous pressures of the heart [3]. This experiment, amongst others, fueled the suspicion that the right heart was not essential. The Fontan procedure, which involves the diversion of blood from the vena cava to the pulmonary arteries in the process bypassing the morphological RV, also contributed to the assumption that the RV was merely a bystander in the systemic circulation.

1.2 Right Heart Failure

With the advent of advanced cardiovascular imaging, a progressive appreciation of the right heart has emerged due to a clearer understanding of RV anatomy and physiology. In the last few decades, the RV has increasingly been the target of research as right heart failure (RHF) has been shown to be associated with significant morbidity and mortality. In 2006, the National Heart, Lung, and Blood Institute tasked a working group with identifying research opportunities in RHF [4]. In 2014, the International Right Heart Failure Foundation Scientific Working Group defined RHF as a clinical syndrome caused by an alteration of structure and/or function of the right heart circulatory system that leads to

suboptimal delivery of blood flow (high or low) to the pulmonary circulation and/or elevated venous pressures at rest or with exercise [5]. In 2019, the American Heart Association (AHA) published a Scientific Statement on the Evaluation and Management of Right Heart Failure. Thus, the importance of the RV's central role in cardiovascular physiology is becoming recognized.

RHF is associated with reduced exercise capacity, worse NYHA functional class, and decreased survival [6]. Multiple studies have shown an independent association of RHF with mortality in patients with left heart disease [7–9]. Not only is RV dysfunction detrimental in HF with reduced ejection fraction (HFrEF), RHF is an independent risk factor for CV mortality in HF with preserved EF (HFpEF) [10]. After cardiopulmonary bypass or valve replacement surgery, right ventricular dysfunction is associated with elevated risk of mortality [11]. In patients with inferior myocardial infarction with RV involvement, the risk of death, shock and arrhythmias is elevated [12]. In the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, RV failure was associated with similar in-hospital mortality (53.1%) as left ventricular failure (60.8%, $p = 0.296$) [13]. In both acute and chronic RV pressure overload, RHF increases the risk of mortality. In patients with pulmonary embolism triggered right ventricular cardiogenic shock, the mortality rate is as high as 20–50% compared to <4% in hemodynamically stable patients [14]. In pulmonary hypertension, mortality is most closely related to the RV function [15].

1.3 Anatomy and Embryology of the Right Ventricle

Although the RV and LV are coupled together, the RV has a separate and distinct anatomy and physiology. Morphologically, the three-dimensional shape of the RV is complex. The RV has a triangular appearance from the side and that of a crescent moon when viewed in cross section as

its' septal contour is indented by the LV [16]. The interior of the RV has coarse trabeculae, a moderator band, papillary muscles, tricuspid valve, and a thin 3–5 mm free wall due to the low-pressure pulmonary circulation. Anatomically, the RV is divided into three components: (1) an inlet (sinus) portion, which consists of the tricuspid valve apparatus, including the chordae and papillary muscles, (2) An outlet portion (infundibulum/conus) portion, which includes the pulmonary valve, and (3) the trabeculated apex which is often very thin [17].

Both the RV and LV are comprised of a network of muscle fibers formed by layers of muscle. The RV is composed of two layers of superficial and deep muscle fibers as opposed to the 3 layers of the LV. The superficial layer is arranged circumferentially, such that it is parallel to the AV groove while the deep layer is arranged longitudinally from base to apex extending into the LV. This extension contributes to ventricular interdependence between the RV and LV along with the septum and pericardium. The circumferential fibrous layer found in the LV is absent from the RV [18]. Longitudinal shortening contributes more to RV stroke volume than the short axis [19]. The RV and LV are more easily distinguished based on the moderator band, tri-leaflet atrioventricular valve, uniformly coarse trabeculations, apically displaced septal tricuspid valve in relation to the anterior mitral valve, and more than two papillary muscles in the RV [17]. The blood supply to the RV free wall is predominantly from the right coronary artery. The posterior descending artery supplies the inferoposterior one-third of the septum while the left anterior descending artery perfuses two-thirds of antero-septum.

Embryologically, the RV and LV also differ. During gastrulation, myocardial cells are derived from the mesoderm. The left sided chambers have origins from the "primary heart field", which are the first population of cells to migrate into the region forming the heart. This field contributes to the formation of the LV, interventricular septum, and the atria. The "secondary heart field", which is medial and anterior to the primary heart field, migrate anteriorly and posteriorly to the

heart tube, contributing to the future outflow tract and the right sided chambers [20]. In week 4 of embryogenesis, a muscular septum arises to give the earliest distinction between both ventricles, while by week 8 there is distinction between the pulmonary and systemic circulations.

1.4 Physiology of the Right Ventricle

The RV has three mechanisms of contraction [17]: (1) The longitudinal fibers shorten pulling the tricuspid annulus and apex together along with pulling on the free wall from the LV. Contrarily, the LV contracts through a complex series of twisting and rotational movements. (2) The RV has a bellows like effect where the free wall moves inward (3) Traction of the RV free wall from septal LV attachment. RV contraction is believed to be in peristaltic movement since contraction occurs 20–50 ms earlier in the sinus and apex than the conus [21]. Through septal contraction, the LV contributes to RV ejection.

The LV and RV differ physiologically. In the embryo and fetus, the RV contributes to 60% of the cardiac output due to right to left shunting through the ductus arteriosus and patent foramen ovale, and serve as the systemic ventricle. Postpartum, the LV and RV have similar cardiac output but the LV becomes the work horse for the heart. The RV generates one sixth of the LV energy expenditure because it only has to work against a highly compliant, low resistance pulmonary circulation [14]. Despite this difference in pressure, both the RV and LV eject the same stroke volume.

1.5 Right Ventricular Pressure Volume Loop and Cardiodynamics

The ventricular pressure volume (PV) loop relation reflects both RV and LV function. The differences in the LV and RV pressure and volume are reflected in the shapes of their PV

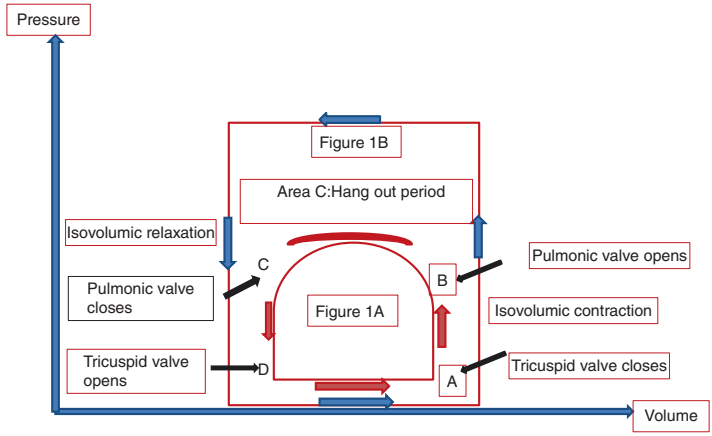

FIGURE 1.1 Pressure and volume loop of the (**a**) the right ventricle (**b**) the left ventricle

loops. As shown in the example of the PV loop in Fig. 1.1a, the RV has brief isovolumic periods of contraction and relaxation resulting in a trapezoidal configuration. In comparison, the LV (Fig. 1.1b) has a rectangular shape as the stages of the cardiac cycle have clearly defined periods of isovolumic contraction and relaxation.

At the end of diastole, point A in Fig. 1.1a, the tricuspid valve (TV) closes with initiation of systole. A short isovolumic contraction time (upward red arrow) occurs. When RV pressure supersedes the pulmonary artery pressure, the pulmonic valve opens (point B), and the RV ejects blood. RV ejection is known to extend (Area C) despite the pressure decline due to the high momentum of blood into the low resistance pulmonary circulation [16]. The pulmonic valve then closes (point C) as the volume falls to mark the end of systole and the beginning of diastole with isovolumic relaxation (downward red arrow). Subsequently, the tricuspid valve opens (point D) for diastolic filling. The cardiac cycle then repeats. Shaver et al. noted that the pulmonic valve closes well after the onset of the RV pressure decline in the normal right heart, evident by a time difference between pul-

monary arterial dicrotic notch and the right ventricular pressure measurement [22]. The extension of blood momentum in to the right ventricular outflow tract in spite of the closed valve is termed the "hangout period" [22]. The aortic hang out period is negligible due the higher systemic impedance.

Right ventricular function is dependent on both its systolic and diastolic function. RV systolic function is dependent on contractility, preload, and afterload. The RV end systolic pressure volume relationship (ESPVR) shown in Fig. 1.2 is considered the most reliable marker of contractility [23]. The slope of the ESPVR is the end systolic elastance (*Ees*), which is an index for RV contractility. The maximal elastance (*Emax*) is the point in the cardiac cycle when the pressure is highest in the RV and volume is decreased. Arterial elastance (*Ea*) refers to the pressure that the RV must overcome to eject blood into the pulmonary circulation. *Ea* which is a marker of RV afterload refers to the line that extends from the end diastolic volume (EDV) to *Emax* as shown on Fig. 1.2.

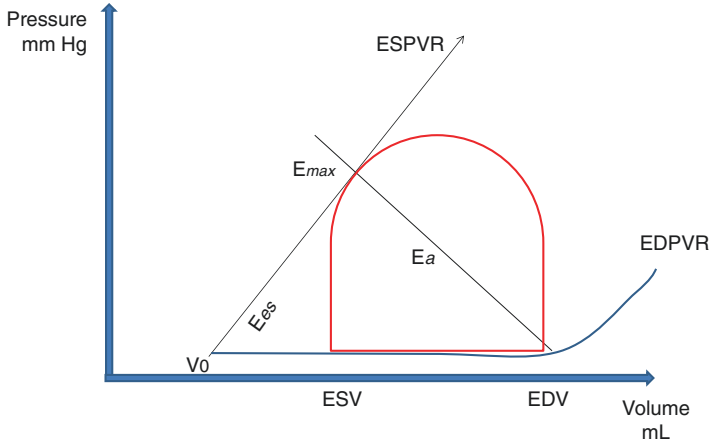

Figure 1.2 The right ventricular pressure volume loop. *ESPVR* end systolic pressure volume relationship, *Emax* maximum elastance, *Ees* end systolic elastance, *Ea* arterial elastance, *ESC* end systolic volume, *EDV* end diastolic volume, *EDPVR* end diastolic pressure volume relationship

The curvilinear line also shown in Fig. 1.2, delineating the relationship between the RV pressure and volume in diastole is the end diastolic pressure volume relationship (EDPVR). This line is tangential to the PV loop at end diastole and is a measure of right ventricular compliance. The ESPVR and EDPVR serve as the boundaries of the PV loop.

When faced with changes in preload and afterload, the RV has two autoregulatory mechanisms, which are intrinsic to the myocardium, to preserve cardiac function—heterometric autoregulation and homeometric autoregulation. Heterometric autoregulation (Fig. 1.3a) occurs with changes in preload to preserve RV function as per the Frank Starling mechanism. When the EDV increases, an equivalent increase in stroke volume occurs to maintain end systolic volume (ESV). Homeometric autoregulation is governed by the Anrep effect [24]. Gleb von Anrep experimentally demonstrated that increasing afterload causes a linear increase in ventricular contractility to maintain stroke volume [24]. The physiologic adaption of RV function to changes in rising pulmonary arterial (PA) vascular load is known as RV-PA coupling.

The RV adapts more easily to preload than afterload. Preload is the EDV present before isovolumic contraction. Increasing preload causes the cardiomyocytes to stretch and increase the sarcomere length. In the sarcomere length-tension relationship, fiber tension increases the overlap of actin and myosin filaments bridges as well as increases the sensitivity of troponin C to calcium. Thus, stronger contraction occurs during systole. Likewise, when preload is decreased, the stroke volume decreases and force of contraction is less.

The ESV is maintained by the heterometric response when preload increases and is the first response to increased afterload. RV afterload is the resistance or pressure increase during contraction that the RV must overcome to eject blood into the pulmonary vasculature. Unlike preload which is easily defined as EDV, there are many markers of RV afterload. Factors which impact RV afterload include pulmonary vascu-

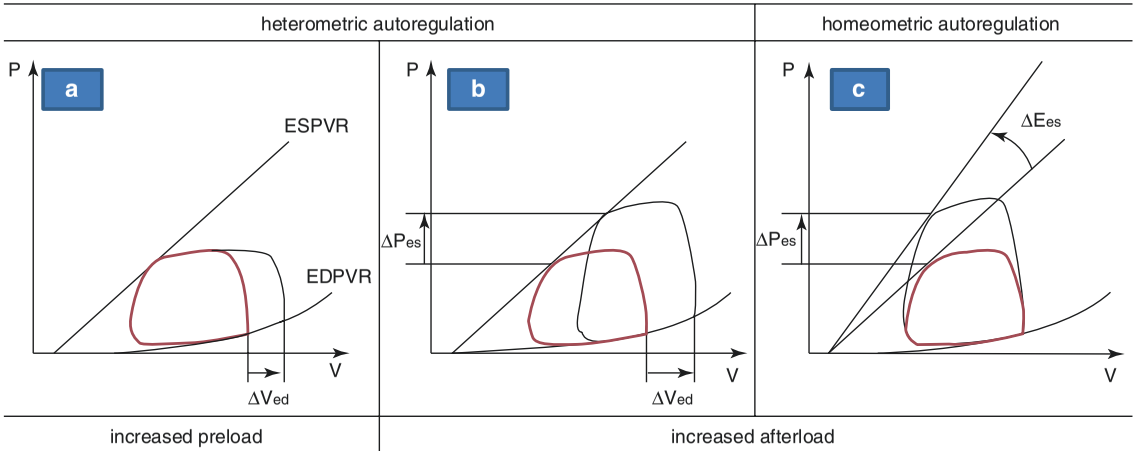

FIGURE 1.3 Representation of heterometric (left and center plot) and homeometric autoregulation (right plot). If preload is increased (**a**) heterometric autoregulation increases SV by the same ΔVed. If afterload is increased, both heterometric and homeometric responses are activated. In heterometric autoregulation (**b**), an increase in EDV (ΔVed) leads to an increase in pressure (ΔPes) with no change in SV and inotropy. In homeometric autoregulation (**c**), a pressure increase (ΔPes) to match increased afterload is achieved by increasing RVcontractility (ΔEes) with no change in SV and preload. The baseline loop is sketched in red. The end-systolic pressure-volume relationship (ESPVR) line and the end-diastolic pressure volume relationship (EDPVR) line define the limits of RV working conditions. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Annals of Biomedical Engineering, Methods for Measuring Right Ventricular Function and Hemodynamic Coupling with the Pulmonary Vasculature, Alessandro Bellofiore, Naomi C. Chesler. Copyright 2013

lar resistance (PVR), *Ea* (end-systolic pressure divided by the stroke volume), maximum wall tension, and hydraulic power [25]. A detailed discussion of the various contributors to RV afterload is beyond the scope of this chapter.

The RV is sensitive to changes in both acute and chronic afterload. When afterload is increased, the stroke volume (SV) should decrease but heterometric autoregulation (Fig. 1.3b), preserves SV. Within minutes, homeometric autoregulation (Fig. 1.3c) kicks in with normalization of EDV. The primary RV adaptative mechanism to increased afterload is concentric remodeling with an increase in the number of cardiac sarcomeres. Thus, the RV can maintain adequate pressure to overcome the increase in afterload. As increased afterload persists, maldaptive remodeling occurs through eccentric hypertrophy leading to progressive RV dilatation and shifting of the septum to the LV with resultant decrease in LV filling and dyssynchrony. Wall stress also increases leading to decreased coronary perfusion and ischemia. Subsequently, contractility declines with uncoupling of the RV and PA [18] and loss of cardiac output.

Contractility or inotropy is based upon the assumption that the RV will stiffen and relax upon a predictable time course and is dependent on the ESPVR (Fig. 1.2). When the RV is faced with chronic increases in afterload, the pressure volume relationship changes to one similar to the LV PV loop with an increase in isovolumic contraction and relaxation times. Over time, changes in preload, afterload, and contractility causes RV dilatation. The RV cannot relax as the pressure and volume increases. The greater the EDV, the stronger the contraction until a physiologic limit has been exceeded. The sarcomeres are essentially overstretched and myosin and actin cannot interact. Thus, contractility decreases and right ventricular dysfunction ensues with resultant RV-PA uncoupling. In addition, due to the restraint imposed by the pericardium and interventricular dependence, LV dysfunction develops as discussed in the pathophysiology section.

The PV loops of the RV reveal how the RV and pulmonary vasculature are coupled. Effective RV and PA coupling maintain cardiac function. When the RV and PA uncouple, RV function deteriorates and predicts clinical outcomes. This

uncoupling is detrimental and most clear seen in pulmonary hypertension. This concept is explored in detail in Chap. 7.

1.6 Pathophysiology of Right Heart Failure

RHF occurs due to states of pressure or volume overload or from a direct insult to the myocardium. A direct insult to the myocardium could be from right ventricular myocardial infarction, myocarditis, right ventricular myopathy such as arrhythmogenic right ventricular cardiomyopathy, and right ventricular contusion among others. The RV is sensitive to changes in both acute (pulmonary embolism, acidosis, hypoxia, acute respiratory distress syndrome, cardiac contusion and increased positive end expiratory pressure) or chronic injury (pulmonary hypertension, left heart disease, pulmonary stenosis, outflow tract obstruction, or double chambered RV). In the acute setting, the RV is incapable of generating a mean pulmonary artery pressure >40 mmHg [26]. The RV as mentioned above is not as sensitive as the LV to changes in preload. Increased preload further dilates the RV, leading to tricuspid regurgitation, through the dilation of its annulus. Other conditions that cause RV dysfunction include massive blood or fluid infusion, tricuspid or pulmonary regurgitation, carcinoid syndrome, and atrial septal defect.

The hemodynamic adaptation of the RV to injury includes:

1. *Systolic Ventricular Interdependence*: The change in the compliance of one ventricle affects the other, through a process called ventricular interdependence. An acute or chronic rise in right ventricular afterload or excessive increase in right ventricular volume, results in the bowing of the interventricular septum to the LV. The LV assumes a "D shaped" formation, which results in the reduction of the LV diastolic filling pressure leading to a decline in LV stroke volume and an increase in LV end diastolic pressure [27].
2. *Diastolic ventricular interdependence*: is mediated through pericardial constraint. An increase in RV pressure and volume overload leads to an increase in right ventricular

EDV. A negative diastolic interaction through intact pericardial constraint results in an increased left ventricular EDPVR which contributes to the decrease in LV output [28, 29].

According to Laplace's Law, RV wall stress is directly proportional to intracavitary pressure (right ventricular afterload), internal ventricular diameter (from increased RV preload) and inversely related to ventricular wall thickness (thin wall from RV myocardial infarction). The formula for Laplace's Law is Pressure = (2 × wall stress × wall thickness)/radius. The pathogenesis of RV wall stress is based on the complex interaction between neuro hormonal and cytokine activation, gene profiling, and RV remodeling) [4]. Figure 1.4 summarizes the pathophysiology of right heart failure.

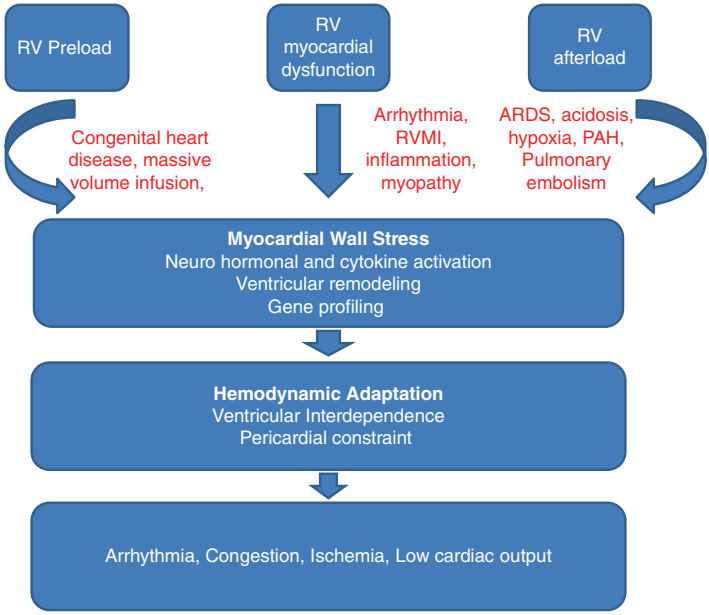

Figure 1.4 The pathophysiology of right heart failure. *RV* right ventricle, *RVMI* right ventricular myocardial infarction, *ARDS* acute respiratory distress syndrome, *PAH* pulmonary arterial hypertension

1.7 What Are the Clinical Manifestations of Right Heart Failure?

The clinical manifestations of right heart failure are multifold. Presenting symptoms can include chest pain (ischemia), palpitations (arrhythmia), shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, ascites, anasarca (fluid retention), lightheadedness, diaphoresis (low cardiac output), and right upper quadrant pain (hepatic congestion).

Three clinical syndromes (Cardiorenal, Cardiohepatic, Cardiogastric) are considered direct consequences of chronic RHF (Fig. 1.5). Cardiorenal syndrome (CRS) refers to a heterogeneous syndrome involving the interplay of the kidneys and the heart leading to HF and kidney dysfunction. CRS I is characterized by acute HF causing acute kidney injury while chronic kidney disease in CRS II is the result of chronic HF [30]. The mechanism for kidney dysfunction is through (1) inadequate renal perfusion from low cardiac output [31],

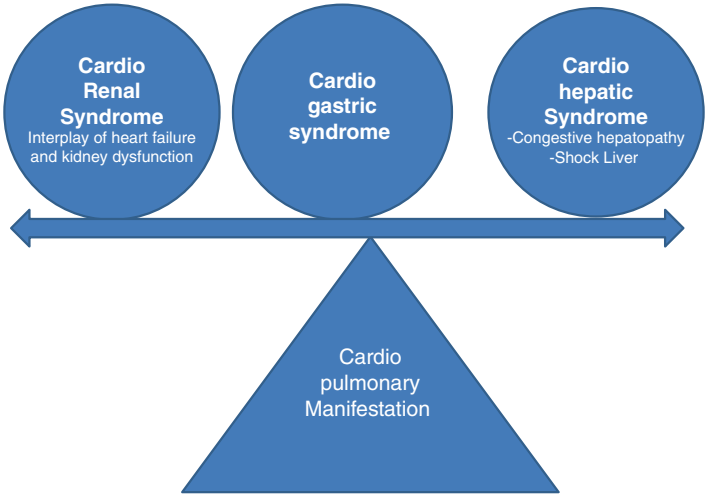

Figure 1.5 Clinical syndrome of right heart failure

or (2) increased renal vein pressure from elevated central venous pressure(CVP) [32]. Irrespective of cardiac output, elevated CVP is a predictor of worsening kidney function [33], which is manifested as decreased urine output, rising blood urea nitrogen (BUN) and creatinine, and increased fluid overload. The rising BUN or creatinine in RHF could erroneously be interpreted as a need to decrease diuretics.

Cardiohepatic RHF is caused by back pressure from an elevated CVP to the hepatic system. Two types of cardiohepatic syndrome exist (A). Cardiogenic shock liver injury, also known as shock liver or ischemic hepatitis is defined by acute decrease in blood flow to the liver leading to acute hepatic congestion and hypoxia [34]. Two out of the following three criteria are required to make the diagnosis: (1) Heart failure (2) aminotransferase levels >20 times the upper limit of normal (3) exclusion of other causes of liver failure [35]. (B) Congestive hepatopathy is a consequence of chronic congestion leading to a decrease in blood flow to the liver, increased hepatic venous pressure, hepatic hypoxia and necrosis [36]. Prolonged hepatic congestion eventually leads to cardiac cirrhosis.

Finally, RHF can also present with gastrointestinal manifestations. Chronic CVP elevation and decreased cardiac output leads to decreased abdominal absorption, also called "gut edema" [37]. Splanchnic venous congestion from RHF can cause increasing abdominal girth leading to cardiorenal syndrome from elevation in intra-abdominal pressure [38].

1.8 Evaluation and Management of Right Heart Failure

The evaluation and management of RHF is extensively discussed in the proceeding chapters in a variety of clinical scenarios. As with all disease states, the most important facet of RHF management is to tailor treatment to the underlying cause. Unlike Heart Failure with reduced Ejection Fraction, which has an armamentarium of guideline directed medical

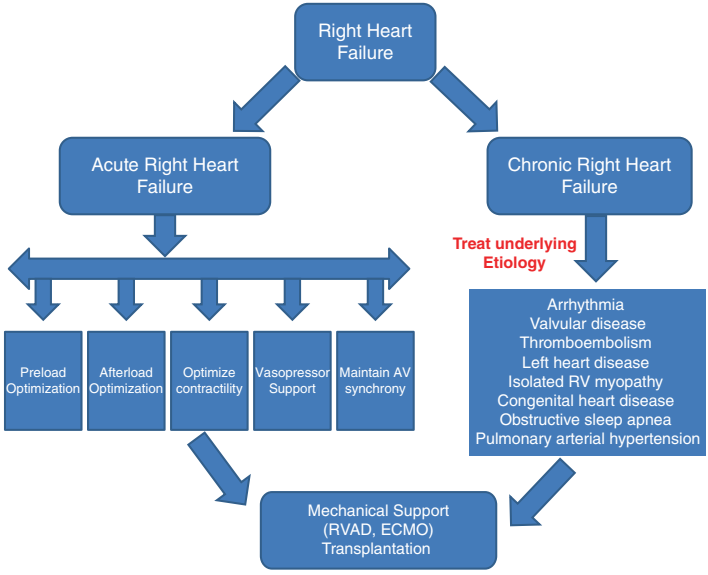

FIGURE 1.6 Management of acute and chronic right heart failure. *RVAD* right ventricular assist device, *ECMO* extracorporeal membrane oxygenation

therapy, a lack of evidence based medical therapy exists for RHF, confirming the neglect of the right heart in clinical trials focused on HF. Management is also dependent upon whether the patient presents with acute or chronic heart failure as summarized in Fig. 1.6.

1.9 Conclusion

After decades of neglect, the RV is moving to center stage in importance. Despite advancements in the management of left HF, the RV ultimately determines outcomes. As we develop a more comprehensive understanding of the RV in cardiovascular physiology and cardiodynamics, intense focus is turning to the RV's role in cardiovascular disease. Right ventricular dysfunction is a predictor of survival and progresses to RHF, which

is associated with significant morbidity and mortality. To date, management of RHF has been limited as the focus of clinical research has been on left HF. Further research is needed to better understand and tailor the management of RHF with the hope of improving patient survival and quality of life.

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Chapter 2
New Onset Heart Failure: Which Side Is It, Right or Left?

Christopher P. Blomberg, Wajih A. Syed, and Lana Tsao

Case

A 65-year-old woman presented with no reported past medical history as she had avoided medical care for the past 20 years. She has had mild-to-moderate (1–2+) lower extremity edema up to her knees for at least the past 10 year. During which time, she slept in a recliner, and was able to complete her activities of daily living (ADLs) with intermittent breaks to rest. In the past 6 months, she has needed to rest more frequently while performing her ADLs and usually took 2–3 naps per day. Her abdomen had become firmer than normal,

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with an associated 15 lb weight gain. She was morbidly obese with a BMI of 45 kg/m^2 and stated that she primarily ate frozen or take-out meals on a daily basis. For a number of years, she has complained of palpitations that seemed to gradually worsen. She has become increasingly reliant on her children to assist in household chores due to progressive fatigue. At her daughter's insistence, she finally established care with a primary care provider, who promptly referred her to the cardiology clinic for evaluation and management.

2.1 What Is the Clinical Presentation of Chronic Right Heart Failure?

This patient presented with clear evidence of volume overload and suspected heart failure (HF), but the distinction between right heart failure (RHF) and left heart failure (LHF) based on the history alone is often difficult. Many of the symptoms of RHF are indistinguishable from LHF. The absence of orthopnea, paroxysmal nocturnal dyspnea (PND), and shortness of breath may suggest a right-sided etiology but is not diagnostic. Early signs and symptoms of RHF typically include fatigue and lower extremity edema. The distinction between RHF and LHF is often made after left-sided pathologies are excluded, and the underlying pathology is identified.

In the setting of chronically elevated central venous pressure (CVP), chronic vascular congestion of end organs can lead to progressive dysfunction. As RHF progresses, the forces of ventricular interdependence skew in favor of right ventricle (RV) predominance in both pressure and volume overload, which in later stages may lead to a reduced cardiac output and end organ ischemia [1]. The hepatic, renal, and gastrointestinal systems are primarily affected by these deleterious effects.

In the early stages of hepatic congestion, right upper quadrant discomfort from liver capsule stretching and nausea may be present, which may indolently progress to early satiety and anorexia. It is important to note that these symptoms are indistinguishable from primary hepatic conditions such as

cholestasis with the determination of volume status usually being the delineating factor [2].

Decreased urine output and/or increasing diuretic requirements may be early signs of renal involvement [3]. As renal dysfunction progresses, reports of fatigue, nausea, anorexia, and ultimately confusion may develop. The development of cardio-renal syndrome is associated with a poor prognosis [4].

Increased intra-abdominal pressures due to ascites may develop as systemic congestion overwhelms the capacitance of the splanchnic vasculature, which can lead to renal dysfunction secondary to compression of the renal vasculature and reduced renal perfusion [5]. Effects on gastric and colonic function leading to early satiety, anorexia, and constipation are also seen.

Upon further interrogation, our patient denied any history of orthopnea, PND, or chest pain. She admitted to symptoms of daytime somnolence and a history of morbid obesity since she was a teenager. Her husband and daughter both confirmed the presence of loud night-time snoring and choking spells. She denied any history of tobacco, alcohol, or illicit drug abuse, but admitted to drinking nearly a pot of coffee every day.

2.2 What Is the Next Step in Evaluation?

When a patient presents with signs and/or symptoms of HF, after a comprehensive history, the initial diagnostic approach always begins with a thorough physical exam.

Her vitals were significant for a pulse of 135 beats per minute, blood pressure of 130/80 mmHg, and a respiratory rate of 20 breaths per minute. Using the bell of the stethoscope with the patient sitting in the upright position, her cardiac exam was significant for a holosystolic III/VI murmur best heard at the middle left sternal border. The murmur was louder with inspiration. Her rhythm was tachycardic and irregular. The first heart sound (S1) was not appreciated, the second heart sound (S2) was variable, and a right-sided S3 was present. Her lungs were clear with equal inspiratory and expiratory times. An estimation of her jugular venous pressure (JVP) was at least 15 cm H_2O. No right ventricular heave

was present but the apical impulse of the left ventricle (LV) was displaced laterally. Hepatomegaly, a pulsatile liver, and a slightly tender right upper quadrant were present in the absence of an abdominal fluid wave. Her lower extremity edema was pitting, 3+, and symmetric. Figure 2.1 depicts an example of a patient with RHF.

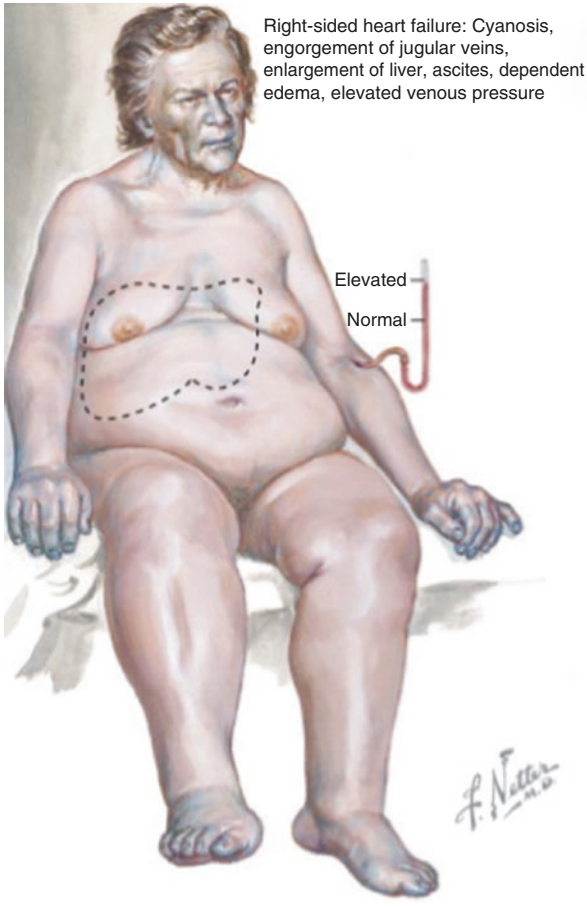

Figure 2.1 Schematization of a patient with a classic presentation of right heart failure. Netter illustration used with permission of Elsevier Inc. All rights reserved. www.netterimages.com

2.2.1 Cardiac Findings

Cardiac auscultation, when the time is invested to perform correctly, can identify significant valvular pathologies. It is important to listen directly on the skin with both the bell and the diaphragm as well as to purposefully listen for the presence of each of the possible murmurs. One of the most important auscultatory findings to distinguish left versus right-sided murmurs is how it varies with respiration. Deep inspiration lowers intrathoracic pressure and increases venous return to the right side of the heart. Therefore, right-sided murmurs will typically *increase* in severity with inspiration and *decrease* with exhalation, commonly referred to as Carvallo's sign. This sign was present in our patient and suggestive of tricuspid regurgitation (TR).

Palpation for an RV heave is performed by placing the heel of the hand on the left sternal border and is present when the heel of the hand is lifted off the chest with each systole. This typically represents significant RV hypertrophy, but in rare cases may also represent marked right atrial enlargement.

2.2.2 Pulmonary Findings

Her clear lung sounds may reduce one's suspicion of a left-sided pathology. However, this cannot absolutely distinguish between right and left-sided HF as patients with chronic LHF can also lack pulmonary edema if they are well compensated and euvolemic. Due to compensatory mechanisms including increased lymphatic drainage [6], increased thickness of alveolar basal membrane reducing capillary filtration [7], and enhanced alveolar fluid clearance [8], lung fields could be clear.

2.2.3 Jugular Vein Assessment

Estimation of a patient's CVP is commonly performed via jugular venous pressure (JVP) assessment and is an important tool to assist in quantifying the degree of volume overload. Typically, this evaluation begins with the patient supine and the head of

the bed elevated at a 45° angle. With the head turned towards the left shoulder, the right side of the neck should be closely inspected to observe for the leading edge of the distended jugular vein. A vertical measurement in centimeters is then taken from this point to the Angle of Louis, to which 5 cm is added (an estimation of the depth of the right atrium from the angle of the sternum). Sometimes the leading edge of the distended jugular vein cannot be appreciated. If the right atrial pressure is low then the jugular venous distension is located below the clavicle. Gentle pressure applied to the right upper quadrant/liver may bring the vessel into view, commonly referred to as hepatojugular reflux. If the right atrial pressure is markedly elevated, the patient may be asked to sit upright with the feet dangling off the exam table. This allows the blood to pool in the lower extremities to lower the venous waveforms in the neck below the angle of the jaw for measurement. The right-sided pressures vary based on the respiratory cycle and typically fall with inspiration. Kussmaul's sign is a rise, or failure to fall, of venous pressure with inspiration and represents right-sided volume overload as well as reduced ventricular compliance.

If the CVP cannot be estimated by the jugular vein, then assessment of peripheral venous collapse may be considered. With the patient supine and the head of the bed at a 45° angle, if the veins are distended on the dorsum of the hand, then the arm may be passively elevated until the hand veins are no longer visible. If this transition point occurs when the arm is elevated above the level of the sternal angle, then the CVP is likely elevated. Similarly, the Anthem or Rizkallah sign may be employed during which the patient is in the same position, but instead of the arm being passively raised it is instead placed directly over the sternum. If the hand veins remain distended then an elevated CVP is suspected [9].

2.2.4 Hepatic Findings

The majority of patients with RHF develop hepatic congestion with resultant hepatomegaly. The liver may feel firm and is often tender to palpation. Splenomegaly is characteristi-

cally absent. The increase in venous pressure causes perisinusoidal edema and hepatocyte atrophy leading to impaired diffusion of oxygen and nutrients in the liver [10]. The "backward" failure is also responsible for the compression of lymphatics and the impaired capability of lymph drainage may lead to ascites in 25% of the patients [11]. In patients with considerable TR, a prominent systolic pulsation of the liver may be appreciated due to an enlarged right atrial 'v' wave. A presystolic pulsation of the liver, attributable to an enlarged right atrial 'a' wave, can occur in tricuspid stenosis, constrictive pericarditis, restrictive cardiomyopathy involving the RV, and pulmonary hypertension. The slow flow within hepatic sinusoids favours thrombosis within the hepatic venules and portal tracts, promoting fibrosis and ultimately leading to cirrhosis [12].

2.3 What Is the Pathophysiology of Chronic RHF?

The RV is connected to the low impedance, highly distensible pulmonary circulation that allows efficient transfer of blood to maintain the same stroke volume as the LV. Since the RV and LV are connected in series, the cardiac output is essentially the same, but the afterload is significantly different.

The RV adaptation depends on the presence of the pressure or volume overload that it encounters. Because of its greater compliance, the RV can adapt tremendously and increase its contractility by up to fivefold in response to rising afterload [13]. When faced with an even higher load, the RV starts to dilate in order to maintain adequate cardiac output and ventriculo-arterial coupling. Under normal conditions, the RV impact on the LV is minimal but as the RV pressure rises, ventricular interdependence results in movement of the interventricular septum to the left. This causes mechanical inefficiency which impairs LV diastolic filling and stroke volume [13]. Dilatation of the RV results in tricuspid regurgitation, which further increases preload. Finally, as the wall tension continues to rise, molecular changes of RV myocyte

loss and fibrosis occur that will eventually result in right ventricular failure [14].

The most common cause of RHF is LHF secondary to post-capillary pulmonary hypertension and chronically elevated right ventricular afterload. Causes of chronic right ventricular dysfunction can generally be divided into three categories: (1) Increased afterload, (2) Increased preload, and (3) Primary RV cardiomyopathies. The etiologies of RHF are outlined in Table 2.1.

Since the RV is coupled to a high compliance, low impedance pulmonary system, it is better suited to handle volume overload (preload) than pressure overload (afterload). An

Table 2.1 Causes of right heart failure

Increased afterload	Increased preload	Primary cardiomyopathy
• Left heart disease	• Tricuspid regurgitation	• Ischemia/infarct
• Pulmonary hypertension	• Pulmonic regurgitation	• ARVC
• Acute PE	• ASD	• Myocarditis
• Pulmonic stenosis (valvular or subvalvular)	• TGA	• Amyloidosis
• ARDS	• ToF	• Sarcoidosis
• COPD	• Ebstein anomaly	• Dilated CM
• CTEPH	• Anomalous pulmonary venous return	• Hypertrophic CM
• Pulmonary artery stenosis		• Cardiotoxic medications

PE pulmonary embolism, *ARDS* acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *CTEPH* chronic thromboembolic pulmonary hypertension, *ASD* atrial septal defect, *TGA* transposition of the great arteries, *ToF* Tetralogy of Fallot, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *CM* cardiomyopathy

increase in afterload causes an exaggerated work load on the RV by impeding forward flow and reducing RV stroke volume. Common causes of increased RV afterload include pulmonary hypertension, acute pulmonary embolism, pulmonic stenosis (valvular or sub-valvular), as well as lung pathologies such as acute respiratory distress syndrome, chronic obstructive pulmonary disease, and chronic thromboembolic pulmonary hypertension (CTEPH).

Congenital heart disease such as the presence of an atrial septal defect, transposition of the great arteries, Tetralogy of Fallot as shown in Chap. 4. Ebstein anomaly, anomalous pulmonary venous return as well as pulmonary and tricuspid regurgitation can lead to an increased preload.

Primary RV cardiomyopathies can result in reduced contractility and include viral myocarditis and arrhythmogenic right ventricular cardiomyopathy (ARVC), the latter of which is reviewed in Chap. 5. Impaired contractility of the RV due to an ischemic cardiomyopathy can result in a decrease in LV preload leading to systemic hypotension and a reduction in cardiac output. This can be seen in the post-cardiotomy patient or RV myocardial infarction patient discussed in Chap. 9. Restoration of blood flow is the mainstay of treatment which improves both right ventricular systolic and diastolic function.

2.4 What Is the Recommended Diagnostic Work Up?

2.4.1 Laboratory Tests

There are no laboratory tests that are specific for RHF. On the initial presentation of a patient with previously undiagnosed HF, routine labs are checked including a complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, a B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), as well as an assessment for ischemia through troponin level.

Depending on the clinical history, specialized testing may be considered such as a d-dimer to assess for the presence of a DVT and/or PE. This patient's labs are listed below.

Hemoglobin/ Hematocrit	10.3/33.1	(ref 11.8–15.8 g/dL/35–47%)

Her labs were significant for a mildly reduced hemoglobin and hematocrit, which may be at least in part dilutional from volume overload. Anemia and iron deficiency can also be associated with cardiorenal syndrome [15]. The risk of mortality is also increased in HF associated with anemia [16].

Bilirubin 1.8 (ref 0.0–1.0 mg/dL), AST 30 (ref 0–37 U/L), ALT 35 (ref 0–40 U/L), Alkaline phosphatase 248 (ref 39–117 u/L), γ-glutamyl transpeptidase (GGT) 65 (ref 9–48 U/L)

Jaundice is not commonly reported, with total bilirubin levels rarely exceeding 3 mg/dL (ref 0.0–1.0 mg/dL) [17]. A cholestatic pattern is significantly more prevalent than elevated transaminases, with elevated GGT and alkaline phosphatase most closely correlating with adverse outcomes in RHF [18]. Protein-losing enteropathy is classically associated with patients who have undergone Fontan surgery, but rarely can be seen with pericardial and valvular etiologies such as severe tricuspid regurgitation and can lead to cardiac cachexia [19]. In advanced disease, liver synthetic function may also become impaired as suggested by reduced albumin levels and an elevated international normalized ratio. Jaundice may become evident suggesting cardiac cirrhosis.

Creatinine	1.7	(ref 0.50–1.30 mg/dL)

As previously noted, passive venous congestion and or compression of the renal vasculature from increased abdominal pressures can contribute to abnormal kidney function. Several non-hemodynamic pathways can also exacerbate

cardiac or kidney injury, which include the persistent activation of the renin–angiotensin–aldosterone system and chronic inflammation. This leads to imbalance in the proportion of reactive oxygen species/nitric oxide production, elevated circulation levels of tumor necrosis factor-α (TNFα), interleukin-1 (IL-1), and interleukin-6 (IL-6) [20]. An increase in blood urea nitrogen (BUN) and serum creatinine level can occur, which are independent markers of adverse outcome and results in diuretic resistance [21]. In some cases, diuretics may lead to further worsening of renal function and present a challenge in treatment.

Troponin T	0.08 ng/mL	(ref 0.000–0.030 ng/mL)

If the ECG is not suggestive of an acute coronary syndrome, then once the patient is stabilized an ischemia workup can be pursued. It is common for patients with volume overload to have a mildly elevated troponin when superimposed on reduced renal clearance in the setting of acute and or chronic kidney disease.

NT-proBNP	1845 pg/mL	(ref 0–900 pg/mL)

Elevated levels of BNP and NT-proBNP are supportive, but not necessarily diagnostic of HF. These biomarkers do not distinguish RHF from LHF. BNP has emerged as a useful marker of prognosis in RHF accompanying pulmonary arterial hypertension (PAH) [22–24]. It is important to note that the NT-proBNP, more so than BNP, may be inappropriately elevated due to reduced renal clearance in the setting of significant kidney dysfunction or paradoxically low in obese patients [25].

2.4.2 Electrocardiography (ECG)

Her ECG on presentation demonstrated atrial fibrillation at 135 beats per minute with low voltage throughout and a right

bundle branch block (RBBB).The QT interval was normal with no significant ST-T wave abnormalities. Q waves were not present.

ECG is a quick and simple tool to aid in the assessment of RV dysfunction. The RBBB is suggestive of right ventricular strain. Other prominent findings may include right axis deviation, RV hypertrophy, and/or inferior Q waves suggestive of prior RV infarct. Atrial fibrillation is also common in patients with right ventricular dysfunction.

2.4.3 Imaging

Her echocardiogram showed a normal LV ejection fraction (LVEF) of 65% without mitral or aortic valve pathologies, mild LV diastolic function, no LV hypertrophy. The RV was moderately dilated with abnormal systolic function. Moderate-to-severe tricuspid regurgitation was present as well as a flattened interventricular septum during systole and diastole, and a fixed and dilated inferior vena cava (RA pressure of at least 15 mmHg).

Doppler and 2D echocardiography is recommended as the first imaging modality. This can help to assess for left-sided pathologies and determine the size and function of the RV, along with the assessment of right ventricular and pulmonary pressures. Tricuspid annular plane systolic excursion (TAPSE) is an M-mode derived measurement of RV longitudinal motion. A low TAPSE has been shown to predict prognosis related to right ventricular dysfunction, especially in patients with pulmonary hypertension [26]. However, 2D echocardiography is limited in its' ability to comprehensively assess right ventricular dysfunction due to the RV's thin wall, peculiar morphology, and anterior location.

Although not currently indicated in this patient, cardiac magnetic resonance (CMR) imaging provides an advantage over echocardiography due to its superiority in anatomic, volumetric, and quantitative analysis of the RV. It is also more sensitive in the assessment of congenital heart diseases,

pulmonary hypertension, and evaluation of intra-cardiac shunts. CMR is crucial in the diagnosis of ARVC, since there is a lack of established and definite "gold standard" test [27]. Chapter 3 elaborates on the role of diverse imaging tools in RHF.

2.4.4 Invasive Testing

A right heart catheterization (Swan-Ganz) may be considered if her creatinine does not improve or actually worsens with diuresis, or as a way to identify the underlying pathology causing RHF. This tool provides a more accurate assessment of right-sided filling pressures as well as determines cardiac output and systemic vascular resistance. PAH can be diagnosed and concurrently assessed for response to treatment, evaluate for intracardiac shunts, and provide an estimation of the left atrial pressure.

Table 2.2 outlines findings that may suggest right ventricular dysfunction and RHF. It is important to note, however, that not all of the listed findings will be present in every patient nor does the presence of one or a few of these findings dictate that right-sided dysfunction is the sole pathology. Rather, these findings may support the diagnosis when combined with the history, physical exam, and multiple data points.

2.5 How Is Chronic RHF Managed?

Generally, the treatment of RHF is focused on treating the underlying pathology. However, the first step is to stabilize symptoms. In the case of our patient, this involves a trial of diuresis and rate control of her atrial fibrillation. The current HF guidelines primarily focus on the management of LV dysfunction. There is a paucity of data demonstrating efficacious therapies directed towards treatment of isolated RV dysfunction. The mainstay of therapy for RV dysfunction is to identify and treat the underlying disorder [3].

Table 2.2 Diagnostic findings that support right heart failure

Test	Findings to support right ventricular dysfunction or RHF
Electrocardiogram	• RBBB • RV hypertrophy • Right atrial enlargement • Right axis deviation • S1Q3T3 in acute pulmonary embolus • ST elevation, more elevated in lead III than lead II (acute RV infarct)
Chest X-ray	• RV and/or pulmonary artery (PA) enlargement • Hyperinflated lungs (COPD) • Absence of pulmonary vascular congestion or Kerley "B" lines • Wedge-shaped absence of pulmonary vasculature (pulmonary infarct)
Echocardiography	• Absence of left-sided pathologies • Dilated RV and/or reduced systolic function (low TAPSE, S′, or RV fractional area change) • Elevated RV systolic pressure • RV free wall hypertrophy • Tricuspid stenosis/regurgitation • Pulmonic stenosis/regurgitation • Hepatic vein flow reversal • Ventricular septal interdependence (volume and/or pressure overload) • McConnell's sign or apical "wink" (acute PE) • Atrial septal defect • Ventricular septal defect
Cardiac MRI	• Dilated RV • Reduced RV systolic function/ejection fraction • Increased late gadolinium enhancement (LGE) • RV free wall hypertrophy • Myocardial edema

Table 2.2 (continued)

Test	Findings to support right ventricular dysfunction or RHF
Right heart catheterization	• Pulmonary hypertension (pre- and/or post-capillary) • Constriction (prominent 'x' and 'y' descents with a square root sign, elevation and equalization of diastolic pressures) • Elevated RA pressure (equivalent to JVP) • Kussmaul's sign • Ventricular interdependence (requires concurrent LV pressure monitoring) • Shunt run may show a "step up" in oxygenation levels in the right heart chambers, suggestive of a left-to-right shunt
CTPA	• Acute and/or chronic pulmonary emboli • COPD/emphysema
Pulmonary function tests or high resolution CT of the chest	• COPD/emphysema
Labs	• Elevated BNP or NT-proBNP • Abnormal liver function tests • Elevated INR • Reduced albumin • Elevated Creatinine and BUN • Elevated D-dimer

RBBB right bundle branch block, *RV* right ventricle, *COPD* chronic obstructive pulmonary disease, *TAPSE* tricuspid annular plane systolic excursion, *PE* pulmonary embolus, *RA* right atrium, *JVP* jugular venous pressure, *CTPA* computerized tomography pulmonary angiogram, *CT* computerized tomography, *INR* international normalized ratio, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *BUN* blood urea nitrogen

2.5.1 Diuretics

Loop diuretics such as furosemide, torsemide, and bumetanide are the key to treatment in both acute and chronic RHF. Gastrointestinal absorption of furosemide is reduced in the setting of significant gut edema, often prompting escalation to torsemide or bumetanide due to their increased absorption and better oral bioavailability. Patients who do not respond to escalating doses of oral diuretics may require intravenous diuretics. Diuretic resistance may also result from chronic and or acute renal disease, and low cardiac output resulting in renal arterial hypoperfusion combined with renal venous congestion, and/or intense neurohormonal activation.

Intermittent dosing of thiazide diuretics, such as metolazone or chlorothiazide, may help to "prime" the kidneys in an effort to augment the diuretic response by being administered approximately 30 min prior to the loop diuretic. The use of an aldosterone antagonist in conjunction with loop or thiazide diuretics can also be effective. There is a growing body of evidence regarding the role of aldosterone antagonism in patients with RV dysfunction [28, 29]. Renal replacement therapy with either continuous veno-venous hemofiltration (CVVH) or hemodialysis can be the last resort in patients who are resistant to escalating doses of diuretics.

2.5.2 Digoxin

Digoxin has been shown to contribute to improvements in acute hemodynamic abnormalities in RHF but no data exists on the long-term benefits [30].

2.5.3 Invasive Therapies

In the presence of ischemia, coronary revascularization should always be considered. As noted above, evaluation with

a PA catheter can help to diagnose an underlying disorder (such as PAH or a shunt), as well as assess for a response to treatment.

2.5.4 Pulmonary Vasodilators

Pulmonary vasodilators have been shown to improve WHO functional status and mortality in patients with group I PAH. However there have been no proven therapies to reduce mortality in patients with group II, III, IV, or V pulmonary hypertension. This is discussed in detail in Chap. 7.

2.5.5 Surgery

In the setting of symptomatic RHF, tricuspid valve surgery may be considered for primary tricuspid regurgitation if unresponsive to medical therapy, or in the setting of at least moderate right ventricular dilatation and/or systolic dysfunction [31].

Case Conclusion: Her symptoms and physical exam responded well to aggressive oral diuresis. Her labs were closely monitored, demonstrating improvement in her creatinine and LFT abnormalities. She was then started on a low-dose beta blocker for rate control. Her cardiac stress test did not show evidence of ischemia. A sleep study was performed that revealed an Apnea–Hypopnea Index (AHI) of 45, which is consistent with severe obstructive sleep apnea, and she was promptly started on continuous positive airway pressure (CPAP) therapy. The patient was provided extensive education and reinforcement on HF management throughout this process. After treatment, her follow-up echocardiogram showed normalized RV systolic function but remained moderately dilated. Her TR improved to moderate severity. The cause of her sleep apnea was likely related to her morbid obesity, and she was subsequently referred to the local weight loss center for further evaluation and management, including consideration for bariatric surgery.

Clinical Pearls

- Right heart failure is most commonly caused by left heart disease.
- The right ventricle can adapt to volume overload better than pressure overload.
- Assessment of right ventricular failure requires a careful history and physical examination as well as a high index of suspicion.
- Achieving euvolemia and treating the underlying disorder are key to the management of RHF.
- The presence of right ventricular dysfunction, independent of the etiology, is associated with an increased mortality.

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Chapter 3
Multimodality Imaging of the Right Heart

Edith Liliana Posada-Martinez, Xochitl A. Ortiz-Leon, Lissa Sugeng, and David J. Hur

Case

A 29-year-old gentleman presented with atypical chest pain associated with shortness of breath, but no nausea or diaphoresis. He also reported a history of palpitations since age 16, but no cyanosis. Physical exam revealed normal rate, regular rhythm with widened split S1, a 2/6 early systolic ejection murmur at the mid sternal border, and no gallop or friction rub. His abdomen was normal. Examination of his extremities revealed no signs of cyanosis or edema. Electrocardiogram was normal sinus rhythm with incomplete right bundle branch block, troponin within reference range, and chest radiograph showed cardiomediastinal silhouette within normal limits.

In the course of his workup, he underwent transthoracic echocardiogram (TTE) that demonstrated blood flow through mainly the upper portion of the interatrial septum, suggesting

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a wide atrial septal defect (ASD) with superior extension (Fig. 3.1a) and concern for minimal to no tissue rim at the superior aspect; the right ventricular systolic pressure (Fig. 3.1b) was 28 mmHg (including a right atrial pressure of 5 mmHg). The right ventricle (RV) appeared mildly dilated (diastolic internal diameter 4.5 cm and indexed 2.25 cm/m^2) but still with preserved function (Figs. 3.2 and 3.3).

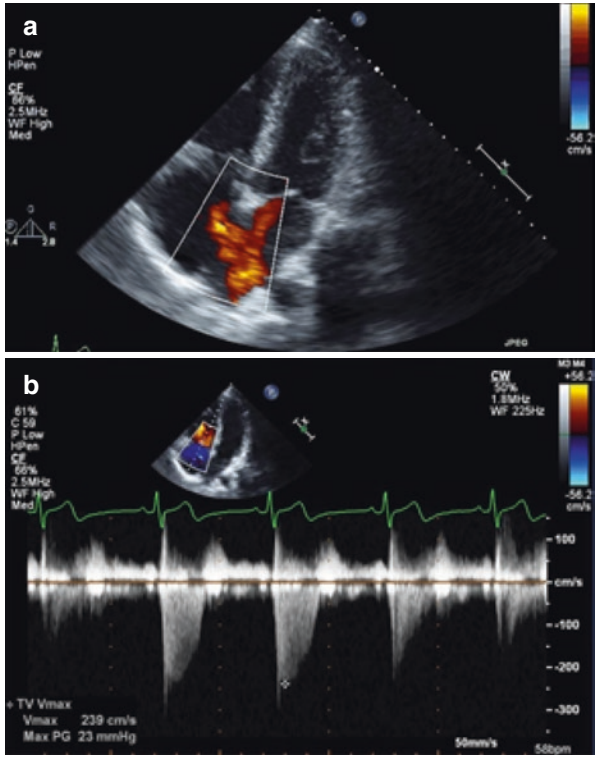

Figure 3.1 (**a**) Modified four-chamber view showing the atrial septal defect with colour Doppler flow coming from left atrium into right atrium. (**b**) Continuous-wave Doppler of tricuspid regurgitant jet for calculating the right ventricular systolic pressure by modified Bernoulli equation (23 mmHg), plus estimated right atrial pressure 5 mmHg, to get 28 mmHg

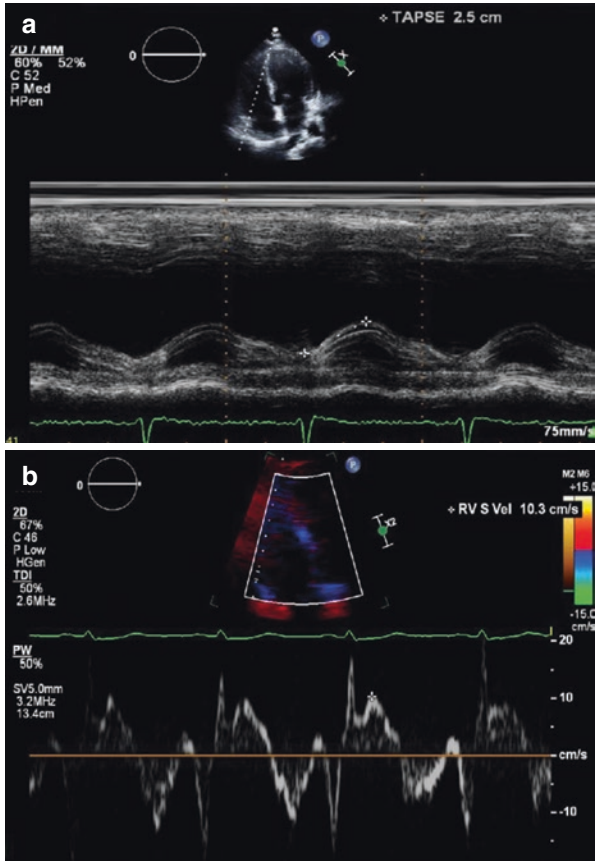

FIGURE 3.2 (**a**) Tricuspid annular plane systolic excursion (TAPSE) >1.7 cm. (**b**) Doppler tissue imaging-derived tricuspid lateral annular systolic velocity wave (S′) >9.5 cm/s

Because of the importance of the anatomic evaluation of the defect, the patient underwent cardiovascular magnetic resonance (CMR) imaging, which visualized a secundum ASD seen in the superior portion of the interatrial septum (Fig. 3.4). The ASD measured 1.4 cm in the superior-inferior axis (Fig. 3.5); there was approximately half a centime-

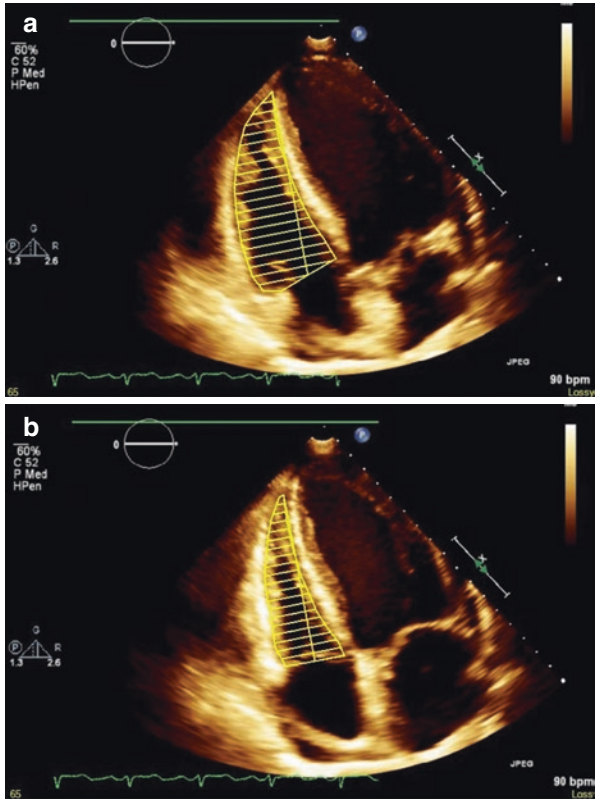

FIGURE 3.3 Fractional area change (FAC) >35%. (**a**) End-diastolic area. (**b**) End-systolic area

tre of surrounding tissue rim superiorly and the Qp:Qs was 2.3:1 (Fig. 3.6), consistent with a hemodynamically significant left-to-right shunt. The systemic and pulmonary venous return was normal. There were no atrioventricular or ventricular defects found. There was moderately enlarged right ventricular size (end-diastolic volume 342 mL and indexed 173 mL/m^2) with normal right ventricular systolic function

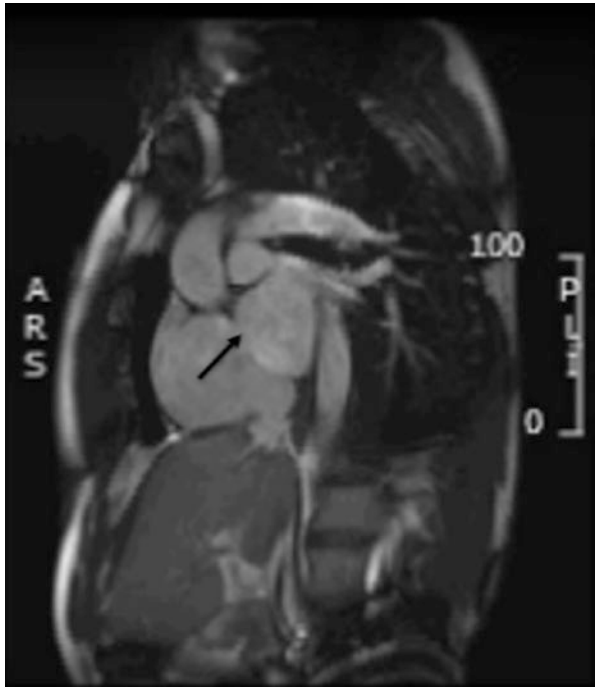

FIGURE 3.4 Cine imaging in the short-axis orientation at the level of the atria depicts the secundum atrial septal defect (arrow) with a small rim of superior septal tissue that was sufficient for placement of percutaneous septal occluder device

with right ventricular ejection fraction (RVEF) of 52%. Tricuspid regurgitation (TR) was mild (regurgitant fraction 14%), and right atrium (RA) was moderately enlarged. There was no delayed enhancement.

Given that there was a sizeable ASD with hemodynamic left-to-right shunting with enlarged right heart size but still normal right ventricular function, it was felt that it was time to intervene, and close the defect before the development of

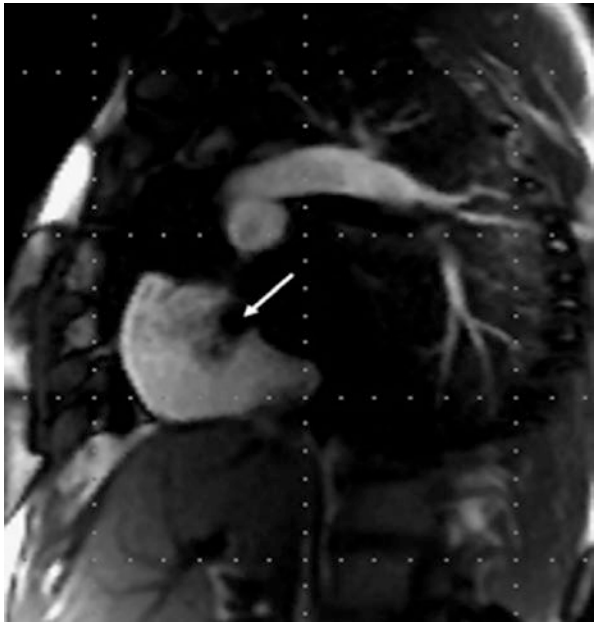

FIGURE 3.5 First-pass perfusion imaging with real-time injection of contrast depicts the ASD (arrow) with left-to-right shunting (non-contrast-mixed blood from the left atrium shunting across the ASD to the right atrium containing contrast-mixed blood, yielding a "negative contrast" void). The length of the ASD measures up to 1.4 cm

right ventricular dysfunction and subsequent right heart failure. The patient underwent transoesophageal echocardiogram (TOE) in order to characterize the defect and assess if he was a candidate for a percutaneous septal occluder device. The TOE confirmed a large secundum ASD, measuring 5×2.5 cm with adequate tissue rim at the superior aspect. He was referred to the Structural Heart Interventional Cardiology team for closure.

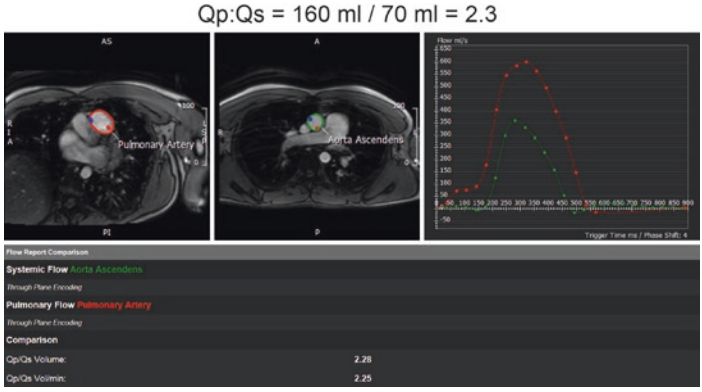

Figure 3.6 PC-CMR performed in the pulmonary artery (red contour) and the ascending aorta (green contour) to measure the respective flows. There was no significant pulmonic or aortic regurgitation. The absolute flow detected in the pulmonary circulation as evidenced in the pulmonary artery (Qp) is 160 mL and in the systemic circulation as evidenced in the ascending aorta (Qs) is 70 mL. Thus, the ratio (Qp:Qs) is 160 mL/70 mL, which is 2.3, signifying a significant left-to-right shunt

3.1 Echocardiographic Assessment of RV Function

3.1.1 RV Systolic Function

The complex crescent shape of the RV hinders its evaluation, therefore in some cases a multimodality approach with echocardiography, cardiac computed tomography and CMR is required. The echocardiogram is the first step in the imaging evaluation of right heart pathology [1]. The systolic function of the RV is an important parameter in clinical practice that has shown its usefulness in the whole spectrum of cardiac

pathology: ischemic cardiomyopathy, non-ischemic heart failure, congenital heart disease, and pulmonary hypertension (PH), as well as prior to cardiac surgery, and in recent years, percutaneous transcatheter cardiac interventions [2, 3].

The systolic function of the RV can be evaluated through different echocardiographic parameters; including tricuspid annular plane systolic excursion (TAPSE), RV myocardial performance (RIMP) or Tei index, fractional area change (FAC), Doppler tissue imaging (DTI)-derived tricuspid lateral annular systolic velocity wave (S′), and with novel echocardiographic techniques such as global longitudinal strain (GLS) and three-dimensional (3D) RVEF [1, 4].

The TAPSE represents a measure of RV systolic longitudinal function. According to the recommendations, it is measured in the apical RV-focused four-chamber view [5] by M-mode with the cursor positioned in the tricuspid lateral annulus; it measures the distance between end-diastole and peak systole in millimetres. TAPSE is a straightforward parameter that is easy to perform; however, it is angle-dependent and may be affected by the cardiac translation. The cut-off value for RV dysfunction by TAPSE is <17 mm [4].

Similarly to TAPSE, peak systolic velocity of tricuspid annulus (S′) is a measure of the systolic longitudinal function of the RV. S′ is measured from the apical four-chamber view by pulsed-wave DTI in cm/sec. This parameter is also easy to measure and reproducible, but it has the main disadvantage of being angle-dependent [4]. An S′ velocity <9.5 cm/s indicates RV systolic dysfunction.

The FAC is the percentage of area change in systole with respect to diastole and is also measured in a RV-focused apical four-chamber view. It is calculated subtracting end-systolic area (ESA) from end-diastolic area (EDA) divided by EDA: FAC = [(EDA – ESA)/EDA] × 100. This parameter includes the longitudinal and radial function of the RV. Thus, it is considered a parameter of global systolic function. This is still a single-plane measure of the RV function and has a fair inter-observer reproducibility. A value <35% indicates systolic dysfunction of the RV [4].

The RIMP or Tei index can be measured using either pulsed-wave (PW) spectral Doppler or DTI velocity of the lateral tricuspid annulus. It is calculated by adding the isovolumic contraction time (IVCT) to the isovolumic relaxation time (IVRT) divided by the ejection time (ET) interval: RIMP = [(IVCT + IVRT)/ET]. This parameter is considered also a measure of global RV performance since it includes parameters of systolic function and also the isovolumic relaxation. A RIMP >0.43 by PW Doppler and >0.54 by DTI suggests RV dysfunction. Tei index is unreliable when the right atrium (RA) pressure is high, which will shorten the IVRT [4].

The rate of increase in ventricular pressure (dP/dt) is a contractility index, which measures the rate of increase in the ventricle's pressure during the period of isovolumic contraction, when atrial pressure remains relatively constant and changes in the regurgitant flow velocity reflects the ventricular contractility [6]. In the right side, dP/dt measures the time required for the TR velocity to increase from 1–2 m/s. The increase in pressure (dP) is calculated using the modified Bernoulli principle ($P = 4\ V^2$), where V is the maximal velocity of the TR jet in meters per second (m/s); therefore $4\ (2)^2 = 16$ and $4(1)^2 = 4$, so dP = 16–4; dP = 12 mmHg. The time interval (dt) is measured between 1 and 2 m/s. Finally, the dP/dt is calculated as 12 mmHg divided by this time (in seconds). The recommendation for dP/dt of the RV has been defined as the lower normal limit to be approximately 400 mmHg/s [1, 7]. The main limitation of this parameter is its load-dependency.

3.1.2 RV Diastolic Function

The parameters for the assessment of the RV diastolic function are basically those used for the left side; however, important considerations should be addressed. The parameters should be acquired from the apical four-chamber view and must be taken at held expiration or the average of at least five consecutive beats due to respiratory variation. Moreover, these parameters can be affected by age, respiration, heart rate, and loading

conditions. Assessment of RV diastolic function is carried out by pulsed Doppler of the tricuspid inflow (E and A waves), tissue Doppler of the lateral tricuspid annulus (e′ and a′ waves), pulsed Doppler of the hepatic vein, and measurements of IVC size and collapsibility. The quantification of RV diastolic function include the following parameters: E/A ratio (1.4 ± 0.3), E wave deceleration time (180 ± 31 ms), e′/a′ ratio (1.18 ± 0.33), e′ (14.0 ± 3.1 cm/s) and E/e′ ratio (4.0 ± 1.0) [4]. In addition, estimation of RA pressure by measurement of IVC diameter and collapse with inspiration should be considered in the determination of RV diastolic function. According to guidelines for the echocardiographic assessment of the right heart in adults by the American Society of Echocardiography, the RV diastolic dysfunction should be graded as follows: tricuspid E/A ratio <0.8 suggests impaired relaxation, a tricuspid E/A ratio of 0.8–2.1 with an E/e′ ratio >6 or diastolic flow predominance in the hepatic veins suggests pseudonormal filling, and a tricuspid E/A ratio >2.1 with a deceleration time <120 ms suggests restrictive filling [1].

There are few studies that have evaluated the clinical impact of RV diastolic dysfunction. The E/e′ has a high sensitivity and specificity for predicting RA pressure ≥10 mmHg in non-cardiac surgery and in cardiac transplantation [8, 9]. In patients with PH and chronic heart failure, diastolic dysfunction was associated with worse functional class and was an independent predictor of mortality [10, 11]. In addition, diastolic RV dysfunction may be considered a marker of early RV dysfunction because it is often present before systolic function drops [1].

3.2 Echocardiographic Assessment of RV Size and Hemodynamics

3.2.1 RV Chamber Assessment

The RV is a crescent-shaped structure, anteriorly located, and smaller than the left ventricle but with a thinner free wall that

receives venous circulation through the vena cava and continues with the pulmonary artery [12, 13]. The RV is divided in three components based on their embryological origins: the inlet (which includes tricuspid valve, tendinous chords, and papillary muscles); the apex (a portion very trabeculated); and the infundibulum or conus (which includes the pulmonary valve). The crista supraventricularis separates the RV inlet and outlet portions.

Unlike the left ventricle, the RV has only two myocardial layers, the superficial and subendocardial. The superficial RV layer (approximately 25% of wall thickness) is arranged circumferentially in a parallel direction with the atrioventricular groove, and extends toward the left ventricle and contributes along with the septum to the biventricular interdependence [14]. On the other hand, the subendocardial RV layer (approximately 75% of wall thickness) has the myocytes arranged in a longitudinal direction and contributes in greater proportion to the systolic function of the RV [14, 15].

Because of the complexity of the RV geometry, the RV size is often evaluated by conventional 2D echocardiography through multiple acoustic windows; however, the accuracy of these parameters may be limited when the free wall is not well defined, such as in patients with dilated RVs. RV-focused apical four-chamber view is considered the best approach for these measurements. Recent studies have shown ultrasound enhancing agents improve the visualization of RV endocardial borders by decreasing inter-observer variability and resulting in more accurate evaluation of RV size and function [16, 17]. The reference values commonly used in 2D echocardiography to indicate RV dilation are: diameter >41 mm at the base and >35 mm at the midlevel in the RV-focused four-chamber view [4].

3.2.2 Right Heart Pressures Assessment

Echocardiography allows estimation of the right ventricular systolic pressure (RVSP), which in the absence of pulmonary stenosis will be the same as pulmonary artery systolic pressure

(PASP). The RVSP is determined from the TR jet using continuous-wave Doppler plus the right atrial pressure (RAP). The peak pressure gradient (ΔP) is calculated through the modified Bernoulli equation: $\Delta P = 4\ V^2$ as described above [1]. The RAP is determined by the diameter of the inferior vena cava (IVC) evaluated in a subcostal view, 1–2 cm from the IVC-RA junction and its percentage of collapsibility during an inspiratory sniff [4]. According to these parameters the values for the RAP are as follows: IVC diameter <2.1 cm with collapse >50% suggest mean RAP of 3 mm (range between 0 and 5 mmHg); IVC diameter >2.1 cm with collapse <50% suggests mean RAP of 15 mmHg (range between 10 and 20 mmHg); for the remaining combinations an intermediate mean value of 8 mmHg (range between 5 and 10 mmHg) may be assumed.

3.3 Novel Echocardiographic Assessment of the RV

3.3.1 Speckle Tracking/Strain

The study of myocardial fibers has been carried out with different techniques by echocardiography. Nowadays, the most widely used technique is speckle tracking on the basis of displacement measurements. Speckle tracking analyses different parameters of cardiac mechanics such as displacement, velocity, strain, and strain rate. Strain is the fractional change in the length of a myocardial segment, expressed as a percentage, unitless, and can analyse these changes in the longitudinal, circumferential, and radial direction. The GLS, which is the average of the segmental strain, is the parameter most widely used and has shown the most clinical implications [18]. The RV GLS, measured in the RV-focused four-chamber view, is calculated as the average of the three segments of the free wall (basal, mid, and apical) or can include the three segments of the septal wall and be calculated as the average of the six segments. Most of the studies showing the clinical applications of RV GLS measured the free wall longitudinal

strain (FWGLS) because it is considered that the septal wall is mostly affected by LV mechanics; however, both methods seem to have excellent agreement [19]. This technique is considered angle-independent and reproducible, but it is influenced by load conditions, image quality, and artefacts. An important limitation for this technique is the variability among vendors and the lack of multiple studies with larger populations to determine normal values [20, 21]. The current cutoff value established by the guidelines for RV GLS is >−20 (<20 magnitude with the negative sign) [4].

RV strain has shown prognostic value in different clinical scenarios such as heart failure [22–24] or myocardial infarction [25, 26]. In the PH setting, a RV GLS <10% of the basal segment of the RV free wall was a predictor of poor prognosis [27]. In addition, RV strain predicts RV failure after extracorporeal membrane oxygenation [28] as well as being a predictor of worse outcomes in patients who undergo cardiac surgery [29, 30].

3.3.2 3D Echocardiography

Although the above mentioned parameters have shown their usefulness in assessing and predicting outcomes in different cardiac pathologies, they are based on geometrical assumptions of the RV and do not include the complete analysis of all parts of the RV (inlet, apex, and the infundibulum). The TAPSE, S′, RIMP, and RV FWGLS are focused on the longitudinal function and lacking in the evaluation of transverse (radial) function. On the other hand, the FAC can determine the RV function in both directions; however, it does not include the infundibular portion of the RV, which accounts for around 20% of the end-diastolic volume [31]. So far 3D echocardiography has become the most accurate tool for the evaluation of RV function and has been validated against CMR, which is considered the gold standard for measuring volumes and EF [32]. Despite this, few studies have analysed the clinical

impact of 3D RV volumes and RVEF [33, 34]. This may be due to less availability of the software and the lack of training in the acquisition and analysis of 3D data. Nevertheless, 3D RV analysis is a promising tool in patients with right heart disease.

3.4 The Role of Cardiac MRI in Investigating the RV

3.4.1 Function/Volume Assessment

CMR is a non-invasive 3D tomography technique considered the standard of reference for the evaluation of cardiac volumes and systolic function [35]. In the right heart, CMR has demonstrated to be accurate and reproducible for the quantification of RV function including volumes and EF [36–38]. In addition, CMR allows for the assessment of morphology, quantification of RV mass, tissue characterization and valvular function through the analysis of transvalvular flows [39, 40].

In general, CMR scans include different phases. First, the cine sequence allows the assessment of morphology and the calculation of volumes, size, and EF [41]. Next, the phase contrast (PC) is useful in the analysis of valvular function such as quantification of TR or pulmonic regurgitation (PR) severity. Ultimately, post-contrast sequences can be performed. Delayed enhancement with gadolinium (DEG) imaging is a very useful technique that can evaluate myocardial scar or fibrosis [35].

CMR cine imaging allows hemodynamic evaluation of the RV through the quantification of end-diastolic, end-systolic, and stroke volumes, and ultimately RVEF. Additionally, right-sided cardiac output can be calculated by multiplying the stroke volume by the heart rate. Cine imaging allows for evaluation of right heart morphology and identification of RV hypertrophy [36], RA enlargement [42], and RV wall motion abnormalities. For example, in

patients with inferior myocardial infarction with extension to the RV or septal abnormalities due to volume overload (flattening or leftward bowing during diastole) or pressure overload (flattening or leftward during systole) that may suggest associated PH. Septal bowing is indicative of PASP ≥67 mmHg, leading to impaired filling and reduced LV end diastolic volume and decreased cardiac output [42, 43]. The RV volumes measured by CMR are an important predictor of outcomes in patients with right side pathology [44]. For example, patients with repaired tetralogy of Fallot, who frequently have PR, severe RV dilation (RV end-diastolic volume index ≥160 mL/m^2, or RV end-systolic volume index ≥80 mL/m^2, or RV end-diastolic volume ≥2× LV end-diastolic volume) aids in the timing of pulmonary valve replacement [45] as discussed in Chap. 4, Born with a Failing Right Heart. RV volumes have shown to be an independent risk factor of cardiac tachyarrhythmia in those patients [46]. Additionally, the function of the RV is a predictor of outcomes in chronic systolic heart failure [47] and non-ischemic dilated cardiomyopathy [48].

3.4.2 Flow Analysis

PC velocity mapping (PC-CMR) is used to analyse blood flow velocity through the cardiac chambers and vessels. In the right side, the peak velocity of TR can be used to calculate the RVSP based on the modified Bernoulli equation, similar to the method used in echocardiography. In the setting of congenital heart disease with PH, CMR allows the quantification of cardiac shunts with the pulmonary-to-systemic flow ratio (Qp:Qs) by performing PC-CMR at the main pulmonary artery and ascending aorta [36], which is an important parameter in the timing of shunt closure. PC-CMR is also able to assess coronary perfusion and identify ischemia of the RV not only in patients with coronary artery disease but also in PH patients [41]. Moreover, the evaluation of the systolic flow in the right coronary artery (RCA) has been reported,

and it is related to RV mass and RV pressure [49]. Intracardiac shunts can also be visualized in a real-time fashion with first-pass perfusion imaging with injection of contrast.

3.4.3 Tissue Characterization

Because of its high definition and ability to characterize myocardial tissue [36], in addition to the quantification of RV volumes, CMR can identify intramyocardial edema and fibrosis, which play an important role in the differential diagnostic work-up of cardiomyopathies. The pattern of fibrosis on DEG imaging can give clues about the differentiation between ischemic and non-ischemic cardiomyopathy. Subendocardial to transmural DEG with a location that is in keeping with an epicardial coronary artery territory is typically described as an ischemic pattern, whereas mid-wall or epicardial DEG (with sparing of the subendocardium) are typically described as a non-ischemic pattern.

Myocardial fibrosis is common in patients with right heart disease; therefore, DEG has an invaluable role in the identification of RV pathology. In patients with PH, DEG located at the right ventricular insertion sites with the interventricular septum (IVS) near the basal segments [50–52] has been related with parameters of RV dysfunction [52]. In Ebstein's anomaly, myocardial fibrosis has been associated with worse clinical status [53].

3.5 The Role of Multi-Detector Computed Tomography

Multi-detector computed tomography (MDCT) is considered the reference standard for anatomical information. Current CT scanners have evolved to more detector rows (up to 128-, 256-, and 320 slice) and dual-source, leading to higher spatial and temporal resolution [54]. This newer generation of scanners has increased the z-axis coverage allowing shorter

breath-hold duration and lower radiation dose, as well as contrast volume with an excellent spatial resolution [55]. However, the images can be suboptimal with fast and irregular cardiac rhythms. MDCT scans include non-contrast high-resolution CT and contrast-enhanced CT angiography (CTA) [56].

Evaluation of volumes and function of the cardiac chambers by CTA involves semiautomated segmentation of the ventricles, using at least ten phases of the cardiac cycle (5–95% phase of the R-R interval) [57, 58]. ECG-gated CTA allows the evaluation of RV function and size, including chamber dilation and wall thickness hypertrophy [59]. The correlation between CT, CMR, and echocardiography modalities has been investigated. MDCT volumes are slightly higher (4%) compared with CMR [32]. Therefore, MDCT is an alternative for the evaluation of RV volumes in patients with devices (cardiac defibrillators or resynchronization therapy) who cannot readily undergo CMR scanning.

Because of its invaluable differentiation of anatomic structures in patients with PH and RV dysfunction, MDCT is most indicated to assess the cardiopulmonary structures in order to investigate the underlying cause of PH (e.g., lung disease, pulmonary embolism, left-to-right shunt as a patent ductus arteriosus or atrial and ventricular septal defect, rheumatologic diseases) and also the secondary changes, allowing for the evaluation of disease severity [60, 61].

In the setting of acute pulmonary embolism, the IVS deviation, RV diameter/LV diameter ratio and the main pulmonary artery diameter (MPAD)/ascending aorta diameter (AOD) ratio evaluated by MDCT can be useful for predicting right ventricular dysfunction [62].

In the new era of percutaneous transcatheter interventions for valvular disease, specifically in TR, multimodality cardiac imaging is a vital component in the selection of the patient and for procedure planning. MDCT is the preferred modality for the anatomic evaluation of the tricuspid annulus, subvalvular apparatus, trabeculations, coronary visualization, vena cava, and femoral venous access, also in addition to right heart size and function [63]. Finally, even though direct quantification

of tricuspid valvular insufficiency is not feasible with CTA, there are anatomical surrogates of valvular regurgitation severity that can be derived, such as the measurement of anatomic regurgitant orifice area during systole and quantification of the tricuspid annular area in diastole [64].

3.6 The Complementary Role of Radionuclide Scan and PET-CT

Radionuclide imaging was the first non-invasive modality for the evaluation of RV function [65]. However, the advent of other non-invasive imaging methods and their technological advances have displaced radionuclide scintigraphy as the first line test in diagnostic work-up. Nevertheless, this technique is able to assess RV function, perfusion, and metabolism, which can provide a comprehensive evaluation of the RV and also be integrated with other non-invasive imaging methods. Through molecular imaging, RV oxygen consumption has been measured with positon emission tomographic (PET) imaging to gain insight onto the pathophysiology of right heart dysfunction [66, 67]; however, the clinical importance of these findings needs to be further assessed.

Case Conclusion

The presented case of a 29-year-old male with diagnosis of secundum ASD shows the important role of multimodal imaging evaluation. The TTE diagnosed the ASD, assessed the RV function, and ruled out PH, which would have been contraindication for the closure of the defect. Next, CMR confirmed the dilation of right heart cavities but still normal RV function, determined significant left-to-right shunting, and visualized the defect from multiple views, providing evidence of feasibility of a percutaneous approach. Tissue characterization showed no ventricular DEG. Additional visualization by both CMR and TOE (Figs. 3.7, 3.8, and 3.9) provided more detailed anatomical information about the defect, complementary imaging of the superior rim, and

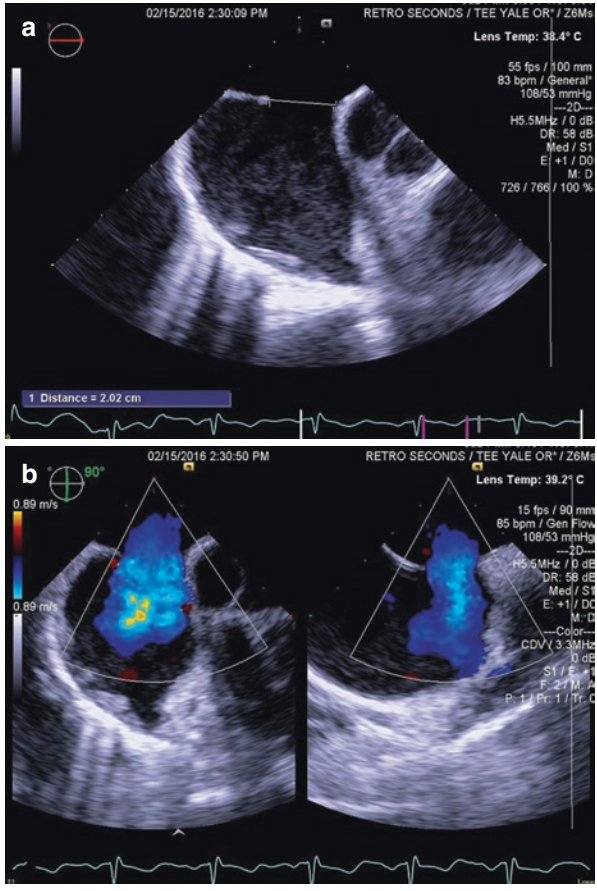

FIGURE 3.7 Transoesophageal echocardiogram (**a**) 2D Mid-oesophageal 0° view showing the ASD measuring 2.0 cm without anterior border. (**b**) 2D colour at mid-oesophageal 0° view showing the flow through the ASD

ruled out any other associated congenital heart disease, in order to provide the highest confidence that the patient was a candidate for percutaneous closure of the defect. Ultimately, the patient underwent successful percutaneous device closure of the defect, avoiding the risks of an open surgery.

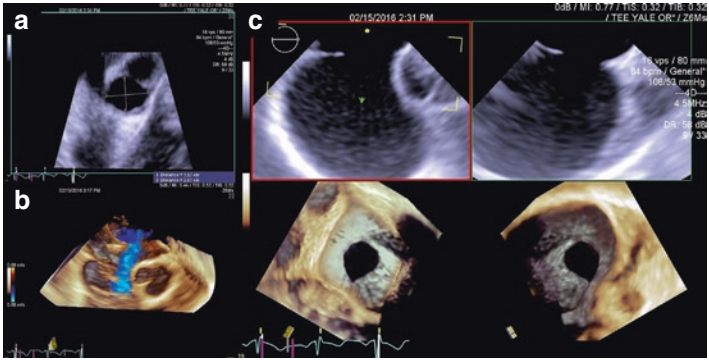

Figure 3.8 Three-dimensional transoesophageal echocardiogram. (**a**) Planimetry of the ASD measuring 2.1 cm in the major diameter and 1.6 cm in the perpendicular diameter. (**b**) 3D short axis at 0° showing the jet trough the ASD. (**c**) 3D short axis at 0° showing the ASD from left atrium (left) and right atrium (right)

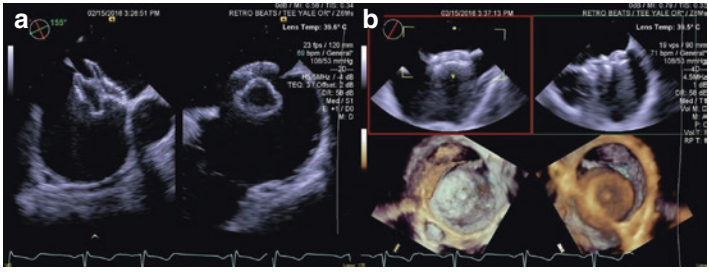

Figure 3.9 Transoesophageal echocardiogram during the ASD closure. (**a**) Bi-plane imaging at 65° and 155° showing when the device is being placed. (**b**) 3D imaging after the deployment of the device from the left atrium (left) and the right atrium (right)

Clinical Pearls

1. The right ventricle has a complex shape and structure, making it challenging to image and assess; as a result, more than one modality may be needed for evaluation.
2. Transthoracic echo remains first-line for cardiac imaging of the right side.

3. Magnetic resonance and transoesophageal echo are often subsequently pursued for complementary information regarding size, function, tissue characterization, and planning for invasive therapeutic procedures.
4. In select cases, additional imaging by computed tomography offers incremental information on structural relationships and procedural planning.
5. Moving forward into the future, emerging and novel parameters of echo and CMR are attempting to further provide new ways to assess the right ventricle as part of diagnostic and prognostic work-up.

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Chapter 4
Born with a Failing Right Heart

Matthew R. Carazo, Michael J. Landzberg, and Maan Jokhadar

Case Presentation

A 37-year-old woman with repaired Tetralogy of Fallot (ToF) was admitted for increased dyspnea on exertion. At age 22 months, she underwent ventricular septal defect (VSD) patch closure and right ventricular outflow tract (RVOT) transannular patch repair and felt well until age 18 years when she noted increased dyspnea on exertion and early fatigue with daily activities. Evaluation at the time revealed severe pulmonary regurgitation (PR), leading to recommendation to undergo surgical pulmonary valve replacement (PVR). This was pursued with successful valve implantation that was complicated by complete atrioventricular (AV)

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node block requiring placement of permanent pacemaker with atrial and ventricular epicardial leads. Her pacemaker was changed to a transvenous dual-chamber pacemaker at age 24 years.

4.1 What Are the Initial Thoughts?

The potential for lifelong heart failure (HF) for patients with congenital heart disease begins at birth. Symptoms and signs of HF depend on the complexity of the anatomic and physiologic disease—with more severe cases presenting at birth or shortly thereafter, necessitating urgent intervention. For those born with a failing right heart, all procedures, regardless of timing and type, should be considered palliative and not curative; despite repeated procedures, cumulative myocardial damage often occurs due to congenital pathophysiology, deranged hemodynamics, and the therapeutic procedures themselves.

4.2 What Is TOF?

Tetralogy of Fallot (ToF) is the most frequent cyanotic congenital heart disease with almost 33 cases per 100,000 live births [1]. The four fundamental features of ToF, first described in detail by Fallot in 1888, comprise of unrestrictive malalignment VSD, pulmonary outflow tract obstruction (which may vary and contribute to relative direction and degree of intra-cardiac shunting), overriding aorta, and right ventricular (RV) hypertrophy [2] (Fig. 4.1). Given the advancements in surgical techniques since Lillehei first began operating on patients in 1955, there more patients are surviving, and even thriving, well into adulthood [3, 4]. Because of these advancements, physicians of all fields will encounter these patients.

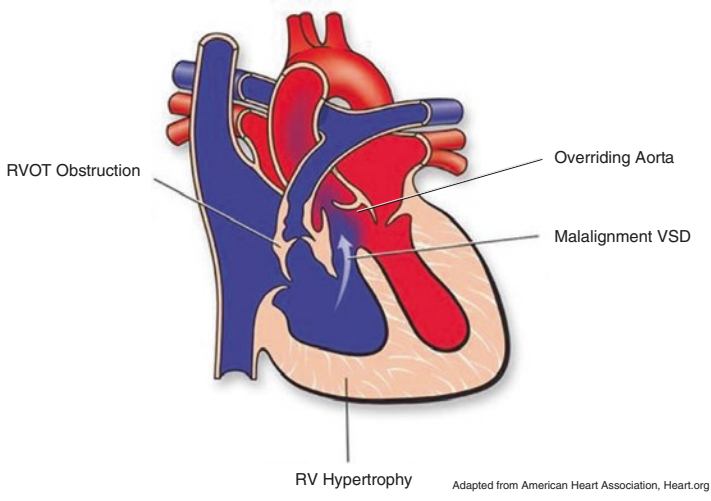

FIGURE 4.1 The four fundamental features of Tetralogy of Fallot (ToF). Tetralogy of Fallot is comprised of malalignment ventricular septal defect (VSD), right ventricle outflow tract (RVOT) obstruction, overriding aorta, and right ventricular (RV) hypertrophy. Adapted from American Heart Association, Heart.org

4.2.1 Anatomy and Physiology

Van Praagh et al. describes ToF as one basic abnormality—the inadequate development of the subpulmonary infundibulum (which may or may not involve the pulmonary valve itself) from which all pathophysiology results [2, 5]. The key to understanding the features of ToF is knowledge of RV anatomy: the inlet portion, the apical trabecular component, and the outflow. The embryology and anatomy of the RV is discussed in Chap. 1.

The hypoplastic infundibulum itself creates the obstruction within the pulmonary outflow tract. The VSD results because the displaced infundibulum no longer fills the area above the septal band and ventricular septum. The hypoplas-

tic infundibulum, which contains the infundibular septum as its floor, does not develop normally in a rightward, posterior, and inferior direction. Consequently, the aortic valve, which attaches to the infundibular septum, is malaligned anteriorly and superiorly, and thus overrides the aorta. In this case, the pulmonary valve (if developed) is often thickened and stenotic. RV hypertrophy occurs in the postnatal period if the RV is exposed to both a significant pulmonary outflow tract obstruction and a large non-restrictive VSD as pulmonary vascular resistance begins to fall [2].

Also in the postnatal period, the ductus arteriosus closes, and infants are solely reliant on the blood exiting the RV and flowing throughout the pulmonary vascular bed for systemic oxygenation. Thus, the degree of RVOT obstruction dictates the postnatal pathophysiology—the greater the obstruction, the less flow into the more distal pulmonary artery (PA). In infants born with significant obstruction (and/or if the pulmonary vascular resistance does not fall), there will be a net right-to-left shunt with flow of deoxygenated (blue) blood across the VSD, especially if it is large and unrestricted, into the systemic circulation, resulting in cyanosis [6].

4.3 What Are the Expected Physical Examination Findings in ToF?

In the post-operative adult, the physical exam directly correlates with the residual sequelae of the surgical intervention. A single S2 is due to the absence of functional pulmonary valve leaflets. A loud P2 may be due to a replaced pulmonic valve and/or pulmonary hypertension. A systolic ejection murmur can be heard if there is a residual outflow tract obstruction or abundant flow due to a regurgitant pulmonary valve. An early diastolic murmur denotes pulmonary regurgitation (PR) while flow due to tricuspid regurgitation (TR) or residual VSD can be heard throughout systole. A diminished or absent unilateral radial pulse and ipsilateral thoracotomy scar are key to the exam for patients who underwent subcla-

vian artery-to-pulmonary artery anastomosis (classic Blalock-Taussig-Thomas {BTT} shunt) in early childhood [7].

4.3.1 Case Continued

On physical examination, the patient's vital signs were normal, and she appeared comfortable. Well-healed sternotomy, abdominal, and deltopectoral scars were noted. The jugular venous pressure was elevated at 10 cm H_2O, and her lungs were clear. Cardiovascular examination revealed an RV heave, normal S1, split S2 with loud P2, a grade II/VI systolic murmur at the left upper sternal border, and a grade II/IV diastolic murmur at the left lower sternal border. Peripheral pulses were normal.

4.4 What Is the Approach to ToF?

The goal for all surgical repair of ToF involves relief of RVOT muscular bundles and/or pulmonary valve annular obstruction, VSD closure, and main PA augmentation (and branches as needed).

Early surgical repair involved an anastomosis of the subclavian artery to the ipsilateral PA in order to augment pulmonary blood flow in those with severe RVOT obstruction (BTT shunt) [8]. The procedure then evolved into the modern approach using a modified BTT shunt with a polytetrafluroethylene interposition graft between the subclavian and pulmonary arteries, which may be taken down surgically later at the time of repair of the infundibulum and relief of the subpulmonary obstruction [8].

Earlier generations of patients may have undergone central shunt placement with anastomosis of the aorta to one of the branch pulmonary arteries in order to augment flow. Use of these shunts such as the Waterston (right PA to ascending thoracic aorta connection) and Potts (left PA to descending thoracic aorta anastomosis) has fallen out of favor as sys-

temic to pulmonary flow is difficult to control, potentially leading to pulmonary overcirculation, iatrogenic ligation of nearby branch upper PA segments, or early shunt closure [9].

For those undergoing neonatal surgical repair with a narrowed infundibulum, the transannular approach to repair involves a full thickness incision along the infundibulum, effectively splaying it open to relieve the obstruction, followed by patch augmentation at the level of the pulmonic annulus, which fundamentally disrupts the valve architecture in order to provide this relief—sometimes with extension of the patch into the main PA—and VSD patch closure [6, 7, 10].

A valve-sparing technique has been advocated but still involves infundibulotomy or ventriculotomy to access the right ventricular outflow tract and resect obstructive muscle bundles [11]. Full relief of the infundibular obstruction may not result, cumulating in RV hypertrophy, fibrosis, recurrent RVOT obstruction, and a higher chance of reoperation [6, 10, 12].

The use of RV to PA conduit (cadaveric homograft or xenograft) may be necessary if the pulmonary arteries are diffusely small or if the location of the coronary arteries preclude infundibular repair [6]. PA reconstruction may also be required [12].

Non-surgical approaches including transcutaneous balloon valvuloplasty and stenting of the infundibulum have been used; the associated sequelae include residual RVOT obstruction, pulmonary regurgitation, tear within the infundibulum/main PA, and aneurysms and pseudoaneurysms within the outflow tract [13].

4.5 What Is the Pathophysiology of Right Heart Failure (RHF) in TOF?

ToF is an excellent model for RHF as the pathology begins before birth and has ramifications throughout life. In utero, the RV undergoes abnormal volume and pressure loading [14]. Concomitant poor development of pulmonary vascula-

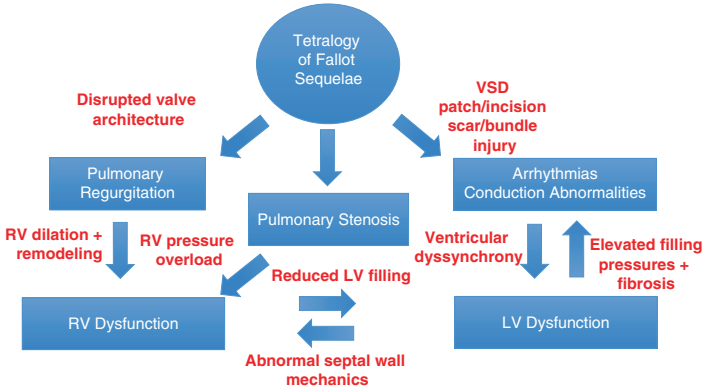

FIGURE 4.2 Pathophysiology of ToF sequelae. *RV* right ventricle, *LV* left ventricle, *VSD* ventricular septal defect

ture capacitance has significant long-term effects, and measurement of this value as a surrogate for RV afterload has noted implications for ventricular failure later on in life [15].

The six key sequelae of repaired ToF include pulmonary regurgitation, pulmonary stenosis, impaired RV function, LV dysfunction, arrhythmias, and conduction abnormalities; these contribute to the increasing morbidity and mortality seen in adulthood [16] (Fig. 4.2 and Table 4.1).

4.5.1 Pulmonary Regurgitation and Biventricular Dysfunction

Relief of RVOT obstruction often comes at the price of PR, resulting in adverse remodeling—as a compensatory measure to preserve stroke volume—due to volume, pressure, or mixed pressure/volume overload [1] (Fig. 4.3). Influential factors include: the duration of diastole, size of the orifice of regurgitation, the capacitance of the PAs, RV diastolic afterload, compliance of the RV, and the diastolic pressure gradient between the main PA and the RV [17, 18]. Alterations in pulmonary vascular resistance affect differential branch PA

Table 4.1 The six key sequelae of repaired ToF

Sequelae of ToF repair	Mechanism	Effect
Pulmonary regurgitation	Patch augmentation of the infundibulum → distortion of the annular architecture	Right ventricle dilation + decreased compliance + increased diastolic afterload → decreased global function
Pulmonary stenosis	Residual obstruction in the RVOT, at or above the level of the pulmonary valve, or within the pulmonary vascular bed	RV pressure load → eccentric and concentric hypertrophy → ventricular failure
Impaired RV function	Dilation + remodeling due to increased preload and afterload	Septal bulge → impaired contraction and decreased LV filling
Left ventricle dysfunction	Abnormal septal mechanics	Arrhythmias + symptoms of HF + SCD
Arrhythmias	Elevated filling pressures + scar at surgical site + ventricular fibrosis	HF symptoms, worsening ventricular function, SCD
Conduction abnormalities	Bundle branch injury due to VSD patch or suture placement + scar/fibrosis	Impaired ventricular synchrony → decreased RV + LV function

RVOT right ventricle outflow obstruction, *RV* right ventricle, *HF* heart failure, *SCD* sudden cardiac death, *VSD* ventricular septal defect, *LV* left ventricle

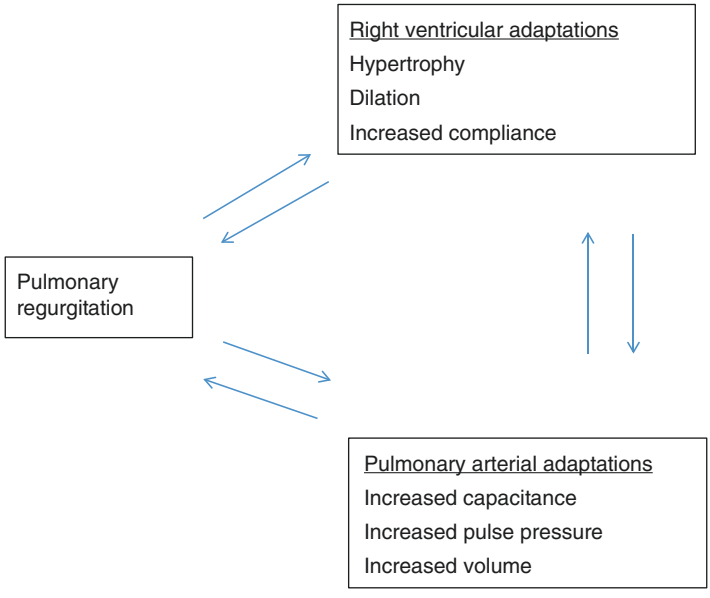

FIGURE 4.3 Effects of pulmonary regurgitation on right ventricular failure. Adapted from Geva, JCMR 2011, 13:9

regurgitation with etiologies ranging from prior unilateral central shunt placement to external compression of the left lung by an enlarging heart [19].

Similar to LV adaptation to chronic volume loading in the setting of aortic valve regurgitation, the RV undergoes a pathophysiologic response to PR after ToF repair. First, there is a compensated stage during which end diastolic volume (EDV) increases, and eccentric and concentric hypertrophy occurs with maintenance of global systolic function and mass-to-volume ratio [20]. These mechanisms eventually fail (often years to decades later), leading to further ventricular dilation but with decreased mass-to-volume ratio (insufficient hypertrophy) and increased afterload with an associated decrease in global systolic function [17]. Eventually, these sequelae culminate in irreversible myocardial injury, characterized by

increased wall stress, interstitial fibrosis, and dyssynchrony both within the RV and between the ventricles [1, 20]. This remodeling influences ventricular-ventricular interaction on the basis of mechanical and hemodynamic factors through septal geometry changes and chronically reduced left ventricular filling, respectively [21].

4.5.2 Pulmonary Stenosis

Residual obstruction in the RVOT, at or above the level of the pulmonary valve, or within the pulmonary vascular bed, can all result after ToF repair as a consequence of surgical intervention itself and/or be inherent within the patient's anatomy. Pulmonary stenosis will result in additional RV pressure load. Animal models with surgically induced pressure overload demonstrate increases in contractile indices, systolic and diastolic reserves, and enhanced contractility via the Anrep effect [22]. This compensation may provide patients with an early protective effect on remodeling by preserving circumferential and radial myocardial strain while also negatively affecting LV intraventricular synchrony [23].

4.5.3 Arrhythmias and Conduction Abnormalities

In ToF, the His-Purkinje conduction pathway moves along the inferior aspect of the malalignment VSD, and therefore is often vulnerable to damage during surgery, resulting in classic postoperative right bundle branch block [24]. Atrial and ventricular arrhythmias late after repair are prevalent and correlated with a time-dependent risk of sudden cardiac death (SCD) [7]. Typical atrial flutter is the most common type of atrial arrhythmia in patients with repaired ToF [24]. SCD is the most common mode of death in ToF patients; the overall incidence ranges from 0.15% to 1.2% [25–28]. Risk scoring has been proposed for appropriate ICD shocks in primary prevention for patients with these variables: prior palliative

shunt, inducible sustained ventricular tachycardia (VT), QRS duration ≥180 ms, ventriculotomy incision, nonsustained VT, and LV end-diastolic pressure ≥12 mmHg; a lower risk score confers a lower risk of annualized rate of appropriate shocks [29, 30].

4.6 What Diagnostic Work Up Would You Recommend?

As shown in Chap. 3, serial imaging studies are required to assess RV size and function. Color Doppler echocardiography provides visualization of regurgitation jets, and pulsed wave Doppler demonstration of diastolic flow reversal in the main or branch PAs, regurgitant fraction >40%, and jet pressure half-time of <100 ms are all indicative of severe regurgitation [31].

Data suggest ventricular size and function predict major cardiac outcomes. Increases in RV volumes and reductions in biventricular ejection fraction by cardiac magnetic resonance imaging (MRI) correlate well with decreases in tricuspid and mitral annular plane systolic excursion (TAPSE and MAPSE respectively). Right and left ventricular peak longitudinal 2-dimensional strain imaging on echocardiography is suggestive of adverse ventricular-ventricular interaction and interrelation of biventricular function [32, 33]. Similarly, myocardial deformation parameters of ventricular longitudinal and circumferential strain as measured by cardiac MRI feature tracking—a technique that assesses strain function—are predictors of outcome of a combined endpoint of death, successful resuscitation, or ventricular tachycardia [34, 35].

RV end-diastolic volume (EDV) dilation (with Z-scores based on published normal values ≥ 7) along with right and/or left ventricular dysfunction as measured on cardiac MRI are predictive of death, sustained ventricular tachycardia, and worsening functional status [36]. A pre-operative indexed RV end-systolic volume (ESV) of >95 mL/m^2, older age, lower RV ejection fraction, and lower LV ejection fraction are all

associated with adverse outcomes, including death, HF, and sustained VT; an indexed RV ESV < 80 mL/m^2 is predictive of RV volume and function normalization after PVR [37].

Echocardiography is useful to identify the level of stenosis as well as severity. Moderate stenosis of a native valve is associated with a peak velocity of 3–4 m/s (or 36–64 mmHg) while velocities above 4 m/s (or 64 mmHg) indicate severe stenosis [38]. If an RV-PA conduit is used as part of the original repair, leaflet fibrosis and calcification of the conduit can degrade valve function and/or obstruct blood flow at any location along the entire conduit length [39].

ECG and Holter monitoring can be utilized for surveillance of arrhythmias and have been useful for clinical decision-making, such as referral for electrophysiology study and/or placement of ICD [40]. For patients undergoing programmed ventricular stimulation following ToF repair, inducible monomorphic VT and polymorphic VT predict future clinical VT and SCD [27]. Lengthening of the QRS interval on ECG reflects mechanical asynchrony present within the RVOT (and not within the RV body itself) resulting from prior surgical repair and fibrosis at the surgical site [41].

4.6.1 Case Continued

Our patient's electrocardiogram revealed sinus rhythm with a first-degree AV block, right bundle branch block, and left posterior fascicular block. Interrogation of the pacemaker device showed no arrhythmias. An echocardiogram showed normal LV size and systolic function, grade 1 diastolic dysfunction, moderately enlarged RV with moderately reduced systolic function, flattening of the interventricular septum, and a maximum instantaneous Doppler gradient of 53 mmHg across the RVOT, severe PR, and moderate TR with an estimated RV systolic pressure of 55 mmHg. Cardiac computerized tomography demonstrated unobstructed RVOT, no coaptation of pulmonary valve leaflets, a dilated RV with indexed RV EDV of 140 mL/m^2 (53.6 ± 10.5 mL/m^2)

and indexed RV ESV of 80 mL/m^2 (22 ± 7 mL/m^2), a reduced RV ejection fraction of 42%, normal LV size with ejection fraction of 51%, normal sized main and branch PAs, and normal coronary artery course without stenosis.

4.7 What Are the Management Strategies for this Patient?

Patients often enjoy an asymptomatic period that lasts for several decades before manifesting signs of HF similar to their counterparts with acquired heart disease [42]. Archetypal HF symptoms such as exercise intolerance, dyspnea on exertion, volume overload, and fatigue may not be as overt in ToF patients [43].

Medical therapy often includes the same drug classes within the acquired LV HF armamentarium: diuretics; beta-blockers for myocardial preservation and arrhythmia management; and angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), aldosterone antagonists, and angiotensin receptor-neprilysin inhibitor (ARNi) for afterload reduction and prevention of adverse ventricular remodeling [44]. However, the evidence for HF drugs in ToF is lacking in randomized, double-blind placebo-controlled trials [45]. For ToF patients who develop pulmonary vascular disease, disease-targeting drug therapies have been used to decrease pulmonary vascular resistance and improve functional class [46]. Cardiac resynchronization therapy (CRT) has been shown to improve LV ejection fraction with favorable trends in LV volumes in repaired ToF patients who met clinical criteria for upgrade or implantation of CRT pacemaker [47]. Electrophysiological studies and ablative therapies are also employed for arrhythmia management as needed [43]. Additionally, any modifiable HF risk factors, such as tobacco use, obesity, diabetes, or hypertension, should also be addressed [16].

Residual obstructive or regurgitant lesions may require catheter-based or surgical interventions. PVR often improves symptoms in those with combined pulmonary stenosis and regurgitation rather than regurgitation alone and is reasonable in patients with symptoms and/or evidence of RV and/or LV dysfunction [48] (Fig. 4.4). PVR can be performed surgically or percutaneously; transcatheter PVR (TPVR) can be placed valve-in-valve (Medtronic Melody or Edwards SAPIEN valves) within existing RVOT conduits or previously placed surgical valves [49, 50]. Branch PA balloon dilation and stenting may be used for relief of stenosis while collaterals causing pulmonary vascular overcirculation or hemoptysis may require catheter-based coiling or vascular plug deployment [49]. Residual VSD(s), RVOT obstruction(s), PA stenosis, significant aortic regurgitation, RVOT aneurysm, and enlarged aortic root with diameter ≥ 55 mm also may require surgical intervention [51].

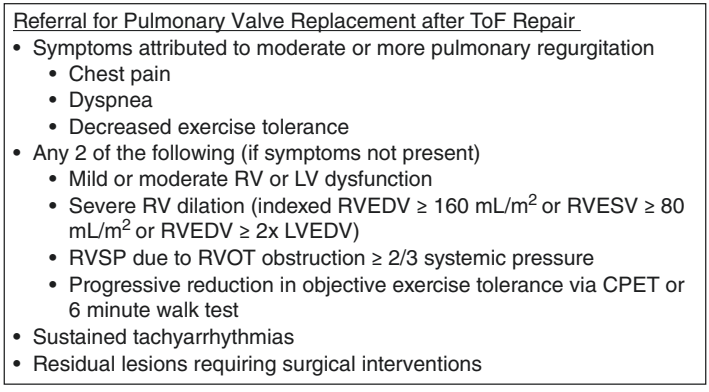

Figure 4.4 Referral for pulmonary valve replacement after ToF repair. *ToF* tetralogy of fallot, *RV* right ventricular, *LV* left ventricular, *RVEDV* right ventricular end diastolic volume, *RVESP* right ventricular end systolic volume, *RVSP* right ventricular systolic pressure, *RVOT* right ventricle outflow tract, *CPET* cardiopulmonary exercise testing. Adapted from Stout et al., JACC 2019;73:e81–e192

4.8 What Are the Options for Advanced Therapies?

Advanced HF therapies have been employed in repaired ToF patients, including inotrope and vasopressor therapy, ventricular assist device (VAD), and heart transplantation [52, 53].

VAD placement for a subpulmonic RV is technically challenging given the anterior position of the RV, and its use is limited [54]. Data for the use of a subaortic LV VAD is also limited, though mortality is similar to those without congenital heart disease [55–57]. RV dysfunction often precludes LV VAD therapy. Cardiac transplantation may also be used in severe HF, but patients often have longer wait-list times and congenital heart disease-specific factors that may affect transplant candidacy, such as allo-sensitization, pulmonary hypertension, surgical challenges (e.g. adhesions, collateral vessels, PA reconstruction), and liver dysfunction [52, 58, 59]. Palliative care may be appropriate for those who are not candidates for advanced HF therapies [52] as discussed in Chap. 12.

4.9 What Is the Prognosis?

The utility of cardiopulmonary exercise testing (CPET) has been highlighted as a tool in the management of patients with HF. CPET provides insight into cardiac physiology as well as the response of pulmonary and musculoskeletal systems to the metabolic demands of exercise; use of peak VO_2 (peak oxygen consumption) and V_E/VCO_2 slope (minute ventilation-carbon dioxide output relationship, a measurement of ventilation-perfusion matching) has been described in risk stratification for patients with repaired ToF [60]. Multiple factors associated with repaired ToF influence myocardial reserve, including pulmonary and tricuspid valve regurgitation, RV-LV interactions, wall motion abnormalities due to surgical patches within the RVOT and ventricular septum, conduction abnormalities, neurohormonal imbalances, and myocardial architectural damage.

In turn, these factors affect the hemodynamic disturbances seen during exercise as noted by changes in submaximal and maximal CPET measurements [61].

Use of HF tools, such as the Seattle Heart Failure Model, for risk stratification in adults with congenital heart disease can help identify populations at high-risk for death and cardiovascular hospitalization [62]. Biomarker measurements may also be helpful as elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T, and growth-differentiation factor 15 have been associated with cardiovascular events [63, 64].

4.9.1 Case Conclusion

On the basis of the findings above, the patient underwent TPVR with a bovine pericardium bioprosthetic valve with a valve-in-valve approach. Her post-procedural course was uncomplicated, and on clinic follow up, her symptoms had resolved.

Clinical Pearls

- Heart failure in repaired ToF manifests as volume overload, atrial and ventricular arrhythmias, and decreased exercise tolerance.
- ToF results from infundibular septum hypoplasia, and surgical repair focuses on relieving RVOT obstruction, often at the expense of pulmonary regurgitation.
- Exam findings directly correspond to the sequelae of surgical repair, including single S2, murmurs of pulmonary stenosis and/or regurgitation, diminished or absent radial pulse due to prior BTT shunt, and residual VSD murmur.
- Electrocardiogram and echocardiogram are important diagnostic tools in patients with acute HF symptoms. Cross-sectional imaging, such as CT and MRI, is utilized for interventional planning. CPET can be used for prognostication. Invasive assessment of hemodynamics may be of particular utility when RHF is longstanding or concomi-

tant liver impairment is suspected, given the propensity towards low systemic vascular resistance in these cases.

- Diuretics and antiarrhythmics may be given in the acute presentation of HF. Standard HF guideline-directed medical therapy is often used for afterload reduction and prevention of adverse remodeling, though compelling data supporting long-term use are lacking. Pulmonary vasodilators are utilized in concomitant pulmonary hypertension management. Ablative therapies may be beneficial in specific instances of tachyarrhythmia; pacemakers and ICDs may be useful to treat bradyarrhythmias and to reduce incidence of sudden cardiac death.
- Advanced therapies, including inotrope infusion, mechanical circulatory support, and heart transplantation are generally offered for refractory heart failure.
- Diagnostic evaluation and therapeutic strategies for patients with RHF associated with congenital heart disease should be reviewed in conjunction with expert clinicians in the management of congenital heart disease.

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Chapter 5
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Nath Zungsontiporn and Mark S. Link

Case Presentation

A 20-year-old man with history of cardiac arrest, status post implantable cardioverter defibrillator (ICD) presented for an evaluation after his ICD discharge. One year ago, he was shocked by the defibrillator and started on amiodarone 200 mg/day. On the day of presentation, two ICD shocks were delivered and he passed out. After regaining consciousness, he called emergency medical service and was brought to the emergency room. He reported no other symptoms at the time of initial evaluation. He had no family history of sudden cardiac death (SCD), premature coronary artery disease or familial cardiomyopathy.

Initial physical examination was notable for parasternal lift, grade 2/6 pansystolic murmur that was accentuated by inspiration on left lower sternal border, and the presence of palpable implanted device on left upper thorax. ECG shows sinus rhythm (Fig. 5.1) remarkable for right ventricular

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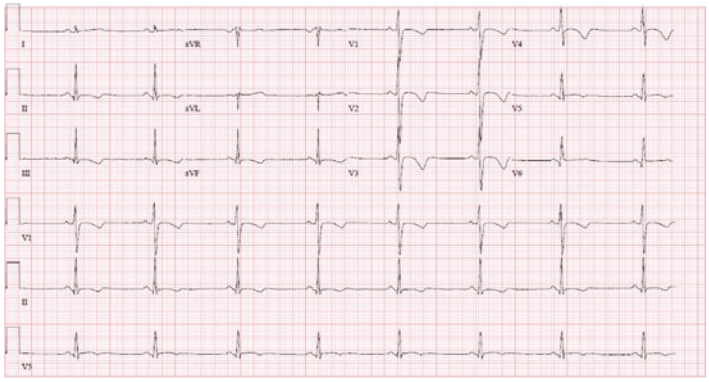

Figure 5.1 Sinus rhythm ECG. Note the T-wave inversions from V1 to V5, which are distinctly abnormal

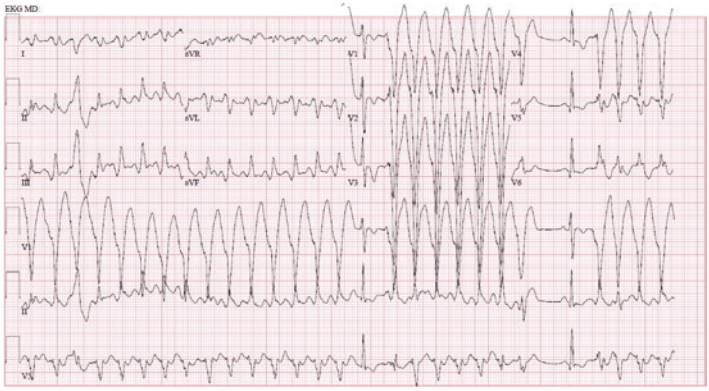

Figure 5.2 Wide complex tachycardia ECG. Note the left bundle branch block pattern which signifies that the arrhythmia is coming from the right ventricle

hypertrophy and T wave inversion in several leads (V1–V5, II, III, aVF). He was also noted to have intermittent non-sustained wide complex tachycardia (WCT) on telemetry, which was also captured by a 12-lead ECG (Fig. 5.2).

5.1 Our Initial Approach for Evaluation of this Patient

This patient presented with reported multiple ICD shocks associated with syncope. Thus, an ICD interrogation was indicated to confirm the presence of ICD shocks and to evaluate its cause. However, even before the interrogation, the presence of non-sustained WCT provided us an important clue of the underlying arrhythmia that may have caused the ICD shocks. The main differential of WCT includes ventricular tachycardia (VT), supraventricular tachycardia (SVT) with conduction delay, SVT with pre-excitation, and ventricular paced rhythm (Fig. 5.3).

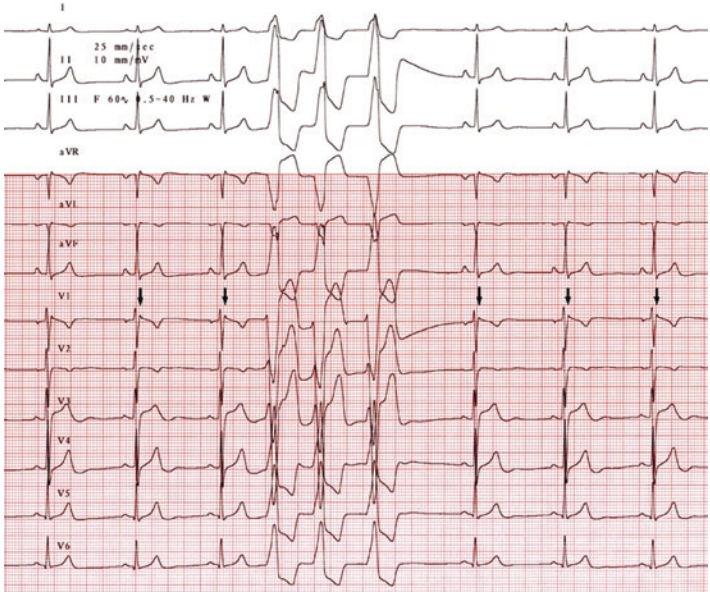

FIGURE 5.3 Epsilon waves. This 12-lead ECG from a *different* patient with ARVC demonstrates epsilon waves (arrow head). Also, 3-beat non-sustained VT with LBBB-like morphology/inferior axis is also demonstrated in the middle of the tracing

Given the history of heart disease, associated abnormal physical signs and ECG findings, as well as the presence of an ICD, the clinical likelihood that the WCT was a VT was already high. Although there were no ECG signs of atrioventricular dissociation (dissociated P wave, fusion beats, and captured beats), the QRS complex morphology during the tachycardia was more consistent with VT than SVT given (1) left bundle branch block (LBBB)-like QRS complex with RS > 70 ms in V2 and (2) initial r wave with duration >40 ms in aVR. Paced rhythm is highly unlikely at the rate of almost 180 beats/min as the upper tracking rate of the device is generally not programmed to exceed 150 beats/min. The subsequent ICD interrogation showed that the patient was shocked three times for a sudden onset, regular WCT with distinctly different QRS morphology from the recorded baseline. This was consistent with our suspicion of VT causing ICD shocks.

In patients with structural heart disease, VT with LBBB-like QRS morphology generally originates from right ventricle (RV) or interventricular septal myocardium. Various pathological processes can lead to the development of VT in these areas. However, in this patient with physical signs and electrocardiographic findings suggestive of predominant RV structural abnormalities, arrhythmogenic RV cardiomyopathy (ARVC) needs to be considered.

5.2 Terminologies: ARVC, ARVD, and ACM

ARVC, also termed arrhythmogenic right ventricular dysplasia (ARVD), is a genetic cardiomyopathy characterized by myocardial atrophy and fibrofatty replacement. This results in increased arrhythmogenicity and ventricular contractile dysfunction. The majority of ARVCs are caused by pathogenic mutations in genes encoding protein components of intercalated discs, such as desmosome [1]. Although ARVC was initially described as a disease of the (RV) [2], left ventricular involvement by the disease is not uncommon.

As the disease involvement is not limited to the RV, some authors use the term arrhythmogenic cardiomyopathy (ACM) instead of ARVC when referring to the disease. However, in the recent Heart Rhythm Society (HRS) expert consensus statement, this term is used more broadly to conceptualize a group of primary cardiomyopathies of various etiologies. This terminology excludes heart diseases due to coronary artery disease, hypertension, and valvular heart diseases that have arrhythmias as prominent presenting clinical features. Thus, ARVC represents one type of ACM [1]. To be consistent with this conceptual framework, the term ARVC will be used to refer to the disease in this article.

Also, some authors consider an ACM with predominant LV involvement a "variant" of ARVC. Although this might be true in some scenarios, in our opinion, there is insufficient evidence at this point to make a generalized conclusion. Thus, this article will focus on ARVC as diagnosed based on 2010 revised Task Force criteria.

5.3 What Is the Epidemiology and Pathophysiology of ARVC?

The prevalence of ARVC is not entirely clear and varies in different ethnic populations. The reported prevalence ranges from 0.6 to 1 case in 1000 persons [3, 4].

5.3.1 Pathology, Genetics, and Pathophysiology of ARVC

The pathological hallmark of ARVC is myocardial tissue atrophy and replacement by fibrofatty tissue [5–8]. The cardiomyocytes in the affected areas show degenerative features, apoptosis, and/or necrosis [7]. The degree of fibrosis in the affected tissue varies from minimal (*fatty variant*) to significant (*fibrofatty variant*) [5, 6, 8]. On electron microscopic

examination, intercalated disc structural abnormality and remodeling can be seen on the affected cardiomyocytes [9].

Intercalated discs are specialized structures on the cell membrane that connect adjacent cardiomyocytes and play vital roles in mechanical and electrical coupling as well as regulating cellular signaling pathways. They comprise of three main structures: desmosomes, fascia adherens, and gap junctions. The intercalated discs rely on orchestrated functions of these components [10].

In ARVC patients, pathogenic mutations in genes encoding components of the intercalated disc leads to qualitatively and/or quantitatively abnormal production of such proteins and, consequently, impaired functions of intercalated discs. Impaired mechanical coupling leads to cardiomyocyte detachment, death, and, in conjunction with abnormal cellular signaling, fibrofatty replacement [7, 11]. Impaired electrical coupling and fibrofatty tissue interposed between adjacent cardiomyocytes lead to slow, non-uniform electrical conduction, which predispose patients to the development of reentry arrhythmia [7, 11]. As the disease progresses, resulting in increased cardiomyocyte loss, ventricular wall motion abnormality, systolic dysfunction, and dilation ensue.

The pathogenic mutation of ARVC was first identified in junction plakoglobin (JUP) gene, encoding desmosomal proteins [12]. Subsequently, mutations were identified in other desmosomal genes, namely plakophilin-2 (PKP2), desmoglein-2 (DSG2), desmoplakin (DSP), and desmocollin-2 (DSC2). Overall, pathogenic desmosomal gene mutations were identified in approximately 50% of ARVC patients [13, 14]. Mutations in genes encoding non-desmosomal proteins have also been reported to cause ARVC but were identified in less than 10% of patients [13–15]. Most pathogenic mutations identified were heterozygous. Multiple mutations (homozygous, compound heterozygous, or digenic) were found in only approximately 6% of patients [7, 13, 16].

Given the incomplete penetrance and variable phenotypic expression of ARVC, environmental factors have been pro-

posed to play a role in its pathogenesis. Exercise has been associated with increased penetrance of ARVC in pathogenic desmosomal gene mutation carriers [17, 18]. Increased myocardial wall stress associated with exercise in conjunction with underlying impaired cardiomyocyte adhesion is hypothesized to accelerate cardiomyocyte detachment and death; thus, promoting the disease manifestation.

ARVC was initially thought to almost exclusively involve the RV, especially in the inflow, outflow, and apex, collectively called the "triangle of dysplasia" [2, 7]. However, LV involvement was found in 47% to 76% on pathological examination of the examined hearts (post-mortem or explanted) with ARVC [5, 8]. ARVC pathology generally progress from the subepicardial to subendocardial myocardium [7, 8].

5.4 What Are the Clinical Manifestations and Prognosis of ARVC?

ARVC patients usually present for clinical evaluation between the ages of 20–50 years with symptoms relating to ventricular arrhythmia (VA), such as palpitations, chest discomfort, presyncope, and syncope. Cardiac arrest and SCD can be the first presenting symptom in approximately 10% of patients [13, 19, 20]. VAs due to ARVC generally have LBBB-like morphology [20, 21], reflecting their RV origins, but can have superior or inferior axis [21]. VAs frequently recur during follow up and can lead to SCD [13, 19–21].

Most patients do not have heart failure symptoms early in the course of the disease [13, 20, 21]. As the disease progresses, symptoms of heart failure, especially right-sided (fatigue, exertional intolerance, lower extremity edema, and abdominal bloating), may subsequently develop from progressive contractile dysfunction and dilatation of the RV [13, 20]. Increasingly recognized is involvement of the LV, and dilation and subsequent left heart failure is seen as patients are not dying of arrhythmias. A small number of these patients require heart transplantation [13, 20].

ARVC is found to be familial in approximately 50–70% of patients [11, 13]; mainly inherited in an autosomal dominant pattern with incomplete penetrance and variable phenotypic expression [22, 23]. Autosomal recessive ARVC is rare and typically associated with characteristics cutaneous manifestation in the form of keratoderma striate on palmar and plantar surfaces as well as wooly hair [12, 24]. This constellation of abnormalities is named "Naxos syndrome" [24].

Overall, the prognosis of patients with ARVC in contemporary cohorts with utilization of ICD is reasonable [13, 19]. In a large cohort study of 439 ARVC patients with median follow up of 7 years, cardiac mortality and the need for cardiac transplantation occurred in 6% and 4% of patients, respectively [13]. SCD is the most important cause of death and is responsible for almost all deaths in patients without an ICD. In those with an ICD, deaths are more commonly due to heart failure and non-cardiac causes.

5.5 What Are the Diagnostic Tests Recommended for ARVC?

5.5.1 Electrocardiography (ECG)

Various ECG abnormalities reflect delayed/fragmented activation of the myocardium affected by ARVC. As ARVC predominantly involves the RV, these ECG abnormalities are most commonly observed in the right precordial leads (V1–V3) [25]. If they present on left precordial leads, LV involvement should be suspected [25]. Normal ECG can be seen in up to 12% of ARVC patients, especially in earlier stages [26]. ECG abnormalities are generally classified into depolarization and repolarization abnormalities [14].

Epsilon wave, prolonged terminal activation duration (TAD) of QRS complex, and late potentials on signal averaged ECG, are depolarization abnormalities that are relatively specific for ARVC. Thus, they are incorporated in the revised Task Force criteria for diagnosis of ARVC (see Table 5.1) [14, 25]. QRS fragmentation, incomplete and com-

Table 5.1 Revised task force criteria for diagnosis of ARVC

Criteria categories	Major criteria	Minor criteria
Global or regional dysfunction and structural alterations	• *By 2D echo* Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): – PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥ 19 mm/m^2) – PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥ 21 mm/m^2) – Or fractional area change ≤33% • *By MRI* Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: – Ratio of RV end-diastolic volume to BSA ≥ 110 mL/m^2 (male) or ≥ 100 mL/m^2 (female) – Or RV ejection fraction ≤40% • *By RV angiography* Regional RV akinesia, dyskinesia, or aneurysm	• *By 2D echo* Regional RV akinesia or dyskinesia and 1 of the following (end diastole): – PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥ 16 to <19 mm/m^2) – PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥ 18 to <21 mm/m^2) – Or fractional area change >33% to ≤40% • *By MRI* Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: – Ratio of RV end-diastolic volume to BSA ≥ 100 to <110 mL/m^2 (male) or ≥ 90 to <100 mL/m^2 (female) – Or RV ejection fraction >40% to ≤45%

(continued)

Table 5.1 (continued)

Criteria categories	Major criteria	Minor criteria
Tissue characterization of wall	• Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	• Residual myocytes 60–75% by morphometric analysis (or 50–65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Repolarization abnormalities	• Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥ 120 ms)	• Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6 • Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete right bundle-branch block

Table 5.1 (continued)

Criteria categories	Major criteria	Minor criteria
Depolarization/ conduction abnormalities	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1–V3)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG – Filtered QRS duration (fQRS) ≥ 114 ms – Duration of terminal QRS < 40 μV (low-amplitude signal duration) ≥ 38 ms – Root-mean-square voltage of terminal 40 ms ≤ 20 μV • Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete right bundle-branch block
Arrhythmias	• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 ventricular extrasystoles per 24 h (Holter)

(continued)

Table 5.1 (continued)

Criteria categories	Major criteria	Minor criteria
Family history	• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria • ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation[a] categorized as associated or probably associated with ARVC/D in the patient under evaluation	• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative • ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

PLAX indicates parasternal long-axis view; *RVOT* RV outflow tract, *BSA* body surface area, *PSAX* parasternal short-axis view, *aVF* augmented voltage unipolar left foot lead, *aVL* augmented voltage unipolar left arm lead, and *SAECG* signal averaged ECG
Adapted from Marcus et al. [37]
[a]A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non–ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree

plete right bundle branch block (RBBB) can be seen in ARVC but do not have adequate specificity for diagnostic purpose.

The epsilon wave is defined as reproducible, low-amplitude signals between the end of QRS complex to the onset of T wave. It represents delayed epicardial activation of the basal RV (near the tricuspid valve) and is associated with advanced conduction delay in the RV [27]. Although highly specific for ARVC, epsilon wave can be seen in cardiac sarcoidosis, acute myocardial infarction, and Brugada syndrome [25]. It is seen in approximately 5–20% of ARVC patients during their initial evaluation [19, 28, 29].

TAD of QRS complex is measured from the nadir of the S wave to the end of the QRS. Prolonged TAD (≥55 ms) in right precordial leads reflects delayed endocardial activation at RV outflow tract (RVOT) and basal RV inferior wall [27]. It is found in approximately 30–60% of ARVC patients during their initial evaluation [20, 28, 29].

Signal averaged ECG is a specialized ECG technique that generates averaged ECG signals by mathematically combining signals of 3 Simson's orthogonal bipolar leads: X, Y, and Z. This technique allows the detection of small amplitude, slowly conducting signals from pathologic myocardium ("late potentials") by analyzing filtered QRS duration (fQRSD), low amplitude signal duration below 40 μV (LAS) and root mean square voltage in last 40 ms of the QRS (RMS-40). In a study comparing signal averaged ECG in ARVC patients and healthy control, the detection of late potentials by fQRSD >114 ms, LAS > 38 ms, and RMS-40 < 20 μV was found to be high specificity for the diagnosis of ARVC [30].

The only repolarization abnormality incorporated in the revised Task Force diagnostic criteria is T-wave inversion. T-wave inversion can be seen in leads V1 and, sometimes V2, in healthy adults but rarely extends to V3 [31]. In ARVC

patients, T wave inversion in V1–V3 can be seen in approximately 30–80% patients during their initial evaluation [19, 20, 28, 29] and reflects RV dilation [14]. Other pathologic conditions that can cause T wave inversion in right precordial leads include RV cardiomyopathies from other causes, RBBB, and acute pulmonary embolism [14].

5.5.2 *Cardiac Imaging*

Echocardiography is generally the first imaging study used to evaluate suspected patients given its low cost and broad availability. Abnormal cardiac morphology and function associated with ARVC, such as RV dilation, global systolic dysfunction, and regional wall motion abnormalities can be detected by two dimensional (2D) echocardiography. The revised task force criteria rely on various degrees of these echocardiographic abnormalities to diagnose ARVC (see Table 5.1). However, evaluation of RV abnormalities by standard 2D echocardiography is limited by the retrosternal location and complex geometry of the RV as well as the RV wall motion assessment [14, 32, 33]. Three dimensional (3D) echocardiography [34] and assessment of tissue deformity by quantitative techniques, such as tissue Doppler imaging and strain imaging [35, 36] have been developed to overcome these limitations. However, whether addition of these newer techniques improve diagnostic accuracy beyond standard 2D echocardiography in ARVC patients remains to be validated.

Cardiac magnetic resonance imaging (MRI) techniques can characterize myocardial tissue composition in addition to cardiac morphology and function. However, the use of cardiac MRI to detect the fibrofatty replacement of RV myocardium (Fig. 5.4) is limited by inadequate specificity of such findings (fat infiltration of RV myocardium can be seen in healthy population) and the technical challenges of detecting fibrosis in thin RV wall by current MRI techniques [32]. Currently, the diagnosis of ARVC by cardiac MRI mainly

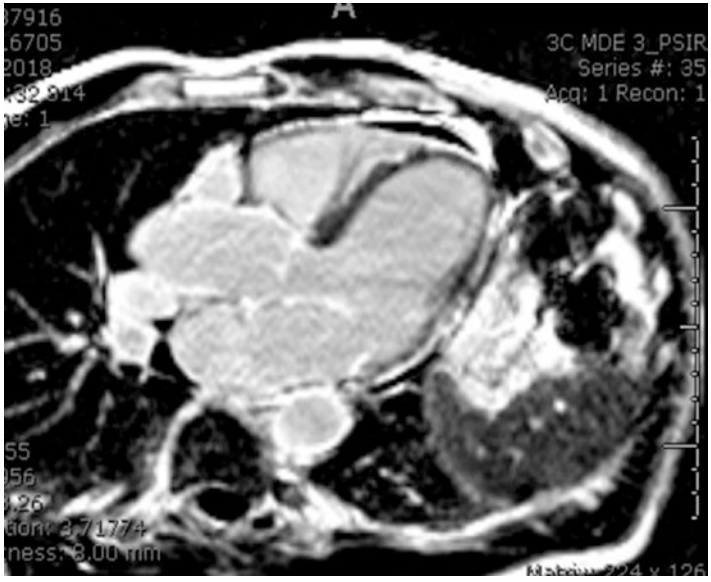

Figure 5.4 Subepicardial late gadolinium enhancement (LGE). Cardiac MRI from a *different* patient with ARVC demonstrates diffuse subepicardial LGE on both LV and RV. Although this finding represents myocardial fibrofatty replacement due to pathological process of ARVC in this particular patient, subepicardial LGE is not specific for ARVC and is not part of the diagnostic criteria

relies on the demonstration of regional wall motion abnormalities in association with RV dilation or global systolic dysfunction (see Table 5.1) [37]. The main advantage of cardiac MRI over echocardiogram is that the assessment of right ventricular structure and function is less limited by the retrosternal location and complex geometry of the RV. However, similar to echocardiogram, the evaluation of regional wall motion abnormalities by cardiac MRI remains challenging and is limited by subjectivity. Cardiac MRI tissue tracking technique can quantify regional ventricular function and may overcome this limitation [37].

5.5.3 *Electrophysiologic Study (EPS)*

EPS can demonstrate areas of low-voltage electrogram in the RV (reflecting RV myocardium loss) (Fig. 5.5), right ventricular VT with macroscopic re-entry mechanism, and multiple inducible right ventricular VT morphologies. These findings support the diagnosis of ARVC in suspected patients [38, 39]. In addition, the demonstration of inducible VT in ARVC patients can facilitate SCD risk stratification and guide ICD decision (see Table 5.2). EPS is generally most useful in patients with uncertain diagnosis or SCD risk despite comprehensive non-invasive testing and in patients that catheter ablation is planned.

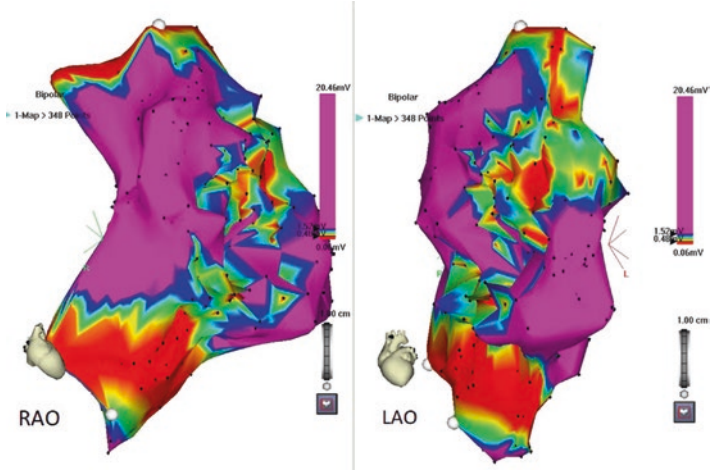

FIGURE 5.5 Low voltage areas on RV endocardial surface. Right anterior oblique (RAO) and left anterior oblique (LAO) views of endocardial RV bipolar voltage mapping from a *different* patient with ARVC demonstrates low voltage areas (<1.5 mV, represented by non-purple colors) on RV apex, inflow, and outflow tracts

Table 5.2 HRS expert consensus statement recommendations on ICD implantation in patients with ARVC

Class I	Class IIa	Class IIb
An ICD is recommended in patients with ARVC • Who have suffered a cardiac arrest with VT or VF • Who have sustained VT not hemodynamically tolerated • Or with LVEF 35% or lower and NYHA class II–III symptoms and an expected meaningful survival of greater than 1 year	An ICD is reasonable in patients with ARVC • Who have syncope suspected to be due to a ventricular arrhythmia • With hemodynamically tolerated sustained VT • With LVEF 35% or lower and NYHA class I symptoms and an expected meaningful survival of greater than 1 year • With three major, two major and two minor, or one major and 4 minor risk factors for ventricular arrhythmia[a] • With phospholamban mutation and LVEF<45% or NSVT • With Lamin A/C mutation and two or more of the following: LVEF<45%, NSVT, male sex • Or with Lamin A/C mutation and an indication for pacing	An ICD may be reasonable in patients with ARVC and two major, one major and two minor, or 4 minor risk factors for ventricular arrhythmia[a]

Adapted from Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy. Heart Rhythm. 2019. *ICD* implantable cardioverter defibrillator, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *VT* ventricular tachycardia, *VF* ventricular fibrillation, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *NSVT* non sustained ventricular tachycardia

[a]Major criteria: NSVT, inducibility to VT at EPS, LVEF ≤ 49%. Minor criteria: male sex, >1000 premature ventricular contractions (PVCs)/24 h, RV dysfunction (as per major criteria of the 2010 Task Force Criteria, see Table 5.1), proband status, 2 or more desmosomal variants. If both NSVT and PVC criteria are present, then only NSVT can be used

5.5.4 Endomyocardial Biopsy

Histological examination of biopsied endomyocardial tissue can demonstrate (1) the degree of myocardium loss and fibrosis, which forms the basis of diagnostic criteria for ARVC (see Table 5.1), and (2) other pathological conditions, such as myocarditis or sarcoidosis, that may mimic ARVC. Conventional RV septal biopsy has limited sensitivity to diagnose ARVC given the segmental nature of the disease and its predominant RV free wall involvement [40]. Electroanatomic mapping or cardiac imaging can be used to identify affected areas and guide the biopsy to improve diagnostic yield [40]. Endomyocardial biopsy is generally performed when the diagnosis remains uncertain despite comprehensive non-invasive testing.

5.5.5 Genetic Testing

The main purpose of genetic testing in ARVC patients is to support the diagnosis when a pathogenic mutation is demonstrated in suspected patients and to facilitate family member screening in ARVC patients with pathogenic mutations. Genetic testing may also be used to facilitate phenotype risk stratification in certain scenarios (see Table 5.2) [1]. To be considered pathogenic and fulfill a major diagnostic criteria, the identified mutations must be categorized as associated or probably associated with ARVC, which are defined as American College of Medical Genetics and Genomics (ACMG) class 5 (>95% likelihood of being pathogenic) or class 4 (>90% likelihood of being pathogenic) mutations, respectively [1].

Collectively, the presence of identifiable pathogenic mutations in patients with ARVC is associated with earlier onset of symptoms and VAs but not with cardiac death and transplantation rates [13]. Specific gene mutations have been observed to be associated with certain phenotypes and severities of ARVC. LV dysfunction is common in ARVC patients with LMNA, PLN (founder variants), TMEM43 (founder variants), DSP, DSG2, and DSC2 mutations but is

uncommon in PKP2 and JUP mutations [1, 14, 16]. Patients with LMNA, PLN, and DSP gene mutations seem to be at a higher risk of Vas [1, 14, 16]. In addition, those with more than one pathogenic mutation have a higher risk of developing VAs, LV dysfunction, and heart failure [1, 14, 16].

The specific intricacies and methods of genetic testing are beyond the scope of this article. In general, the genetic testing should be done by a team of providers with expertise in genetics and cardiology. The genes tested should be focused on those with sufficient evidence to be ARVC-related [1].

5.6 What Is the Diagnostic Criteria and Differential Diagnosis of ARVC?

A definitive pathological diagnosis of ARVC is based on histological demonstration of transmural fibrofatty replacement of right ventricular myocardium [41]. This method requires a sizable piece of myocardial tissue; thus, it is not clinically feasible in most patients. Given the lack of a "gold standard" clinical test, the clinical diagnosis of ARVC relies on a set of criteria. The international task force criteria were revised in 2010 to improve its sensitivity to diagnose ARVC and utilizes six categories of major and minor criteria to diagnose ARVC (see Table 5.1) [37]. The diagnosis of definite ARVC is based on fulfilling 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline ARVC: 1 major and 1 minor or 3 minor criteria from different categories; and possible ARVC: 1 major or 2 minor criteria from different categories.

ARVC should be suspected in apparently healthy patients who developed VAs, especially those originating from the RV. The diagnosis is relatively straightforward in patients with LBBB-like morphology/superior axis VAs, characteristic ECG abnormalities, and/or consistent RV abnormalities on imaging. In those with LBBB-like morphology/inferior axis VA without major ECG or echocardiographic abnormalities, the diagnosis is more challenging. The majority of these patients have idiopathic RV outflow tract (RVOT) VA and

are unlikely to benefit from more exhaustive evaluation. However, in those with family history of ARVC and/or SCD as well as those with VA features not typical for idiopathic RVOT (intrinsicoid deflection time >80 ms, QS pattern in lead V1, and/or QRS axis >90° [42]), additional evaluation with cardiac MRI, EPS, and/or endomyocardial biopsy may be pursued. In patients who undergo EPS, ARVC should also be considered when macroscopic re-entry mechanism of VT, multiple inducible VT morphologies, and low-voltage electrogram are demonstrated [38]. In rare circumstances, cardiac sarcoidosis involving the RV has been reported to mimic ARVC and idiopathic RVOT VA [43, 44]. Extracardiac manifestation and the presence of AV block can be a clue to consider cardiac sarcoidosis (Figs. 5.6 and 5.7).

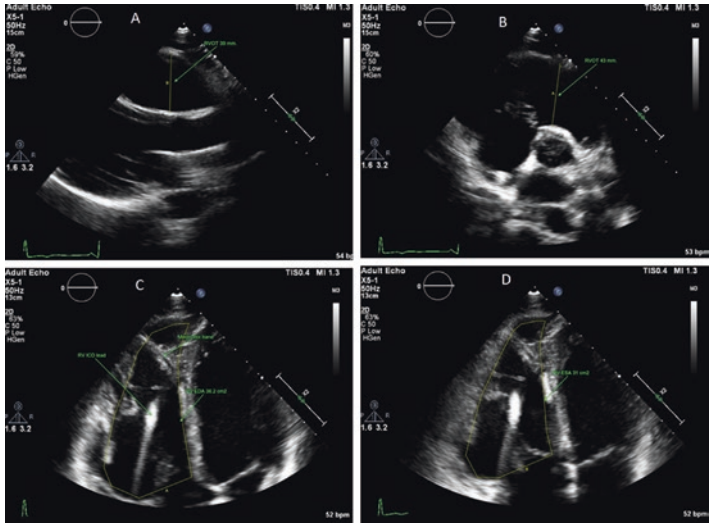

Figure 5.6 Echocardiographic criteria for ARVC. (**a**) Parasternal long-axis view demonstrates RVOT diameter of 39 mm. (**b**) Parasternal short-axis view demonstrates RVOT diameter of 43 mm. (**c**, **d**) RV focused four-chamber views demonstrates severely dilated RV with RV EDA of 36.2 cm^2 and ESA of 31 cm^2. PLAX indicates parasternal long-axis view; *PSAX* parasternal short-axis view, *RVOT* RV outflow tract, *EDA* end-diastolic area, *ESA* end-systolic area

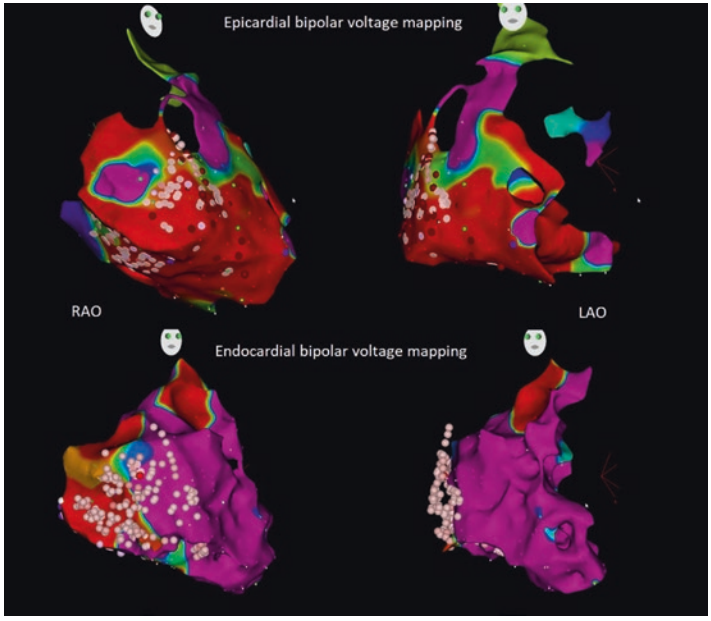

FIGURE 5.7 Low voltage areas demonstrated on both RV epicardial and endocardial surfaces. Right anterior oblique (RAO) and left anterior oblique (LAO) views of epicardial and endocardial RV bipolar voltage mapping. The low voltage areas (<1.5 mV) are represented by non-purple colors

In patients that were incidentally found to have abnormal right ventricular morphology and/or function on imaging studies, congenital heart disease with right ventricular volume and/or pressure overload, pulmonary hypertension, RV infarction, and other cardiomyopathies that may involve the RV should also be considered in addition to ARVC. If the diagnosis remains unclear after reviewing the initial imaging studies, additional imaging with different modalities and/or cardiac catheterization can be helpful. Lastly, patients with advanced stage ARVC can have significant LV involvement and may present with heart failure symptoms. The differential in this scenario is broad, and other causes of left ventricular cardiomyopathy need to be considered.

5.7 How Are Patients Selected for ICD Implantation?

The use of an ICD is associated with significant reductions in SCD in a large cohort study of patients with ARVC [13]. Although data from randomized controlled studies are lacking, an ICD is likely valid given that the patients who were selected to receive an ICD are generally perceived to be at higher risk; thus, biasing against the effectiveness of ICD. As ICD only benefits patients who will develop SCD and is associated with significant cost and complications, SCD risk stratification is necessary. A previous history of sustained VA, especially those associated with hemodynamic instability, is the most important risk factor [45]. Other risk factors include significant RV and LV dysfunction, history of cardiac syncope, non-sustained VT, frequent PVCs on 24-h Holter, male sex, and certain high-risk genetic mutations [45]. The HRS Expert Consensus Statement recommended ICD implantation in ARVC patients who have suffered a VT/VF cardiac arrest, have sustained VT (not hemodynamically tolerated), with LVEF 35% or lower, NYHA class II–III symptoms, and an expected meaningful survival of greater than 1 year [1]. Table 5.2 lists other recommendations regarding ICD implantation in ARVC patients.

5.8 What Is the Management of ARVC?

Competitive sport and high intensity endurance exercises are associated with increased risk of VA, SCD, and progression of structural changes in ARVC patients [18, 46]; Thus, participation in such activities should be avoided by the patients [1, 47]. Participation in recreational sport with a limited exertional component likely does not increase these risks [46].

Antiarrhythmic drugs have been used to decrease VA in ARVC patients based on the results of non-randomized studies and anecdotal experiences given the lack of data from randomized controlled studies. Amiodarone and sotalol have

been inconsistently associated with VA suppression (approximately 70–80%) in ARVC patients [29, 48, 49] and have been suggested by the HRS expert consensus to be used to control arrhythmic symptoms or reduce ICD shocks (class IIb) [1]. As VA and SCD in ARVC frequently occur with adrenergic stimulation, such as during exercise, the use of beta blocker has been recommended by some experts [47]. However, the benefit of beta blocker in reducing life-threatening arrhythmic event has not been demonstrated [29].

There is also a paucity of data demonstrating the efficacy of medications in improving the RV function or slowing the progression of right ventricular failure in ARVC patients. An animal model demonstrated that preload-reduction using a combination of diuretics and isosorbide dinitrate prevented the development of ARVC induced by endurance exercise training [50]; thus, HRS expert consensus suggests that the use of isosorbide dinitrate to reduce preload may be considered in symptomatic ARVC patients with RV dysfunction [1]. Medical treatment to optimize volume status and slow/improve LV dysfunction in ARVC patients is similar to that of heart failure due to other conditions. However, there are some that advocate beta-blockers for all patients with ARVC, regardless of LVEF, to both reduce arrhythmias and prevent RV and LV dysfunction. In addition, and somewhat unique to ARVC is the exercise restriction. It is reasonably well established that more than moderate intensity exercises increases the risk of the development of heart failure.

5.9 What Is the Role of Catheter Ablation?

Catheter ablation aims to eliminate scar-related reentry circuit of VT. It is generally recommended in patients who have failed or unable to tolerate at antiarrhythmic drugs. However, if antiarrhythmic drugs are not desired, it can be used as a first line treatment [51]. In ARVC patients with VT, VT-free survival after at least one catheter ablation was reported to be 83% and 56% after 1 and 3 years, respectively [52, 53]. As

subepicardial scar is usually more prominent in ARVC, combined epicardial and endocardial ablation has been shown to be superior to endocardial only ablation (approximately 40% reduction in VT recurrence [54]) but is associated with higher risk of acute procedural complications [54]. Combined epicardial and endocardial ablation has been recommended as the initial ablation strategy by some experts [47].

5.10 What Are the Recommendations for Screening of Family Members?

As ARVC is mostly transmitted in an autosomal dominant pattern, HRS expert consensus statement recommends that first-degree relatives of ARVC patients (proband) undergo clinical evaluation every 1–3 years starting at 10–12 years of age. The evaluation should include 12-lead ECG, ambulatory ECG, and cardiac imaging. If the ARVC patient (proband) has identifiable pathogenic mutations (ACMG class 4 or 5 mutations), genetic testing can be used to facilitate family member screening. In this case, it may be reasonable for asymptomatic members of a family who do not have the familial variant and have a normal cardiovascular evaluation to be released from regular screening and educated to return if disease symptoms occur [1].

5.10.1 Case Conclusion

After initial evaluation, the patient met 1 major (T wave inversion in V1–V3) and 1 minor diagnostic criteria (nonsustained VT with LBBB-like morphology/inferior axis) for ARVC. At this point, cardiac imaging was needed to evaluate for structural abnormalities that would support our suspicion for ARVC or suggest an alternative diagnosis. TTE was obtained and demonstrated (1) severely dilated RV with RVOT diameter of 39 and 43 mm in parasternal long and short axis views, respectively (Fig. 5.4), (2) severe RV systolic

dysfunction with fractional area change of 14% (Fig. 5.4). (3) Akinetic RV apical and inferior walls (other RV walls are severely hypokinetic). Of note, LV size and systolic function were normal. As TTE findings fulfilled additional major diagnostic criteria, the diagnosis of definite ARVC was made. In fact, this patient subsequently fulfilled 3 major criteria as the genetic screening test also showed heterozygous PKP2 disease causing mutation (c.2146-1 G>C). Neither cardiac MRI nor endomyocardial biopsy was obtained as the diagnosis of ARVC was quite certain and the patient already had an ICD (he is unquestionably high risk for SCD).

This patient had recurrent VT causing multiple ICD shocks despite taking amiodarone. We initially increased his amiodarone for acute VT control. However, neither increasing amiodarone dose nor switching to sotalol would be an optimal long-term strategy given side effects of amiodarone and questionable incremental efficacy of sotalol. Thus, we decided to perform combined epicardial and endocardial EPS with plan for an ablation. Bipolar voltage mapping during EPS showed areas of low voltage electrograms (<1.5 mV) along the free wall, apex, and inferior wall on RV epicardium as well as inferior wall of RV endocardium (Fig. 5.5). Several different VTs were induced and mapped to multiple epicardial RV locations. Overall result of EPS was consistent with ARVC. Extensive ablation was performed on these areas. After the ablation, amiodarone was gradually reduced to 100 mg/day over the following 6 months. The patient had no recurrent VT after 12 months of follow up. He walks in a park for exercise but avoids higher intensity endurance exercise.

Clinical Pearls

- ARVC is a genetic cardiomyopathy caused by pathogenic mutations in genes encoding components of intercalated discs, such as desmosomes.
- ARVC most commonly presents with symptoms of ventricular arrhythmias, such as palpitations, presyncope, syncope, and SCD.

- Heart failure symptoms, especially right-sided, may develop later in the course of ARVC.
- ARVC is diagnosed by a set of criteria incorporating ECG, cardiac imaging, and genetic findings.
- ICD implantation and avoiding high intensity endurance exercise play a central role in reducing sudden cardiac death risk.

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Chapter 6
Right Heart Failure from Pulmonary Embolism

Peeyush Grover, Alireza Vaziri, and Lawrence A. Garcia

Case 1

A 76-year-old female after total knee replacement surgery, presented with sudden onset shortness of breath and pleuritic chest pain. She was noted to have worsening right lower extremity swelling for 3 days prior to presentation. Her initial vital signs included blood pressure of 90/60 mmHg, heart rate of 110 beats per minute (bpm) and an O2 saturation of 90% on room air. She had no personal or family history of venous thromboembolic events (VTE). A computed tomographic pulmonary angiogram (CTPA) demonstrated a saddle pulmonary embolism (PE) with extension into both the right and the left main pulmonary arteries (PA) (Fig. 6.1). The right ventricle (RV) at its largest cross-sectional diameter was 1.8 times the size of the left ventricle. Transthoracic echocardiogram (TTE) demonstrated a dilated RV with reduced right ventricular systolic function and septal flattening consistent with acute elevation of PA systolic pressure.

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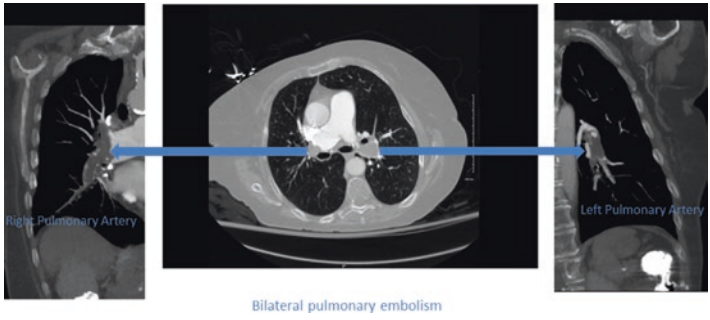


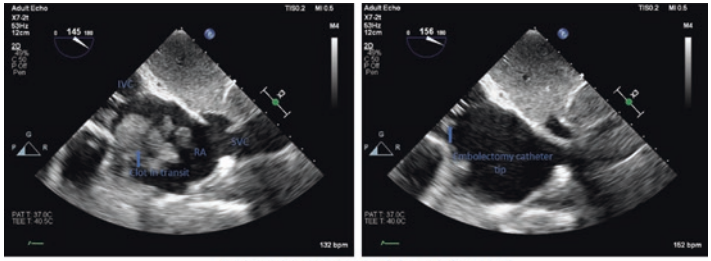
FIGURE 6.1 A computed tomographic pulmonary angiogram demonstrating a saddle pulmonary embolism. The blue arrows show the extension of the clot into bilateral pulmonary arteries

Case 2

A 56-year-old male patient with prior history of alcohol abuse, was found unconscious at home in a disheveled state. Emergency responders reported the patient to be hypotensive (80/50 mmHg) and in atrial fibrillation with rapid ventricular response (>140 bpm). In the hospital, initial resuscitation was performed with intravenous fluids and vasopressor support. An early diagnosis of alcohol intoxication was made. He was also noted to have bilateral lower extremity swelling on physical examination. TTE showed a serpiginous mass extending from the inferior vena cava (IVC) into the right atrium and across the tricuspid valve into the RV (Fig. 6.2). CTPA confirmed the diagnosis of acute PE and also demonstrated a massive thrombus in the left main PA, along with sub segmental thrombus in the right PA branches.

Case 3

A 65-year-old male with past medical history of diabetes mellitus and essential hypertension presented with sudden onset chest pain and shortness of breath at rest. He had no known past medical history of VTE or abnormal bleeding. When initially assessed in the emergency room, he had normal vital



Clot in transit in the right atrium before and after retrieval

FIGURE 6.2 Transthoracic Echocardiogram showing a clot in transit. The clot extends from the IVC into the right atrium across the tricuspid valve and into the right ventricle

signs. Initial work-up including ECG and serum troponin levels ruled out cardiac etiologies of chest pain. He was then noted to become progressively tachypneic and tachycardic. Arterial Blood Gas (ABG) analysis demonstrated a pH of 7.6 with PaO2 of 65 mmHg on 4 L of inhaled oxygen by nasal cannula and increased A-a gradient. CTPA demonstrated a right ventricle/ left ventricle (RV/LV) cross sectional diameter ratio of >2:1. PE was involved in both the right and left PAs. TTE demonstrated the presence of McConnell's sign. He was started on anticoagulation with IV unfractionated heparin. His hypoxemia continued to worsen over the next few hours, warranting urgent intubation and vasopressor support.

6.1 Introduction

Acute PE is a major cause of acute RHF. VTE occurs when thrombi commonly arising from the proximal lower extremity deep veins, pelvic veins or less commonly the gonadal or renal veins, travel through the inferior vena cava (IVC) to the RV via the right atrium and tricuspid valve to eventually lodge in the PA. Acute PE originating from the upper extremities or thoracic veins, is rare and usually not large enough to cause hemodynamic derangement. Acute PE follows the

same etiologic classification as VTE. It is considered a provoked event if it is due to the presence of an identifiable risk factor within the last 6–12 weeks prior to the event and is unprovoked in the absence of such. The risk factors for acute PE are similar to the risk factors for VTE.

Common presenting symptoms range from a subclinical asymptomatic condition to shortness of breath and/or chest pain that is typically pleuritic in nature [1]. Less common symptoms of acute PE include cough, wheezing or syncope. Syncope indicates a more serious form of acute PE with high clot burden causing hypotension. Less commonly, a massive PE can also present as obstructive shock or sudden cardiac death [2].

PE is classified into massive, submassive, or low risk [3]. The European Society of Cardiology classifies sub-massive PE into *intermediate high risk* or *intermediate low risk* based on the presence of one/none or both of the following indicators: (a) imaging evidence of RV dysfunction; (b) cardiac biomarkers of RV strain [4].

Untreated massive PE has a high mortality rate of 25–30% [5]. A Hemodynamically Unstable presentation of PE is found in 10–12% of patients with underlying saddle pulmonary emboli [6, 7]. Adequately treated hemodynamically unstable PE carries a mortality rate of approximately 5%. A clot-in-transit has been reported to be associated with a mortality rate as high as 40% [7]. This type of clot is often identified on an echocardiogram and is located either in the RV or in the IVC (Fig. 6.2), [6]. Anatomy and pattern of lodgment of the embolus plays a role in hemodynamic derangement. For example, a saddle PE would typically lodge at the bifurcation of the right and left main PA and is more often associated with hemodynamically unstable PE.

Right ventricular failure is defined as the inability of the RV to maintain adequate pulmonary arterial blood flow in spite of normal central venous pressures [8]. Acute right ventricular pressure overload is the main pathophysiologic event during massive PE which results in acute RHF. Ultimately, obstructive shock occurs. The pathophysi-

ology of acute RHF in PE differs from chronic RHF as seen in pulmonary hypertension (Chap. 7).

The RV, as discussed in Chap. 1; Introduction to the Right Heart, is composed of a thin crescent shaped free wall which ejects nearly the same volume of blood as the LV into a high compliance, low resistive pulmonary arterial system with only 1/6 of the energy expenditure of the LV. RV end systolic and end diastolic pressures are 15–28/0–8 mm Hg respectively. The vascular resistance of the pulmonary arterial system is 123 ± 54 dyne s cm^{-5} m^2. In contrast, systemic LV vascular resistance is 10–20 times greater at 2130 ± 450 dyne s cm^{-5} m^2. The pulmonary vascular system has a large buffer of partially collapsed or unused vascular beds, and proximal PA vascular tone is very low [9]. RV geometry is suitable to adapt to large increases in venous return but is incapable of generating systolic pressures >40 mmHg in an acute setting [5].

6.2 What Is the Pathophysiology of Acute Right Heart Failure in Pulmonary Embolism?

The right ventricular response to pressure overload of massive clot burden is primarily via a mechanism called *homeometric autoregulation* or *the Anrep effect.* This refers to the rapid increase in contractile ventricular function after abrupt increase in afterload and is mediated by cytosolic ionized calcium [8, 10]. The coronary perfusion pattern of the normal RV free wall differs from that of the LV. Intramural RV free wall pressure does not normally rise above systemic arterial pressure, therefore, RV free wall coronary perfusion happens in both systole and diastole. In acute PE, a sudden decrease in LV preload due to obstruction of the principal pulmonary arteries, causes dramatic decline in systolic aortic root pressure. With sudden increase in RV wall tension due to acute RV dilation, RV free wall coronary perfusion declines precipitously resulting in myocardial ischemia [11]. RV dilatation also causes tricuspid valve insufficiency that result in further

decrease in RV ejection flow. When all the contractile reserve mechanisms are exhausted, a catastrophic spiral of events—including acute myocardial inflammation, hypoxic injury and focal RV myocyte necrosis—will cause irreversible RV damage. The clinical outcome is hemodynamic collapse. This pattern is collectively called obstructive shock and carries a high risk of mortality. Patients with prior RV damage including RV infarct or hypoxic pulmonary vascular vasoconstriction are more prone to acute RHF with lower clot burden.

In acute RV failure due to massive PE, pharmacologic or mechanical debulking of the pulmonary clot burden is the only known intervention that may increase the chance of survival [12].

6.3 What Is the Initial Approach?

Initial assessment should identify hemodynamically unstable patients from hemodynamically stable ones. Massive PE is a hemodynamically unstable condition defined as acute PE with sustained hypotension (systolic blood pressure <90 mmHg for at least 15 min) despite adequate volume resuscitation or requiring inotropic support. Alternative causes of hypotension such as hemorrhage, arrhythmia, left ventricular [LV] dysfunction, pulseless electrical activity, bradycardia ≤40 bpm or sepsis need to be ruled out. Sub-massive PE is less clearly defined. It is a hemodynamically stable condition defined by the absence of systemic hypotension but with either RV dysfunction or biochemical evidence of myocardial necrosis. Low risk PE is a hemodynamically stable PE with the absence of the clinical markers of adverse prognosis that define massive or submassive PE [3].

All three case presentations (Cases 1–3), had a varying degree of hemodynamic instability. Resuscitative therapy should be the initial focus of therapy for hemodynamically unstable PE. The first steps should involve oxygenating or ventilating the patient and hemodynamic stabilization with IV fluids and/or pressor support.

The patient in Case 1 required 2 L of O_2 to maintain a goal saturation above 92% and fluid resuscitation with normal saline for hemodynamic stability. The patients in Cases 2 and 3 required extreme measures of hemodynamic support with intubation and pressors. Extra corporeal membrane oxygenation (ECMO) was utilized in Case 3.

Whenever PE is suspected, the pretest probability for PE should be estimated by a scoring method such as the Modified Wells score [13]. The modified Wells score (See Table 6.1) is a clinical scoring system based on physical examination findings and risk factors for PE. A low score is considered to be <2, an intermediate score is between 2 and 6, and a high score is usually >6. The modified Wells criteria have been best validated in the outpatient setting; however, prior meta-analysis has demonstrated sensitivity for acute PE amongst inpatients with the addition of the D-dimer test [14]. Case 1 had a calculated modified Wells score of 4.5. Both cases 2 and 3 had a score of 7.5. The D dimer level in Case 1 was elevated at 800 ng/mL (reference <500 ng/mL), suggesting the need for further testing. Cases 2 and 3 did not need to be tested for D dimer given the high probability of acute PE.

Table 6.1 Modified Wells Criteria (A low score is considered to be <2, an intermediate score is between 2 and 6 and a high score is usually >6)

Criteria	Points
Clinical symptoms of DVT	3
Immobilization of 3 days or more	1.5
Surgery in previous 4 weeks	1.5
History of hemoptysis	1
Malignancy	1
History of previous DVT/PE	1.5
Heart rate > 100 beats/min	1.5
Other diagnosis less likely than PE	3

An initial assessment of a patient with a suspected PE should include ABG as well as basic chemistries. Common abnormalities seen on ABGs include hypoxemia (Pa O2 < 80 mmHg), a widened Arterial-alveolar gradient for oxygen (>20 mmHg), respiratory alkalosis and hypocapnia (<40 mmHg) [15–17]. All of our cases had findings of hypoxemia and respiratory alkalosis on ABG's, making the diagnosis of acute PE very likely.

ECG abnormalities are non-specific in patients with suspected PE. The most common findings are sinus tachycardia and nonspecific ST-segment and T-wave changes (70% of patients). Other abnormalities include an S1Q3T3 pattern, a RV strain pattern and a new incomplete right bundle branch block. These findings are very uncommon (<10%), but are associated with poor prognosis [18, 19]. All three patients presented with sinus tachycardia.

In patients with a low and intermediate risk of PE, a D-dimer test is very sensitive. Therefore, a normal D-dimer (<500 ng/mL) effectively excludes PE. No further testing is required in low risk patients. A D-dimer test is best used in conjunction with the clinical probability assessment [20]. When the D-dimer level is elevated, a diagnostic imaging study should be performed, preferably with a CTPA. As Case 1 had an elevated D Dimer with an intermediate pre-test probability, CTPA was urgently ordered, which confirmed the diagnosis of PE. The other cases had a high probability of PE, therefore, the initial test was CTPA from the start.

Right heart catheterization (RHC) can monitor pressures in the PAs after catheter based lysis or thrombectomy [21]. All our patients underwent RHC which demonstrated a PA systolic pressure between 40 and 50 mmHg and an elevated PA diastolic occlusion pressure gradient (>10 mmHg). The Pulmonary Artery Pulsatility index (PAPi), defined as the ratio of pulmonary artery pulse pressure to right atrial pressure, has emerged as a powerful predictor of right ventricular failure in patients with acute inferior myocardial infarction and those undergoing left ventricular assist device placement. PAPi can serve as a

useful marker of RV dysfunction in patients with PE as well [22]. PAPi is discussed in more detail in Chap. 9.

6.4 Which Imaging Modalities Should Be Pursued for Definitive Diagnosis?

The Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED) study conducted between 1985 and 1986 confirmed the value of high and low probability scintigraphy lung ventilation perfusion (V/Q) scan. Corresponding V/Q scan results, when combined with high and low clinical suspicion (Modified Wells scores) for acute PE, have a 96% positive predictive value and 96–98% negative predictive value [23].

PIOPED II conducted between 2001 and 2003 demonstrated 83% sensitivity and 96% specificity of CTPA in detecting PE [24].

Selective pulmonary angiography has been considered the gold standard imaging test for diagnosing PE in the past. However, this test is invasive, involves use of large doses of potentially nephrotoxic iodinated radio contrast and is not readily available in all hospitals. Hence, CTPA is currently considered the imaging modality of choice for detecting PE if not otherwise contraindicated. CTPA should be performed in all patients with an intermediate probability of PE and in those with a D-dimer level ≥500 ng/mL where the diagnostic pretest probability is moderate to high. A prospective, multicenter cohort study of 3306 patients with clinically suspected PE from both an inpatient and outpatient setting, categorized patients according to the modified Wells score—as PE "likely" (score > 4) or PE "unlikely" (score ≤ 4). Patients underwent D-dimer testing and PE was considered excluded when the D-dimer level was <500 ng/mL. Both PE "unlikely" patients who had a D-dimer level ≥500 ng/mL, and PE "likely" patients, underwent CTPA (a total of 1939 patients). CTPA excluded PE in 1505 patients who were 45.5% of the study population. In these patients, the 3-month incidence of

VTE was 1.3%, and PE was considered a possible cause of death in seven patients (0.5%) after a negative CTPA [20]. CTPA is considered most accurate for the detection of large, main, lobar, and segmental PE, and less accurate for the detection of smaller, peripheral, subsegmental PE Newer generation CTPA scanners have increased detection rates of smaller emboli.

Estimates of the incidence of PE in the general population have increased following the introduction of higher resolution CTPA; however, PE related mortality remains unchanged despite the use of CTPA [25]. In patients who cannot undergo CTPA (such as renal failure or contrast allergy), a V/Q scan is a viable option. The results of the V/Q scan should be considered along with the clinical probability of having PE. Amongst patients with a normal V/Q scan and any clinical probability, no further testing is needed. In patients with a low-probability V/Q scan and low clinical probability (Wells score < 2) no further testing is required. In patients with a high-probability V/Q scan and high clinical probability (e.g, Wells score > 6), immediate treatment with anticoagulation is indicated. All other combinations of V/Q scan results and clinical pretest probabilities are indeterminate and further testing is often recommended [26].

Magnetic Resonance Pulmonary Angiography (MRPA) can substitute for CTPA to avoid radiation exposure for young or pregnant patients. However, MRPA is less sensitive and more dependent on the experience of the technologist performing the scan, compared with CTPA. MRPA requires no ionizing radiation, and the examination can be combined with MR venography in the same setting. MRPA was studied prospectively in 371 adults with suspected PE. Among the 75% of patients who had technically adequate images, MRPA alone showed a sensitivity and specificity of 78% and 99%, respectively [27].

Catheter-based pulmonary angiography is more invasive and slightly less sensitive than CTPA, and is usually reserved for patients undergoing concurrent therapeutic interventions. In emergent circumstances, TTE can also be used when a

rapid or presumptive diagnosis for PE is considered. TTE findings of PE include a dilated RV, reduced right ventricular systolic function, and elevated PA systolic pressure. McConnell's sign is an echocardiographic finding of PE whereby the RV free wall is akinetic, while the RV apex is spared [28]. In most cases however, particularly those who are hemodynamically stable, echocardiography is generally considered insensitive, since abnormalities are frequently absent in patients with PE [29].

6.5 What Is the Contemporary Management of Acute Pulmonary Artery Embolism?

For most patients who become hemodynamically stable following resuscitation, and in whom the clinical suspicion for PE is high, immediate anticoagulation (AC) is recommended [3, 30]. While results are pending, AC must be individualized according to the clinical suspicion for PE, hemodynamic status, and contraindications to anticoagulation. A prior study has demonstrated a clear improvement in in-hospital mortality and a long term reduction in pulmonary hypertension from AC amongst such group of patients [31]. The choice of AC depends on multiple factors including hemodynamic stability, renal function, and whether an invasive procedure is anticipated. The option include low molecular weight heparin, IV unfractionated heparin or long acting oral anticoagulants (Direct Oral Anticoagulant: DOAC or Vitamin K Antagonists: VKA) [32, 33].

For patients with a high clinical suspicion for PE, empiric administration of systemic thrombolytic therapy can be lifesaving as an adjunct to any AC. A recent meta-analysis showed that amongst massive (high-risk) PE patients, systemic thrombolytic therapy versus no therapy decreased the composite endpoint of death and recurrent thromboembolism (9.4% versus 19%) [34]. Another large trial compared placebo plus heparin with thrombolytic therapy plus heparin in 1005 patients with acute PE who were normotensive and had evi-

dence of RV dysfunction [35]. Compared with heparin alone, thrombolysis resulted in a reduction in the primary endpoint of death and hemodynamic decompensation at 7 days following randomization. The thrombolysis arm was associated with increased extracranial bleeding, major bleeding and hemorrhagic stroke (2% versus 0.2%). The use of thrombolytic therapy as a life-saving measure should be individualized and based on the clinical setting and results of available investigational test results. The initiation of AC should never be delayed while considering other, more aggressive interventional therapies [36]. It is important to keep in mind that sometimes a clear diagnosis could be difficult to make and may require a multidisciplinary team approach. Some highly specialized centers have incorporated a "Pulmonary Embolism Response Team" (PERT) to facilitate this process rapidly [32, 33] with a high success rate. PERT consists of emergency room physicians as well as a radiologist, pulmonologist, intensivist, pharmacist, vascular and interventional cardiologist.

For patients who have contraindications to AC or have an unacceptably high bleeding risk, placement of an IVC filter may be considered. An IVC filter can be considered in patients with significant DVT clot burden who are at risk of pulmonary artery embolism but with no active PE or those patients with a clot in transit after successful clot retrieval [37]. Retrievable filters are generally preferred. They should be removed after the patient can be safely anticoagulated, and the burden of clot has resolved. IVC filters are associated with multiple complications including thrombosis, migration, injury to the IVC and fractures; therefore the retrieval should be within 2–3 months after deployment [38].

6.6 What Are the Endovascular Strategies for Pulmonary Artery Embolism?

Systemic thrombolytic therapy is a widely accepted treatment for patients with PE who subsequently develop hemodynamic instability [39]. Multiple catheter-based techniques

have been developed for the management of PE. These techniques offer the benefits of less risk of bleeding and localized treatment of a formed clot along with reduced pulmonary arterial hypertension in the long term, when compared with systemic thrombolysis [40]. The techniques include manual thrombus breakdown and aspiration (embolectomy), localized treatment with a thrombolytic agent such as tPA (tissue plasminogen agent) or a combination of these therapies. Techniques utilized are ultrasound guided thrombolysis, rheolytic embolectomy, rotational embolectomy and suction embolectomy. The data behind these techniques are based on small observational studies, and the superiority of one over the other has not been validated [41, 42]. Typically, rotational devices do not require venotomy, thus avoiding the additional risk of vascular complications. More advanced catheter techniques have been used for the removal of large fresh thromboemboli in the IVC or right heart chambers (clot in transit) or for use during extracorporeal bypass. Such devices cannot easily access the distal PAs due to the small sized caliber of these vessels.

The use of catheter-directed thrombus removal or thrombolysis, should be limited to patients with high risk of bleeding, in shock, or who have failed systemic thrombolysis.

Lower doses of systemic thrombolytic therapy could help expedite the resolution of pulmonary hypertension amongst patients with PE. In the Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) trial [40], 121 patients were randomly assigned to receive either heparin alone—unfractionated or low molecular weight—or the combination of half of the standard dose of tPA plus heparin. Compared with conventional therapy, this lower-dose regimen of tPA resulted in lower rates of pulmonary hypertension and similar rates of bleeding, recurrent PE, and mortality (5% versus 1.6%).

The Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) study randomized 59 patients with acute intermediate risk PE to IV heparin alone or ultrasound-assisted catheter-directed thrombolysis (USAT) followed by

IV heparin [43]. The USAT regimen consisted of high frequency ultrasound combined with 10–20 mg of tPA infused over 15 h. At 24 h, compared to conventional anticoagulation, USAT resulted in an improved RV:LV ratio (mean difference 0.3 versus 0.03), suggesting a hemodynamic benefit. At 90 days, there was no difference in mortality or major bleeding between the groups. Another single-arm prospective trial in a similar population, the Submassive and Massive Pulmonary Embolism Treatment with Ultrasound Accelerated Thrombolysis Therapy (SEATTLE II) trial described similar results [44].

6.7 What Are the Surgical Options for Pulmonary Embolism?

Surgical embolectomy, usually the last resort, is reserved as an option in specialized centers with available expertise. Considerations for surgical embolectomy are hemodynamic instability due to acute PE for patients in whom thrombolysis (systemic or catheter-directed) is contraindicated, and/or has failed [45, 46]. Additional indications may include echocardiographic evidence of an embolus trapped within a patent foramen ovale or present in the right atrium or RV [47]. The surgical approach is commonly associated with high mortality, particularly in the elderly (up to 46%) [45, 46]. Proximal emboli are usually amenable to surgical removal whereas distal thrombus is generally not amenable to surgery. Prior data has not demonstrated any difference in 30-day mortality amongst patients who underwent surgical embolectomy compared with patients who underwent thrombolysis (15% versus 13%) [48]. Some retrospective series have supported the role of surgical embolectomy amongst only unstable PE patients [49].

Complications include those associated with cardiac surgery and anesthesia as well as embolectomy-specific complications, such as perforation of the pulmonary artery and cardiac arrest.

6.8 What Is the Prognosis of Acute Pulmonary Embolism?

Massive PE has a mortality rate of approximately 8%. Amongst patients presenting with shock or hemodynamic collapse, the mortality has been reported to be as high as 40% [50]. RV dysfunction, RV dilatation and elevated PA pressures can be used to assess the prognosis for patients [51]. Factors that may contribute to early morbidity include alveolitis from an evolving pulmonary infarction, superimposed pneumonia, and medical comorbidities [52]. For subsegmental PE, the prognosis is better and is largely determined by comorbidities including malignancy, older age, male gender, chronic obstructive pulmonary disease, and heart failure [53].

Case Conclusion

- *Case 1*:

  The patient was assessed in the emergency room and was diagnosed with a massive PE requiring anticoagulation with IV unfractionated heparin. Due to persistent hypotension and tachycardia, she was considered a candidate for systemic thrombolysis. She was considered low risk for major bleeding, including intra cranial bleeding. The PERT favored catheter directed thrombolysis using low dose tPA for the next 12 h. She stabilized with significant improvement in RV size and function within 24 h of tPA infusion. She was maintained on a DOAC for the next 3 months.
- *Case 2*:

  The patient underwent suction embolectomy with removal of the serpentine mass from the IVC/RA and RV. An IVC filter was deployed and catheter directed thrombolysis was then performed for the following 12 h. Marked improvement in the RV size and function was noted 24 h, post procedure. The patient was successfully weaned off vasopressors and extubated. He was anticoagulated for a total of 6 months and the IVC filter was retrieved 3 months post procedure.

- *Case 3*:

  The patient had a worsening course and required mechanical ventilation and multiple inotropic/ vasopressor support. The decision was made to advance therapy to veno-arterial (VA) ECMO support. Catheter directed thrombolysis was performed. His RV dysfunction and hemodynamics improved. He was weaned off VA ECMO support, but developed a left facial droop later during the course of the hospitalization. Urgent CT scan showed no areas of hemorrhage, although MRI revealed a right thalamic stroke. Transesophageal echocardiogram failed to show any PFO or aortic atheroma. The likely cause of the stroke was thought to be a complication related to ECMO. He underwent extensive physical and occupational therapy and was able to return to work with minimal residual deficit.

Clinical Pearls

- Acute right heart failure is the major pathophysiologic manifestation of massive Acute Pulmonary Embolism.
- Whenever PE is suspected, the pretest probability for PE should be estimated by a well validated scoring method such as the Modified Wells Score.
- CTPA is currently considered the imaging modality of choice for detecting PE.
- For patients with acute PE who are hemodynamically stable, immediate AC is recommended, if not otherwise contraindicated.
- For patients with acute PE who are hemodynamically unstable, systemic thrombolysis should be considered. The use of catheter-directed thrombus removal or thrombolysis should be limited to select patient population and centers.
- Patients with Acute PE who develop acute right heart failure and shock usually carry a poor prognosis.

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Chapter 7
The Failing Right Heart from Pulmonary Hypertension

Andrea Shioleno and Aaron Waxman

Case

This is a 42-year-old Caucasian female with a past medical history of asthma who presented with dyspnea on exertion. She was previously active without limitations but 1 year ago noticed progressive dyspnea after a flight of stairs. She was evaluated by her primary care physician (PCP) and diagnosed with asthma. She was prescribed inhalers initially and a trial of steroids but experienced no improvement in her symptoms. She was referred after her PCP found enlarged pulmonary arteries on a Chest X-ray (Fig. 7.1). She denied a history of miscarriages. Her family history is negative for clotting disorders, pulmonary, cardiac or auto-immune disease. She is a lawyer who denies the use of alcohol, tobacco, intravenous drugs, or diet medications. She took no additional medications or supplements.

On exam, she was well appearing with a heart rate of 107 beats per minute (bpm), blood pressure 112/78 mmHg, O2 saturation 93% on room air, and temperature of 37 °C. She had clear breath sounds bilaterally on lung exam.

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Cardiovascular exam revealed jugular venous distension (JVD) of 12 cm H2O, a loud second heart sound (P2) with a faint holosystolic murmur radiating to the lower right sternal border louder with inspiration, and no edema. Her dermatologic and musculoskeletal exams were negative for joint deformities, rashes, clubbing or cyanosis.

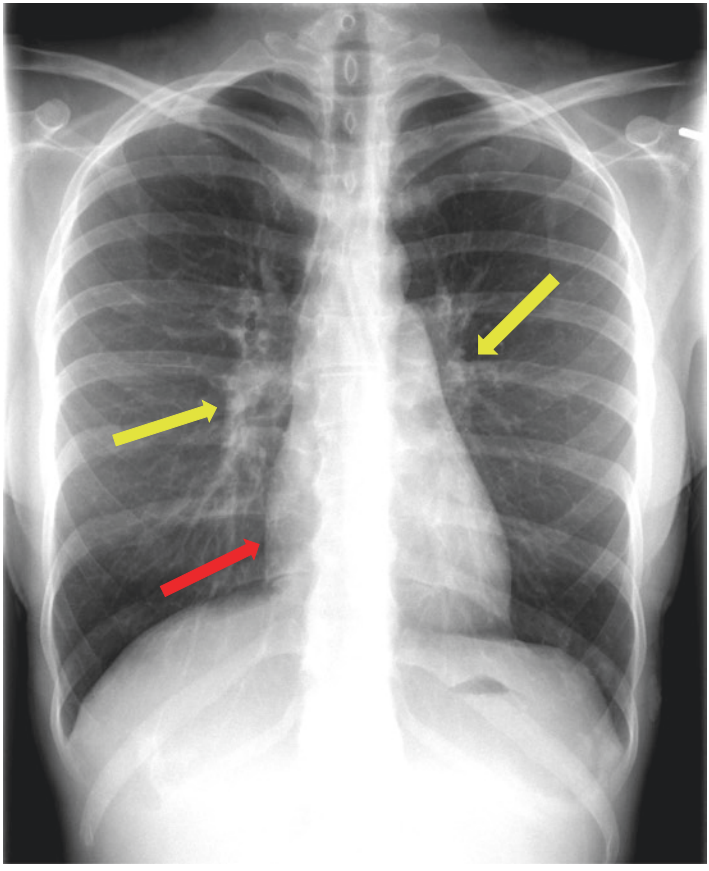

Figure 7.1 Chest X-ray shows a slightly enlarged right atrial silhouette (red arrow), prominent central right and left main pulmonary arteries (yellow arrows), and peripheral hypovascularity

7.1 What Are the Clinical Manifestations of Pulmonary Hypertension?

There are a range of clinical manifestations of pulmonary hypertension (PH), therefore a thorough exam should focus on evaluating for the disease, its severity, and different etiologies. Patients typically present with shortness of breath on exertion, but more severe disease can include weight gain, lower extremity swelling, palpitations from tachyarrhythmias, hemoptysis, and syncope [1]. The cardio-pulmonary exam is particularly important. Key findings on the cardiac exam include an accentuated second heart sound (P2) from increased flow across the pulmonary valve; a right ventricular third heart sound (S3) auscultated at the lower right sternal border due to right ventricle (RV) dysfunction; a palpable RV heave at the lower left sternal border associated with an enlarged RV; a pan-systolic murmur over the lower left sternal border that is more accentuated on inspiration from tricuspid regurgitation; or an early diastolic crescendo murmur from pulmonary regurgitation at the upper left sternal border. If right atrial pressures (RAP) are increased, JVD will be present when evaluating the lateral neck with the head of the bed at a 30° angle. In addition, peripheral edema, hepatomegaly, or ascites may also be seen.

The lungs are typically clear in Group 1 pulmonary arterial hypertension (PAH) patients. However, the lung exam could present with 'dry crackles' in the setting of interstitial lung diseases (ILD) or rales and decreased breath sounds from pleural effusions when PH develops from left sided heart disease. It is also important to evaluate for other systemic illnesses that can cause PH. Telangiectasias, digital ulceration and sclerodactyly can be seen in scleroderma patients. Swan neck deformities and bilateral joint tenderness and swelling may be suggestive of rheumatoid arthritis. Pericardial or pleural rubs and a malar rash are concerning for systemic lupus. Spider nevi, palmar erythema, and ascites may suggest underlying liver disease. Finally, digital clubbing should prompt consideration of ILD, cyanotic congenital heart disease, and pulmonary veno-occlusive disease (PVOD) [1].

Case Continued

She was referred for pulmonary function testing (PFT), a six-minute walk test (6MWT), chest imaging, and laboratory studies to investigate for PAH. Her 6MWT test revealed desaturation to 89% with a Borg score of 3 after 442 m. Her Ventilation Perfusion (VQ) scan was low risk for pulmonary embolism. The computed tomography (CT) scan of her Chest with contrast was negative for acute pulmonary embolism, ILD, nodules, or lymphadenopathy but did show an enlarged main pulmonary artery and RV (Fig. 7.2). Her PFT showed

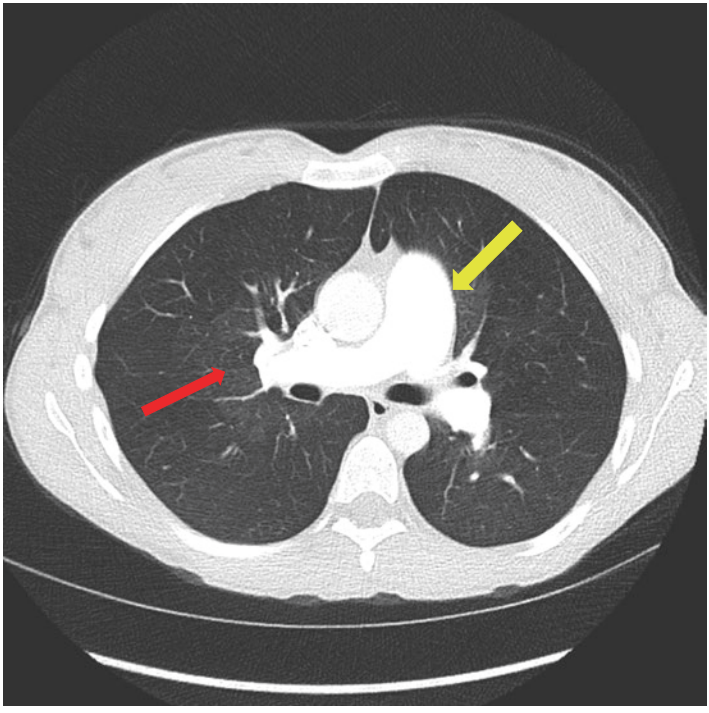

FIGURE 7.2 CT Chest with pulmonary embolism protocol reveals an enlarged pulmonary artery (yellow arrow) compared to the aorta and bilateral peripheral mosaicism (red arrow) which are both seen in pulmonary hypertension

normal spirometry with no significant reversibility with bronchodilators and a DLCO 40% of predicted. An arterial blood gas showed pH 7.42, pCO2 31, PaO2 70. Her complete blood count, complete metabolic profile, HIV test, urine drug screen, thyroid studies and auto-immune panels were negative. Her BNP was elevated at 500 pg/mL (reference <100 pg/mL).

7.2 How Does the Right Ventricle Fail in Pulmonary Hypertension?

Right ventricular failure is the ultimate fatal consequence of pulmonary hypertension. In PH the right heart fails overtime due to increasing afterload which leads to maladaptive changes in the RV. Typically, the pulmonary vascular bed is a high-flow, low resistance, and low-pressure circuit with distensible vessels that dilate and recruit to accommodate increases in flow. However, in PAH, the small arteries undergo remodeling caused by vasoconstriction, in situ thrombosis, and proliferation of smooth muscle and endothelial cells which become resistant to apoptosis [2]. This remodeling causes increased pulmonary vascular resistance (PVR) which directly impacts the pulmonary artery pressure (PAP). PAP = LAP + (CO × PVR)/80, where LAP equals left atrial pressure and CO represents cardiac output. As a result, increasing PVR leads to elevated PAP over time and thus increased afterload, which the RV must pump against.

The RV's geometry is adapted to variations in venous return, but it is not designed to operate against a high resistance and poorly compliant system. The RV's first response to this increasing afterload is enhanced systolic contraction, known as the Anrep effect [3]. To accomplish this, the RV undergoes concentric remodeling with an increase in the number of cardiac sarcomeres [3]. As afterload continues to increase, this adaptive hypertrophy fails as the RV reaches its limit of enhanced contractility. A second maladaptive remodeling begins to occur, right ventricular dilation.

Right ventricular dilation is problematic for several reasons. First, it supersedes the Frank-Starling mechanism and results in a dramatic and irreversible decrease in RV contractile function. Second, it pushes the interventricular septum toward the left ventricle (LV) reducing LV filling. As the RV dilates further, it prolongs its time in systole leading to more compression of the LV as it is trying to fill since both ventricles compete for space within the pericardium [1]. Finally, right ventricular dilation increases wall stress leading to increased oxygen demand and reduced coronary perfusion. As the RV fails to maintain forward flow, cardiac output is reduced which can progress to systemic hypotension, right ventricular ischemia, and a downward spiral of shock leading ultimately to death [4, 5].

Case Continued

Her transthoracic echo (TTE) revealed a normal left atrium and ventricle with intact systolic and diastolic function (LVEF 60%). There was systolic and diastolic flattening of the interventricular septum consistent with right ventricular pressure and volume overload, a dilated right atrium, moderately dilated right ventricular cavity with moderately reduced function, an estimated RV systolic pressure (RVSP) of 63 mmHg, moderate tricuspid regurgitation, and no pericardial effusion (Figs. 7.3 and 7.4). She was referred for right heart catheterization (RHC) which revealed RAP 12 mmHg, RV pressure 53/12 mmHg, pulmonary capillary wedge pressure (PCWP) 10 mmHg, PAP 62/30 mmHg with a mean PAP (mPAP) 40 mmHg, Cardiac output (CO) 4.1 L/min and Cardiac index (CI) 2.5 L/min/m^2, PVR 10 wood units (WU), systemic vascular resistance (SVR) 1100 dynes s cm^{-5}, and a mixed venous saturation (SVO2) 66%. She had no significant change in mPAP with oxygen or inhaled nitric oxide but her PVR did improve to 7 WU and her CO improved to 6 L/min.

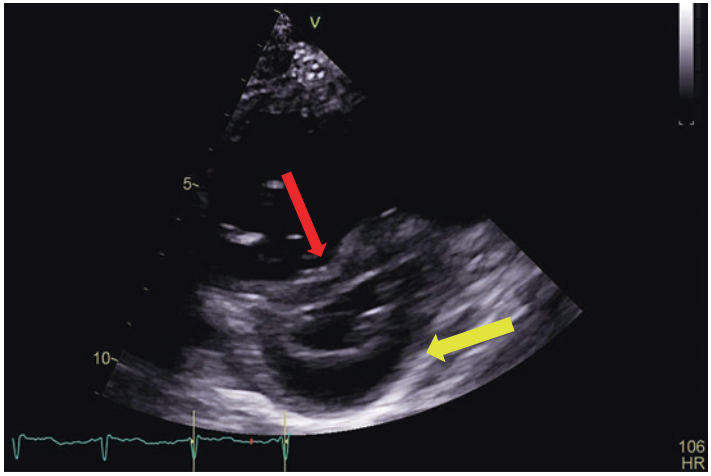

FIGURE 7.3 Parasternal short axis view on TTE showing flattening of the interventricular septum (red arrow) causing a "D" shape of the LV (yellow arrow) due to right ventricular pressure and volume overload

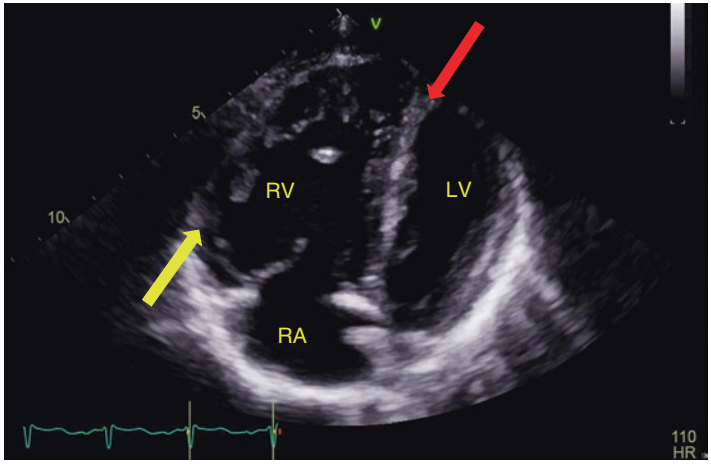

FIGURE 7.4 Four Chamber View on TTE demonstrating RV and RA enlargement, with notable RV hypertrophy (yellow arrow) and bowing of the interventricular septum (red arrow) toward the LV

7.3 What Is the Initial Approach to Evaluate Right Heart Failure?

Initial evaluation for right heart failure (RHF) in PH involves a combination of clinical exam, imaging and hemodynamics. Since the RV fails overtime, the symptoms of dyspnea and decreased exercise tolerance occur before the physical exam signs of RHF develop [4]. A good physical exam as previously mentioned is important to assess for RHF as well as a laboratory assessment for end organ damage of the liver and kidneys. Although not specific to the RV, a brain natriuretic peptide (BNP) is also helpful because it correlates with hemodynamic severity and prognosis in patients with PAH [6].

A TTE is the first non-invasive imaging that is utilized to evaluate the RV's size, shape, and function. Two-dimensional (2-D) TTE can be used to directly visualize RV enlargement, thickening of the right ventricular wall, and reduced systolic function. It is also important to assess the septum for flattening or impinging on the LV, which is a sign of right ventricular pressure overload [7]. Quantitative measurements of RV size can also be made at the basal and middle segments to measure chamber width as well as RV free wall thickness [7]. M-mode and tissue doppler are useful tools to evaluate RV systolic function. Specifically, the tricuspid annulus plane systolic motion (TAPSE) measures the movement of the tricuspid annulus on M-mode to assess systolic function with a value of <1.8 mm considered abnormal [7]. Tissue doppler peak systolic velocity of the tricuspid annulus assesses apical motion of the tricuspid annulus with a value of <10 cm/s considered abnormal [7]. Chapter 3 reviews echocardiographic findings in RHF.

Estimates of RVSP obtained by echocardiogram correlate well with measurements made by RHC, but the variance can be >10 mmHg in up to 50% of cases [8]. Therefore, RHC is the gold standard not only for diagnosing PH but also for assessing the severity of RHF. A mPAP >20 mmHg at rest with a PVR ≥3 wood units and a PCWP ≤15 mmHg is diagnostic for "pre-capillary" PAH. A mean PAP >40 mmHg is

considered severe but clinical outcomes and severity are based on assessing the impact this is having on the RV and not just the mPAP. An RV pressure >17–32/10–12 mmHg suggests RV overload. This leads to elevated RV end diastolic pressure which is transposed onto the right atrium making RA pressures >12 mmHg an important indicator of RHF. As the RV fails to adapt to increased afterload in PH, CO and SVO2 begin to fall signifying failure of the right heart.

7.4 Discuss the Hemodynamic Assessment of Afterload Induced Right Heart Failure?

It is not the PVR and mPAP which dictate clinical outcomes in PH, but instead the interplay between the RV and its ability to adapt to these changes in the pulmonary circulation. As previously described, the RV hypertrophies to increase contractility against this rising afterload. However, there is a point at which afterload overcomes this compensatory contractility, which has been described as "RV-PA uncoupling" [9–11].

To quantify RV-PA coupling, one must first understand how RV contractility and afterload are measured from RV pressure volume loops (Fig. 7.5). Systole begins when there is a rise in pressure caused by actin-myosin cross bridging without a change in volume, known as isovolumic contraction. Pressure rises until it supersedes pulmonary arterial pressure, causing the pulmonic valve to open and the RV to eject blood into the pulmonary circulation. Ultimately the RV empties and diastole begins. Elastance is defined as the pressure divided by volume, so the point in the cardiac cycle at which pressure is the highest and volume is low is considered the point of maximal elastance ($E_{max)}$. This point occurs during systolic ejection and is important because E_{max} is the gold standard for determining RV systolic function [11, 12]. The standard measurement of afterload is labeled arterial elastance (E_a), which is measured from a line that transects the

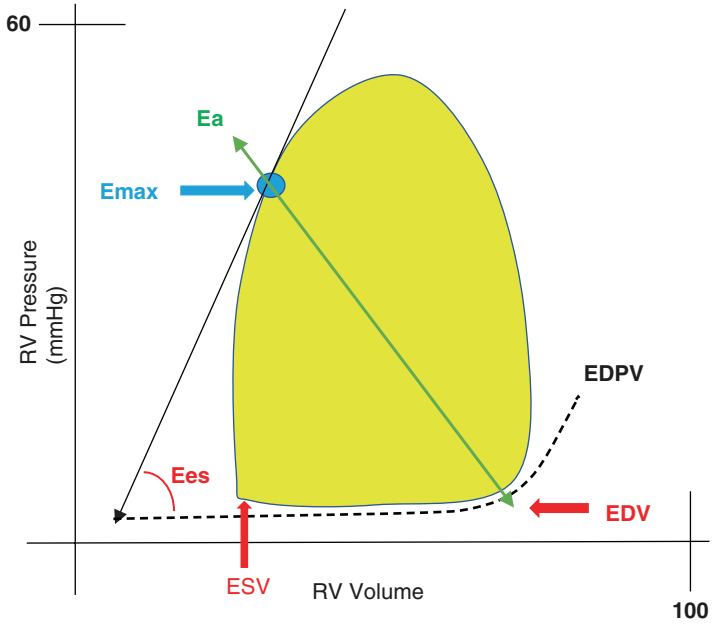

FIGURE 7.5 RV pressure volume loop. RV Afterload (E_a) is measured by drawing a line between the point of end diastolic pressure volume relationship (EDPVR) and the point of maximum elastance (E_{max}). Contractility (E_{es}) is determined using the slope of the line connecting the E_{max} to the end systolic volume (ESV). Ultimately, using the E_{max} we can determine RV contractility (E_{es}) and RV afterload (E_a) and use it to assess RV-PA coupling (E_{es}/E_a)

end diastolic volume and E_{max} [11, 13, 14]. The E_a is more reflective of right ventricular afterload during resistive, pulsatile and passive flow of blood out of the RV compared to static measures of mPAP and PVR [12]. Finally, contractility is determined by the slope of the line connecting the E_{max} to the end systolic volume since a 'stronger' ventricle with increased contractility will generate larger pressures. Contractility is labeled end systolic elastance (E_{es}) [11]. These values are used to assess, RV-PA coupling, which is defined as E_{es}/E_a with the understanding that the RV and PA circulation act together as a unit to maintain cardiac output [3, 5, 11, 14–16].

Although measuring RV pressure and volume loops are considered the gold standard, it requires multiple measurements to be taken while occluding venous return to the heart, making it an impracticable maneuver in human studies. Therefore, Bellofiore et al**.** investigated 'the single beat method', which was first studied in the LV and applied it to the RV in both animal and human models [9, 10]. This method measures RV pressure during isovolumic contraction and relaxation and determines RV contractility without relying upon measuring RV volume [5, 9]. Graphing these pressures enables calculation of a maximum-pressure (*Piso*) which is used to calculate E_{es} and E_a [9, 11] (Fig. 7.6). This method was

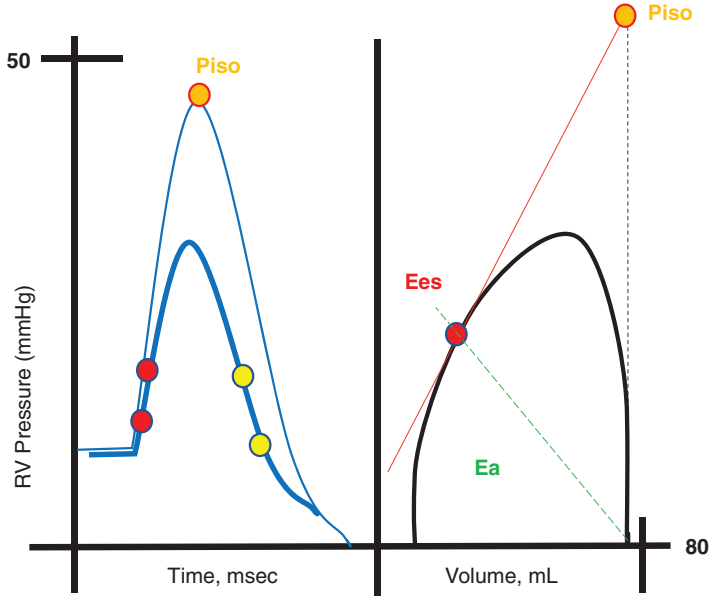

Figure 7.6 Single Beat Method. Pressures measured in the early and late portions of the RV pressure curve during isovolumic contraction (red dots) and relaxation (yellow dots) are used to determine the maximum pressure that can be reached by an isovolumic contraction (Piso). Piso is then used to defined the end systolic pressure volume relationship and ultimately to calculate E_{es} and E_a

validated and ultimately used to assess PH patients during RHC [10, 13–15, 17]. Vanderpool et al. demonstrated that in a mix of pre-capillary PH patients, RV-PA coupling based on this method was the only independent predictor of transplant-free survival [17]. The optimal coupling occurs at an E_{es}/E_a ratio between 1.5 and 2 and studies have found that a ratio <0.805 was associated with onset of RV failure [15, 16].

In addition, RV-PA coupling has been found to be an earlier marker of disease even in patients with normal RHC data at rest. In studies of patients with chronic thromboembolic disease and normal RHC, they evaluated RV-PA coupling and found a ratio of <0.68 demonstrated a lack of RV reserve during exercise [18]. Exercise studies measuring RV-PA coupling in PH have shown that progressive exercise intolerance is due to a decline in the efficiency of the hemodynamic interaction between the RV and pulmonary vasculature, rather than either ventricular or vascular impairment alone [10]. Sing et al. demonstrated that even in exercise PH, an early form of PH, RV-PA uncoupling is seen during incremental increases in load during exercise suggesting that this phenomenon is present early in the disease state [13, 14]. One major mechanism for this uncoupling appears to be a loss of pulmonary artery distensibility. In patients with exercise PH and PAH there was an increased RV-PA uncoupling with exercise which correlated with decreased measured pulmonary distensibility [14]. It appears that vascular remodeling in PH leads to a loss of pulmonary distensibility which becomes evident during exercise when increased volume and flow are delivered to the pulmonary circulation.

Case Continued

She was considered an NYHA Functional Class II and initiated on dual therapy with an oral PDE5 inhibitor (tadalafil) and an endothelin receptor antagonist (ambrisentan) with good clinical response. On a repeat 6MWT 3 months later she could complete 492 m with a Borg Score of 2. Her repeat TTE showed RVSP 45 mmHg and RV with improved function to mildly reduced function. Repeat RHC showed RAP 6 mmHg,

RV pressure 43/6 mmHg, PAP 44/24 mmHg, mPAP 30 mmHg, PCWP 13 mmHg, CO 7 L/min, CI 5 L/min/m^2, PVR 3 WU, SVR 900 dyne s/cm^{-5}, SVO2 70%.

7.5 How Do You Prognosticate RV Failure Induced Pulmonary Hypertension?

RV function is one of the major factors determining morbidity and mortality in PH patients. In addition to RV-PA coupling discussed above, a combination of tools is used to prognosticate mortality in these patients and guide medical management. The 2015 ERC/ERS guidelines have divided PH patients into three categories based on one-year mortality: Low risk is defined as <5%; intermediate risk 5–10%; and high risk is >10% [1].

The low risk patients lack clinical signs of right heart failure, progressive symptoms, or syncope. They are NYHA Class I or II and have a 6MWD of >440 m [1, 19]. If cardiopulmonary exercise testing is done, testing shows peak VO2 > 15 mL/min/kg and VE/VCO2 slope <36. TTE assessment would show right atrium area <18 cm^2 on imaging. Laboratory studies show a BNP <300 pg/mL. Finally, RHC shows RAP <8 mmHg, CI >2.5 L/min/m^2 and a SVO2 > 65% [1]. Since our patient fit into this category, she was initiated on dual oral therapy.

Comparatively, high-risk patients have signs of RHF with rapid progressive symptoms or syncope. These patients are defined as NYHA functional Class IV with a 6MWD of <165 m. However, it is important to note that response to treatment on follow up has more valuable prognostic information. Patient with a good baseline functional class who progress on treatment to a functional class of III or IV have worse survivals than those who started at NYHA Class III or IV but improved with therapy [20]. A peak VO2 < 11 mL/min/kg and VE/VCO2 slope > 45 on cardiopulmonary exercise testing correlates with poor prognosis. Laboratory studies show a BNP >300. TTE reveals an right atrium area

>26 cm^2 on imaging and the presence of a pericardial effusion, which is an independent predictor of morality [19, 21]. Finally, a RHC with RAP >14 mmHg, CI <2 L/min/m^2, and an SVO2 <60% are consistently associated with worse survival in PAH patients [1, 7, 22]. This patient group requires evaluation for IV drug therapy [1, 23].

Case Continued

One year later she presented to clinic with worsening shortness of breath on exertion and pre-syncope. She was afebrile with a new 6–8 L O_2 requirement to keep her O_2 saturation >90%. Her heart rate was 124 bpm with a blood pressure of 95/62. Exam revealed JVD to 15 cm H2O, an RV heave, a loud P2, and peripheral edema with cool extremities. She denied fever, chills, cough, hemoptysis, chest pain, or palpitations but has been light-headed with exertion and noted new ankle swelling. She was sent to the emergency department. Her initial labs revealed a BNP 4000 pg/mL, Arterial blood gas pH 7.28/25/70 with an elevated lactate, new acute kidney injury, and elevated transaminases. An EKG revealed new atrial flutter with 2:1 block with rapid ventricular rate of 124 with no ischemic changes. A computed tomography pulmonary embolism protocol was unremarkable. A TTE with bubble study was negative for intracardiac shunt or left ventricular systolic heart failure (LVEF 60%) but there was new systolic and diastolic flattening of the interventricular septum consistent with RV pressure and volume overload. The ventricle was severely dilated with severely reduced function; TAPSE 1.10 cm. Right atrium was also moderately dilated, RSVP 80 mmHg, severe tricuspid regurgitation, and a small pericardial effusion. She was admitted to the intensive care unit and a Swan-Ganz Catheter was placed. Initial measurements revealed RAP 20 mmHg, RV 80/20 mmHg, PCWP 12 mmHg, PAP 90/35 with a mPAP 65 mmHg, CO 3.1 L/min and CI 1.5 L/min/m^2, PVR 13 WU, SVR 1800 dynes s/cm^{-5}, SVO2 40%. A central line, arterial line, and foley catheter were placed and she was initiated on furosemide drip. However, her heart rate increased to 140 bpm and blood

pressure dropped to 72/50 mmHg, prompting initiation of norepinephrine to maintain mean arterial pressure >65 mmHg. She was then started on IV dobutamine and inhaled Epoprostenol (iPGI2) through a high-flow nasal cannula. An amiodarone drip was also started for atrial flutter with rapid ventricular rate.

7.6 Discuss the Management of the Failing Right Heart from Pulmonary Hypertension?

Progressive PH leads to RHF and end organ damage from decreased cardiac output and venous congestion making it a challenging disease to manage with a high mortality rate. As with any patient in shock, it is important to evaluate for other causes of shock and treat factors that may contribute to worsening RHF. Arrhythmias, common in RHF, reduce effective coronary filling in diastole and should be treated aggressively with consideration of amiodarone or electrical cardioversion [24]. Acidosis, hypoxemia, and hypercapnia can worsen pulmonary vasoconstriction therefore it is important to keep O2 saturation >92% and aim for a normal pH and pCO_2. Although it is preferable to avoid intubation since anesthetics and positive pressure ventilation can cause hypotension and reduce preload to an already pre-load dependent LV, intubation is sometimes necessary. Avoiding high tidal volumes and excess positive end-expiratory pressure (PEEP) may help reduce the risk of significantly worsening PVR in this setting [25].

Treatment should focus on improving RV contractility, reducing excess preload, and preventing RV ischemia. The placement of a Swan-Ganz Catheter can be useful to understand the hemodynamics and assess the impact of each medical intervention. One of the first steps to improving RV contractility in PH is to reduce excess preload. Unlike other forms of RHF where fluid administration may enhance right ventricular output, in PH the RV is already dilated and fluid administration will further displace the interventricular

septum, impair LV diastolic filling, and reduce cardiac output. Since the RV has a flatter Frank-Starling curve than the LV, a considerable amount of volume unloading may be necessary before any improvement in RV function is seen [24]. This unloading can be accomplished with diuretics or dialysis to keep the CVP 8–12 mmHg with adjustments to optimize RV function and cardiac output [24].

A failed response to diuretics and especially hypotension warrants initiation of vasopressors and ionotropic agents. Stabilizing systemic blood pressure with vasopressors above the RVSP is critical to provide a pressure gradient for right coronary artery perfusion. Current recommendations include the use of norepinephrine to accomplish the goal as it has α1 agonism to improve SVR, β1 stimulation to enhance contractility, and has been shown to improve RV-PA coupling in animal models [26, 27]. Additional vasopressors which can be used include epinephrine and vasopressin, which can induce pulmonary vasodilatation by stimulating endothelial nitric oxide at doses ≥0.04 units/min [28–30]. Phenylephrine and dopamine should be avoided as the former increases PVR without improving RV contractility and the latter causes excess tachycardia that reduces LV filling and worsens demand ischemia [24, 26, 27, 31, 32]. Inotropic agents such as dobutamine and milrinone are also helpful in the setting of acute RV failure especially in conjunction with vasopressors since they can cause vasodilation. Animal studies have shown that dobutamine and milrinone are effective at improving CO and even RV-PA coupling [33, 34]. In general, norepinephrine, vasopressin, and epinephrine can be used in combination with dobutamine or milrinone in PH with right ventricular failure as long as the focus remains on titrating medications based on hemodynamic monitoring.

In addition to improving RV contractility and preventing ischemia, it is important to treat afterload with pulmonary vasodilator therapy. IV prostacyclin (Epoprostenol and Treprostinil) is the drug of choice for any patient considered to be NYHA Class III or IV since it has been shown to improve not only CO, PVR, and RV-PA coupling but also

functional status and survival [23, 35, 36]. Although studies are limited in acute RHF, the short half-life makes IV therapy a titratable option in the ICU with close monitoring for side effects of hypotension, gastrointestinal symptoms, and headaches [5]. In acute and chronic PH, the combination of dobutamine and inhaled nitric oxide (iNO) improved CO, decreased PVR, and increased the PaO_2/FiO_2 ratio in animal studies [37]. As a result, inhaled prostacyclin (iPGI) and iNO have been utilized in ICUs to treat RV failure since they are effective at improving CO, oxygenation, and PVR in cardiothoracic surgery patients with elevated PAP. They have the theoretical advantage of reduced risk of VQ mismatch and hypotension compared to IV therapy [38–42]. Although promising, neither of these inhaled drugs has been studied extensively in PAH patients with acute RHF. Other classes of PH medications have not been tested at length, but it is currently recommended to avoid endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and guanylate cyclase stimulators given the long half-life and risk of hypotension [24].

Case Continued

Initially the transplant and ECMO teams were consulted. After several hours on iPGI2, dobutamine, and norepinephrine, her urine output began to improve and her lactate normalized. A furosemide drip was re-initiated. After 48 h, norepinephrine was weaned down to 2 μg/min and the decision was made to trial IV treprostinil starting at 2 ng/kg/min with careful up-titration.

7.7 What Are the Surgical and Interventional Alternatives for Pulmonary Hypertension?

Given the complexity of decompensated RV failure from PH, other advanced interventional and surgical options may be investigated in select patients. These options are intended for

patients that have potentially reversible RV failure or who fail maximal medical therapy. Right ventricular assist devices (RVADs) have been designed for use in RV failure, but in patients with RHF due to increased afterload, there is limited data and potential harm with their use [5]. As a result, current options are limited to extracorporeal membrane oxygenation (ECMO) and transplant.

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) should be considered in certain patients who fail medical therapy. Since it relies on an intact RV to pump blood to the LV, Veno-venous ECMO (VV-ECMO) is generally reserved for patients with preserved RV function who have intractable hypoxemia. VA-ECMO, however, oxygenates venous blood and delivers it directly to the arterial circuit. The data for VA-ECMO in PAH patients is based on case reports where it has been utilized as a bridge for patients undergoing pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension (CTEPH) and for a treatment naïve PH requiring hemodynamic support until clinical recovery with PH therapy [5, 24, 43–45]. More studies are needed to fully evaluate its role in the management of decompensated PH with RV failure.

Finally, transplant should be a consideration in patients with RHF who have failed medical therapy. As noted before, PH patients with high RA pressures and low cardiac output have worse outcomes, therefore a transplant referral is appropriate for those with a RAP >15 mmHg and a cardiac index <2.0 L/min/m^2 [5, 24, 46]. Despite the fact that PH leads to RHF, these patients do not necessarily need a dual heart-lung transplant [22]. In fact, most PH patients with lung transplant alone have a rapid decrease in their PA pressures immediately post-op with significant improvement in their RV function a year after transplant [22]. The data suggests that a dual lung transplant is more effective than single lung transplant [22]. Overall, although post-transplant PAH patients had a higher early mortality, after 5 years they had similar outcomes compared to other matched lung transplant patients and a dramatic improvement in their quality of life [22, 47].

Case Conclusion

After 3 weeks in the hospital, she was weaned off dobutamine and norepinephrine, her treprostinil dosing was titrated to 24 ng/kg/min, and her oxygenation improved to 2 L nasal cannula. Transplant was delayed given her recovery. She was discharged to cardiopulmonary rehab with close follow-up.

Clinical Pearls

1. The RV in PH fails due to rising afterload from increased resistance and reduced distensibility in the pulmonary vasculature.
2. Outcomes in PH patients are based on the RV's ability to adapt to rising afterload and maintain contractility.
3. Assessments of RV-PA coupling have demonstrated that dysfunction occurs early in PH and impacts exercise tolerance and transplant free survival.
4. The focus of treating RV failure in PH is to reduce excess preload, improve RV contractility, prevent RV ischemia, and decrease afterload in the pulmonary vasculature.
5. In patients with severe RHF who have failed medical therapy or are bridging to therapy, transplant and VA-ECMO should be considered at an expert center.

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Chapter 8
Right Heart Failure from Carcinoid Syndrome

Melissa A. Lyle and Heidi M. Connolly

Case

A 64-year old female with a history of a neuroendocrine tumor presents with exertional dyspnea and progressive lower extremity edema. Four years prior she presented with frequent diarrhea and abdominal pain. Abdominal computed tomography revealed a cecal mass and multiple hepatic lesions. Colonoscopy identified the mass located at the ileocecal valve, and biopsy revealed a well-differentiated neuroendocrine tumor. Liver biopsy was consistent with metastatic neuroendocrine tumor, and monthly octreotide injections were started. Despite octreotide injections, she continued to experience flushing and severe diarrhea, with greater than ten bowel movements per day.

Progressive lower extremity edema, exertional dyspnea, and fatigue raised the concern for carcinoid heart disease (CHD). Physical exam illustrated an elevated jugular venous pressure around 15 cm of water, with a prominent "V" wave and a parasternal impulse. Auscultation revealed single first and second heart sounds, grade 2 systolic and grade 2 diastolic murmurs, best heard at the left sternal border, with an

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increase in intensity with inspiration. A transthoracic echocardiogram was ordered to evaluate for CHD.

8.1 What Is the Initial Approach to Evaluating Right-Sided Valvular Disease?

When a patient present with signs of right-sided heart failure, including increasing dyspnea, lower extremity edema, and ascites, the initial evaluation should include a physical examination (see Chap. 2). And if physical exam confirms suspicion of right-sided valvular disease, then a transthoracic echocardiogram should be performed to further elucidate pathology. Cardiac magnetic resonance imaging and computed tomography can serve as valuable adjuncts for the assessment of right-sided valvular disease in select cases.

8.2 Discuss the Pathophysiology of Carcinoid Heart Disease

Neuroendocrine tumors are rare, with an incidence ranging from 2.5 to 5 per 100,000 people [1]. These tumors arise from enterochromaffin cells; they can occur anywhere in the body, but have a predilection for the gastrointestinal tract. Gastrointestinal neuroendocrine tumors were originally described as "carcinoids," with the "midgut carcinoid," originating from the distal small intestine to the proximal colon [2]. Primary midgut carcinoid tumors can metastasize to the liver and regional lymph nodes. Thirty to forty percent of patients with carcinoid tumors present with carcinoid syndrome, and the most common manifestations are vasomotor changes such as flushing and hypotension, gastrointestinal hypermotility with diarrhea, and bronchospasm. Carcinoid tumors release vasoactive substances, such as serotonin (5-hydroxytryptamine), 5-hydroxytrptophan, histamine, bradykinin, and prostaglandins, responsible for the

vasomotor changes. Carcinoid syndrome frequently occurs in the setting of primary midgut carcinoid tumor metastases to the liver because the vasoactive substances reach the systemic circulation quickly via the hepatic vein [3].

CHD occurs in over 50% of patients with carcinoid syndrome and [4, 5] is characterized by plaque-like depositions on the endocardial surface of heart valves, most frequently the right-sided valves, the subvalvular apparatus, cardiac chambers, and even occasionally the intima of pulmonary arteries and aorta [6, 7]. The pathogenesis of CHD is still not completely understood. It is speculated that the vasoactive substances, particular serotonin (5-HT), secreted by the neuroendocrine tumor induce proliferative effects on fibroblasts, upregulate transforming growth factor-β1, and activate inflammatory cytokines by activating the 5-HT receptors. The 5-HT_{2B} receptors are most prevalent on heart valves. The resulting plaque-like deposits are comprised of myofibroblasts, smooth muscle cells, and an extracellular matrix composed of collagen, microfibrils, and mucopolysaccharides [7]. In approximately 90% of CHD cases, the right-sided valves are primarily affected [3]. It is thought that the left-sided valves are often spared because of the inactivation of vasoactive substances by the lungs. When left-sided valve pathology occurs, it is often associated with an atrial level right-to-left shunt [5], which allows the vasoactive substances to reach the left sided cardiac chambers without undergoing inactivation in the pulmonary capillaries. Recent investigations have also revealed that bronchopulmonary carcinoid is not associated with left-sided involvement in the absence of a patent foramen ovale as previously suspected [8].

The affected right-sided valves have a typical thickened white appearance. The carcinoid plaques typically deposit on the ventricular aspect of the tricuspid valve leaflets, resulting in leaflet thickening, reduced mobility, and thickening of the subvalvular apparatus and papillary muscles. In severe cases, there is reduced excursion and the leaflets become retracted and do not coapt. This is associated with severe tricuspid valve regurgitation, with a classic dagger-shaped profile on Doppler echocardiography, and occasionally mild tricuspid stenosis [1, 3, 9].

The carcinoid plaques frequently affect the arterial aspect of the pulmonary valve cusps. In a similar pattern to the tricuspid valve, the pulmonary valve cusps can become diffusely thickened in CHD. This progressive thickening results in straightening of the cusps, leading to retraction and severe pulmonary valve regurgitation [3]. Pulmonary annular stenosis is also associated with CHD, and can be visualized by 2D echocardiography and may cause increased velocities noted on continuous wave Doppler echocardiography in the right ventricular outflow tract.

8.3 What Are the Clinical Manifestations of Carcinoid Heart Disease?

The clinical manifestations of CHD include features of right-sided heart failure. Early symptoms may include progressive fatigue and dyspnea on exertion. As the right-sided heart failure progresses, patients can present with increasing dyspnea, ascites, early satiety, and lower extremity edema. Physical exam will frequently illustrate elevated jugular venous pressure, with a prominent "V" wave in the setting of severe tricuspid valve regurgitation. On palpation, a right ventricular heave is often noted, and a pulsatile liver can be felt in the setting of severe tricuspid valve regurgitation. Auscultation will reveal the holosystolic murmur of tricuspid valve regurgitation and the diastolic murmur of pulmonary regurgitation, and occasionally the diastolic murmur of tricuspid stenosis and the systolic pulmonary stenosis murmur. The valve murmurs are often subtle due to the low pressure right-sided system.

8.4 What Is the Diagnostic Work Up?

The initial diagnostic work-up includes a detailed history and physical exam. Chest radiography may illustrate enlargement of the right-sided chambers, with right ventricular enlargement often indicated by a decreased retrosternal space noted on the lateral view. An electrocardiogram often illustrates

ST-T wave abnormalities and some demonstrate low voltage QRS, but most electrocardiograms in patients with CHD demonstrate nonspecific findings.

Laboratory evaluation, specifically biomarkers, can aid in the initial diagnosis of CHD. The most useful biomarker is N-terminal pro-B-type natriuretic (NT-proBNP), which does have diagnostic and prognostic importance [10]. In the absence of known CHD, it is recommended that yearly NT-proBNP levels be obtained in patients with carcinoid syndrome to monitor for CHD. Urinary 5-hydroxyindoleacetic acid (5-HIAA), the result of serotonin metabolism by monoamine oxidases in the liver, also serves as a biomarker for CHD [11]. Plasma and urinary 5-HIAA levels are elevated in patients with CHD, and higher levels are associated with an increased risk of progression of disease [12]. Finally, chromogranin A (CgA) is a glycoprotein released by the neuroendocrine tumor and is increased in a majority of patients with CHD. This biomarker is quite sensitive, up to 100% for detection of CHD, but only 30% specific. Therefore, CgA levels are more helpful for detection of recurrence of the neuroendocrine tumor rather than initial screening for CHD [10, 13].

Transthoracic echocardiography (TTE) remains the gold standard for diagnosis and evaluation of CHD. Frequently, TTE can illustrate characteristic features, such as the thickened and retracted tricuspid valve with associated severe regurgitation, as well as the immobility of the pulmonary valve cusps and pulmonary annular constriction, resulting in pulmonary valve regurgitation and outflow tract obstruction. However, when the pulmonary valve cusps are severely thickened and retracted, it may be difficult to visualize them by standard TTE, and 3D echocardiography can enhance visualization of the cusps. 3D echocardiography can also aid in right ventricular volume and function assessment [14]. Several echocardiographic scoring systems have been created in an attempt to further define prognostic features in CHD, and it was determined that the scoring system that focuses mainly on tricuspid valve anatomy and regurgitation is best for screening, with more complex scoring systems reserved for monitoring pro-

gression of disease in patients with established heart disease [15]. An agitated saline shunt study should be performed during the initial echocardiogram for CHD to identify any potential right-to-left atrial level shunt, given the risk of left-sided valve involvement in patients with a patent foramen ovale or atrial level right-to-left shunt.

Multimodality imaging echocardiography (as shown in Chap. 3) is often utilized to refine the diagnostic assessment of CHD, and can be complimentary to initial echocardiography. Cardiac magnetic resonance (CMR) imaging can further define CHD, particularly assisting in delineating the degree of pulmonary valvular involvement and right ventricular volume and function assessment. CMR can also further define other morphologic features of CHD, such as myocardial metastases [3, 16]. Cardiac computed tomography (CT) is a valuable tool for assessing the degree of valvular pathology in CHD, and aids in evaluation of right ventricular size and function [17], similar to CMR. Cardiac CT can also provide a pre-operative assessment of coronary artery anatomy.

Functional imaging with radiolabeled somatostatin analogues, such as gallium-68-DOTATOC/DOTATATE positron emission tomography CT scanning, can help localize the primary tumor, and occasionally this type of functional imaging can be useful in the assessment of carcinoid cardiac metastases to the pericardium and myocardium. However, in general, cross-sectional imaging of the heart, in the form of echocardiography, CMR, and cardiac CT, are the optimal modalities to assess right-sided valvular pathology and right ventricular size and function [3].

Case Continued

A transthoracic echocardiogram was obtained for our patient, and this revealed features of classic CHD. She was found to have a severely thickened tricuspid valve with immobile leaflets (Fig. 8.1a). There was lack of tricuspid leaflet coaptation with severe tricuspid valve regurgitation (Fig. 8.1b). Continuous wave (CW) Doppler echocardiography illustrated a dagger-shaped

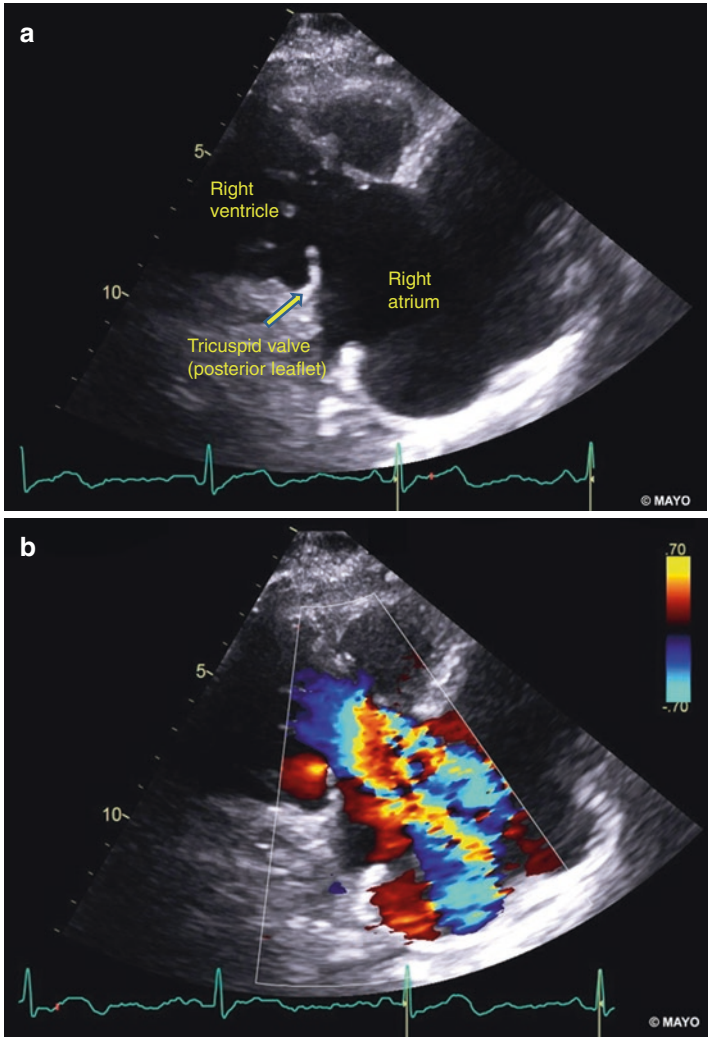

FIGURE 8.1 (**a**) Right ventricular inflow view illustrating thickened and retracted tricuspid valve leaflets. (**b**) Right ventricular inflow view illustrating severe tricuspid valve regurgitation

profile, consistent with severe tricuspid valve regurgitation. The tricuspid valve regurgitant velocity jet was only 2.4 m/s, which is in the setting of rapid equalization of pressures between the right atrium and right ventricle (Fig. 8.2). The inferior vena cava was dilated and non-collapsible, consistent with severely elevated central venous pressures. Systolic flow reversals were visualized in the hepatic veins in the setting of severe tricuspid valve regurgitation (Fig. 8.3). The pulmonary valve cusps were not well visualized by TTE, which is suspicious for severe pulmonary pathology (Fig. 8.4). Color flow imaging illustrated flow acceleration through the pulmonary valve (Fig. 8.5a) and also was suggestive of severe pulmonary valve regurgitation (Fig. 8.5b).There was also a rapid deceleration of the CW Doppler regurgitant signal with termination of flow in mid-diastole (Fig. 8.6). The right ventricle was severely enlarged, with a basal right ventricular diameter of 54 mm (upper normal 42 mm) and a mid-right ventricular diameter of 51 mm (upper normal 35 mm). There was mild-moderate dysfunction based on quantitative and qualitative assessment (Figs. 8.7 and 8.8).

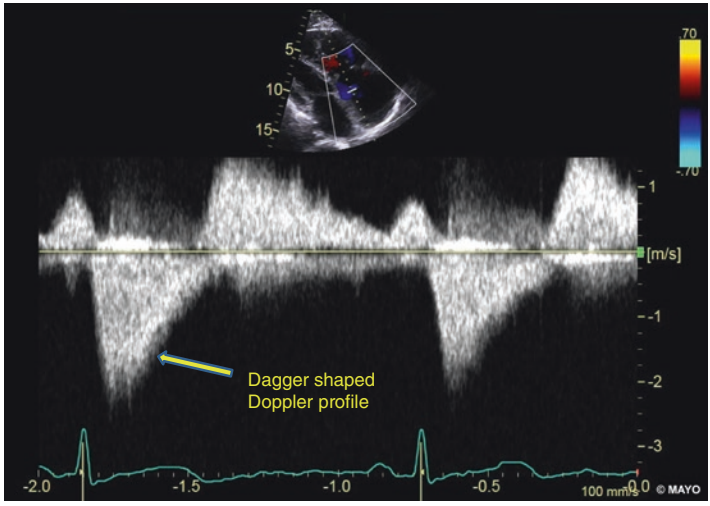

Figure 8.2 Continuous wave Doppler demonstrating severe tricuspid valve regurgitation with a dagger shaped Doppler profile, consistent with rapid equalization of pressures between the right atrium and right ventricle

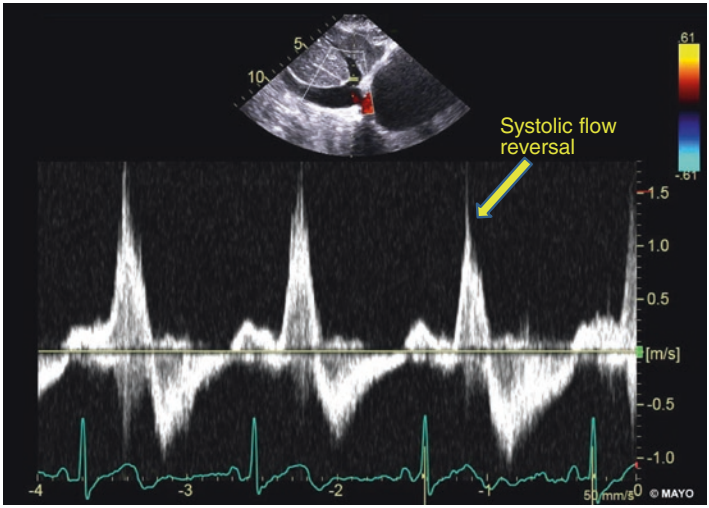

FIGURE 8.3 Hepatic vein pulsed wave Doppler with systolic flow reversals in the setting of severe tricuspid valve regurgitation and elevated right atrial pressure

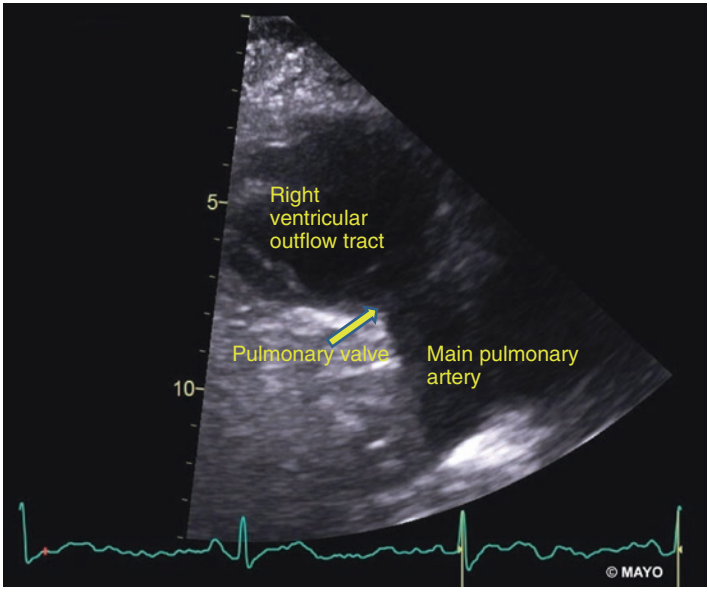

FIGURE 8.4 Right ventricular outflow view

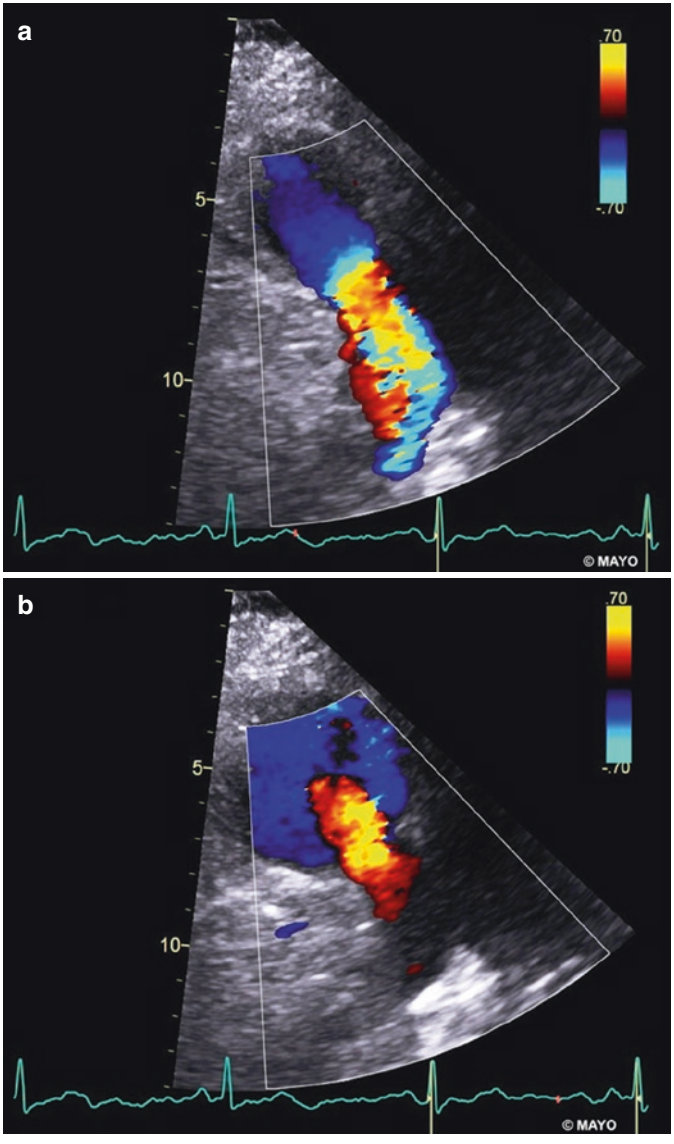

FIGURE 8.5 (**a**) Right ventricular outflow view illustrating flow acceleration through the pulmonary valve. (**b**) Right ventricular outflow view illustrating severe pulmonary valve regurgitation

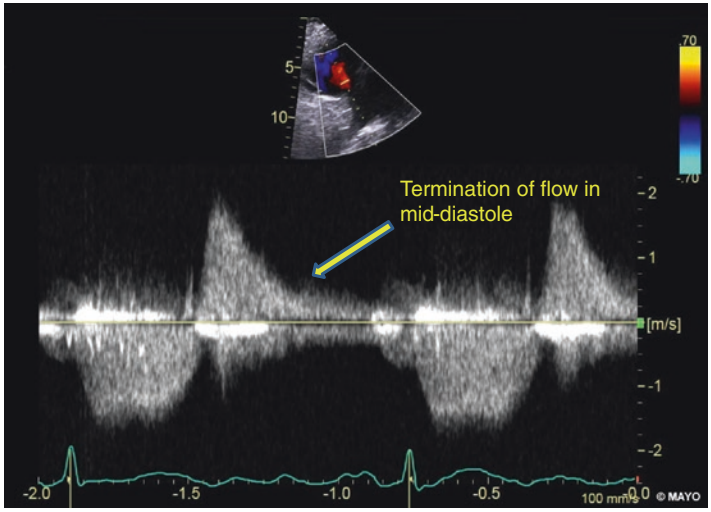

FIGURE 8.6 Continuous wave Doppler through the pulmonary valve, illustrating severe pulmonary valve regurgitation with a rapid deceleration time and termination of flow in mid-diastole

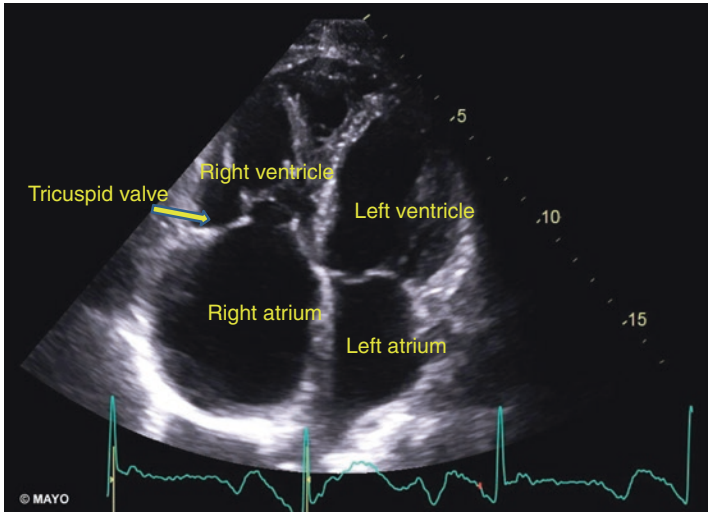

FIGURE 8.7 Apical four chamber view demonstrating right atrial and ventricular enlargement

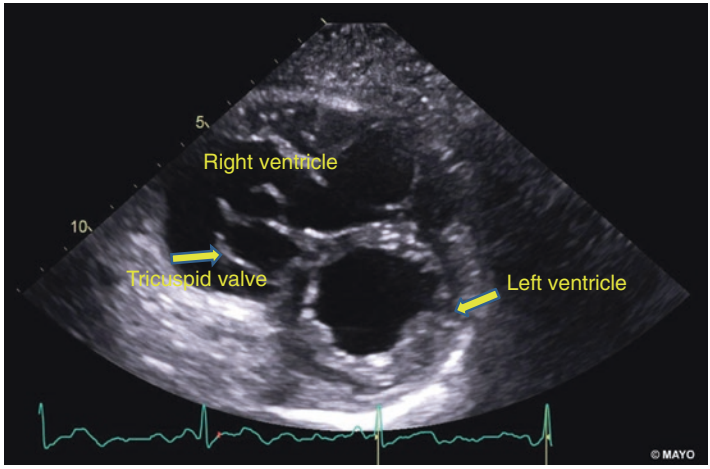

FIGURE 8.8 Short axis view illustrating right ventricular enlargement and lack of coaptation of tricuspid leaflets

Following the echocardiogram, a cardiopulmonary exercise test was completed to assess functional capacity. She exercised for only 4 min and had a low peak VO2 (11.9 mL/(min kg), 55% predicted), despite maximal effort. These findings were consistent with cardiac output impairment in the setting of her CHD. She also underwent a PET DOTATATE scan, which illustrated extensive metastatic disease with progression, despite long-term therapy with a somatostatin analogue. Peptide Receptor Radionuclide Therapy (PRRT) is planned to slow the progression of her metastatic disease.

8.5 Discuss Medical Management

With regard to medical therapy for carcinoid syndrome, somatostatin analogues are the treatment of choice, and are even used in asymptomatic patients in an attempt to prevent or slow the progression of CHD [18, 19]. By decreasing the circulating serotonin levels, there could be added benefit of

somatostatin analogues for reducing risk of development and progression of CHD. Interferon alpha can be used in conjunction with somatostatin analogues for refractory carcinoid syndrome or in patients who do not tolerate somatostatin analogues [20]. In patients with advanced disease with limited response to somatostatin analogues, peptide receptor radionuclide therapy can be utilized in an attempt to control tumor growth. Finally, transcatheter arterial embolization (TAE) and surgical debulking have both served as effective treatments of advanced disease with predominant liver metastases. Embolization can be effective at reducing symptoms in 50–100% of patients with hepatic lesions [21]. Other studies have shown that patients with CHD who undergo liver resection have reduced risk of progression and an overall improved prognosis [22]. However, in patients with severe heart disease, it is important to exercise caution before undergoing hepatic resection, given the significant increased bleeding risk at the time of surgery. In patients with severe CHD with significant right-sided valvular pathology, right heart dysfunction, and elevated right atrial pressure, it may be prudent to address the right-sided valves prior to undergoing surgical intervention for hepatic metastases.

In regard to CHD, the first step in medical management is the treatment of right-sided failure. Unfortunately, medical therapy is mostly limited to loop diuretic therapy, which can improve lower extremity edema, ascites and shortness of breath, but may further decrease cardiac output by decreasing preload, leading to increased fatigue. The mainstay of therapy for severe right-sided valvular disease in the setting of CHD remains surgical intervention.

8.6 What Are the Indications for Tricuspid Valve Replacement?

Cardiovascular surgery with valve replacement is still the most effective treatment for advanced CHD and severe right-sided valvular pathology, most frequently severe regurgita-

tion. Valve surgery can dramatically improve symptoms in patients with severe CHD [23] and is the only treatment that improves survival [24]. Without surgical intervention, there is only an estimated 10% survival at 2 years once patients develop New York Heart Association (NYHA) functional Class III/IV symptoms [23, 25]. Tricuspid valve regurgitation is typically the main lesion in CHD, and therefore patients with CHD and severe tricuspid valve regurgitation are frequently evaluated for tricuspid valve replacement [26].

With severe pulmonary valve regurgitation occurring in conjunction with the tricuspid valve disease, it is preferable to proceed with pulmonary valve replacement rather than resection [27]. Given there is an association with pulmonary annular stenosis, a patch enlargement of the right ventricular outflow tract is often performed to alleviate any right ventricular outflow tract obstruction. Balloon valvuloplasty is not recommended for treatment of the pulmonary annular stenosis given the frequent presence of concomitant pulmonary regurgitation. If a patent foramen ovale is present, it should be closed at the time of surgery.

Two questions that surround the surgical treatment in CHD are the optimal timing of surgery and the choice of prosthesis type. Timing of surgery is difficult, and should involve a multidisciplinary approach. Patients with severe tricuspid and/or pulmonary valve regurgitation who develop cardiac symptoms and do not respond to medical therapy, should be referred for surgical consideration if the metastatic carcinoid disease is controlled. When observation rather than operation is chosen, it is important to continue monitoring patients for evidence of right ventricular dysfunction, and multimodality imaging can be helpful for further assessment of right ventricular size and function. Valve replacement should be considered for medication refractory right-sided heart failure. A final indication for cardiac valve replacement is prior to consideration of liver metastasis resection or liver transplantation to avoid excessive bleeding risk at the time of hepatic intervention [3].

There still remains some controversy regarding the choice of valve prosthesis, but the decision should always include shared

decision making. One disadvantage of mechanical valves is the need for continued systemic anticoagulation, which can be cumbersome when additional surgical interventions may be warranted. Another disadvantage is the known increased risk of thrombosis associated with mechanical valves in the tricuspid and pulmonic position, which approaches 4% per year [26, 28]. Bioprosthetic valves are usually preferred for patients with CHD, although there have been concerns for premature degeneration of the valve prostheses, thought to be hastened by the carcinoid syndrome [29, 30]. However, improvements in the treatment of carcinoid syndrome, with focus on optimization before and after surgery, may help protect the bioprosthetic valves from premature degeneration secondary to vasoactive substances [23]. Recent investigations have also shown that structural valve deterioration secondary to the carcinoid process is in fact rare. Another, concern is bioprosthetic valve dysfunction secondary to thrombosis [25, 31]. Therefore, we recommended continued systemic anticoagulation for at least 3–6 months after bioprosthesis implantation.

Prior reports of operative mortality for valve replacement in CHD have ranged from 18 to 63% [32]. Recent studies have shown that early operative mortality has improved to approximately 5% in patients undergoing surgery at an experienced center since 2005 [33]. Overall, early mortality in cardiovascular surgery for CHD has improved, and it remains the most effective treatment to provide symptomatic improvement. However, overall survival for these patients still depends on tumor progression and their underlying neuroendocrine tumor prognosis [33].

8.7 Which Interventional Percutaneous Strategies Are Available?

While surgical valve replacement remains the gold standard for treatment of severe, symptomatic CHD, transcatheter valve replacement may become an attractive option for patients considered too high risk for cardiac surgery [34].

There have been case reports describing percutaneous pulmonic valve implantation in patients with native CHD [35], but experience appears to be more robust with transcatheter valve-in-valve replacement [36], with case reports describing valve-in-valve replacements in both the pulmonary and tricuspid positions [37]. Currently, percutaneous valve prostheses are not clinically available in the United States for treatment of native tricuspid valve disease.

Case Conclusion

Given overall survival still depends on tumor progression, the decision was made to initially treat our patient's metastatic carcinoid disease with PRRT. Following PRRT, she will complete a surgical evaluation, with potential tricuspid and pulmonary valve bioprosthetic replacements. In the interim, symptoms of right-sided heart failure will be palliated with loop diuretic therapy.

Clinical Pearls

1. Patients with carcinoid heart disease (CHD), which is characterized by plaque-like depositions on the endocardial surface of heart valves, most frequently right-sided valves, often present with symptoms of right-sided heart failure, including progressive dyspnea on exertion and fatigue.
2. Physical exam findings include elevated jugular venous pressure with a prominent "V" wave in the setting of severe tricuspid valve regurgitation, right ventricular heave on palpation, and the holosystolic murmur of tricuspid valve regurgitation and diastolic murmur of pulmonary regurgitation.
3. Transthoracic echocardiography can illustrate characteristic features, such as the thickened and retracted tricuspid valve with associated severe regurgitation, as well as the retracted pulmonary valve cusps and pulmonary annular constriction, resulting in pulmonary valve regurgitation and outflow tract obstruction. Multimodality imaging with CT and MRI can help further define valvular pathology and assess right ventricular enlargement and function.

4. Somatostatin analogues are the main medical treatment for carcinoid disease, but medical therapy for right sided heart failure in the context of CHD is limited to loop diuretic therapy.
5. Cardiovascular surgery with valve replacement is the gold standard treatment for advanced CHD and severe right-sided valvular pathology, most frequently for severe tricuspid regurgitation.

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Chapter 9
Mechanical Support of the Failing Right Heart

Sunu S. Thomas, Maxwell E. Afari, and Erin Coglianese

Case

A 66-year-old man with diabetes mellitus, hypertension, and tobacco use presented with 1 week of exertional chest pain, progressive shortness of breath, and orthopnea. In the Emergency Department (ED), blood pressure was 80/60 mmHg, heart rate 40 beats-per-min, respiratory rate of 20 breaths-per-min and oxygen saturation of 88% in ambient air. Initial labs were remarkable for N-terminal pro b-type natriuretic peptide (Nt-pro BNP) of 5000 pg/mL (normal < 400 pg/mL), troponin T of 5 ng/mL (normal < 0.04 ng/mL), and lactic acid of 5.5 mmol/L (normal < 2.2 mmol/L). The bedside electrocardiogram revealed new Q waves in the inferior leads. Physical examination revealed poor mentation, elevated jugular venous pressure (JVP) of >15 cm H2O with

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positive hepatojugular reflux, clear lung fields, and cold and clammy lower extremities.

9.1 What Is the Initial Assessment?

The first step towards managing this patient was recognizing that he was in cardiogenic shock. In the 1970s, Forrester et al. demonstrated four hemodynamic profiles in patients with acute myocardial infarction [1]. These profiles were based on congestion (pulmonary artery capillary pressure: PCWP > 18 mmHg) and perfusion (cardiac index: CI > 2.2 L/min/m^2). Profile IV patients (those with congestion and hypoperfusion), representing those in cardiogenic shock, have an increased risk of mortality [1, 2].

The coldness and clamminess in the lower extremities suggested decreased tissue perfusion. This suspicion corroborated with the narrow pulse pressure (difference between systolic and diastolic blood pressures) of 20 mmHg (normal ~40 mmHg). A pulse pressure less than 25% of systolic blood pressure is indicative of decreased left ventricle (LV) stroke volume [3].

The elevated JVP in this patient served as evidence for elevated filling pressures which was consistent with his symptoms of shortness of breath and orthopnea. In the Forrester classification system he would be classified as "cold and wet", which supports the clinical suspicion of cardiogenic shock in this hypotensive patient. Q waves in the inferior leads (II, III, avF), imply a late presentation of inferior ST elevation myocardial infarction. This patient was stabilized, then referred to the cardiac catheterization laboratory for ongoing chest pain.

Case Continued

In the ED, he was given ASA 325 mg and atorvastatin 80 mg. He was placed on 3 L per min of oxygen delivered through a nasal cannula with oxygen saturation of 94%. Norepinephrine

was started at 0.1 mcg/kg/min to maintain systemic perfusion. Left heart catheterization (LHC) revealed a right-dominant system with 90% stenosis of the right coronary artery (RCA), status post drug eluting stent to the subtotal occlusion of the ostial RCA. Right heart catheterization (RHC) revealed: Right atrium pressure (RAP): 20 mmHg, Pulmonary artery pressures (PAP): 38/19 [25] mmHg, PCWP: 20 mmHg, cardiac output (CO): 3.8 L/min, CI: 1.9 L/min/m^2, blood pressure:75/60 mmHg. Bedside transthoracic echocardiogram (TTE) at the coronary care unit revealed a preserved left ventricle ejection fraction (LVEF) with a severely hypokinetic right ventricle (RV).

9.2 What Should Be the Next Steps in the Management of this Patient?

The first step would be to either increase the norepinephrine (and/or add vasopressin) to achieve a MAP >65 mmHg. The pulse pressure of 15 mmHg (20% systolic blood pressure) and cardiac index of 1.9 (<2.2 L/min/m^2) were concerning for ongoing cardiogenic shock. An inotrope (dobutamine or milrinone) needed to be started to improve myocardial contractility. Despite the LVEF being normal, the severe RV dysfunction on echocardiogram raised the suspicion of RHF in the setting of right ventricle myocardial infarction (RVMI). Chapter 3 extensively reviews the different imaging findings in RHF. On the hemodynamic profile, the pulmonary artery pulsatility index (PAPi) < 1.0 and the right-left heart pressures mismatch evidenced by RAP/ PCWP >0.86 confirmed RHF. The hemodynamic assessment of RHF is reviewed later in this chapter.

The correction of metabolic derangements such as acidosis, alkalosis or anemia is essential in RHF. It is imperative that appropriate oxygenation is delivered to promote decreased myocardial oxygen demand. Hypoxia and hypercapnia would cause an acute increase in RV afterload which would decrease RV stroke volume [4]. In intubated patients,

elevated positive end-expiratory pressure (PEEP) increases intrathoracic pressure, which can reduce venous return leading to a decrease in preload, thus exacerbating RHF [5].

The failing RV is sensitive to arrhythmias, especially those that cause atrioventricular (AV) dyssynchrony such as atrial fibrillation, supraventricular tachycardia, and ventricular arrhythmias. Anti-arrhythmic agents or direct current cardioversion or defibrillation should be used to ensure sinus rhythm. Our patient was bradycardic, which likely reflected the poor AV nodal conduction due to RVMI. Atrial pacing could be used to increase his heart rate to augment the cardiac output [6] in patients who have epicardial wires or permanent pacemakers in place. Pharmacological strategies include chronotropic agents such as dopamine, isoproterenol, epinephrine, and theophylline.

Although, only 5% of patients in the "Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock" (SHOCK) trial had predominant RV failure, their in-hospital mortality (53.1%) was comparable to patients with LV failure [60.8% p = 0.296] [7]. This observations speaks to the need to be proactive and aggressive in the management of RV failure. However, it needs to be pointed out that "Isolated" RV shock was an exclusion criteria in the SHOCK trial, hence the findings cannot be directly applied to our patient.

9.3 What Is the Pathophysiology of RHF?

The etiology for acute RHF in this patient is RVMI. The pathologic signature of RVMI is necrosis of the LV posterior/inferior wall, septum, and posterior right ventricular free wall. The latter is usually contiguous with the septum and in rare occasions to the anterior right ventricular free wall [8, 9]. The RCA is the most common culprit vessel; however, the involvement of the RV free wall is dependent on the location of the occlusion relative to the RV branches. The occlusion must be proximal to the RV branches to cause RVMI. In a

left dominant system, the left circumflex and the left anterior descending artery could cause RVMI depending on the epicardial vessel giving rise to the RV branches. Cohn et al., were the first to demonstrate the hemodynamic profile of RVMI when they showed RAP >15 mmHg [10]. The distinctive hemodynamic profile is characterized by RHF, low output and clear lungs.

The pathophysiology of RHF is explored in Chap. 1. RHF starts with an initial insult (such as ischemia) to the RV as seen in our patient or as a result of trauma/surgery, air embolus during cardiac surgery, and inflammation (myocarditis). Other potential etiologies include pulmonary arterial hypertension, pulmonary embolism, and acute respiratory distress through the increase of RV afterload. The RV is also preload sensitive, hence the progressive dilatation and worsening tricuspid regurgitation from massive blood transfusion or fluid infusion could cause ventricular interdependence.

The mechanisms for RV failure include: (a) Ventricular interdependence: An increase in RV pressure and volume results in a left shift of the interventricular septum. The consequence of this shift is the reduction of the LV diastolic filling, which contributes to the decline of cardiac output [11]. (b). Pericardial constraint: An acute increase in RV volume can worsen the pericardial constraint, which is transmitted to the septum causing the interventricular septum to shift to the left, thus increasing the LV filling pressure and decreasing the effective cardiac output [12]. (c) Finally, an increase in the RV filling pressures results in the reduction of coronary flow, due to coronary sinus congestion. The reduced coronary flow would contribute to further ischemia [13].

9.4 What Is the Medical Management of RV Cardiogenic Shock?

The medical management of acute RHF should focus on treating the underlying cause. In acute RVMI, coronary artery reperfusion is essential. Management should target

the optimization of preload, contractility, and afterload. In cases with low intravascular volume, cautious fluid infusion is required to increase contractility as per the Frank Starling curve. The central venous pressure (CVP) should be monitored closely during fluid infusion to ensure that it does not exceed 12–15 mmHg in those who are volume depleted [14]. On the other hand, RV volume overload from excess preload can shift the interventricular septum to the left resulting in interventricular interdependence as discussed above.

This patient had elevated right and left filling pressures, so his fluid status needed to be optimized with a diuretic. Optimally, intravenous diuretics should be titrated to keep the CVP between 8 and 12 mmHg and PCWP <18–22 mg Hg [14]. In the setting of fluid overload refractory to diuresis, continuous veno-venous hemofiltration (CVVH) or ultrafiltration might be needed to achieve negative fluid balance. Inotropes such as epinephrine, dobutamine or milrinone can be used to keep cardiac index >2.2 L/min/m^2. Inotrope choice can be institution-dependent and stylistic. Dobutamine acts via β1 receptor stimulation, but may also cause vasodilatation due to β2 effects. We opted to not use dobutamine as an initial strategy in this patient because he was hypotensive. Epinephrine was not a first choice either due to the concern for demand ischemia. Inhaled and parenteral epoprostenol and nitric oxide would be the agents of choice in cases with elevated pulmonary artery pressures to decrease the RV afterload [15].

Case Continued

Despite maximal medical therapy (norepinephrine 1 mcg/kg/min, vasopressin 0.04 units/min, milrinone 0.5 mcg/kg/min, inhaled epoprostenol 30 ng/kg/min), the patient continued to have unfavorable RHC hemodynamics: RAP 18 mmHg, PA 30/18 [12] mmHg, PCWP 15 mmHg, CO 4.3 L/min, CI 2.1 L/min/m^2. The Shock Team was consulted for the consideration of RV mechanical support.

9.5 Which Percutaneous Mechanical Support Options Are Available for Acute RHF?

Intra-aortic balloon pump (IABP) is the most commonly used percutaneous mechanical support in LV failure. IABP has no direct effect on RHF; however, indirect support is achieved through the promotion of coronary perfusion during diastole. IABP's utilization in biventricular failure is based on the concept that its LV afterload reduction effect will reduce the RV filling pressures. In the SHOCK Trial, IABP usage was similar between RV and LV cardiogenic shock [7].

The axial flow Impella RP (Abiomed Inc., Danvers, Massachusetts-USA) and extracorporeal centrifugal flow TandemLife Protek Duo (TandemLife, Pittsburgh, PA) bypass the RV by delivering blood from the right atrium to the pulmonary artery. The Impella RP (shown in Fig. 9.1) is placed through the femoral vein into the inferior vena cava (IVC)/right atrial junction (inlet), and then advanced through the tricuspid valve into the main pulmonary artery (outlet). In the RECOVER RIGHT trial, which included 30 patients with cardiogenic shock post left ventricular assist device (LVAD) implantation, cardiotomy or myocardial infarction, Impella RP was shown to improve the hemodynamic profile of patients through the decrease in RAP and increase in CI [16]. The overall survival at 30 days was 73.3% post device explant or hospital discharge.

In the United States, the Federal Food and Drug Administration (FDA)'s mandated post approval study (PAS) showed approximately 29% (12/42) survival. The disparity between the pre-market approval (PMA) study and the PAS mortality was attributed to patient selection. The survival rate was 64.3% in the PAS cohort who strictly met the PMA criteria [17]. Patients with cardiogenic shock >48 h, cardiac arrest, or with pre-implant hypoxic or ischemic neurologic event were not in the PMA; hence, appropriate patient selection is imperative for Impella RP use. Impella RP is European CE marked.

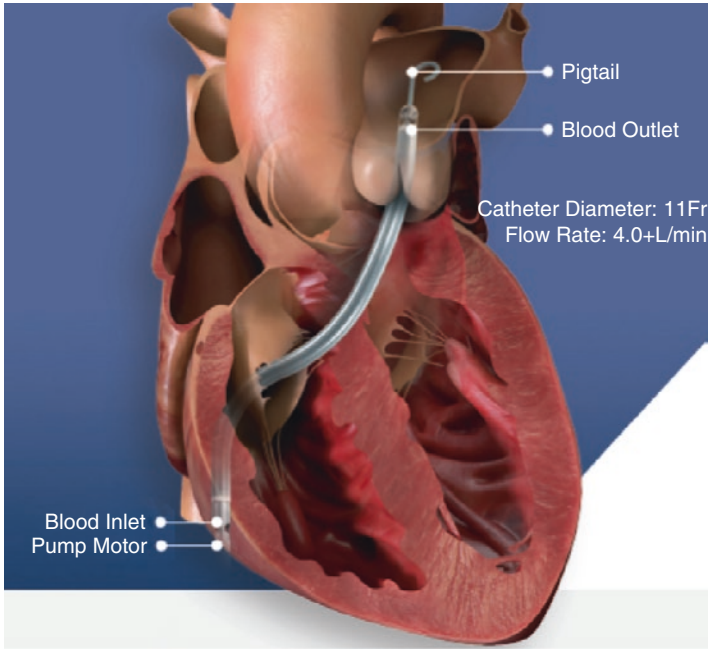

FIGURE 9.1 Schematized Impella RP. Blood is drawn from the inlet (sits in the inferior vena cava) and then delivered at the outlet (in the pulmonary artery). This figure is courtesy of Abiomed Inc., Danvers, Massachusetts-USA

The TandemLife Protek Duo (TandemLife, Pittsburgh, USA), shown in Fig. 9.2 has a proximal lumen in the right atrium while the distal lumen is in the pulmonary artery. The dual lumen cannula is inserted through the right internal jugular vein and the TandemLife Protek Duo can provide up to 4.5 L/min of flow. Blood is drained from the right atrium into an extracorporeal centrifugal pump and then delivered into the pulmonary artery. It provides the advantage of groin-free insertion, allowing patients to be mobilized and rehabilitated while in the hospital. In cases of lung failure, an oxygenator can be added to the TandemLife Protek Duo [18].

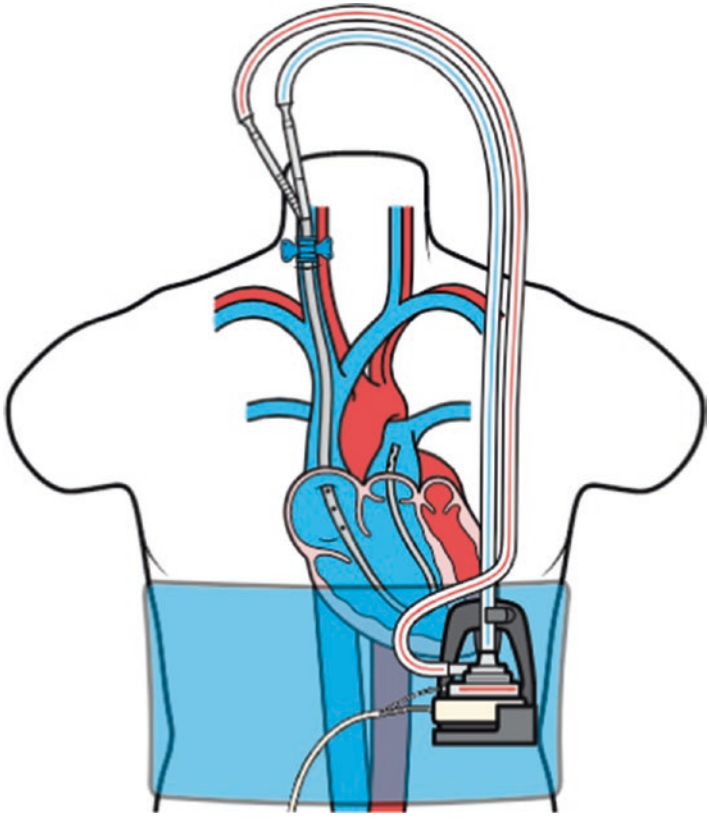

FIGURE 9.2 Schematization of blood circulation through the TandemLife Protek Duo. Venous blood (blue color) is drawn from the right atrium into an extracorporeal centrifugal pump (shown on the right). Oxygenated blood (red color) returns through the dual lumen cannula into the pulmonary artery. This Figure is courtesy of TandemLife, Pittsburgh, USA

Recently, a two-center, retrospective review of 17 patients showed successful wean of TandemLife Protek Duo in 23% (n = 4) patients. Although the device served as a bridge to right ventricular assist device (RVAD) in 35% (n = 6) of the cohort, the mortality rate was still high (n = 7) [19]. In the trial

above, the indications for TandemLife included elevated RAP despite aggressive medical therapy; inability to wean inotrope or vasopressor support while on continuous flow LVAD; and clinical signs of RV failure. Most of the patients in this series had RHF after LVAD implantation.

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) takes blood from the right atrium (via the femoral vein), passes through the oxygenator and then delivers oxygenated blood to the femoral artery (percutaneous) or the aorta (surgical). Sometimes, a distal perfuser is placed in the superficial femoral artery or the posterior tibial artery to overcome lower extremity ischemia from the large-bore cannulas. Although VA-ECMO reduces preload to both ventricles, it causes elevation of LV afterload.

The Impella RP and TandemHeart Protek Duo tend to decrease the RV preload but increase the left ventricle preload since the outlet or distal lumen is located in the pulmonary artery. In biventricular failure, increasing the LV preload (Impella RP and TandemHeart) or LV afterload (VA-ECMO) could worsen pulmonary edema.

Case Continued

Based on the patient's tenuous hemodynamic values, an Impella RP was implanted through the right femoral vein. Over the next week, vasopressors as well as inhaled epoprostenol were weaned off. Despite this, he remained on a high level of support with RAP 16 mmHg, PA 34/18 [23] mmHg, PCWP 18 mmHg, CO 4.2 L/min, CI 2.1 L/min/m^2, MAP 70 mmHg on milrinone 0.5 mcg/kg/min and the Impella RP. Due to the duration of support required by the patient (the Impella RP is FDA approved for up to 14 days of support), the Advanced Heart Failure Team was consulted for the placement of an RVAD.

9.6 Which Hemodynamic Parameters Are Useful for the Assessment of RV Function?

Invasive hemodynamic monitoring with a pulmonary artery catheter is critical to understanding RV pathology. Cohn et al. identified RAP>15 as a marker of hemodynamically significant RVMI [10]. Presence of RAP >15 mmHg is a risk factor in for RHF in continuous flow-left ventricular assist devices (CF-LVAD) [20]. A right–left heart pressure mismatch is another clue to RHF. The normal RAP is ~5 and PCWP ~10, therefore a normal RAP/PCWP is ~0.5. Lopez-Sendon et al. demonstrated that an RAP/PCWP >0.86 correlated with pathologic evidence of RVMI [21]. Subsequently, RAP/ PCWP have been shown to be associated with increased mortality or hospitalization in patients with advanced heart failure [22]. In a study involving contemporary LVAD, a CVP > 15 and an RAP/PCWP > 0.63 accurately predicted RHF [23].

Recently, pulmonary artery pressure index (PAPi) has been proposed as a marker of RHF and is defined as the pulmonary artery systolic pressure minus the pulmonary artery diastolic pressure divided by the RAP (PASys-PADia)/RAP. In a retrospective study of an inferior wall myocardial infarction cohort, hemodynamically derived RAP/PCWP, PAPi and the right ventricular stroke work (RVSW) were compared to qualitative echocardiographic grading of RV systolic function. RVSW was calculated as Stroke Volume/[mean PA pressure − PCWP] × 0.0136. PAPi appeared to have the strongest association with the echocardiographic estimates of RV systolic function ($r = -0.731, p < 0.001$) [24]. In the aforementioned study, PAPi showed a high sensitivity (88.9%), specificity (98.3%) and accuracy (97.1%) in predicting the need for a percutaneous RV support device.

Similarly, PAPi < 1.85 was shown to have the highest predictive value in predicting RHF (94% sensitivity and 81%

Table 9.1 Hemodynamic parameters used to evaluate right ventricular failure

Hemodynamic parameter	RAP (mmHg)	RAP/ PCWP	PAPi	RVSWI
Without LVAD	>15(10)	>0.86(21)	<1.0(24)	
With LVAD	>15(20)	>0.63(23)	<1.85(25)	<0.3–0.6 (25)

LVAD left ventricle assist device, *RAP* right atrial pressure, *PCWP* PA capillary wedge pressure, *PAPi* pulmonary artery pulsatility index = (PA systolic pressure – PA diastolic pressure)/RAP, *RVSWI* right ventricle stroke work index = [mean PA pressure – mean RA] × stroke volume index
Stroke volume index = cardiac index/heart rate

specificity) in a cohort of patients with RHF after CF-LVAD implantation [25]. Other hemodynamically derived parameters evaluated in this study included: pulmonary artery elastance (PAE): [PA systolic pressure/stroke volume]; pulmonary artery compliance (PAC): stroke volume/(PA systolic pressure—PA diastolic pressure); and RV stroke volume index (RVSWI): [mean PA pressure—mean RA] x stroke volume index. The stroke volume index is calculated from cardiac index/ heart rate. These other hemodynamic parameters were not as sensitive as PAPi. Table 9.1 reflects the hemodynamic parameters used in the clinical setting to define RHF.

9.7 What Are the Surgical Options for RV Failure?

Our patient was in persistent cardiogenic shock (cardiac index of 2.1 L/min/m^2) despite being supported on an Impella RP. In the RECOVER-RIGHT Trial, which led to FDA approval of the Impella RP, the average time of support was 3.0 ± 1.5 days [16]. FDA approval of Impella RP is up to 14 days. Since our patient had been on Impella RP support for 14 days, it was appropriate to consider alternative therapies. Although there are clear indications for LVAD implantation [26], there are no

guidelines for RVAD implantation. The indications for isolated RVAD implantation in the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) include acute myocardial infarction, failure to wean from cardiopulmonary bypass and post-cardiotomy RV failure [27].

9.7.1 Right Ventricular Assist Device

The CentriMag Right Ventricular Assist device (RVAS) [St. Jude, Minneapolis, MN, USA) has an inflow cannula in the right atrial appendage while the outflow cannula is in the pulmonary artery. The RVAS is an investigational device approved for humanitarian use in the United States for acute RV failure up to 30 days. This device can be used temporarily for isolated RV support, biventricular support, or for RHF after LVAD implantation.

The reported prevalence of RHF after LVAD implantation is approximately 20–30%. The 30-day survival of patients receiving CentriMag RVAS in an LVAD cohort (n = 12) is 50%, while on support for an average of 14 days [28]. CentriMag biventricular support in 12 patients (for a range of 4–22 days) confirmed its utility as a bridge to LVAD (n = 8), bridge to recovery or explant (n = 2), with survival of 83% at 7 and 14 days after implantation [29]. The utility of Centrimag for RV support in post cardiotomy cardiogenic shock, orthotopic heart transplantation (OHT), or LVAD placement has also been shown [17].

There is no approved ambulatory durable RVAD at this time. Contemporary LVADs such as HeartMate III (HM3) [Abbott, North Chicago, IL, USA] and HVAD (Medtronic, MN, USA) have been used in an RVAD configuration. The RV is unloaded by placing the inflow cannula in the right atrium or RV, while the blood is pumped through the outflow graft into the pulmonary artery. The utility of HM3 as an isolated RVAD [speed of 5000 rpm, flow rate of approximately 4.2 L/min], has been shown in a 70-year old male with end stage RHF [30]. To decrease the intraluminal length of the

RVAD inflow cannula, several layers of felt spacers are sutured onto the sewing ring. A query of the EUROMACS registry revealed that a total of eight patients were implanted with the HVAD in the RVAD position for isolated RV failure. 30-day survival was 50%; two patients underwent OHT and the RVAD was explanted in one patient due to RV recovery [27].

Two HM3s were implanted in a biventricular configuration in 14 patients with biventricular failure. Initial RVAD flows were 2.4–5.4 (mean 4.0) L/min at speeds of 4400–6700 (mean 5200) rpm. In this study, eight out of 14 patients continued on BiVAD support for 95–636 (mean 266) days including seven discharges to home [31]. Figure 9.3 shows the chest X-ray of a patient with a biventricular HVAD. The total artificial heart (Syncardia Systems, LLC, Tucson, AZ), a pulsatile device, is another option for biventricular support [32].

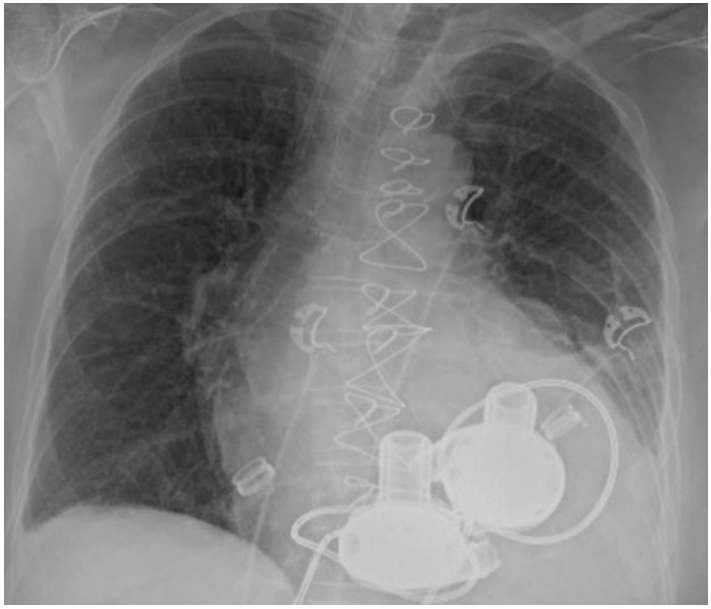

Figure 9.3 Chest radiograph showing a patient with a two HVADs used in a biventricular configuration

9.7.2 *What Are the Indications for Heart Transplant Listing?*

For patients with intractable RHF, heart transplant is the most durable method to correct circulatory dysfunction. Table 9.2 outlines the adapted 2016 International Society for Heart Lung Transplantation (ISHLT) listing criteria for heart transplantation [33]. Advanced age (>70 years), body mass index >35, reversibility of pulmonary hypertension (PVR > 5 wood units), active malignancy, hemoglobin A1C > 7.5, frailty, substance abuse, or red flags on psychosocial assessment could preclude listing for OHT at some heart transplant centers.

A review of the ISHLT registry reveals that 3.1% of patients transplanted were on RVAD prior to transplantation [34]. Limited data exists on the outcomes for OHT in isolated RHF patients. In a series of 12 patients, a mortality rate of

Table 9.2 General indications for heart transplantation

Indications for heart transplant
Refractory arrhythmia
End stage congenital heart disease
Refractory ACC AHA stage D, NYHA class III-IV
Refractory cardiogenic shock requiring continuous inotrope
Refractory angina despite maximal anti anginals or revascularization
Re-transplantation for severe coronary allograft vasculopathy
Estimated Seattle heart failure model 1-year survival of 80% or a heart failure survival score in the high/medium risk
CPET peak VO2 of <14 mL/kg/min without beta blocker, <12 mL/kg/min with beta blockers, young patients <50y (peak VO2 < 50%), BMI > lean body mass–adjusted peak VO2 of <19 mL/kg/min, when RER <1.05, consider VE/VCo2 > 35

NYHA New York Heart Association, *CPET* cardiopulmonary exercise testing, *RER* respiratory exchange ratio, *Vo2* maximum rate of oxygen consumption

50% was reported after OHT, but the majority of these patients were complex congenital patients who are not representative of our patient [35].

Case Conclusion

A Centrimag RVAD was implanted to support the right ventricle. After 5 days, the patient was weaned off all inotropes. A hemodynamic and echocardiographic ramp study revealed a recovered right ventricle. The Centrimag was subsequently decannulated uneventfully, and he was successfully discharged home.

Clinical Pearls

- Initial management of acute RHF should focus on treating the etiology of RHF. Patients need to be stabilized by correcting metabolic derangements, ensuring AV synchrony, appropriate systemic perfusion (MAP > 65 mmHg) and appropriate ventilation.
- Medical management should focus on optimizing the right ventricular preload, afterload and contractility.
- The hemodynamic parameters suggestive of RHF are RAP>15, RAP/ CWP > 0.86 or >0.63 (with LVAD), PAPi <1.0 or <1.85 (with LVAD) and RVSWI <0.3–0.6 (with LVAD).
- Percutaneous mechanical support for acute RHF includes Impella RP, TandemHeart Protek Duo, and ECMO.
- Surgical Options are (1) contemporary durable LVADs implanted as ambulatory RVAD (2) total artificial heart for biventricular support (3) Centrimag RVAD used for temporary support while the RV recovers and (4) heart transplantation for intractable RVF.

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Chapter 10
Right Heart Failure After Cardiac Transplantation

Taylor Lebeis and Gregory Lewis

Case

A 40-year-old woman with history of Hodgkin's lymphoma, status post mediastinal radiation at ages 8 and 11, complicated by development of coronary artery disease and valvular heart disease, initially presented to the surgical intensive care unit (SICU) after aortic valve replacement, mitral valve replacement and tricuspid valve annuloplasty. She developed cardiac arrest and was cannulated for veno arterial extracorporeal membrane oxygenation (VA ECMO). She was urgently listed as a United Network for Organ Sharing (UNOS) status 1 candidate for orthotopic heart transplantation (OHT). She underwent OHT with a cold ischemic time of 200 min and warm ischemic time of 60 min. While in the

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operating room following heart transplantation, her hemodynamic data were as follows: right atrial pressure (RAP) 20 mmHg, right ventricular (RV) pressure 50/20 mmHg, and pulmonary artery (PA) pressure 50/36 mmHg, cardiac output 4 L/min, and cardiac index of 1.9 L/min/m^2. Her pulse was 100 bpm, blood pressure was 89/50 (MAP 63) mmHg, O_2 saturation 89% on a combination of epinephrine 6 mcg/min, milrinone 0.5 mcg/kg/min, norepinephrine 8 mcg/min, and inhaled epoprosterenol 30 ng/kg/min.

10.1 What Is the Differential Diagnosis?

The initial hemodynamic data suggests acute post-operative RV failure. The differential diagnoses in right heart failure (RHF) in a transplanted heart include: primary graft dysfunction (PGD), hyperacute rejection (HAR), post-operative pulmonary embolism and surgical complication.

PGD has been reported in 2.3–28.2% of patients undergoing OHT [1–5]. This range reflects the various definitions of PGD prior to the consensus definition established by the International Society of Heart and Lung Transplantation (ISHLT) in 2014 [6]. Of patients with PGD, isolated RV graft dysfunction and combined biventricular dysfunction occur in about 45% and 47% of patients respectively [7].

The diagnosis of PGD must be made within 24 h of OHT. The ISHLT hemodynamic definition of PGD-RV, shown in Table 10.1, refers to a right atrial pressure greater than 15 mmHg or a pulmonary capillary wedge pressure (PCWP) less than 15 mmHg, and cardiac index (CI) less than 2.0 L/min/m^2. A transpulmonary gradient (TPG) less than 15 mmHg with pulmonary artery systolic pressure (PASP) less than 50 mmHg is also suggestive. The need for a right ventricular assist device (RVAD) clearly suggests RV failure [6].

The RV is vulnerable to injury during the transplantation. Severe RHF can result from mechanical trauma, air embolism of the right coronary artery, severe tricuspid regurgitation and cardiac tamponade leading to increased RV filling

Table 10.1 Criteria for primary graft dysfunction—right ventricle

1. RAP >15 mmHg PCWP <15 mmHg CI <2.0 L/min/m^2
2. TPG <15 mmHg ± PASP <50 mmHg
3. Need for RVAD

RAP right atrial pressure, *PCWP* pulmonary capillary wedge pressure, *CI* cardiac index, *TPG* transpulmonary pressure gradient, *PASP* pulmonary artery systolic pressure, *RVAD* right ventricular assist device
Adapted from Kobashigawa et al. [6]

pressures and RV dysfunction [8–10]. Immediately after OHT, there can be reperfusion and ischemic injury to the procured heart leading to right ventricular dysfunction [8, 11, 12]. Efforts are made to reduce ischemic time as much as possible, but may be limited in several situations.

Hyperacute rejection (HAR) is a rare and devastating complication that can occur post OHT with a mortality rate of about 70% [13, 14]. Its occurrence has been dramatically reduced by ensuring ABO compatibility among donors and recipients, though this complication can occur in the setting of preformed anti-HLA antibodies to the donor heart. HAR typically causes biventricular dysfunction.

Severe deconditioning postoperatively can predispose to pulmonary emboli. The incidences of venous thromboembolism (VTE) and pulmonary emboli have been reported as frequent complications [15, 16]. Acute pulmonary emboli can cause elevated pulmonary artery pressures leading to RHF. Chapter 6 highlights three cases of RHF due to pulmonary embolism.

10.2 What Is the Initial Approach in Elucidating the Etiology?

The initial assessment of post-transplant cardiac function is completed while the patient remains on cardiopulmonary bypass in the operating room. Per ISHLT guidelines, peri-

operative monitoring should include continuous ECG-monitoring, post-operative 12-lead ECG, invasive arterial pressure monitoring, direct measurement of RAP or central venous pressure (CVP), intermittent measurement of cardiac output, continuous measurement of arterial oxygen saturation, transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE), and continuous measurement of urinary output [17].

If there is allograft dysfunction of unclear etiology, a TTE or TEE may need to be repeated. In the event that there is hemodynamic compromise without a clear cause, particularly if filling pressures are equalized and elevated, the patient should return to the operating room to exclude cardiac tamponade by direct surgical exploration. If the patient requires mechanical support, a myocardial biopsy should be considered during the operation to evaluate for significant rejection [17].

Screening panel reactive antibodies are performed in all patients being considered for OHT [17]. Postoperatively, an immediate retrospective donor recipient crossmatch is run to screen for anti-HLA antibodies that can cause antibody mediated rejection (AMR). Donor-specific antibodies should be sent when there is a high suspicion for AMR, in which case an endomyocardial biopsy may need to be performed sooner than the periodic post-transplant schedule established by transplant centers.

10.3 What Is the Hemodynamic Assessment in a Transplanted Heart?

On invasive hemodynamic monitoring, attention should be given to the ratio of the right-sided compared with the left-sided pressures as well as pulmonary pressures in order to monitor for significant right-sided heart cardiac dysfunction. Chapter 9 also discusses the hemodynamic assessment in right ventricular cardiogenic shock. A normal RAP/PCWP ratio is about 0.5; an elevated ratio along with absolute elevations in RAP is suggestive of significant RV dysfunction [18, 19].

Pre-existing pulmonary hypertension can predispose to PGD. The exposure of an RV accustomed to normal pulmonary vascular resistance (PVR) in the donor to elevated pulmonary pressures in the recipient can result in circulatory collapse, which was first demonstrated in the 1950s in an animal model [20].

Preoperative PVR ≥ 3.0 Wood units or TPG ≥ 15 mmHg should warrant a vasodilator challenge [21–24]. PVR is calculated by taking the difference between the mean PA pressure and the PCWP and dividing that by the cardiac output (Eq. (10.1)). Preoperative PVR elevation is associated with increased mortality even when reversible [23, 25, 26]. PVR is useful to monitor the need and effectiveness of pulmonary vasodilators postoperatively. TPG is the difference between the mean pulmonary arterial pressure and PCWP (Eq. (10.2)). Additionally the pulmonary artery pulsatility index (PAPi), which is calculated by dividing the difference between the systolic pulmonary artery pressure and diastolic pulmonary artery pressure by the mean RAP (Eq. (10.3)), is predictive of RHF when using a cut off <1.0 [27]. While these values have not been studied in RHF with heart transplant specifically, it is reasonable to consider these parameters when evaluating the status of the right ventricle.

$$TPG = PA_{mean} - PCWP \tag{10.1}$$

$$PVR = \frac{PA_{mean} - PCWP}{CO} = \frac{TPG}{CO} \tag{10.2}$$

$$PAPi = \frac{\left(PA_{systolic} - PA_{diastolic}\right)}{RAP} \tag{10.3}$$

Case Discussion

Intraoperative TEE revealed preserved LV ejection fraction (EF) but severely hypokinetic RV. There was no evidence of cardiac tamponade or perforation. The clinical picture at this point was consistent with right ventricular dysfunction post-OHT.

10.4 What Are the Predictors of RHF Post OHT?

The RADIAL score is a validated scoring system that was developed to identify those at risk for PGD [5]. The score is based upon six multivariate risk factors: RAP ≥10 mmHg, recipient age ≥60 years, diabetes mellitus, inotrope dependence, donor age ≥30 years, ischemic time ≥ 240 min. Each criterion is assigned a point with increasing scores being at higher risk of PGD. Although this model was created for PGD, it also applies to isolated RV dysfunction [7].

Alhough the RADIAL score is helpful, it is important to note that it was derived and validated in a population of transplant recipients with a low prevalence of ventricular assist devices (VADs). A more contemporary cohort of patients, including those with continuous flow left ventricular assist devices (CF-LVADs) undergoing heart transplantation, was evaluated to determine risk factors [28]. In this study, patients with bridge to transplantation (BTT) CF-LVADs were at increased risk of PGD. Furthermore, increased time on device support, renal dysfunction, RV dysfunction, and pre-transplant amiodarone were associated with increased risk of PGD. The RADIAL score was evaluated in this study and did not appear to stratify risk in this contemporary cohort of patients.

10.5 Discuss the Pathophysiology of Acute RHF After Heart Transplantation

Early donor heart dysfunction is common as the heart has been denervated by the procurement and is dependent upon circulating catecholamines for chronotropy and inotropy. Initial donor heart dysfunction is common and occurs in up to about 50% of donor grafts [6]. The etiology is often multifactorial given the anatomy, location and physiologic stress experienced by the RV [29]. The RV of the heart graft is

susceptible to periprocedural myocardial strain, ischemia, cardioplegia and surgical trauma.

The donor heart goes through a series of events during procurement and implantation which could trigger RHF. These mechanisms of RHF are summarized in Fig. 10.1. The four main physiologic insults are brainstem death of the donor, hypothermic ischemia during transportation, warm ischemia during surgery, and reperfusion injury upon release of the cross-clamp [6].

The process of brainstem death creates a harsh environment that sensitizes the heart to ischemia-reperfusion injury. During brainstem death, a reduction in vasomotor tone leads to vasodilation. In order to counteract vasodilation, an immediate release of myocardial norepinephrine leads to mitochondrial and cytosolic calcium overload to help improve contractility [30]. This mitochondrial calcium can also trigger autophagy, apoptosis or necrosis. The calcium overload in the contractile proteins leads to contracture and is associated

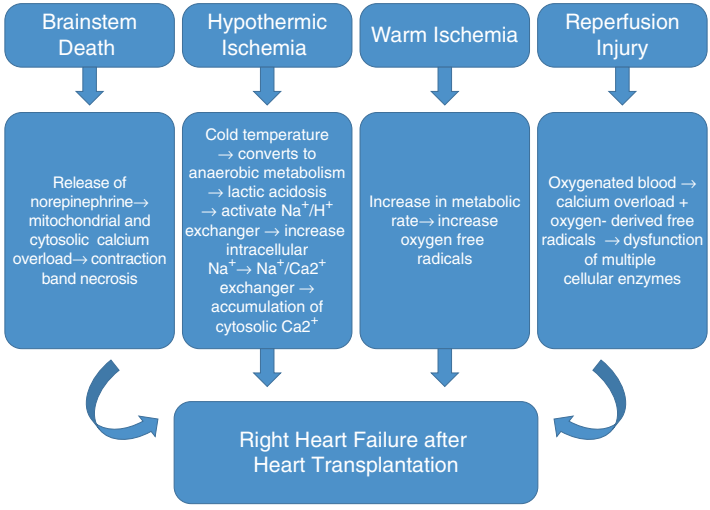

Figure 10.1 Summary of the pathophysiology of right heart failure in the transplanted heart

with the histologic appearance of "contraction band necrosis" [30–33]. During brain herniation, ischemia of the pituitary gland often occurs, leading to the derangement of the endocrine system further causing decreased contractility [34, 35]. In addition, there is a predilection for metabolic derangements to occur due to medications used to treat increased intracranial pressure and impaired myocardial oxygen delivery along with increased myocardial oxygen demand from catecholamine administration [30].

Following cross-clamp, the heart is perfused with a cold cardioplegic solution for transportation. There are several different hypothermic preservation systems available that slow but do not completely stop cellular metabolism [6, 36–38]. The goal is to reduce the formation of mitochondrial metabolism byproducts such as oxygen free radicals. The risk for ischemic injury is higher in older donor organs [39]. This risk may be related to unrecognized coronary artery disease, hypertrophy, or age-related decline in cardioprotective mechanisms [40, 41]. Due to the cold temperatures, around 4 °C, the metabolism is converted from aerobic to anaerobic. The loss of an aerobic environment inhibits the Na^+/K^+ ATP pump leading to cellular swelling. The anaerobic environment leads to lactic acidosis which activates the Na^+/H^+ exchanger increasing intracellular Na^+. The increase in intracellular Na^+ drives the Na^+/Ca^{2+} exchanger which results in accumulation of cytosolic Ca^{2+} [42–45].

When the donor heart is brought into the OR, it is removed from the hypothermic storage system. The donor organ is exposed to higher temperatures and this leads to an increase of the metabolic rate. The increase in metabolic rate increases the production of oxygen free radicals. Multiple studies have demonstrated deleterious effects of warm ischemic time on early survival in patients [3, 46].

Ischemia-reperfusion injury occurs when there is myocyte damage as a result of the restoration of oxygenated blood to the grafted heart. The introduction of oxygenated blood causes further calcium overload and oxygen-derived free radicals that lead to dysfunction of multiple cellular enzymes [47]. The release of calcium and oxygen free radicals activates

the formation of mitochondrial permeability transition pores (MPTP), which are non-specific channels that allow pro-apoptotic factors to be released into cell cytoplasm [48]. These factors lead to a mitochondrial swelling that can cause membrane rupture resulting in necrotic cell death and myocardial damage.

Recipient factors can also contribute to right ventricular failure. Underlying elevated PVR in the recipient along with the potential donor heart too small for a large recipient can overwhelm the RV of the donor heart causing right ventricular failure. Increased recipient PVR can trigger RHF in a donor heart that is in an ischemic state after procurement. Consequently, there is reduction of left-sided preload, which then results in a reduction of coronary perfusion and further decompensation [49].

Activation of the systemic inflammatory response syndrome (SIRS) results in lower systemic vascular resistance from vasodilation in some recipients [50]. Predisposing factors to SIRS activation include prolonged inotropic support, prolonged cross-clamp time, mechanical support prior to transplant, and recipients with high transfusion requirements [51, 52]. The exact pathophysiology is unclear though it is thought to be related to unopposed activation of vascular smooth muscle adenosine triphosphate sensitive potassium channels. Endogenous nitric oxide and vasopressin deficiency have also been considered as causes [52].

Case Discussion

Our patient had an elevated RADIAL score going into transplant based upon the total ischemic time, her inotrope dependence, and elevated RAP $\geq$10 mmHg. Additionally, she was transplanted from mechanical support and had multiple transfusions from her prior surgery. Furthermore, given her history of mediastinal radiation, there was concern that she may have had underlying lung disease.

10.6 How Should Post-operative Acute RHF Be Treated?

The initial management of acute RHF involves four main management strategies: preload optimization, hemodynamic stabilization, maintenance of sinus rhythm and AV synchrony, and ventilatory support. This approach is summarized in Fig. 10.2 [53]. Initially, medical therapy of RHF should be undertaken with inotropic agents to augment RV function and α-adrenergic agonists to support the blood pressure. Systemic vasodilators with pulmonary vasodilating properties can be used in the absence of systemic hypotension to reduce

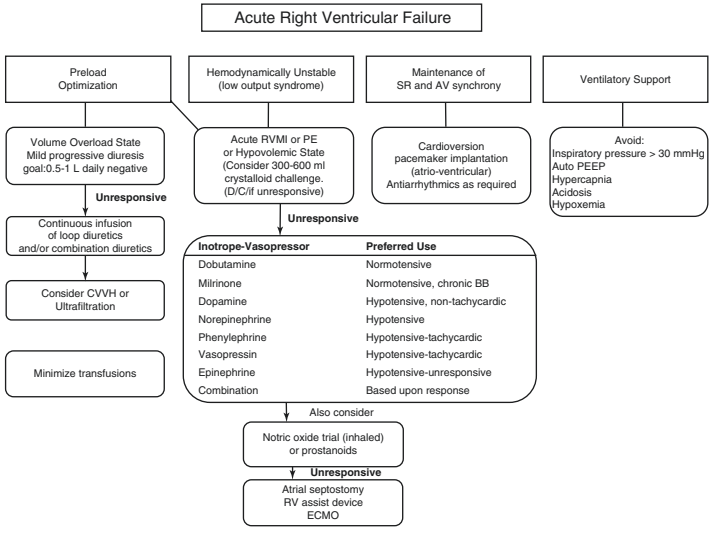

Figure 10.2 Management of right ventricular dysfunction after OHT. *CVVH* continuous venovenous hemofiltration, *RVMI* right ventricular myocardial infarction, *PE* pulmonary embolism, *D/c* discontinue, *BB* beta blocker, *RV* right ventricle, *ECMO* extracorporeal membrane oxygenation, *SR* sinus rhythm, *AV* atrioventricular, *PEEP* positive end-expiratory pressure; Used with permission from Wolters Kluwer Health, Inc. [53]

pulmonary afterload; these include nitroglycerin and sodium nitroprusside. Furthermore, selective pulmonary vasodilators including prostaglandins, inhaled nitric oxide, and sildenafil can be used in the management of RHF [54–62].

After heart transplantation, the preload should be optimized by monitoring invasive CVP. It is critically important to maintain CVP values below 15 mmHg in order to avoid venous congestion of abdominal organs and end-organ dysfunction. This goal can be achieved through initial diuresis to counteract positive fluid balance early in the postoperative course. Ultrafiltration or continuous venovenous hemofiltration may be necessary if there is diuretic refractoriness. If patients are not in sinus rhythm, cardioversion (chemical or electrical) can be considered as well as pacing in order to maintain AV synchrony. Finally, the ventilator settings should be optimized to reduce the workload on the heart including the limitation of inspiratory pressure, avoiding auto PEEP, control of hypercapnia, avoidance of acidemia, and hypoxia.

Prior to the advent of short-term mechanical support, severe PGD was fatal except when salvage re-transplantation was available. At present, both short-term and durable mechanical support should be considered if a patient is unresponsive to medical therapy. The device choice depends on how long the device may need to be in place and whether the patient will be extubated and be ambulated while on mechanical support. Temporary RVADs including RP-impella (Abiomed, Danvers, MA, USA) can be used for a short period of time only. ECMO outcomes have been evaluated in transplant patients with improved survival and ability to wean [1, 63]. More durable temporary RVAD support can be used with Centrimag (Levtronix, Waltham, MA), which allows patients to be extubated and rehabilitated. In the event that there is no recovery of the grafted heart, a redo-OHT can be considered. The key to mechanical support is early intervention when it is required. A delay in the use of mechanical support can to lead to higher mortality [64]. Chapter 9 reviews the indications and role for both percutaneous and surgical mechanical support for RHF. Any patient

who receives mechanical support should have a heart biopsy as discussed earlier [6].

Case Conclusion

Due to refractory RHF despite epinephrine 6 mcg/min, milrinone 0.5 mcg/kg/min, norepinephrine 8 mcg/min, and epoprosterenol 30 ng/kg/min, this patient was centrally cannulated for VA ECMO. RP impella and tandem heart were considered, but given her hypoxia, VA ECMO was selected. She was medically optimized with continuous infusion intravenous furosemide for aggressive diuresis in combination with ECMO to lower her CVP. In this context, inotropes were gradually weaned off, and subsequently, ECMO was decannulated.

Clinical Pearls

- The differential diagnoses for RHF in a transplanted heart include: primary graft dysfunction, hyperacute rejection (HAR), post-operative pulmonary embolism and surgical complication.
- The perioperative assessment of the transplanted heart should include continuous telemetry monitoring, invasive arterial and pulmonary artery catheter pressure monitoring, and urinary output monitoring.
- The pathophysiology of RHF typically involves recipient (elevated PVR, previous mechanical support, blood transfusions), donor (size mismatch, brain stem death) and surgical factors (reperfusion injury, prolonged cold or ischemic time).
- The initial management of acute RHF involves four main management strategies: preload optimization, hemodynamic stabilization, maintenance of sinus rhythm and AV synchrony, and ventilatory support.
- The key to mechanical support is early intervention when it is required.

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Chapter 11
Cardiopulmonary Rehabilitation in Heart Failure

Uyen T. Lam and Philip A. Ades

Clinical Case

A 63-year-old frail woman with a history of coronary artery disease (CAD), poorly controlled type 2 diabetes mellitus, hypertension, ischemic cardiomyopathy [left ventricular ejection fraction (LVEF) of 25%], status post cardiac resynchronization therapy with a defibrillator (CRT-D) presented with acute decompensated heart failure (HF). Bedside echocardiogram revealed biventricular failure with significant anterior wall hypokinesis and no valvulopathy. She underwent percutaneous coronary intervention (PCI) of the left anterior descending artery and was discharged on dual antiplatelet therapy (DAPT), torsemide, metoprolol succinate, sacubitril/valsartan, and spironolactone. She was then referred to cardiac rehabilitation (CR) for exercise training and risk factor modification.

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11.1 What Is the History of Cardiac Rehabilitation?

Prior to the advent of CR and PCI, patients who suffered myocardial infarction (MI) were routinely prescribed 6 weeks of bed rest and inactivity. This strategy sought to minimize further insult to the infarcted cardiac tissue and to closely monitor for ventricular tachyarrhythmia, pump failure, and/or cardiac wall rupture [1]. These patients were hospitalized for upwards of 2 weeks followed by months of activity restriction. CR programs were developed in the 1970s to negate the effects of prolonged inactivity [1]. These programs played an integral role in both preventing deconditioning during inpatient hospitalization and in promoting ongoing reconditioning post-discharge. Over time, there was increased evidence that CR decreased cardiovascular-related and all-cause mortality, cardiovascular events, and hospitalizations [2, 3].

Presently, early ambulation and PCI has shortened the length of stay after MI and patients are typically discharged within 2–3 days. Thus, patients often leave the hospital with relatively little insight into their condition and often struggle to manage their comorbidities. There is strong literature suggesting that CR is a safe, cost-effective, and sustainable adjunct to current therapies to improve quality of life (QoL), morbidity, and mortality in these patients. Unfortunately, CR remains underutilized [4, 5], as only 10% of HF patients are referred to CR at discharge [4].

11.2 What Are the Components of a Cardiac Rehabilitation Program?

Cardiac rehabilitation, in addition to therapeutic exercise, is a comprehensive program designed to improve both the mental and physical health of an individual. Programs that focus only on exercise training without risk factor modification and HF teaching are not considered comprehensive CR. A CR

Phase One
Inpatient physical therapy assessment after acute event, introduction to cardiac rehabilitation program with referral at discharge

Phase Two
Outpatient, closely monitored cardiac rehabilitation and education for management of cardiac conditions and risk factor modification

Phase Three
Outpatient independent self management of cardiac conditions and exercise at a community gym or cardiac rehabilitation facility

FIGURE 11.1 Phases of cardiac rehab

program consists of many phases as shown in Fig. 11.1. Phase one begins during index hospitalization when patients are assessed by physical and occupational therapy for specific needs. At discharge, patients enter phase two, an outpatient monitored program focusing on exercise training and addressing cardiovascular risk factors. Ultimately, the goal after a 12-week program is for patients to enter phase three which is independent lifestyle modification and management of their cardiac conditions.

A baseline assessment of each patient includes an intake history and physical examination followed by a pre-enrollment symptom limited exercise treadmill test (ETT) to assess exercise tolerance and safety prior to initiation of exercise training. Medications and diet should be reviewed and documented. The physician works with exercise physiologists to design an exercise prescription usually based on the peak heart rate (HR). Exercise intensity is targeted between 70 and 85% of peak HR and adjusted according to the Borg perceived exertion scale to a difficulty level of 12–14. This is equivalent to moderate level of activity as shown in Fig. 11.2 [6].

The exercise training regimen typically consists of a 5–10 min warm-up, 20–60 min of aerobic exercise, and a 5–10 min cool down 3 days per week along with resistance training of major muscle groups. Patients are encouraged to maintain physical activity on the days that they are not in

Borg Perceived Exertion Scale	
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	Maximum exertion

Figure 11.2 The Borg RPE scale. Borg Scale is routinely used in cardiac rehabilitation programs to adjust patients exercise prescription ((© Gunnar Borg, 1970, 1998, 2017). Scale printed with permission)

monitored sessions. Cardiac patients also receive either individual or group education regarding how to manage their cardiac condition, the importance of medication adherence, stress management, healthy heart nutrition, and other modifiable risk factors. Assessment for depression and other psychosocial factors interfering with patients' ability to perform self-care is also important and routinely performed by the CR staff. When positive, patients are referred to appropriate professionals for evaluation and treatment. Each patient receives an individualized treatment plan that is reassessed every 30 days for the duration of their participation in CR.

11.3 What Are the Indications for Cardiac Rehabilitation?

Currently there are seven indications for CR that are reimbursed by the Center for Medicare/ Medicaid Services (CMS) (see Table 11.1). Among HF patients, only those with LVEF ≤35% are covered by CMS although there is compelling data

Table 11.1 Reimbursable indications for cardiac rehabilitation (cms.org)

Coronary artery disease (includes stable angina/acute coronary syndrome)
Percutaneous Coronary Intervention (PCI)
Coronary Artery Bypass Graft Surgery (CABG)
Systolic congestive heart failure (EF <35%)
Cardiac transplant and left ventricular assist devices (LVAD)
Valve surgery (includes minimally invasive valve replacements)
Peripheral artery disease (must have claudication)

for benefit in patients with HF with preserved ejection fraction (HFpEF), and the aforementioned indications may expand in the future. Currently no payers cover CR specifically for right sided HF. In Europe, patients with the following conditions are eligible for CR: coronary artery disease, chronic heart failure, left ventricular assist device (LVAD), heart transplantation, peripheral artery disease, post-PCI, after surgical procedures such as coronary artery bypass grafting, valve surgery and correction of congenital heart disease, and those with cardiac devices such as defibrillators, and pacemakers [7, 8].

Case Continued

Our patient qualified for cardiac rehab based on CAD and HF with LVEF<35%. On enrollment in CR, our patient underwent a symptom-limited ETT under the standard Bruce protocol. She walked for 4 min and 35 s and achieved a maximum heart rate of 136 beats per min without any anginal symptoms, but was dyspneic. She underwent diabetes teaching and medication review with the CR nurse. Initial exercise prescription was based on the Karvonen formula. Her estimated maximum heart rate was (220-age) = (220–63) = 157 beats per min. Her heart rate reserve (estimated maximum heart rate- resting heart rate) = 157–87 = 70 beats

per min. We targeted 70% of her heart rate reserve, hence, her targeted heart rate (70% heart rate reserve + resting heart rate) = 49 + 87 = 136 beats per min. She was started on the treadmill walking at a speed of 2.5 mph for 20 min followed by a short break before continuing on the recumbent stationary bike for an additional 20 min. Resistance training was deferred due to fatigue but the plan was to gradually introduce light weights to her routine.

11.4 What Are the Benefits of Cardiac Rehabilitation in Heart Failure with Reduced Ejection Fraction (HFrEF)?

In 2009, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) demonstrated the importance CR in patients with LVEF ≤35%. This landmark trial was the first large-scale study to show the efficacy (11% reduction in 2-year all-cause mortality and hospitalizations) and safety of moderate intensity exercise in patients with HFrEF. Part of the exercise regimen was performed in the home setting [9]. Those who were adherent to their exercise regimen had a lower depression score and also noted improvement in their functional status by at least one NYHA class. These findings subsequently led to the change in the 2013 ACCF/AHA Guideline for the Management of Heart Failure, with Exercise training becoming a Class 1a indication for patients with stable chronic systolic heart failure [10]. CR is recognized as a Class IIa indication in the United States [10], but has a class 1 indication in Europe [11] for HF.

In February 2014, the CMS added HFrEF (EF ≤35%) as a covered indication. The caveat was patients must be stable and on GDMT for 6 weeks prior to enrollment in the program as per the HF-ACTION protocol (Memo: CAD-00437N). Currently only HFrEF is covered by insurers for participation in CR. However, there is compelling evidence that other types of HF also benefit.

Beneficial effects of exercise in chronic heart failure include but not limited to improvement in peak oxygen consumption (VO2), QoL, ventilatory responses, oxidative capacity of skeletal muscle, exercise capacity, endurance, endothelium dependent vasodilation, and muscle strength [12]. Exercise also confers a significant decrease in neurohormonal and sympathetic nervous system activation, HF hospitalizations, and all-cause mortality. It is estimated that the number needed to treat to save one life in HFrEF patients was 17 over 2 years [13].

When compared with CRT, CR appeared to be a non-inferior therapy in a parallel study comparing CRT versus implantable cardioverter defibrillation (ICD) plus supervised rehabilitation in HFrEF with NYHA III class symptoms. Patients in the ICD plus exercise group showed improvement in all parameters on cardiopulmonary exercise testing except for anaerobic threshold. There were similar reductions in right and left ventricular diameters and improvement in LVEF from 25% to 30% in both groups after 6 months of therapy. Thus, CR with target of moderate exertional level and Borg score 11–12 is comparable to CRT [14].

Although a majority of study participants in clinical trials are men, the benefit of CR does not seem to discriminate by gender or age. In HF-ACTION, 28% of participants were women. A post-analysis showed no significant difference in the change in VO2 between men and women, but there was a larger reduction in all-cause mortality and all-cause hospitalization after just 3 months of exercise training in women [15]. Although elderly patients have a greater risk for progressive functional decline, frail patients tend to be excluded from exercise-based clinical trials. Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) studied supervised exercise training in older patients (age > 60 years) with decompensated HF. Investigators initiated inpatient physical rehabilitation and extended it to 12 weeks post discharge. All-cause hospitalization rate decreased by 52% [16]. These findings corroborate the importance of CR in our patient (female, elderly).

Notably, while many of the aforementioned trials showed a positive benefit, there have been some equivocal results as well. ExTraMATCH II, a meta-analysis of 18 randomized exercise training trials of at least 3 weeks, did not show any significant benefit on the risk of mortality and HF hospitalization [17]. A Cochrane Systematic Review by Long et al. of 5783 HFrEF patients with ≥6 month follow up post exercise training showed no impact on short-term (<12 month) mortality. There was a low-moderate evidence of reduction in all-cause hospitalizations and HF-specific admissions [18]. Recently, early hospital-based CR was shown to significantly reduce HF-specific mortality and HF readmissions in a review of 140,552 incident cases of HF admissions. These latter results were consistent with the findings from REHAB-HF [19]. Such conflicting results suggest heterogeneity amongst quality of trials, duration of follow up, variable patient compliance, and perhaps quality of CR centers.

11.5 Is There Evidence for Benefit of CR in Heart Failure with Preserved Ejection Fraction (HFpEF)?

Comorbidities and risk factors such as obesity, obstructive sleep apnea, insulin resistance / diabetes mellitus, hypertension, coronary artery disease, chronic kidney disease, atrial fibrillation, chronic obstructive pulmonary disease, and aging are risk factors for HFpEF. The treatment for HFpEF is targeted at blood pressure control, risk factor modification and the management of underlying conditions.

Existing data has shown that exercise training improves physical function. A meta-analysis of six randomized control trials including 276 patients showed that participation in exercise training improved cardiorespiratory fitness (mean difference + 2.72 L/min) and QoL using the Minnesota Living with Heart Failure score (mean difference −3.97) compared to the control group. There were no changes in LVEF or diastolic function [20]. Similarly, Kitzman et al. randomized 100

patients with HFpEF and obesity into four groups including exercise, caloric restriction, exercise + caloric restriction, and control. While all intervention groups showed improvement in peak VO_2, exercise + caloric restriction group showed the greatest amount of change, 2.5 mg/kg/min increase in VO_2 with no observed serious adverse events [21].

Currently, the ACCF/ AHA and the European Society of Cardiology recommend at least 150 min of moderate level of activity per week. This could be a brisk walk, dancing, active recreation, or any activity that reaches between 3 and 6 metabolic equivalents of task. HFpEF is not a CMS-reimbursable indication for CR in the United States. A large randomized control trial similar to HF-ACTION would likely be required before HFpEF would become a CMS-reimbursable indication in the United States.

11.6 What Is the Effect of Exercise Training on Pulmonary Hypertension and Right Ventricular Failure?

The role of CR in the patients discussed in Chaps. 2 and 7 is highlighted below. To date, there are no clinical trials specifically studying the effects of exercise training on right heart failure (RHF). Most of what is presented in this chapter is extrapolated from the pulmonary hypertension (PH) literature. RHF is a complex disease process and an important predictor of morbidity and mortality. Similar to patients with HF, moderate level exercise training in primary PH patients have been shown in pulmonary rehabilitation (PR) literature to be an effective, safe, and cost-effective treatment [18]. In a large meta-analysis including 784 patients, 6-min walk distance (6MWD) increased by 96 ± 61 m after 15 weeks compared to a control group [22]. The positive effects of exercise are similar to HF patients and appear to be dose-dependent.

In a more recent study, Ehlken et al. studied the impact of exercise training in 85 patients with severe PH due to inoper-

able chronic thrombo-embolic pulmonary hypertension with NYHA class III-IV symptoms [23]. These patients who were stable on targeted medications for at least 2 months were randomized into a control group of usual care versus a 15-week moderate exercise training group. The training program started in a monitored setting for 1.5 h in divided intervals consisting of cycling, walking, dumbbell training with low weights <1 kg for 7 days per week, and respiratory training on 5 days per week for a total of 3 weeks. For the remaining 12 weeks, patients were recommended to continue exercises ≥15 min per day for at least 5 days per week at home. These patients also received counseling and mental training to improve their perception of physical limitations. After the 15 weeks, peak VO_2/kg linearly associated with right ventricular function increased by 15–20%. Cardiac index increased by 1 L/min/m^2 (19%) in the training group versus a decrease in 0.2 L/min/m^2 (−4.3%) in the control group. QoL and perception of physical limitations were also improved in the training group [23]. The results of this hemodynamic study are consistent with prior studies using 6MWD as a surrogate for improvement in functional status during exercise training. More research specifically geared towards RHF with other etiologies is needed. However, it does appear that exercise training may potentially have a positive effect on RV remodeling and function.

11.7 What Is the Evidence of Benefit of CR in Patients with Left Ventricular Assist Devices and Heart Transplant?

Although our patient neither has a left ventricular assist device nor is a heart transplant recipient, it is worth mentioning the role of cardiac rehabilitation in the patient discussed in Chaps. 9 and 10.

These patients' response to exercise can be quite different and requires special consideration before enrollment

into a CR program. The Cardiac Rehabilitation in Patients with Continuous Flow Left Ventricular Assist Devices (Rehab VAD) Trial randomized 26 patients with continuous flow LVAD into 6 weeks of CR or usual care (2:1) [24]. Patients in the CR group engaged in aerobic exercise targeting 60–80% of their heart rate reserve compared to the usual care group who were not prescribed an individualized plan and told to follow physician instructions regarding care as well as to walk daily. A 10% increase in peak VO2, 17% increase in muscle strength, 23% increase in the Kansas City Cardiomyopathy Questionnaire (KCCQ), and 52.3-m increase in 6 MWD were noted in the CR group compared to the control group. These results are consistent with prior studies reporting the safety and improved VO2, pulmonary function tests, muscle strength, QoL while decreasing depression scores in LVAD patients [25]. Reduction of the risk of hospitalization and mortality has also been confirmed with CR [26].

Studies in post-cardiac transplant patients also show similar benefits from CR. Peak VO2 in heart transplanted patients are on average 40–50% lower than normal healthy subjects. This drop in physical function is due to multiple factors including muscle loss due to inactivity and steroid usage, diastolic dysfunction, cardiac rejection, and other systemic derangements. It is important to note that re-innervated hearts have better exercise capacity than denervated hearts, which have higher resting heart rates contributing to chronotropic incompetence [27]. For the most part, the recommended exercise regimen is routine, a combination of aerobic and strength training 3 days per week followed by home maintenance exercise on the remaining days. Exercise training has been shown to increase peak VO2 between 10 and 17%. There is also an improvement in autonomic imbalance, prevention of sympathetic over-activation improving chronotropic responses, and early heart rate recovery [28]. Clearly, exercise training is a crucial element to the recovery of cardiac transplant patients.

11.8 What Are the Barriers to Cardiac Rehabilitation Participation?

There is compelling evidence that comprehensive cardiac rehabilitation is a safe and effective form of therapy to improve functional status and QoL in patients with different forms of HF. Despite clear benefits, there are gaps in referrals, enrollment, and patient retention. Currently, participation in CR remains low, with only about 20–30% of qualified patients enrolled in a program [29].

Medical barriers to referrals include physician misconceptions about benefits of the program, concern for safety in frail and elderly patients, and lack of access to geographically feasible CR programs. Patient barriers to participate include lack of education regarding the benefits of CR, psychosocial determinants such as transportation difficulties or inability to take time off from work, and lack of motivation for exercise training. For CR to be effective, participants must adopt lifestyle changes and continue self-training at home.

Several solutions have been proposed to increase the rates of referral, enrollment, and retention of patients in CR programs. Methods to enhance referrals include integrating an automatic referral into the electronic medical record (EMR) where clinicians must opt out when a qualifying diagnosis has been coded. While this strategy has been effective at capturing many patients, it has not been foolproof. One study compared four different strategies including an automated EMR, use of a CR liaison, a combination of automatic referral + liaison, and usual care. The combination of "automatic referral + a CR program liaison" was more effective at increasing CR participation, increasing participation greater than threefold compared to the control group [30].

This data supports the importance of having a discussion and initiation of enrollment prior to discharge. The Centers for Disease Control and Prevention (CDC) and CMS currently have an initiative called Million Hearts. Their goal is to increase CR participation from 20 to 70% and prevent one million cardiovascular events by 2022. This increase in CR participation is projected to save 25,000 lives and prevent 180,000 hospitalizations annually [29].

Case Conclusion

Our patient completed a 12-week CR program. At the conclusion of the program, she was stable on her heart failure regimen without the need for uptitration of her diuretics and she was able to tolerate 40 min of continuous aerobic exercise in addition to resistance training. Upon discharge, she underwent a second ETT which showed that her exercise capacity had improved. Our patient exercised for 5 min and 49 s on a standard Bruce protocol, which is 1 min and 14 s longer than her pre-CR testing and she has had no hospital admissions for recurrent heart failure since she joined the program.

At this time there are no plans for LVAD or transplantation evaluation because she is stable on guideline-directed medical therapy. Her mood has improved with regular psychiatric follow-up. Her dietary habits have improved, and her A1C declined from 10.2 to 9.1. She feels empowered to make changes and has transitioned to phase 3 of CR.

Clinical Pearls

- Strong data supports improved quality of life and reduced hospital admissions in HFrEF patients participating in CR.
- Exercise training is a Class 1a indication for patients with stable chronic systolic heart failure. CR is recognized as a Class IIa indication in the United States but as a class 1 indication in Europe for HF.
- There are no specific trials studying the effects of CR in right sided HF, but data extrapolated from pulmonary hypertension patients suggests improvement in cardiac output, quality of life, and longer 6MWT.
- LVAD and post-transplant patients participating in CR have improved autonomic dysfunction, chronotropic incompetence, cardiorespiratory fitness, and retention of muscle mass.
- Currently participation in CR remains low, with only about 20–30% of qualified individuals enrolled. Cardiac rehabilitation has highest participation rates when patients are referred while inpatient after the index cardiac event.

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Chapter 12
Palliative Care of the Right Heart

Kristina M. Conner and Michael J. Landzberg

Case

A 57 year-old male with long-standing non-ischemic cardiomyopathy with left ventricle ejection fraction (LVEF) of 10% presented with acute decompensated heart failure (HF) in the setting of atrial fibrillation with rapid ventricular response. Initially, he required inotropic support (milrinone), which was successfully discontinued after atrioventricular node (AVN) ablation with biventricular pacemaker-defibrillator implantation.

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12.1 What Are the Indications for Palliative Care Referral?

Palliative care enables patients to receive goal-directed therapies consistent with their values and preferences. A diagnosis of HF portends an increased mortality risk, high symptom burden, and frequent need for complex medical decision-making throughout the course of the illness. Historically, palliative care and curative treatments have been mutually exclusive, but best practice would involve the provision of symptomatic and disease-directed treatments concurrently. Therefore, palliative care should be integrated early in the disease course and becomes increasingly more important as the illness progresses and/or as the intensity of proposed disease-directed interventions increases [1]. Specific indications for specialty palliative care referral include New York Heart Association (NYHA) Class IV disease, multiple comorbid illnesses (including renal failure, metastatic cancer, and dementia), and frailty or worsening functional status (Fig. 12.1). Another indication for specialty palliative care referral would be at important decision points along the illness trajectory, such as when considering major invasive interventions such as mechanical circulatory support [2] or shifting the focus of care to emphasize the quality of life rather than life prolongation. The patient featured in this case would qualify for palliative care based on multiple factors, including: his acute presentation of symptomatic HF; high mortality risk on the basis of low LVEF; the need for inotropic support; and consideration of invasive procedures and device implantation.

12.2 What Is the Role of Palliative Care in the Management of ACC-AHA Stage C Patients?

Palliative care has a role throughout the trajectory of heart failure regardless of patients' goals of care, and becomes more important as HF progresses [3]. Palliative care in cardiology is unique as the goals of even the most aggressive treat-

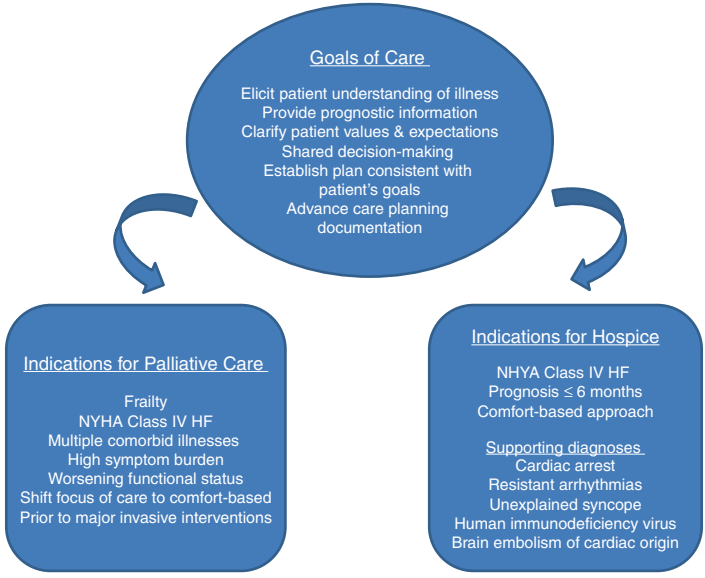

FIGURE 12.1 Description of components of goals of care discussions and indications for palliative care and hospice care in patients with HF

ment of HF are often palliative in nature. Patients classified as ACC-AHA Stage C may benefit from specialty palliative care to help treat symptoms commonly reported in this population, including but not limited to fatigue, dyspnea, depression, and anxiety. Palliative care is also indicated in this stage of disease to help the patient identify surrogate medical decision-makers and complete advance directives, provide anticipatory guidance regarding illness trajectory and prognosis, and participate in shared decision-making around complex medical decisions. Our patient would benefit from early palliative care to assist with both symptom management and medical decision-making, and would continue to benefit from palliative care at varying levels of involvement throughout the disease trajectory (Fig. 12.2) [4].

The traditional model of palliative care involved patients receiving curative care (example: diuresis, inotrope support,

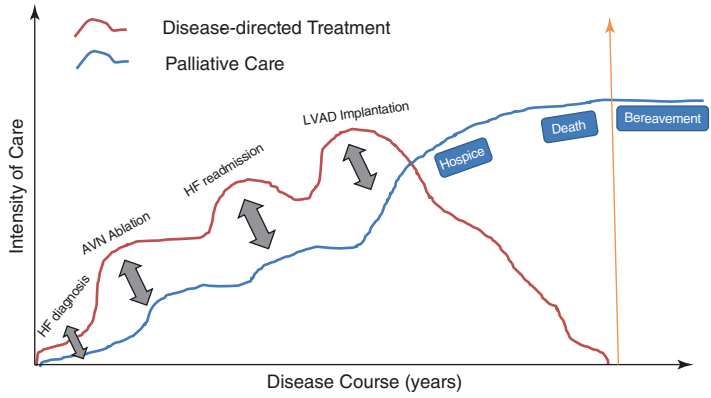

FIGURE 12.2 The contemporary overlapping model of palliative care requires the involvement of palliative care concurrently with disease-directed treatment. The timeline of the patient's disease process is shown with a highlight of the many opportunities that the palliative and supportive care team could be engaged. The x-axis indicates the disease progression over time and the y-axis signifies the intensity of care. The blue line indicates palliative care involvement and the red line indicates heart failure disease trajectory. Arrows indicate opportunities for palliative care involvement

devices for HF patients) until treatment failure, at which point patients received palliative care. The more contemporary overlapping model entails involvement of palliative care concurrently with disease-directed treatment upon diagnosis with a serious illness, with varying involvement of palliative care throughout the disease process (more involvement during disease exacerbations, important decision points, and as disease progresses) [5].

12.3 Which Resources Are Available for Heart Failure Patients and Caregivers?

Caring for patients with HF is time and resource-intensive. The patient in this case may need assistance with instrumental

activities of daily living, transportation to and from appointments and procedures, assistance with medication management, and emotional support as he grapples with adjusting to limitations resulting from his medical condition. Caregivers must be vigilant to avoid caregiver burnout and have access to appropriate resources to support both the patient and themselves. This support may take the form of peer support, palliative and supportive care, and community and governmental resources to help care for patients in the home.

For more information about how to find palliative care: https://getpalliativecare.org/resources/

For information for caregivers: https://www.cardiosmart.org/For-Caregivers/Resources-for-Caregivers

For information on how to get more help in the home: https://eldercare.acl.gov/Public/Index.aspx

For information about planning for advanced heart failure: https://www.heart.org/en/health-topics/heart-failure/living-with-heart-failure-and-managing-advanced-hf/planning-ahead-advanced-heart-failure

Case Continued

Over the next 6 months, the patient was readmitted monthly for decompensated HF. He was typically admitted with worsening shortness of breath and lower extremity edema. His wife noted that he has been depressed lately. On his most recent admission, he was diagnosed with severe biventricular failure requiring milrinone support, and the heart failure specialists initiated a discussion with the patient and his wife regarding whether to place a left ventricular assist device (LVAD).

12.4 What Is the Role of Palliative Care in the Management of Symptoms for ACC-AHA Stage D Patients?

Symptom management is a central tenet of palliative care. The patient in our case is likely to experience a range of

symptoms including depression, anxiety, fatigue, and dyspnea. These symptoms can be optimally managed with a multidisciplinary approach including but not limited to the patient's primary cardiologist, specialty palliative care providers, and a psychosocial support team.

The palliative care team can collaborate with the HF team to facilitate interventions designed to both improve symptoms and optimize treatment of heart failure. As the patient in our case experiences more frequent hospitalizations throughout his illness trajectory, he may benefit from ambulatory intravenous furosemide and or ambulatory inotropes to enhance his quality of life through reduced symptom burden and avoidance of hospitalizations. In clinical practice, subcutaneous furosemide has been used in the hospice population for symptom amelioration for many years and has been helpful to prevent hospital readmission in the palliative care population. There is emerging data to suggest that ambulatory subcutaneous furosemide may benefit patients with decompensated HF [6]. Limited data suggests that ambulatory inotropes may improve ACC-AHA functional class without impacting survival [7]. For patients who are interested in a more comfort-based approach to care and wish to avoid further aggressive disease-directed treatments, we advocate for Palliative Care involvement, including discussion of transition to hospice care [8, 9].

12.5 What Is the Process for Obtaining Informed Consent and Initiating Shared Decision Making for Cardiac Device Implantation?

Ideally, pre-implantation palliative care consultation would result in a comprehensive evaluation of the patient's values and preferences for care along with identification of surrogate decision-makers. These discussions should lead to completion of advance care planning documents such as a healthcare proxy/durable power of attorney for healthcare

(HCP/DPOA) and physician orders for life-sustaining treatment (POLST). Such consultation would also allow for discussion of the tenets of informed decision-making (assessment of patient understanding, involvement of surrogate decision-makers where indicated, discussion of impact of interventions on daily life, and risks, benefits, side effects, and alternatives to the procedure) [10].

In 2013, Centers for Medicare & Medicaid Services (CMS) in the United States of America, issued a national coverage determination with the requirement that patients undergoing surgery for destination LVAD therapy must have access to palliative care prior to device implementation [11]. This mandate has resulted in the widespread integration of palliative care consultation into the workflow at heart transplant centers across the country. Unfortunately, however, palliative care consultation during the pre-implantation period is frequently limited to a perfunctory one-time palliative care encounter, which has not been shown to improve advanced care planning as desired [12].

12.6 How Should Goals of Care Be Approached in this Patient?

All patients with life-limiting or serious illness benefit from goals of care conversations. Early goals of care conversations, preferably with a clinician who is familiar with the patient, are associated with multiple favorable outcomes including improved quality of life and an increase in care concordant with patient wishes [13]. The general approach to a goals of care conversation centers on eliciting patient understanding of illness, providing accurate prognostic information, clarifying patient values, expectations, and hopes, and establishing a plan consistent with patient goals in the context of medical reality.

Unfortunately, initial palliative care consultation frequently occurs in the hospital setting when patients are actively dying or have nearly reached end-of-life. Delayed

Table 12.1 Common barriers to initiation of goals of care conversations related to patient, physician, and system-specific factors

Barriers to goals of care conversations		
Patient	**Physician**	**System**
Lack of knowledge	Lack of training	Lack of infrastructure and training
Unaware of need for conversation	Perceived lack of time	Lack of financial incentive
Cultural barriers	Cultural barriers	Cultural barriers
	Fear of taking away hope	

consultation can deprive patients and their families of the time to build rapport with palliative care providers and comprehensively contemplate, discuss, and document advance directives. The delay in timely palliative care consultation may be due to barriers to effective patient-physician communication stemming from physicians, patients, and the healthcare system (Table 12.1). Medical providers are often hesitant to discuss goals of care for fear of taking away hope or upsetting their patients or families and because of their own discomfort with the conversation due to inadequate training in communicating about goals of care [14]. Physicians also avoid such conversations because of a perceived lack of time or failure to recognize opportunities to have goals of care conversations (such as a significant change in clinical status or important clinical decision point) [15]. Individual physicians may have their own cultural barriers to discussing end-of-life and also frequently lack prognostic awareness. Patients and their families typically do not broach goals of care conversations because they perceive that it is the physicians' responsibility to initiate the conversation; they are unaware of the need for goals of care conversations; or there are cultural barriers to discussing death [16]. Within the United States healthcare system, work is being done to appropriately train

and reimburse clinicians for having goals of care conversations, but currently there are no systematic practices in place to ensure that patients with life-limiting illness consistently engage in advance care planning [17]. The consequences for not discussing goals of care may be emotionally and financially costly to the patient, family, and healthcare system. Negative sequelae include patients receiving burdensome and non-beneficial care at the end of life that is not concordant with their wishes; families experiencing moral distress, depression, and complicated grief as they are forced to make complex medical decisions for their actively dying relatives without their input, and a huge financial burden to the healthcare system as patients receive costly, aggressive treatments at the end of life [18].

In the case of our patient, goals of care conversations should have been initiated early and repeated frequently throughout the clinical course. Upon diagnosis with HF, goals of care conversations to discuss illness trajectory, overall prognosis, and to assign surrogate decision-makers would have been appropriate. Throughout his course, our patient has had several decision points and changes in clinical status where further goals of care conversations would have been appropriate, including prior to pacemaker implantation, during initiation of inotropes, or simply during one of his many inpatient hospital stays (Fig. 12.2). The focus of goals of care conversations changes over time as patients' clinical scenarios and values shift, so frequent re-examination of goals of care is warranted in patients with chronic life-limiting illnesses such as our patient.

Case Continued

Our patient received an LVAD for biventricular failure refractory to inotrope support. His post-operative course was complicated by persistent right ventricular failure despite maximum medical therapy. The patient and his family subsequently decided to avoid further aggressive interventions, including heart transplant.

12.7 What Are the Indications for Hospice in Patients with Heart Failure?

The indications for hospice are, in general, a desire to pursue a comfort-based approach to care and a prognosis of 6 months or less if the disease runs its expected course (Fig. 12.1). Patients with heart disease who meet criteria for hospice care have typically already been optimally treated for heart disease, are not candidates for surgical procedures, or decline these procedures and are NHYA Class IV along with a prognosis of 6 months or less. Supporting diagnoses include history of cardiac arrest, treatment for resistant symptomatic arrhythmias, history of unexplained syncope, history of brain embolism of cardiac origin, and concomitant human immunodeficiency virus. In the United States, criteria for hospice eligibility for cardiac diseases are guided by Medicare and depend on Local Coverage Determination guidelines, which vary regionally.

12.8 What Are the Challenges Associated with Managing an Advanced Heart Failure Patient on Hospice?

Once patients have elected the hospice benefit, they opt to forgo disease-directed treatments in favor of focusing on symptom palliation. Somewhat unique to the field of cardiology is the concept that many interventions that are aggressive disease-directed treatments also result in symptom palliation. Some of these interventions are costly, which can be challenging for hospice agencies to sustain. Additionally, patients who are on hospice typically wish to avoid re-hospitalization, which can be complex as some of the interventions for symptom palliation can only be performed on an inpatient basis or require significant involvement of the primary team. In our patient, for example, continuing to manage his LVAD while on hospice would require seamless communication between

the hospice team and the mechanical support team to ensure appropriate symptom management, device management, and transparency regarding prognosis and goals of care. Furthermore, such management would be costly to the hospice agency, who would bear the full burden of financial responsibility for the patient's care.

12.9 Discuss the Ethical Dilemma Surrounding Cardiac Device Deactivation or Explant?

Whenever considering an intervention, risks and benefits must always be considered. Ethically, discontinuing an intervention is considered to be equivalent to never initiating the intervention in question [19]. Therefore, deactivating an automatic implantable cardioverter-defibrillator (AICD) at the end of life is considered ethically acceptable, and is not considered euthanasia or physician-assisted suicide. When discussing preferences around device deactivation, it is important to be sensitive to cultural considerations and religious beliefs around end-of-life care.

12.10 Palliative Care in Pulmonary Arterial Hypertension and Right Heart Failure

An increasing, though less common, presentation of right heart failure is isolated pulmonary arterial hypertension (PAH) with initiating pathologic changes inherent to the pulmonary vasculature in the absence of precedent left HF. Diagnosis is frequently delayed, as early nonspecific symptomatology of fatigue, anorexia, bloating, dyspnea, and tachycardia may be confused for more common illnesses, adding potential for care provider distrust by the patient and family. Progressive symptom burden, low cardiac output, and mortality have been ameliorated by the advent of disease-

targeting therapies (including endothelin-receptor antagonists, phosphodiesterase-5 inhibitors and prostacyclin analogues), which carry a high burden of side effects and cost. The average survival from the time of diagnosis may reach 7–10 years, with wide variation based upon a variety of biometric factors. Early clinical improvement and sense of well-being despite low physical reserve and overall poor prognosis with such disease-modifying therapies can be accompanied by unrealistic hopes and expectations by the patient and family, as the disease course and trajectory remains unpredictable. The patient in Chap. 7 also needs an early palliative care consult for the reasons enumerated in this chapter.

Patients with right heart failure in the setting of PAH face disease-related symptoms, loss of hope and emotional changes, and waxing and waning functional debility. These challenges are prevalent, yet remain under-recognized, under-reported and under-treated. The progression of PAH is frequently met with multiple-organ system decline, and these patients are considered high-risk for organ transplantation.

Longitudinal palliative care involvement for patients with PAH has been suggested to assist in iterative patient and family prognostic awareness and determination of goals of care and decision-making, development and implementation of coping tools, mood assessment and therapy, non-disease-targeting symptom management, and advanced care planning [20, 21]. Lack of formal PAH-specific criteria for hospice enrollment and the inherent complexities of maintaining or de-prescribing PAH-targeting pharmacotherapies, suggest that palliative care involvement to assist throughout clinical deterioration would be a high-value intervention.

Case Conclusion

After shared decision-making between the patient, his family and the medical staff, he was transitioned to hospice. He reported significant improvement of his quality of life. His family managed his diuretic therapy at home, and despite an overall poor anticipated prognosis of weeks to months, he was still alive 1 year later.

Clinical Pearls

- Palliative Care is indicated upon diagnosis of heart failure and should be provided concurrently with disease-directed treatment.
- Palliative Care is an integral part of the multidisciplinary team caring for patients with HF. Palliative Care can contribute to the interdisciplinary team by providing psychosocial support to the patient and family; initiating symptom management for a range of symptoms including depression, anxiety, fatigue, and dyspnea; and engaging the patient in early and frequent discussion of goals of care.
- Hospice care is appropriate for patients with HF who have a prognosis of 6 months or less who have already been optimally treated for heart disease, are not candidates for surgical procedures, or decline these procedures and have NHYA Class IV disease.
- CMS has issued a requirement that patients undergoing surgery for destination LVAD therapy must have access to palliative care prior to device implementation, which has resulted in palliative care consultation during the preimplantation period that is frequently limited to a perfunctory one-time palliative care encounter and has not been shown to improve advanced care planning as desired. Patients qualifying for mechanical support benefit from early, longitudinal palliative care involvement.
- Patients with right heart failure in the setting of PAH face a high mortality risk, burdensome symptoms, and an unpredictable disease trajectory, and would benefit from early involvement of palliative care.

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