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

M. E. Afari
Cardiovascular Service Line, Maine Medical Center/Tufts University School of Medicine, Portland, ME, USA

L. Tsao (✉)
Division of Cardiovascular Medicine, Steward St. Elizabeth's Medical Center/Tufts University School of Medicine, Boston, MA, USA
e-mail: lana.tsao@steward.org

L. Tsao, M. E. Afari (eds.), *Clinical Cases in Right Heart Failure*, Clinical Cases in Cardiology,
https://doi.org/10.1007/978-3-030-38662-7_1

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

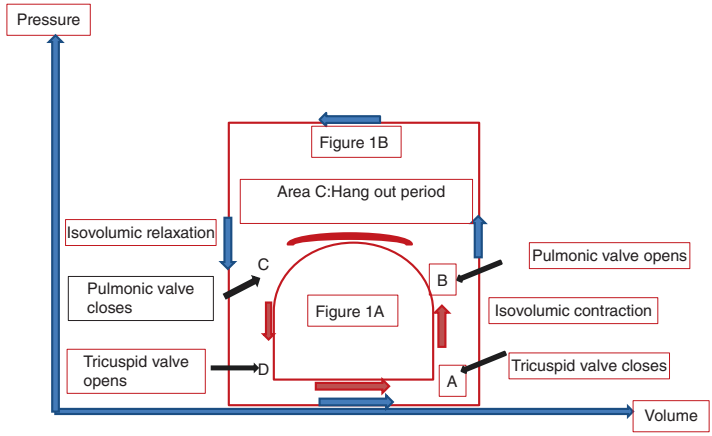

FIGURE 1.1 Pressure and volume loop of the (**a**) the right ventricle (**b**) the left ventricle

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.

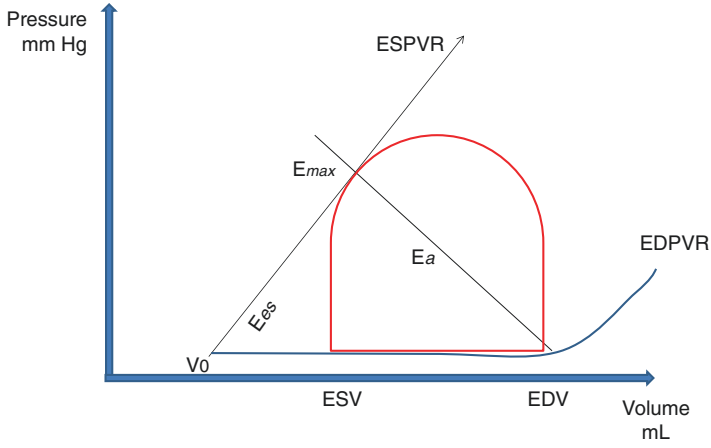

Figure 1.2 The right ventricular pressure volume loop. *ESPVR* end systolic pressure volume relationship, *Emax* maximum elastance, *Ees* end systolic elastance, *Ea* arterial elastance, *ESC* end systolic volume, *EDV* end diastolic volume, *EDPVR* end diastolic pressure volume relationship

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-

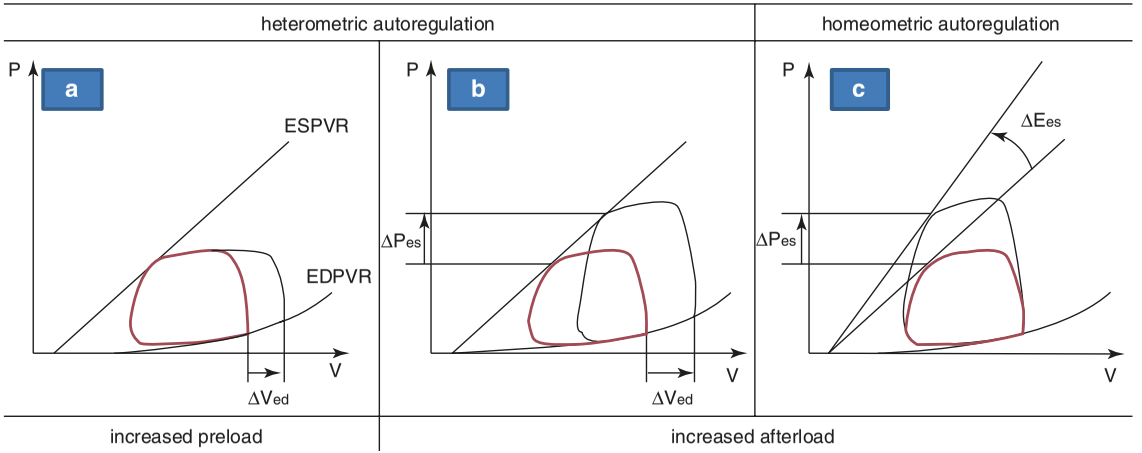

FIGURE 1.3 Representation of heterometric (left and center plot) and homeometric autoregulation (right plot). If preload is increased (**a**) heterometric autoregulation increases SV by the same ΔVed. If afterload is increased, both heterometric and homeometric responses are activated. In heterometric 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.

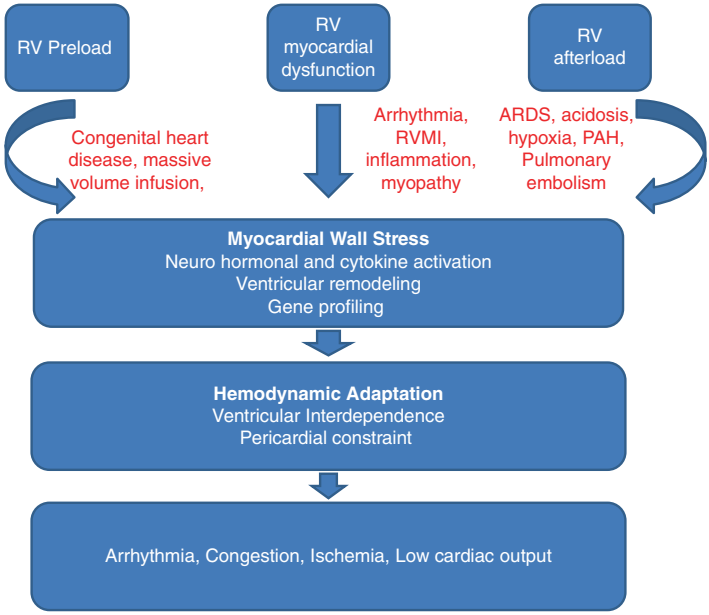

Figure 1.4 The pathophysiology of right heart failure. *RV* right ventricle, *RVMI* right ventricular myocardial infarction, *ARDS* acute respiratory distress syndrome, *PAH* pulmonary arterial hypertension

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],

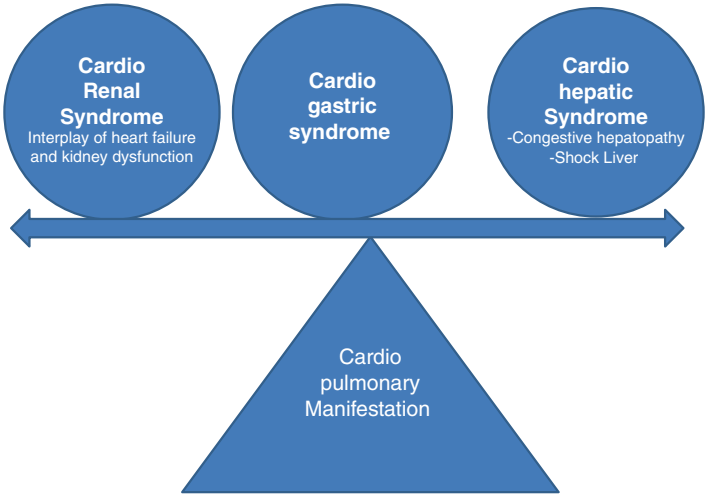

Figure 1.5 Clinical syndrome of right heart failure

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

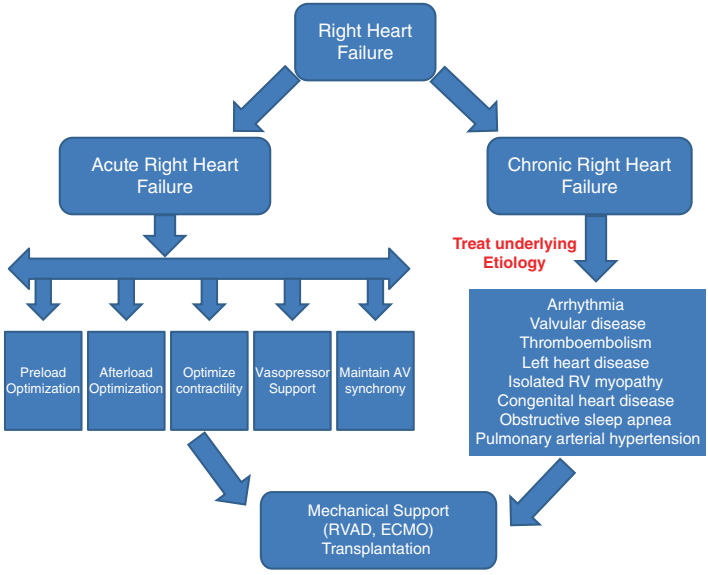

FIGURE 1.6 Management of acute and chronic right heart failure. *RVAD* right ventricular assist device, *ECMO* extracorporeal membrane oxygenation

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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