

## Right Ventricular Function in Cardiovascular Disease, Part II Pathophysiology, Clinical Importance, and Management of Right Ventricular Failure

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Right ventricular (RV) function may be impaired in pulmonary hypertension (PH), congenital heart disease (CHD), and coronary artery disease and in patients with left-sided heart failure (HF) or valvular heart disease. In recent years, many studies have demonstrated the prognostic value of RV function in cardiovascular disease. In the past, however, the importance of RV function has been underestimated. This perception originated from studies on open-pericardium dog models and from the observation that patients may survive without a functional subpulmonary RV (Fontan procedure). In the 1940s, studies using open-pericardium dog models showed that cauterization of the RV lateral wall did not result in a decrease in cardiac output or an increase in systemic venous pressure.<sup>1-3</sup> As was later demonstrated, the open-pericardium model did not take into account the complex nature of ventricular interaction. In 1982, Goldstein and colleagues<sup>2</sup> showed that RV myocardial infarction (RVMI) in a closed-chest dog model led to significant hemodynamic compromise. These findings were further supported by clinical studies demonstrating an increased risk of death, arrhythmia, and shock in patients with RVMI.<sup>4</sup>

The study of the RV is a relatively young field. In 2006, the National Heart, Lung, and Blood Institute identified RV physiology as a priority in cardiovascular research.<sup>5</sup> The goal of this review is to present a clinical perspective on RV physiology and pathobiology. In the first article of the series, the anatomy, physiology, embryology, and assessment of the RV were discussed. In this second part, we discuss the pathophysiology, clinical importance, and management of RV failure.

### Definitions

RV failure is a complex clinical syndrome that can result from any structural or functional cardiovascular disorder that impairs the ability of the RV to fill or to eject blood. The cardinal clinical manifestations of RV failure are (1) fluid retention, which may lead to peripheral edema, ascites, and anasarca; (2) decreased systolic reserve or low cardiac output, which may lead to exercise intolerance and fatigue; or (3)

atrial or ventricular arrhythmias. RV dysfunction, on the other hand, refers to abnormalities of filling or contraction without reference to signs or symptoms of HF. Many indexes can be used to describe RV dysfunction. Among them, RV ejection fraction (RVEF) is the most commonly used index of RV function even though it is a highly load-dependent index of contractility (Table 1).

### Pathophysiology

The RV may be subject to pressure or volume overload, ischemia, intrinsic myocardial disease, or pericardial constraint (Table 2). RV dysfunction begins with an initial injury or a stress on the myocardium and may progress in the absence of a new identifiable insult to the heart (Figure 1). The most common cause of RV dysfunction is chronic left-sided HF. PH is an important cause of RV dysfunction. In 2003, a revised classification of PH was adopted at the Third World Conference in Venice.<sup>6</sup> The revised classification separates causes of PH into those that affect primarily the pulmonary arterial tree (pulmonary arterial hypertension [PAH]), the pulmonary venous system, and the pulmonary vasculature as a result of lung disease, hypoventilation, or pulmonary emboli. RV dysfunction also is a prominent feature of various forms of CHD such as tetralogy of Fallot (TOF), transposition of the great arteries, Ebstein's anomaly, and Eisenmenger syndrome.

RV adaptation to disease is complex and depends on many factors. The most important factors appear to be the type and severity of myocardial injury or stress, the time course of the disease (acute or chronic), and the time of onset of the disease process (newborn, pediatric, or adult years). Other important factors may include the importance of neurohormonal activation, altered gene expression, and the pattern of ventricular remodeling (Figure 2).<sup>5</sup> As emphasized in Figure 2, multiple interactions exist between myocardial injury, neurohormonal activation, altered gene expression, and ventricular remodeling.

In general, the RV adapts better to volume overload than to pressure overload. In atrial septal defect (ASD) and tricuspid

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**Table 1. Selected Markers of RV Dysfunction Associated With Clinical Status and Prognosis**


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|   |
|---|
| Systolic performance indexes                      |
| RVEF  |
| RV fractional area change                         |
| Tricuspid annular plane systolic excursion        |
| RV myocardial performance index                   |
| Hemodynamics                                      |
| Right atrial pressure                             |
| Cardiac index                                     |
| Maximal pressure-time derivative                  |
| Indices derived from pressure–volume measurements |
| Ventricular elastance                             |
| Preload recruitable stroke work                   |
| Diastolic filling profiles                        |
| Tissue Doppler indexes                            |
| Isovolumic acceleration                           |
| Systolic and diastolic myocardial velocities      |
| Right-sided dilation                              |
| RV dilation absolute or relative to LV            |
| Right atrial size                                 |
| Tricuspid regurgitation                           |
| Electrophysiological characteristics              |
| Arrhythmias                                       |
| Inducibility of ventricular tachycardia           |
| QRS duration                                      |
| Neurohormones and cytokines                       |
| B-type natriuretic peptide                        |
| Norepinephrine                                    |
| Endothelin  |
| Tumor necrosis factor                             |

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regurgitation, the RV may tolerate volume overload for a long time without a significant decrease in RV systolic function.<sup>7</sup> Recent studies, however, have demonstrated that long-standing volume overload may lead to an increase in morbidity and mortality.<sup>7,8</sup>

In contrast to volume-overload states, moderate to severe acquired PH in the adult often leads to RV dilatation and failure.<sup>9</sup> Pressure overload of the RV also may lead to RV ischemia, which may further aggravate ventricular dysfunction.<sup>9</sup> Compared with volume-overload states, histological changes are more pronounced in RV pressure-overload states as demonstrated by the increased density of myocardial connective tissue seen in both animal and human studies.<sup>10,11</sup> In acute pressure-overload states such as pulmonary embolism (PE), an adult with a previously normal RV is incapable of acutely generating a mean pulmonary artery pressure >40 mm Hg, and RV failure occurs early in the presence of a significant embolic burden.<sup>12</sup> In most patients with idiopathic PAH, progressive RV dilatation and RV dysfunction occur. Clinical experience suggests, however, that some patients with PH develop RV failure earlier than others with the same degree of pulmonary pressure. Altered gene expres-

**Table 2. Mechanisms and Specific Causes of Right Heart Failure**


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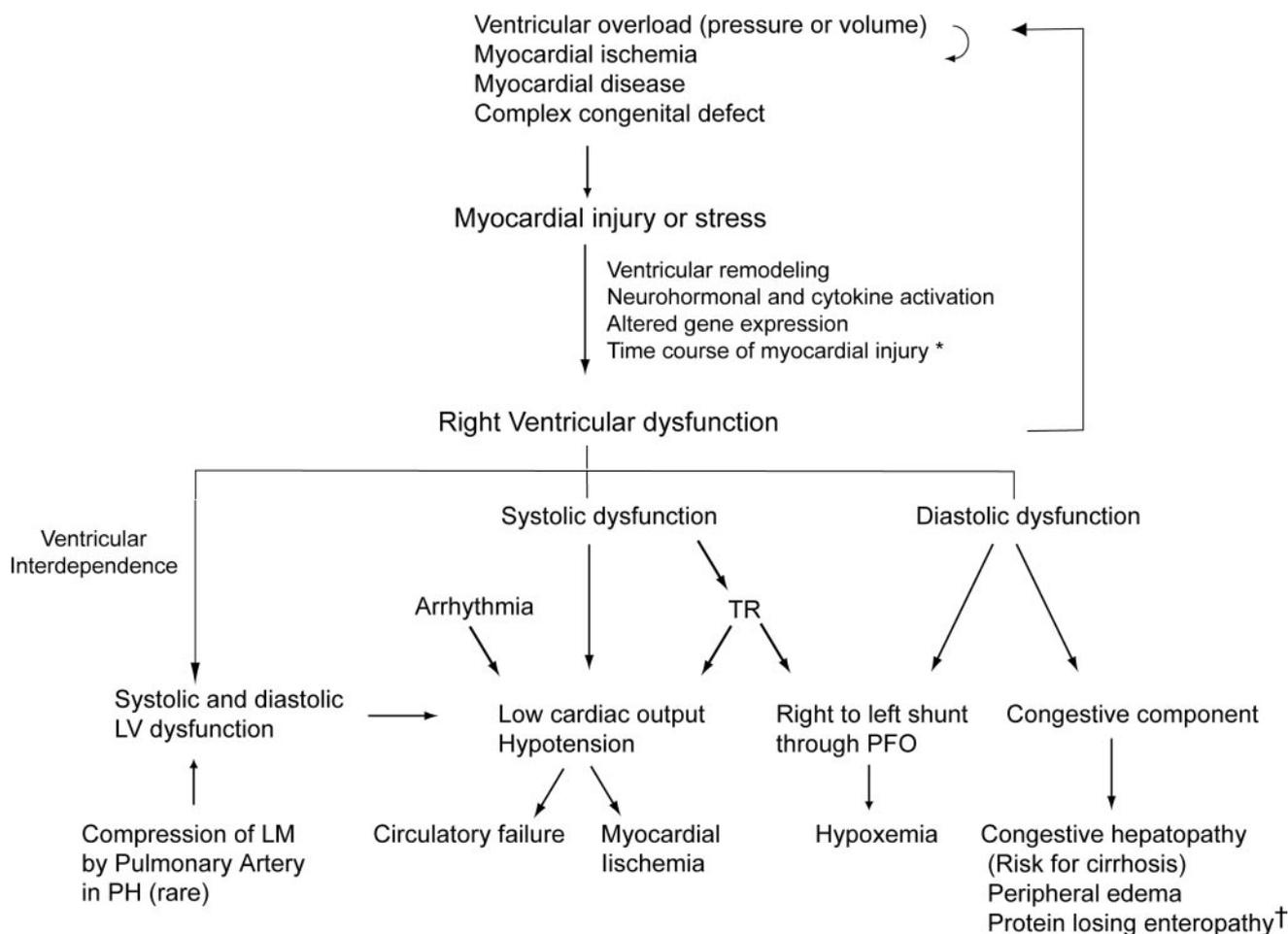
|  |
|--|
| Pressure overload  |
| Left-sided HF (most common cause)  |
| Pulmonary embolism (common)  |
| Other causes of PH   |
| RV outflow tract obstruction   |
| Peripheral pulmonary stenosis  |
| Double-chambered RV  |
| Systemic RV  |
| Volume overload  |
| Tricuspid regurgitation  |
| Pulmonary regurgitation  |
| Atrial septal defect   |
| Anomalous pulmonary venous return  |
| Sinus of valsalva rupture into the RA  |
| Coronary artery fistula to RA or RV  |
| Carcinoid syndrome   |
| Rheumatic valvulitis   |
| Ischemia and infarction  |
| RV myocardial infarction   |
| Ischemia may contribute to RV dysfunction in CHD and RV overload states (especially pressure overload) |
| Intrinsic myocardial process   |
| Cardiomyopathy and heart failure   |
| Arrhythmogenic RV dysplasia  |
| Sepsis   |
| Inflow limitation  |
| Tricuspid stenosis   |
| Superior vena cava stenosis  |
| Complex congenital defect  |
| Ebstein's anomaly  |
| Tetralogy of Fallot  |
| Transposition of the great arteries  |
| Double-outlet RV with mitral atresia   |
| Pericardial disease  |
| Constrictive pericarditis  |

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RA indicates right atrium.

sion and neurohormonal activation may partially account for these differences.<sup>5</sup> Recent studies showed that in some patients with idiopathic PAH, expression and recapitulation of the fetal gene pattern occur as demonstrated by the decreased expression of the  $\alpha$ -myosin heavy chain gene and the increased expression of the fetal  $\beta$ -myosin heavy chain.<sup>5</sup> An association between angiotensin-converting enzyme DD polymorphism and RV adaptation in PAH also has been suggested recently by some investigators.<sup>13</sup>

Two examples of chronic pressure-overload states that are well tolerated by the RV include Eisenmenger syndrome and congenital pulmonary stenosis. In Eisenmenger syndrome, RV failure occurs late in the course of the disease despite having long-standing systemic levels of PH.<sup>14</sup> Compared with other causes of PAH, Eisenmenger syndrome has the best



**Figure 1.** Pathophysiology of RV failure. \*The time course (acute or chronic) and time of onset of the disease process (newborn, pediatric, or adult years) also influence RV adaptation to disease. Neurohormonal activation and altered gene expression modulate the development of RV dysfunction (Figure 2). †Protein-losing enteropathy is multifactorial in the setting of RV failure. LM indicates left main coronary artery; TR, tricuspid regurgitation.

long-term prognosis, with long-term survival of 80% at 10 years, 77% at 15 years, and 42% at 25 years. It has been postulated that the resilience of the RV in Eisenmenger syndrome may be explained by the preservation of the fetal phenotype with equal right and left wall thicknesses throughout life and by the presence of an alternative “outflow,” allowing the RV to shunt to the systemic circuit when the relative ratio of pulmonary to systemic resistance increases as in exercise.<sup>9,14</sup> In congenital pulmonary valve stenosis, the degree of ventricular hypertrophy varies with the severity of obstruction. The RV usually adapts well to pulmonary valve stenosis even when severe, with symptoms being unusual in children and adolescents. Eventually, long-standing untreated severe obstruction may lead to RV failure and tricuspid regurgitation.<sup>7</sup>

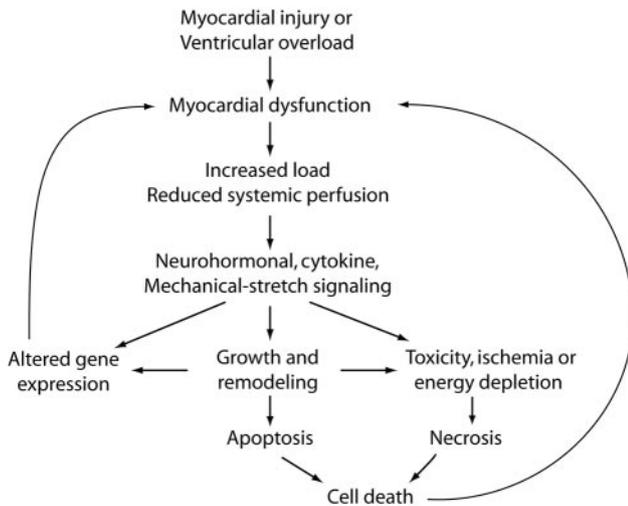
In acute RVMI, the RV shows a remarkable ability to regain systolic function both at rest and during exercise, highlighting its resistance to irreversible ischemic injury.<sup>15</sup>

### Neurohormonal and Cytokine Activation

Numerous studies describe the role of the autonomic nervous system, the renin-angiotensin-aldosterone system, natriuretic peptides, the endothelin system, and cytokines in patients with RV failure.<sup>16–18</sup>

In the failing RV, excessive sympathetic adrenergic stimulation may adversely affect ventricular remodeling and survival.<sup>19,20</sup> In a dog model of RV failure caused by pulmonary artery banding, Fan and colleagues<sup>20</sup> demonstrated a decrease in  $\beta$ -adrenergic receptor density in the stressed RV. Interestingly, the reduced  $\beta$ -adrenergic receptor density was not limited to the failing ventricle but also occurred in the left ventricle (LV). In patients with PAH, elevated catecholamine levels were associated with higher pulmonary vascular resistance and lower cardiac index.<sup>21</sup> In selected patients with CHD and RV failure (TOF, systemic RV), elevated catecholamine levels also were associated with higher New York Heart Association class.<sup>19</sup>

The renin-angiotensin-aldosterone system plays an important role in the pathophysiology of left HF.<sup>22</sup> Many studies also suggest its importance in RV failure. In a rabbit model of RV failure induced by pulmonary artery banding, Rouleau and colleagues<sup>23</sup> demonstrated that RV pressure overload led to a loss of responsiveness to the inotropic effects of angiotensin II and to an uncoupling of angiotensin I receptors to downstream signaling pathways. In patients with cor pulmonale, activation of the renin-angiotensin-aldosterone system also may contribute to fluid retention and ventricular remodeling.<sup>16</sup>



**Figure 2.** Postulated interactions between ventricular remodeling, neurohormonal and cytokine activation, and gene expression in the setting of RV failure. Adapted from Voelkel et al<sup>6</sup> with permission from the publisher. Copyright © 2006, the American Heart Association.

Endothelin system activation may be important feature of pulmonary vascular disease and right HF.<sup>19</sup> In a monocrotaline-induced PAH rat model, an increase in both vascular and RV gene expression of endothelin-1 and endothelin receptors was demonstrated.<sup>24,25</sup> In patients with PAH and CHD (selected forms), elevated endothelin-1 levels were associated with decreased exercise capacity and more severe ventricular dysfunction.<sup>19,25</sup> Modulation of the endothelin system with endothelin receptor antagonists in PAH may lead to an improvement in exercise capacity, a decrease in pulmonary vascular resistance, and better ventricular remodeling (decrease in RV hypertrophy and fibrosis).<sup>17,25</sup> In contrast, endothelin receptor blockade in left HF did not lead to significant clinical benefits even though endothelin levels often are elevated in left HF.<sup>26</sup>

Atrial natriuretic peptide and B-type natriuretic peptide are 2 natriuretic peptides of cardiac origin. B-type natriuretic peptide levels may increase in RV pressure- or volume-overload states such as PH, cor pulmonale, PE, and selected CHD.<sup>18,19</sup> Elevated B-type natriuretic peptide levels also are

associated with an increased risk of mortality in patients with idiopathic PAH.<sup>18</sup>

Activation of cytokines may play an important role in patients with RV failure. In patients with selected forms of CHD and RV dysfunction, elevated levels of tumor necrosis factor and endotoxin were associated with more symptomatic disease (lower functional class or more edema).<sup>19,27</sup>

### Hemodynamic and Systemic Consequences of RV Failure

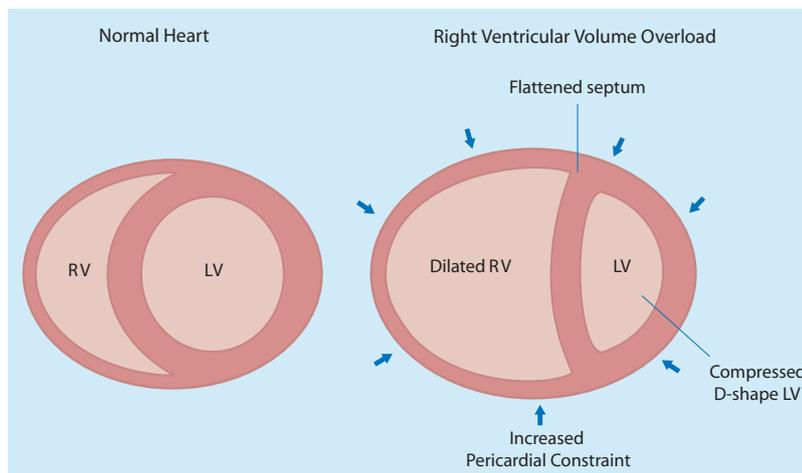
Many factors may contribute to low cardiac output in patients with RV failure such as RV systolic dysfunction, tricuspid regurgitation, ventricular interdependence, bradycardia or tachyarrhythmias, or suboptimal preload (Figure 1). Hypotension may further aggravate RV dysfunction by leading to RV ischemia.

Ventricular interdependence plays an important role in the pathophysiology of RV failure, especially in the acute setting. RV dilatation and/or pressure overload cause a leftward shift of the septum, changing LV geometry; RV dilatation also may increase the constraining effect of the pericardium (Figure 3). These changes contribute to the low-cardiac-output state by decreasing LV distensibility and preload. LV elastance may be decreased through the mechanisms of ventricular interdependence.<sup>15</sup>

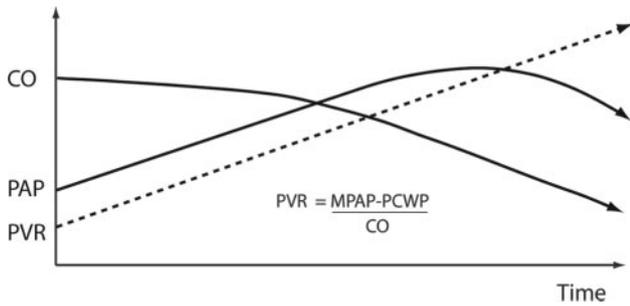
In some patients with severe and progressive RV failure, pulmonary arterial pressure may decrease as a consequence of low cardiac output (Figure 4). Therefore, the interpretation of pulmonary pressure in patients with PH should always take into account the degree of RV failure and effective cardiac output.

RV diastolic dysfunction impairs RV filling and increases diastolic RV pressures and right atrial pressures. This may lead to fluid retention and congestive hepatopathy, as well as cardiac cirrhosis in more advanced cases. RV failure also may lead to significant tricuspid regurgitation, which may further aggravate RV volume overload and decrease cardiac output. Both RV diastolic dysfunction and tricuspid regurgitation may accentuate right-to-left shunting through a patent foramen ovale and lead to hypoxemia.

Protein-losing enteropathy is seen occasionally after the Fontan procedure, in constrictive pericarditis, in severe tri-



**Figure 3.** Ventricular interdependence in RV failure. Dilatation of the RV shifts the interventricular septum toward the left, changing LV geometry. Acute RV distension also may lead to an increase in pericardial constraint (arrows). These changes may contribute to low cardiac output state by decreasing LV distensibility, preload, and ventricular elastance.



**Figure 4.** Hemodynamics in progressive pulmonary vascular disease. A decrease in pulmonary arterial pressure (PAP) in patients with PH may be a sign of low cardiac output (CO) and severe RV failure. PVR indicates pulmonary vascular resistance; PCWP, pulmonary artery capillary wedge pressure; and MPAP, mean PAP.

cuspid regurgitation, and in RV failure. Its origin is multifactorial and cannot be explained simply by elevated right atrial pressure alone. This complex condition may lead to profound hypoproteinemia, malnutrition, and immunological deficiencies.<sup>28</sup>

**Arrhythmias and Sudden Death in RV Disease**

Atrial tachyarrhythmias are the most common arrhythmias encountered in patients with RV failure. In the setting of

acute RV failure or severe RV dysfunction, atrial tachyarrhythmias often lead to hemodynamic instability. Many studies have demonstrated that atrial flutter or atrial fibrillation is associated with an increased risk of morbidity or mortality in patients with RVMI, PH, and CHD.<sup>15,29-31</sup> Right atrial dilatation and remodeling and postsurgical scars within the atria, as in postoperative CHD, represent important substrates for atrial flutter.<sup>30,31</sup>

Ventricular tachycardia arising from the RV may occur in RVMI, PH, CHD, arrhythmogenic RV dysplasia, and idiopathic RV outflow tract tachycardia.<sup>31,32</sup> In patients with CHD, ventriculotomy and/or patching for certain type of ventricular defects are associated with a greater risk of developing ventricular tachycardia.<sup>31</sup> Sinus node dysfunction and conduction blocks also may contribute to exercise intolerance and hemodynamic instability in patients with RV dysfunction (Table 3).

Sudden death in patients with RV disease often is caused by tachyarrhythmia or bradycardia. Other important causes include PE, pulmonary hemorrhage, or mechanical complications associated with RVMI.

**Stages of RV Failure and Prognostic Factors**

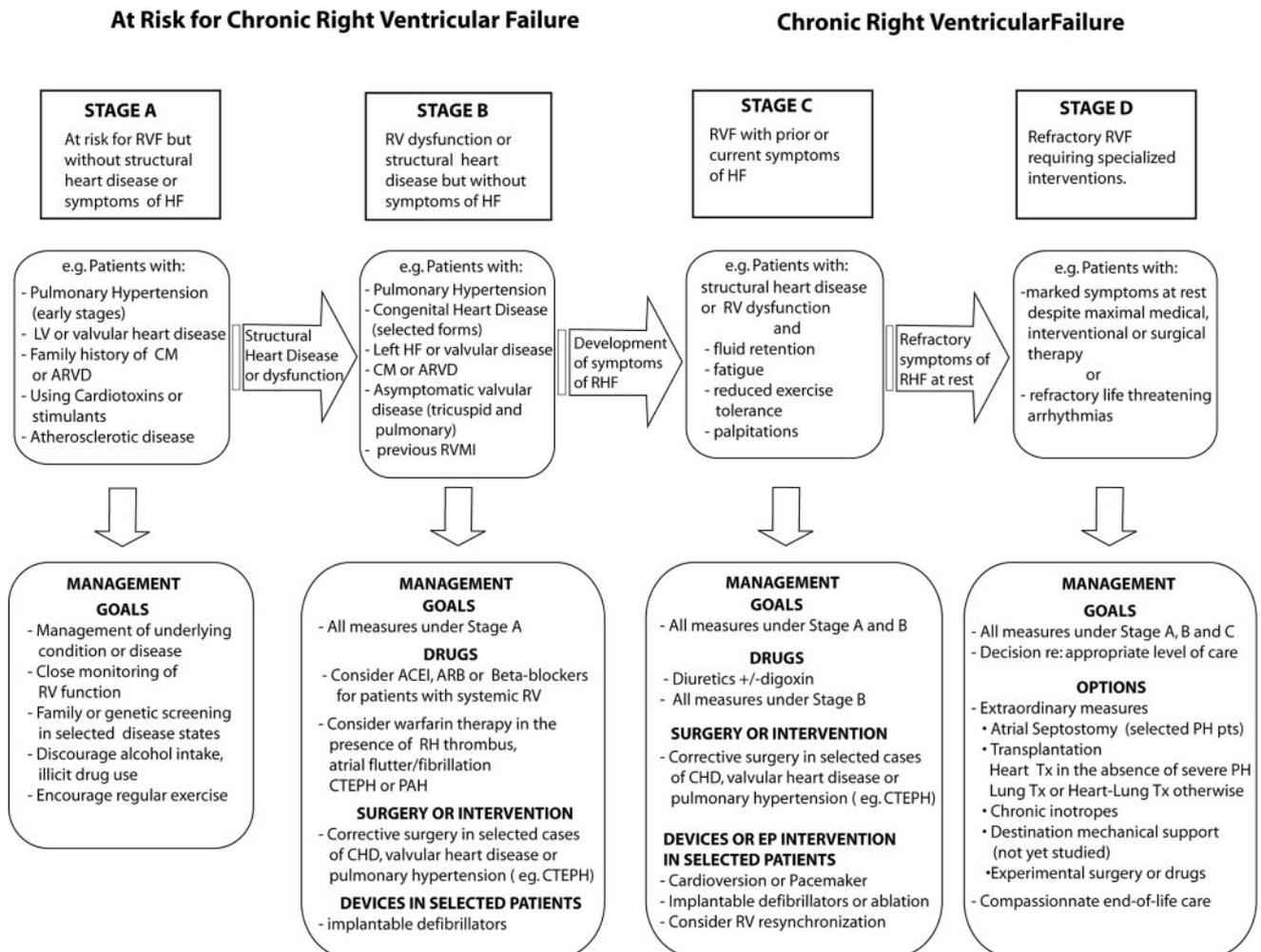
The development of RV failure may be described in terms of progressive stages as it has for left HF. RV failure may

**Table 3. Arrhythmias in Acquired RV Disease and CHD**

| Arrhythmias                   | Selected Forms of Acquired RV Disease   | Selected Forms of CHD   |
|-------------------------------|---|---|
| Supraventricular tachycardia  |   |   |
| Atrial flutter                | Pulmonary hypertension<br>Tricuspid valve disease<br>Advanced lung disease                        | ASD<br>TOF (postrepair)<br>Postoperative atrial switch, Fontan operation                                |
| Atrial fibrillation           | RV myocardial infarction<br>Pulmonary embolism<br>Pulmonary hypertension<br>Advanced lung disease | ASD<br>TOF (postrepair)<br>Unrepaired single ventricle<br>Mitral or aortic valve disease*               |
| Multifocal atrial tachycardia | Advanced lung disease   | ...   |
| Accessory pathways            | ...   | Ebstein's anomaly, L-TGA  |
| Twin AV nodes                 | ...   | Heterotaxy syndrome   |
| Ventricular tachycardia       | ARVD<br>Pulmonary hypertension<br>RV myocardial infarction  | TOF<br>Eisenmenger syndrome<br>Congenital aortic stenosis*  |
| Bradycardia                   |   |   |
| Sinus node dysfunction        | RV myocardial infarction<br>Infiltrative disease  | Heterotaxy syndrome<br>Postoperative atrial switch, Fontan, postoperative Glenn                         |
| AV block                      | RV myocardial infarction<br>Infiltrative disease<br>Myocarditis                                   | Endocardial cushion defect<br>L-TGA, VSD closure<br>AV valve replacement*<br>Subaortic stenosis relief* |

L-TGA indicates L-transposition of the great arteries; AV, atrioventricular; ARVD, arrhythmogenic RV dysplasia; and VSD, ventricular septal defect. The risk of atrial arrhythmias associated with ASD increases with age and pulmonary artery pressure. Adapted from Walsh and Cecchin<sup>31</sup> with permission of the publisher. Copyright © 2007, the American Heart Association.

\*CHD with primary LV or valvular disease.



**Figure 5.** Stages and management of chronic RV failure. The management of chronic RV failure should always be tailored to its underlying cause. ARVD indicates arrhythmogenic RV dysplasia; RH, right heart; CM, cardiomyopathy; CTEPH, chronic thromboembolic pulmonary hypertension; and Tx, transplantation.

progress from asymptomatic RV dysfunction to symptomatic RV failure to refractory RV failure (Figure 5). It is interesting to note that many patients with refractory RV failure associated with PAH may show a significant improvement in RV function after lung transplantation. This finding highlights the potential of recovery of the RV and the marked load dependence of commonly used indexes of RV contractility.

The prognosis of RV failure is strongly associated with its underlying cause. Patients with RV volume overload, pulmonary stenosis, and Eisenmenger physiology usually have the best long-term prognosis. Decreased exercise tolerance represents one of the most important prognostic factors for death or hospitalization in patients with RV failure associated with PH and CHD.<sup>33,34</sup> Other prognostic factors include the severity of RV systolic dysfunction, RV diastolic dysfunction, the extent of neurohormonal activation, chronotropic incompetence, arrhythmias, LV systolic dysfunction, serum uric acid, and bilirubin.<sup>33–36</sup>

## Clinical Importance of RV Function

### Heart Failure

RV dysfunction in left HF may occur in both ischemic and nonischemic cardiomyopathy. RV dysfunction in HF may be

secondary to pulmonary venous hypertension, intrinsic myocardial involvement, ventricular interdependence, neurohormonal interactions, or myocardial ischemia. RV dysfunction appears to be more common in nonischemic cardiomyopathy than in ischemic cardiomyopathy and more closely parallels LV dysfunction.<sup>37</sup>

RVEF represents a strong and independent predictor of mortality in left HF (Table 4).<sup>37–43</sup> Other indexes of RV function that have been associated with worse outcome in HF include RV myocardial performance index and systolic and diastolic tricuspid annular velocities.<sup>43,44</sup> In biopsy-proven myocarditis, tricuspid annular plane systolic excursion is associated with a greater risk of death or heart transplantation.<sup>45</sup>

Exercise capacity, a strong predictor of mortality in HF, appears to be more closely related to RV function than LV function.<sup>39,46</sup> Baker and colleagues<sup>46</sup> and Di Salvo and colleagues<sup>39</sup> observed a significant correlation between RVEF and exercise capacity in HF. On the other hand, Clark and colleagues<sup>47</sup> did not demonstrate such a strong association, highlighting the multifactorial nature of exercise capacity in HF.

**Table 4. Selected Studies Assessing the Prognostic Value of RV Function in HF**

| Study                               | Population | NYHA Class (%) | n   | RV Dysfunction Criteria                     | Main Findings (Significant Findings)                                       |
|-------------------------------------|------------|----------------|-----|---|--|
| Polak et al, <sup>42</sup> 1983     | CAD        | II–IV          | 34  | RVEF <35%                                   | 23% survival (RVD) vs 71% survival at 2 y                                  |
| Di Salvo et al, <sup>39</sup> 1995  | CAD, IDC   | III–IV         | 67  | RVEF <35%                                   | RVD and % $V_{O_2}$ -independent predictors of survival at 2 y             |
| De Groote et al, <sup>38</sup> 1998 | CAD, IDC   | II–III         | 205 | RVEF <35%                                   | RVD, maximal $V_{O_2}$ , NYHA-independent predictors of survival at 2 y    |
| Ghio et al, <sup>41</sup> 2001      | CAD, IDC   | III–IV (70)    | 377 | RVEF <35%                                   | Incremental value of PAP and RV function in predicting event-free survival |
| Sun et al, <sup>44</sup> 1997       | IDC        | III–IV (74)    | 100 | RV area/LV area >0.5                        | RV enlargement independent predictor of survival                           |
| Meluzin et al, <sup>43</sup> 2005   | CAD, IDC   | II–IV          | 140 | RVMPI >1.20, IVA <2.52 cm/s, TAV <10.8 cm/s | RVMPI and TDI indexes were predictive of mortality or event-free survival  |

NYHA indicates New York Heart Association; CAD, coronary artery disease; RVD, RV dysfunction; IDC, idiopathic cardiomyopathy; PAP, pulmonary arterial hypertension; RVMPI, RV myocardial performance index; IVA, isovolumic acceleration; and TAV, tricuspid annular systolic velocity.

Only a few studies have addressed the prognostic importance of RV diastolic function. The difficulty in studying RV diastolic function may be explained the marked load dependence of RV filling indexes. In patients with left HF, Yu and colleagues<sup>48</sup> showed that RV diastolic dysfunction defined by abnormal filling profiles is associated with an increased risk of nonfatal hospital admissions for HF or unstable angina.

### RV Myocardial Infarction

The clinical syndrome of RVMI was first recognized by Saunders in 1930 when he described the triad of hypotension, elevated jugular veins, and clear lung fields in a patient with extensive RV necrosis and minimal LV involvement.<sup>15</sup> The incidence of RVMI in the context of inferior myocardial infarction varies, depending on the diagnostic criteria used, with estimates ranging from 20% to 50%.<sup>4,15</sup> Hemodynamically significant RVMI with hypotension occurs in less than 10% of these patients.<sup>15</sup> The meta-analysis by Mehta and colleagues<sup>4</sup> demonstrated that RVMI was associated with an increased risk of death, cardiogenic shock, ventricular tachycardia or fibrillation, and high-grade atrioventricular block. This increased risk is related to the presence of RV myocardial involvement itself rather than the extent of LV myocardial damage.<sup>15</sup> In survivors of RVMI, RVEF increases significantly during the recovery period in both revascularized and nonrevascularized patients.<sup>15</sup> This suggests that the RV is particularly resistant to irreversible ischemic injury and that myocardial stunning plays an important part in the pathophysiology of RV dysfunction.

### Valvular Heart Disease

RV dysfunction may be seen in both left-sided and right-sided valvular heart disease. Mitral stenosis often leads to PH and RV dysfunction.<sup>49</sup> RV failure, which occurs more commonly in patients with severe mitral stenosis (valve area <1.0 cm<sup>2</sup>) and significant PH (pulmonary vascular resistance >5 Wood units), may be the cause of mortality in 60% to 70% of untreated patients.<sup>50</sup> After mitral valve repair or replacement, RV dysfunction may be reversed to a significant degree.<sup>51</sup>

In chronic severe mitral regurgitation, significant PH at rest (>50 mm Hg) may occur in almost half of the patients, leading to RV dysfunction first during exercise and ultimately

at rest.<sup>52,53</sup> In unoperated patients, subnormal RVEF at rest is associated with decreased exercise tolerance, complex arrhythmias, and mortality.<sup>53</sup> Decreased RV systolic reserve in asymptomatic patients is associated with an increased risk of progression to HF.<sup>53</sup> In patients undergoing mitral valve surgery, Wencker and colleagues<sup>54</sup> demonstrated in a small prospective study that preoperative RVEF  $\leq$ 20% predicted late postoperative deaths.

In patients with aortic stenosis, RV systolic function usually is maintained. RV systolic dysfunction, however, is associated with decreased preoperative cardiac output and a greater requirement of inotropic support after valvular surgery.<sup>55,56</sup> Traditional teaching has been that the RV may sustain severe tricuspid regurgitation for a long time without adverse consequences. Recently, however, Messika-Zeitoun and colleagues<sup>8</sup> have demonstrated that flail tricuspid valve is associated with decreased survival and a high incidence of HF, atrial fibrillation, and need for valve replacement.

### Arrhythmogenic RV Dysplasia and Uhl's Anomaly

Arrhythmogenic RV dysplasia is an unusual myopathy that involves predominantly the RV and results in fibrofatty replacement of the myocardium. Sudden cardiac death frequently is the first manifestation of the disease. Risk factors for sudden death include RV dilatation, precordial repolarization abnormalities, LV involvement, documented or suspected ventricular tachycardia or fibrillation, and  $\geq$ 1 affected family member.<sup>57</sup> Despite the fact that RV dysfunction is a common feature of arrhythmogenic RV dysplasia, symptoms of HF are uncommon (6%).<sup>57</sup> Progressive HF as the cause of death occurs in only a small percentage of patients.<sup>57</sup>

Uhl's anomaly, or parchment heart, consists of aplasia or hypoplasia of most if not all of the myocardium in the trabeculated portion of the RV in the presence of a structurally normal and competent tricuspid valve. The clinical picture of Uhl's anomaly is dominated by congestive HF, which may result in death in infancy.<sup>32</sup>

### Congenital Heart Disease

In patients with CHD, the anatomic RV may support the pulmonary circulation (subpulmonary RV) or the systemic

circulation (systemic RV). RV failure is common in CHD and is closely related to patient outcome.<sup>7</sup>

An isolated large ASD results in left-to-right shunting and volume overload of the RV. Although the RV generally tolerates chronic volume overload well, long-standing volume overload in the setting of an ASD is associated with increased mortality and morbidity (HF, decreased exercise tolerance, and arrhythmias).<sup>7,58</sup> Older age at repair or closure (>40 years of age) also is associated with incomplete RV and right atrial remodeling and an increased risk of arrhythmias.<sup>7,58</sup> In contrast to patients with ventricular septal defects, only a small percentage of patients with ASD develop Eisenmenger syndrome and often do so much later in life.<sup>58</sup> The difference may be related to the timing of shunting, which is delayed in ASD until RV hypertrophy regresses and maturation of the pulmonary vasculature occurs, and to the absence of high-pressure shear forces seen in ventricular septal defects.<sup>58</sup>

In repaired TOF, severe pulmonary regurgitation is the most common cause of RV dilatation and dysfunction and is associated with decreased exercise tolerance, atrial and ventricular arrhythmias, and sudden death.<sup>7</sup> Severe RV dilatation, especially when progressive, may be an early sign of a failing RV and should prompt consideration of pulmonary valve replacement. Pulmonary valve replacement generally results in ventricular remodeling with a decrease in RV volume.<sup>7</sup> Severe preoperative RV dilatation with an end-diastolic volume >170 mL/m<sup>2</sup> or an end-systolic volume >85 mL/m<sup>2</sup>, however, is associated with persistence of RV dilatation after surgery.<sup>59</sup> Some patients with TOF exhibit a “restrictive RV physiology,” which is defined by the presence of forward and laminar late diastolic pulmonary flow throughout respiration.<sup>7</sup> Early after TOF repair, restrictive RV physiology is associated with a low cardiac output and longer intensive care unit stay.<sup>7,60</sup> Late after TOF repair, however, restrictive RV physiology and a less compliant RV counteract the effects of chronic pulmonary regurgitation and are associated with a smaller RV, shorter QRS duration, and increased exercise tolerance.<sup>7,61</sup>

Ebstein’s anomaly is characterized by an apical displacement of the septal and posterior tricuspid leaflets exceeding 8 or 20 mm/m<sup>2</sup> in the adult.<sup>7</sup> The malformation results in an atrialized portion of the RV and moderate to severe tricuspid regurgitation. Associated congenital defects include ASD often with bidirectional shunt, pulmonary stenosis, and accessory pathways.<sup>7</sup> RV failure in Ebstein’s anomaly results primarily from volume overload of the RV and from a hypoplastic RV chamber incapable of adequately handling the systemic venous return. In symptomatic patients, the best surgical approach depends on valve morphology (attachment, commissures, surface) and on the size of the functional RV.

RV outflow tract obstruction may occur in a number of congenital abnormalities, including pulmonary valve stenosis, double-chambered RV, infundibular hypertrophy, or dynamic obstruction of the RV outflow tract. The RV usually adapts well to pulmonary valve stenosis even when severe. In patients with moderate to severe pulmonary valve stenosis, symptoms are unusual during childhood and adolescence.<sup>7</sup> In adults, symptoms of fatigue and dyspnea usually reflect the

inability to increase cardiac output with exercise. Eventually, long-standing untreated severe obstruction may lead to RV failure and tricuspid regurgitation.<sup>7</sup>

In patients with D-transposition of the great arteries who underwent an atrial switch surgery and in patients with congenitally corrected L-transposition of the great arteries, the anatomic RV supports the systemic circulation.<sup>7,62</sup> Because the RV is not well suited to support the systemic circulation, late RV failure usually occurs and is closely related to outcome.<sup>7</sup> In patients who have undergone an atrial switch operation, several factors contribute to the progressive decline in RV function, including myocardial perfusion defects, uncoordinated myocardial contraction, and systemic atrioventricular valve (tricuspid valve) regurgitation.<sup>7,62</sup> In patients with congenitally corrected L-transposition of the great arteries, moderate to severe systemic atrioventricular valve (tricuspid valve) regurgitation is associated with increased mortality.<sup>7,62</sup> Tricuspid valve replacement may slow the progression of RV failure. Late arterial switch operation is considered occasionally in selected patients with transposition of the great arteries.

### Idiopathic PAH

The degree of symptoms and survival in patients with idiopathic PAH are closely related to RV function.<sup>9</sup> In studies assessing hemodynamic variables and survival in idiopathic PAH, high mean right atrial pressures and low cardiac output have consistently been associated with poorer survival.<sup>9,33</sup> In contrast, the level of pulmonary artery pressure has only modest prognostic significance, in part reflecting the decrease in pulmonary arterial pressure that may occur with progressive RV failure (Figure 4).<sup>9</sup> Other direct or indirect parameters of RV function associated with prognosis include right atrial and ventricular size, diastolic eccentricity index, RV myocardial performance index, and tricuspid regurgitation.<sup>9,33,63,64</sup> Other important prognostic factors in idiopathic PAH include exercise tolerance (New York Heart Association class, 6-minute walk test), response to therapy, and the presence of pericardial effusion.<sup>9,33,63</sup>

### Thromboembolic Disease

PE is the most common cause of acute RV pressure overload in the adult. Despite significant advances in cardiovascular medicine, PE remains an important cause of mortality and morbidity. The mortality of PE is closely related to the degree of RV failure and hemodynamic instability. Thus, patients may be divided into 3 groups: (1) hemodynamically stable patients who have an expected mortality of less than 4%, (2) patients with evidence of RV dysfunction but without shock who have an expected mortality between 5% and 15%, and (3) patients in cardiogenic shock who have an expected mortality between 20% and 50%.<sup>12,65,66</sup>

Chronic thromboembolic PH (CTEPH) is characterized by thrombotic obstruction of the main, lobar, or segmental pulmonary arteries.<sup>67</sup> Among patients suffering acute PE, less than 5% go on to develop CTEPH, and two thirds of patients with CTEPH do not have a history of acute PE.<sup>67</sup> Thrombosis in situ plays an important role in the pathophysiology of CTEPH. Compared with patients with idiopathic PAH, pa-

tients with CTEPH tend to have higher right atrial pressure and lower cardiac output for the same level of pulmonary artery pressure.<sup>52</sup> Pulmonary endarterectomy has been demonstrated to improve mortality and exercise capacity in patients with CTEPH.<sup>67</sup>

### Chronic Pulmonary Disease

The generally accepted definition of cor pulmonale is RV enlargement or hypertrophy secondary to pulmonary disease in the absence of LV failure.<sup>68</sup> Patients with cor pulmonale may present with RV hypertrophy, asymptomatic RV dysfunction, or RV failure. Therefore, in studies assessing the relationship between cor pulmonale and prognosis, one has to carefully consider the definition used. Chronic obstructive pulmonary disease (COPD) is the most common cause of cor pulmonale.<sup>68</sup> In patients with COPD, pulmonary arterial pressure usually is only mildly elevated. The development of cor pulmonale is related to the severity of COPD and the degree of hypoxemia (hypoxemic pulmonary vasoconstriction).<sup>68</sup>

Only a few studies have assessed the independent value of RV function in COPD. In a recent study, Burgess and colleagues<sup>69</sup> showed that RV end-diastolic diameter index and the velocity of late diastolic filling were independent predictors of survival. Other important prognostic factors in COPD include the severity of obstructive ventilatory defects and associated comorbidities.<sup>68</sup>

### Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome is a condition associated with a very high mortality rate. Significant RV dysfunction occurs in  $\approx 15\%$  of patients with acute respiratory distress syndrome and usually is related to microvasculature dysfunction and/or the effects of mechanical ventilation.<sup>70</sup> Some studies have demonstrated that RV dysfunction is independently associated with outcome, especially when inspiratory pressures are maintained  $>30$  mm Hg or high positive end-expiratory pressures are tolerated.<sup>70</sup>

### Sepsis

Approximately 50% of patients with severe sepsis and septic shock have concomitant LV systolic dysfunction.<sup>71</sup> RV dysfunction is also common in sepsis and is related to myocardial depression or PH.<sup>72</sup> Persistence of RV dysfunction in sepsis appears to be associated with an increased risk of mortality. In survivors of sepsis, RV dysfunction usually normalizes after 7 to 14 days.<sup>71</sup>

### Cardiac Surgery

The importance of RV function in patients undergoing cardiac surgery has been recognized for several years. In small retrospective studies, preoperative RV systolic dysfunction predicted late survival after coronary artery bypass surgery and mitral valve surgery.<sup>54,73</sup> In the hemodynamically unstable postoperative cardiac patient, Reichert and colleagues<sup>74</sup> showed that RV systolic dysfunction was associated with an increased risk of mortality.

Severe RV failure after cardiac surgery occurs in  $\approx 0.1\%$  of patients and is associated with high mortality rates.<sup>75</sup> Severe RV failure may occur after coronary artery bypass surgery,

valve replacement, heart transplantation, and LV assist device placement. Factors involved in the pathophysiology of RV failure in cardiac surgery include RV ischemia, PH, reperfusion lung injury, pulmonary emboli, sepsis, and acute unloading of the LV after insertion of an LV assist device.<sup>75</sup>

### Management of RV Failure

The management of RV failure should always take into account the origin of and setting in which RV failure occurs. Specific treatment goals include optimization of preload, afterload, and contractility. Maintenance of sinus rhythm and atrioventricular synchrony is especially important in RV failure because atrial fibrillation and high-grade atrioventricular block may have profound hemodynamic consequences. Ventricular interdependence also is an important concept to consider when tailoring therapy. Excessive volume loading may increase pericardial constraint and decrease LV preload and cardiac output through the mechanism of ventricular interdependence. Alternatively, hypovolemia may decrease RV preload and cardiac output. In acute RV failure, every effort should be made to avoid hypotension, which may lead to a vicious cycle of RV ischemia and further hypotension.

The evidence that guides the management of isolated RV failure is not nearly as well established as the evidence that guides the management of chronic HF resulting from LV systolic dysfunction. Most recommendations are based on either retrospective or small randomized studies. An overview of the management of acute and chronic RV failure is presented in Figures 5 and 6.

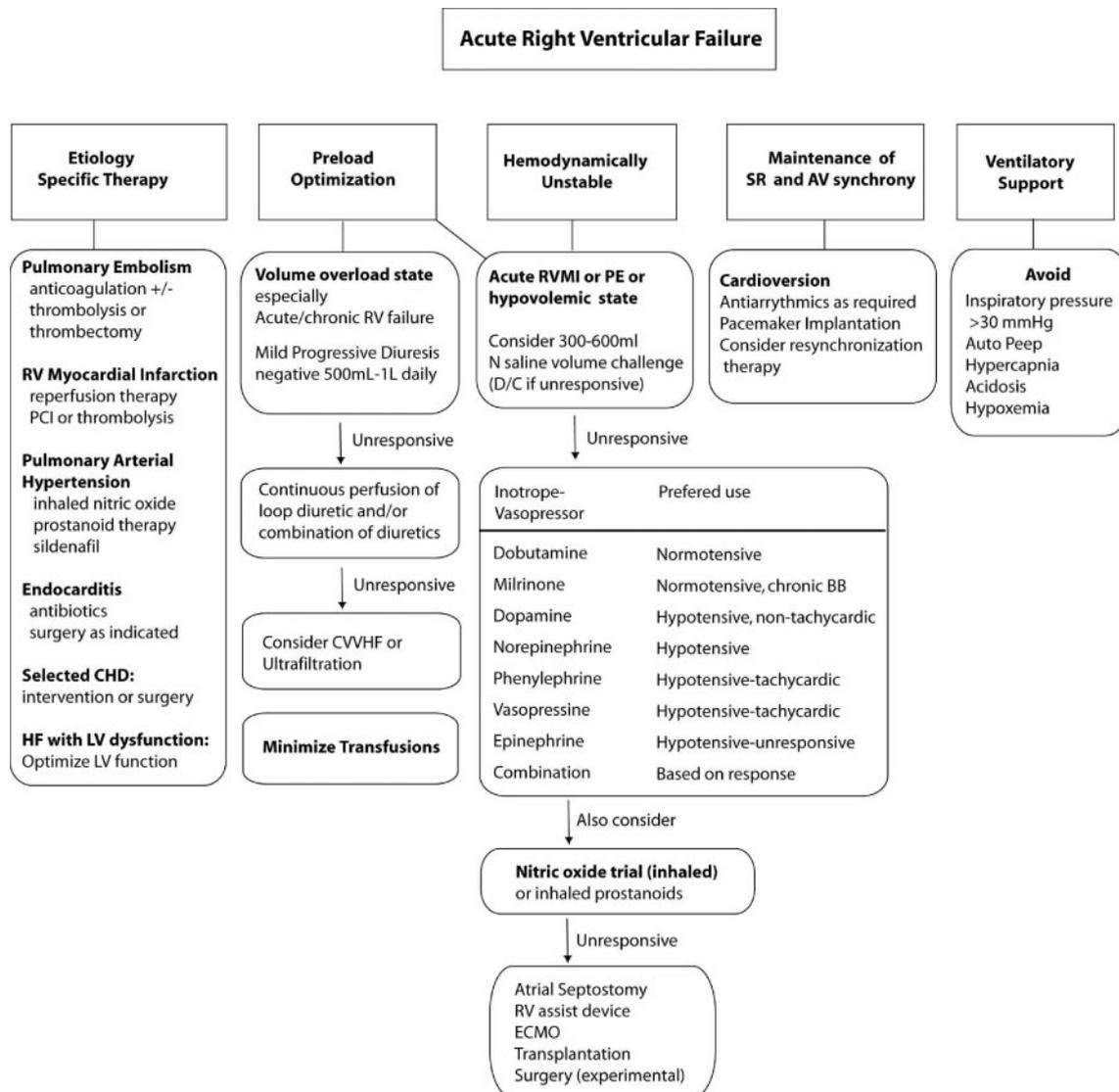
### General Measures

To minimize fluid retention, moderate sodium restriction ( $<2$  g/d), daily measurements of weight, and judicious use of diuretics are recommended. Graded physical activity may be beneficial in patients with PH and RV dysfunction. A recent study in severe chronic PH has shown that moderate exercise training may significantly improve functional capacity and quality of life.<sup>76</sup> Isometric activities may be associated with syncope and should be limited or avoided.<sup>52</sup> Pregnancy in patients with severe RV failure is associated with high maternal and fetal mortality rate. The periods of greater risk are the second trimester and the period of active labor and delivery.<sup>52</sup>

Recognition and management of factors leading to clinical worsening are essential. These factors include noncompliance with medication or diet; use of medications such as nonsteroidal antiinflammatory drugs, nondihydropyridine calcium channel blockers, and antiarrhythmic drugs; systemic factors such as sepsis, anemia, high-output state, hypoxemia, and hypercapnia; cardiovascular factors such as arrhythmias, myocardial ischemia, and pulmonary emboli; obstructive sleep apnea; and high altitude.

### Management Based on the Cause of RV Failure

The most important part of managing RV failure is tailoring therapy to its specific cause. The revised classification of PH provides a framework for treatment of patients with RV failure and PH.<sup>6</sup> Patients with PAH may benefit from prostanoid therapy, phosphodiesterase inhibitors, or endothelin



**Figure 6.** Management of acute RV failure. Hemodynamic instability is defined by hypotension or signs of low cardiac output (eg, renal failure). SR indicates sinus rhythm; PCI, percutaneous coronary intervention; AV, atrioventricular; ECMO, extracorporeal membrane oxygenation; and CVVHF, continuous venovenous hemofiltration.

receptor antagonists. All 3 therapies have led to a significant, although relatively modest, improvement in exercise capacity in patients with PAH.<sup>52</sup> In the acutely decompensated PAH, inhaled nitric oxide, intravenous or inhaled epoprostenol, iloprost, and inotropic support are the most useful agents (Figure 6). In the presence of pulmonary venous hypertension or in patients with HF with biventricular dysfunction, treatment should be directed at optimizing HF management and fluid retention. In patients with PH secondary to various causes of parenchymal lung disease and/or hypoxemia, primary therapy consists of treating the underlying cause of hypoxemia and ventilatory or oxygen support as required. These patients usually do not benefit from treatment with pulmonary vasodilators. In patients with thromboembolic disease, therapy consists of anticoagulation. Thrombolysis or thrombectomy is considered in the presence of hemodynamically unstable patients. The use of thrombolysis in patients with RV dysfunction without shock is still controversial.<sup>65,66</sup>

Pulmonary endarterectomy may be lifesaving in patients with CTEPH.<sup>67</sup>

Patients presenting with RVMI in the context of an inferior ST-elevation myocardial infarction have a significantly higher short-term mortality and therefore should be considered high priority for reperfusion. Only a few studies have assessed the benefits of reperfusion in acute RVMI. Bowers and colleagues<sup>77</sup> showed that patients with successful reperfusion had a better outcome than patients with incomplete reperfusion. Reperfusion therapy also has been shown to improve RVEF and to reduce the incidence of complete heart block.<sup>15</sup> Because thrombolysis in acute RVMI may be associated with a higher failure rate, percutaneous catheter intervention is considered the modality of choice. In survivors of RVMI, recovery of function can occur in a substantial number of patients who were not acutely revascularized, emphasizing the resistance of the RV to irreversible ischemic injury.<sup>15</sup>

In patients with RV dysfunction and valvular heart disease or CHD, corrective surgery or percutaneous intervention should be considered in suitable candidates. Corrective surgery also may be considered in selected patients with CHD, significant PH, and predominant left-to-right shunt.<sup>78,79</sup> Many centers use a preoperative pulmonary vascular resistance <15 Wood units and a ratio of pulmonary to systemic resistance  $\leq 2/3$  as a threshold associated with better surgical outcomes.<sup>78,79</sup> However, individual centers vary these thresholds according to pulmonary vascular reactivity and specific anatomic lesion.<sup>78</sup>

### Optimization of Preload

Clinical assessment of optimal preload in RV failure remains challenging and may differ in the acute and chronic settings. In fact, many studies suggest that both central venous pressure and RV end-diastolic volume may not always reflect RV preload.<sup>80</sup> In general, patients with RV failure and marked volume overload benefit from progressive diuresis. Acute volume loading is sometimes considered in patients with acute RVMI or pulmonary emboli in the absence of marked elevation of central venous pressure (>12 to 15 mm Hg).<sup>81</sup> If no hemodynamic improvement is observed with an initial fluid challenge of 500 mL normal saline, volume loading should not be continued as it may lead to further hemodynamic compromise. Although volume loading is commonly used in severe RVMI, most studies addressing volume loading in RVMI have not demonstrated significant hemodynamic improvement. The clinical response, however, was highly variable among patients. This may reflect different initial volume status, varying baseline end-diastolic volumes, or varying degrees of ischemic burden and injury.<sup>15</sup> In the acute setting, transfusions of packed red blood cells should be minimized to avoid excessive volume loading and exacerbation of PH. A liberal transfusion strategy in critically ill patients also has been associated with increased mortality and morbidity.<sup>82</sup>

### Optimization of RV Afterload

As previously discussed, the approved treatments of PAH often lead to an improvement in exercise capacity and RV function.<sup>9</sup> A recent study has demonstrated that inhaled nitric oxide may be beneficial in patients with RVMI associated with cardiogenic shock.<sup>83</sup> The hemodynamic improvement seen with nitric oxide was most likely secondary to selective pulmonary vasodilatation, resulting in a reduction in RV afterload and subsequent improvement in RV performance.<sup>83</sup>

### Optimization of Contractility

In patients with acute hemodynamically compromising RV failure, inotropic or vasopressor support may be required. Dobutamine is the most commonly used inotrope in RV failure.<sup>84,85</sup> In RVMI, dobutamine increases the cardiac index and stroke volume while maintaining preload.<sup>84</sup> In PH, dobutamine at doses of 2 to 5  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  increases cardiac output while decreasing pulmonary vascular resistance.<sup>85</sup> The combination of dobutamine and nitric oxide in PH also has been shown to be beneficial.<sup>85</sup> Dopamine is used in severely hypotensive patients, whereas milrinone is pre-

ferred in the presence of tachyarrhythmias induced by dopamine or in patients on  $\beta$ -blockers.

Digoxin therapy for RV failure has been studied in PH and chronic pulmonary disease. In PH, Rich and colleagues<sup>86</sup> showed that digoxin given acutely may improve cardiac output by  $\approx 10\%$ . Long-term studies are needed, however, to better define its role in PAH. In COPD, digoxin therapy did not improve maximal oxygen consumption or exercise or RVEF in patients without LV dysfunction.<sup>87</sup>

### Maintenance of Sinus Rhythm

Maintenance of sinus rhythm and heart rate control are important in RV failure. High-degree AV block or atrial fibrillation may have profound hemodynamic effects in RVMI and PH. Sequential AV pacing and cardioversion of unstable tachyarrhythmias should be considered promptly when appropriate.<sup>15</sup>

### Resynchronization of the RV

In recent years, biventricular pacing or cardiac resynchronization therapy has been shown to improve symptoms and survival in selected patients with left HF. The study of RV resynchronization is at its initial stages. Resynchronization of the failing RV may be divided into 2 categories: resynchronization of the systemic RV and resynchronization of the pulmonic RV. In a multicenter international study, Dubin and colleagues<sup>88</sup> demonstrated that cardiac resynchronization therapy was associated with improvement in RVEF in patients with either systemic or pulmonic RV. A small study also suggested hemodynamic improvement with acute RV resynchronization.<sup>89</sup> Future studies will help to determine the long-term effects of resynchronization, the optimal site of pacing, and the optimal outcome variable.

### Prevention of Sudden Death

Predicting sudden death in patients with RV disease remains difficult. Studies have addressed mainly the risk of sudden death in arrhythmogenic RV dysplasia or TOF.<sup>57,90</sup> In patients with TOF, prolonged QRS duration (QRS >180 ms) is a sensitive, although less specific, predictor of sustained ventricular tachycardia and sudden death.<sup>90</sup> Optimal management of RV failure such as revascularization, treatment of PH, and correction of congenital heart defects or valvular disease may decrease the incidence of ventricular tachycardia and sudden death. Implantable defibrillators are considered in patients with arrhythmogenic RV dysplasia and high-risk predictors, in patients who survived a cardiac arrest, in patients with a history of sustained ventricular tachycardia, and in selected patients with inducible ventricular tachycardia (eg, symptomatic TOF).<sup>31</sup> In patients with inducible monomorphic VT, catheter ablation of the ventricular tachycardia circuit also may be considered.

### Anticoagulation

The risk of thromboembolic events in patients with RV failure has not been well established. Although clinical practice varies, anticoagulation usually is recommended in patients with evidence of intracardiac thrombus, documented thromboembolic events (pulmonary emboli or paradoxical

emboli), and PAH (level of evidence fair for idiopathic PAH and expert opinion for PH associated with scleroderma and CHD).<sup>31,52</sup> In patients with paroxysmal or persistent atrial flutter or fibrillation, anticoagulation usually is recommended in the presence of PAH, significant RV dysfunction, or previous thromboembolic events and in the absence of a reversible cause.<sup>31,52</sup> Anticoagulation should be initiated in patients with mechanical tricuspid or pulmonary valves.

### Neurohormonal Modulation of RV Failure: Angiotensin-Converting Enzyme Inhibitors and $\beta$ -Blockers

The effects of  $\beta$ -blockade and angiotensin-converting enzyme inhibition have been studied mainly in HF. In patients with biventricular failure, angiotensin-converting enzyme inhibition has been shown to increase RVEF and to reduce RV end-diastolic volume and filling pressures.<sup>91</sup> Small studies also have demonstrated that  $\beta$ -blockade with carvedilol or bisoprolol improves RV systolic function.<sup>92</sup>

Clinical studies assessing the role of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the systemic RV have not demonstrated improvement in exercise capacity or hemodynamics, although the studies may have been underpowered.<sup>93</sup> At the present time, the role of  $\beta$ -blockade in RV failure is unclear. In a small study in patients with portopulmonary hypertension,  $\beta$ -blockade was associated with worsened exercise capacity and PH.<sup>94</sup>

The role of recombinant human B-type natriuretic peptide (nesiritide) is still controversial in HF with LV dysfunction, and at this moment, its role in RV failure is not defined.

### Supplemental Oxygen Therapy and Ventilation

Hypoxemia may lead to pulmonary vasoconstriction and contribute to PH. On this basis, supplemental oxygen is recommended in patients with evidence of resting or exercise-induced hypoxemia. Patients with hypoxemia associated with pulmonary-to-systemic shunting usually do not benefit from supplemental oxygen therapy. In patients with RV failure who require ventilatory support, every effort should be made to avoid intrinsic positive end-expiratory pressures, inspiratory pressures  $>30$  mm Hg, permissive hypercapnia, acidosis, and alveolar hypoxia.<sup>70</sup>

### Atrial Septostomy

The observation of improved survival of patients with PH and patent foramen ovale has led to the hypothesis that atrial septostomy, which “decompresses” the RV and increases right-to-left shunting, may be helpful in severe RV failure. The response to atrial septostomy in PH is variable. At this time, atrial septostomy should be considered palliative. Predictors of procedure-related failure or death include a mean right atrial pressure  $>20$  mm Hg, a very high pulmonary vascular resistance ( $>30$  to  $55$  Wood units/m<sup>2</sup>), or a predicted 1-year survival of  $<40\%$ .<sup>95</sup>

### Transplantation

Transplantation may be considered in selected patients with advanced refractory RV failure. Originally, it was believed that patients with advanced RV failure secondary to PH could

be candidates only for heart-lung transplantation. However, because of the scarcity of organs, lung transplantation has been tried and has been successful in many patients.<sup>52</sup> Survival in PAH patients who undergo lung transplantation is  $\approx 65\%$  to  $75\%$  at 1 year.<sup>96</sup> Predictors of persistent RV failure after lung transplantation have not been well characterized at this time. Patients with complex CHD with PH should be considered candidates for heart-lung transplantation. Patients with refractory RV failure associated with left HF or patients with arrhythmogenic RV dysplasia and refractory tachyarrhythmias may be considered for heart transplantation in the absence of severe PH.

### RV Assist Device

In patients with acute RV failure refractory to medical treatment, mechanical support with an RV assist device may be used as a bridge to transplantation or to recovery. The most common indications for RV assist device use are severe RV failure associated with LV assist device, heart transplantation, or massive PE.<sup>75</sup> Permanent implantation or “destination therapy” for chronic advanced RV failure has not been studied.

### Conclusions

RV dysfunction is an important predictor of survival and exercise capacity in cardiopulmonary disease. RV failure is a progressive disorder that starts with an initial myocardial injury or stress. Neurohormonal activation, cytokine activation, altered gene expression, and ventricular remodeling may contribute to the progressive nature of the syndrome. Ongoing research will lead to a better understanding of the molecular, genetic, and neurohormonal bases of the syndrome, which will help us tailor the management of RV failure.

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### Disclosures

None.

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KEY WORDS: cardiomyopathy ■ heart defects, congenital ■ heart failure ■ heart ventricles ■ transplantation ■ pulmonary hypertension

## Right Ventricular Function in Cardiovascular Disease, Part II: Pathophysiology, Clinical Importance, and Management of Right Ventricular Failure

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