The Right Heart and Pulmonary Circulation (IV)

Evidence-Based Management of Right Heart Failure: a Systematic Review of an Empiric Field

Mehdi Skhiri, Sharon A. Hunt, André Y. Denault, and François Haddad

Division of Cardiovascular Medicine, Stanford University School of Medicine, Palo Alto, California, United States
Department of Anesthesiology, Montreal Heart Institute and University of Montreal, Montreal, Quebec, Canada

UPDATE

Correspondence: F. Haddad, M.D.
Division of Cardiovascular Medicine, Stanford University School of Medicine, Palo Alto, California, United States of America, 94305.
E-mail: fhaddad@stanford.edu

In recent years, several studies have shown that right ventricular function is an important predictor of survival in patients with congenital heart disease, pulmonary hypertension or left heart failure. Our understanding of right heart failure has improved considerably over the last two decades. In this review article, our objective was to provide a critical summary of the evidence underlying the management of right heart failure. A systematic review of the literature was performed using PubMed and the latest issue of the Cochrane Central Register of Controlled Trials to identify studies conducted between January 1975 and January 2010. The literature search encompassed observational studies, randomized controlled trials and meta-analyses. The evidence underlying the use of beta-blockade, angiotensin-converting enzyme inhibitors, inhaled nitric oxide, hydralazine, warfarin, and resynchronization therapy in right heart failure was systematically reviewed. Emerging new therapies, such as metabolic modulators, and the perils and pitfalls of managing right heart failure are also discussed in the article.

Key words: Heart failure. Acute heart failure. Right heart. Pulmonary hypertension. Systematic review.

Tratamiento basado en la evidencia de la insuficiencia cardiaca derecha: una revisión sistemática de un campo empírico

En los últimos años, varios estudios han indicado que la función ventricular derecha es un factor predictivo importante de la supervivencia en los pacientes con cardiopatías congénitas, hipertensión pulmonar o insuficiencia cardiaca izquierda. Nuestro conocimiento de la insuficiencia cardiaca derecha ha mejorado considerablemente a lo largo de las últimas dos décadas. En este artículo de revisión, nuestro objetivo es presentar de forma crítica la evidencia que subyace en el tratamiento de la insuficiencia cardiaca derecha. Se llevó a cabo una revisión sistemática de la literatura médica, con el empleo de PubMed y el informe más reciente del Registro Central Cochrane de Ensayos Controlados, para identificar estudios realizados entre enero de 1975 y enero de 2010. La búsqueda se centró en ensayos observacionales y en ensayos controlados y aleatorizados, así como en los metaanálisis. Se revisa sistemáticamente la evidencia que subyace en el empleo de bloqueadores beta, inhibidores de la enzima de conversión de angiotensina, óxido nitrico inhalado, warfarina o terapia de resincronización en la insuficiencia cardiaca derecha. Se comentan también los nuevos tratamientos que están surgiendo, como los moduladores metabólicos, así como algunos aciertos y errores en el tratamiento de la insuficiencia cardiaca derecha.


INTRODUCTION

In recent years, several studies have shown that right ventricular function is an important predictor of survival in patients with congenital heart disease, pulmonary hypertension and heart failure (HF). In 2006, the National Heart, Lung and Blood Institute identified right ventricular function and failure as a priority for research in cardiovascular disease. Right ventricular (RV) function may be impaired in several
The search was focused on both observational and randomized controlled trials with a minimum of 5 subjects. Book chapters, meta-analysis, review articles, and editorials were also scanned. The search terms used included, HF, right heart, right ventricle and specific therapies, eg, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), sildenafil, hydralazine, pacemaker, defibrillators, and cardiothoracic surgery. Searches using individual brand names of medications were also conducted.

All studies identified through our searches were assessed by 2 reviewers and consensus was required for inclusion in the review. Data extraction was done independently by the 2 investigators using a pre-defined form. The following data were extracted: methods (study design, method of randomization, concealment of allocation, blinding of the investigators, inclusion and exclusion criteria), populations (sample size, age, and sex), participant characteristics, etiology of heart disease, intervention (agent, dose, timing and duration of therapy, and other medications), control (participants, agent, and dose), and outcomes measures. The main studies relevant to the management of RHF are summarized in table format that summarize study design and main outcome measures. When relevant, we also report recommendations based on the most recently published consensus or guideline statement.1,3,13 When appropriate, we also quote in parenthesis the recommendations of the American College of Cardiology (ACC)-American Heart Association (AHA) or European Society of Cardiology (ESC). The recommendations are classified according to the strength of the recommendation (I, IIa, IIb, III [contraindicated]) and the level of evidence (A, B, C [expert consensus]).

DEFINITION OF RHF AS A SYMPTOMATIC AND PROGRESSIVE DISORDER

RHF is defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the right heart to fill or eject appropriately.1 The cardinal clinical manifestations of RHF are: a) fluid retention manifested as peripheral edema or ascites; b) decreased systolic reserve or low cardiac output syndrome, which may present as exercise intolerance, fatigue or altered mentation; and c) atrial or ventricular tachyarrhythmias. Functionally, the affected right ventricle may be in the subpulmonary (usual) or systemic position (in congenitally corrected transpositions of great vessels (L-TGV) or D-TGV following an atrial-switch repair). Patients may present with a clinical picture of biventricular failure or predominantly RHF.
When considering RHF as a progressive disorder, patients with asymptomatic ventricular dysfunction are considered to be in the early stages of RV failure. 1 Analogous for the staging proposed for left heart failure (LHF), patients may progress from being at risk of RHF (stage A), to asymptomatic RV dysfunction (stage B), to RHF (stage C) and finally refractory RHF (stage D). 1 It is also practical to divide RHF as to whether it is acute or chronic.

**ETIOLOGY AND PATHOPHYSIOLOGY OF RHF**

The clinical syndrome of RHF may result from disorders of the myocardium, the pericardium, endocardium, pulmonary vasculature and pulmonary parenchyma (Table 1). LHF represents the most common cause of RHF. Table 2 summarizes the classification of pulmonary hypertension, a common cause of RHF.

Following initial myocardial stress or injury, several factors may contribute to progression of RV failure, including the timing of myocardial stress (adult period > pediatric), type of stressor (pressure overload > volume overload), and myocardial ischemia, as well as neuro-hormonal and immunologic activation. 7,8 At a molecular level, maladaptative RV remodeling has been associated with a switch in contractile protein isoforms, alteration in cardiac metabolism,

**TABLE 1. Etiology and Mechanisms of Right Heart Failure**

<table>
<thead>
<tr>
<th>Mechanism of RV Dysfunction</th>
<th>Specific Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure overload</td>
<td></td>
</tr>
<tr>
<td>RV myocardial ischemia</td>
<td></td>
</tr>
<tr>
<td>or infarction</td>
<td></td>
</tr>
<tr>
<td>Ischemia and infarction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrinsic myocardial process</td>
<td>Cardiomyopathy or infiltrative process</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflow limitation</td>
<td>Tricuspid stenosis</td>
</tr>
<tr>
<td>Superior vena cava stenosis</td>
<td></td>
</tr>
<tr>
<td>Complex congenital malformation</td>
<td>Ebstein’s anomaly</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td></td>
</tr>
<tr>
<td>Double outlet RV with mitral atresia</td>
<td></td>
</tr>
<tr>
<td>Hypoplastic right ventricle</td>
<td></td>
</tr>
<tr>
<td>Pericardial disease</td>
<td>Constrictive pericarditis</td>
</tr>
</tbody>
</table>

Adapted from Haddad et al8 with permission.

**TABLE 2. Revised World Health Organization Classification of Pulmonary Hypertension**

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic (IPAH)
   1.2. Familial (FPAH)
   1.3. Associated with (APAH):
      1.3.1. Connective tissue disorder
      1.3.2. Congenital systemic-to-pulmonary shunts
      1.3.3. Portal hypertension
      1.3.4. HIV infection
      1.3.5. Drugs and toxins
      1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher’s disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
   1.4. Associated with significant venous or capillary involvement
      1.4.1. Pulmonary veno-occlusive disease (PVOD)
      1.4.2. Pulmonary capillary hemangiomatosis (PCH)
   1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
   2.1. Left-sided atrial or ventricular heart disease
   2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Sleep disordered breathing
   3.4. Alveolar hypoventilation disorders
   3.5. Chronic exposure to high altitude
   3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
   4.1. Thromboembolic obstruction of proximal pulmonary arteries
   4.2. Thromboembolic obstruction of distal pulmonary arteries
   4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous
   Sarcoïdosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Reproduced from Simonneau et al.10
Skhiri M et al. Evidence-Based Management of Right Heart Failure

Helps maintain hemodynamics in early stages of RHF. Experimental studies have shown that in the absence of a dilated RV, LV systolic contraction contributes 20%-40% of RV systolic pressure generation. Diastolic ventricular interdependence contributes to the development of LV systolic dysfunction in patients with RHF. RV enlargement or increased afterload may shift the interventricular septum and increase pericardial constraint on the left ventricle; both of these changes may alter left ventricular geometry and decrease LV preload and contractility (Figure 1).

Compression of the left main coronary artery by a dilated main pulmonary artery, which is occasionally observed in pulmonary arterial hypertension (PAH), may contribute to LV dysfunction. Tricuspid regurgitation and ongoing ischemia may also contribute to the progression of RHF.

DIAGNOSTIC EVALUATION OF PATIENTS WITH RHF

The goals of the initial evaluation of patients with RHF are to better characterize its etiology, severity and functional status, the presence and extent of end-organ damage (renal dysfunction, liver dysfunction)
and the presence of associated conditions. In patients with RHF, physical examination often reveals lower extremity edema, jugular venous distention and a parasternal holosystolic murmur compatible with tricuspid regurgitation. Cyanosis may be observed in patients with right to left shunting or severe low cardiac output.

Echocardiography plays a key role in the diagnosis of right heart disease. Signs of right heart disease on an echocardiogram can include RV enlargement, RV systolic dysfunction, tricuspid regurgitation, and pulmonary hypertension, congenital heart defects, valvular heart disease, or left heart disease. Magnetic resonance imaging (MRI) is becoming the gold standard for evaluating right heart structure and function and is particularly useful in patients with complex congenital heart defects (eg, Ebstein’s anomaly, hypoplastic RV), in patients in whom precise quantification of valvular regurgitation is important, and for planning of a complex surgery or procedure or for research purposes. Recent studies using MRI have also demonstrated the prognostic value of RV end-diastolic volumes and pulmonary compliance assessed by MRI in pulmonary arterial hypertension. Angiography by MRI, computed tomography-angiography or heart catheterization may be of particular value in excluding chronic thromboembolic pulmonary disease, in assessing complex arterio-venous malformations or congenital heart defects. Right heart catheterization is an important part of the evaluation of right heart disease. Indications for right heart catheterization include assessment of pulmonary vascular resistance or impedance, pulmonary pressures, cardiac output shunt fraction, and pulmonary vasoreactivity. Exercise testing is also very useful in objectively assessing clinical deterioration in patients with PAH or congenital heart disease. Caution is, however, advised in performing maximal exercise testing in patients with severe pulmonary vascular disease (contraindicated in the recent AHA consensus on congenital heart disease).

Obtaining baseline renal and liver function tests, albumin, uric acid levels as well as B-type natriuretic peptide levels may be of particular interest in determining prognosis of right heart disease. In patients with severe hypoalbuminemia, protein losing enteropathy should be excluded with the assay of stool alpha-1 antitrypsin. Electrocardiography is part of the routine evaluation and allows assessment of cardiac rhythm, QRS duration or the presence of atrio-ventricular conduction block.

Other studies should be individualized depending upon the suspected etiology of RHF. In patients with PAH, a ventilation perfusion scan, pulmonary function tests, overnight oximetry, serologies for HIV and connective tissue disease (eg, antinuclear antibody test, ANA) are often routinely obtained. Stool alpha-1 antitrypsin are often obtained to rule out protein losing enteropathy. Lung or heart biopsy is rarely indicated in patients with isolated right heart disease. Genetic counseling should be pursued in patients with congenital heart disease or arrhythmogenic right ventricular dysplasia (ARVD). Depending on the etiology and severity of RHF, patients are followed at varying intervals (usually 3 months to 1 year). The recent guidelines for congenital heart disease and PAH offer individualized timing for follow-up depending on conditions.

MANAGEMENT OF RHF

Overview of the Management of RHF

The most important aspect of managing RHF is tailoring therapy to its specific cause. In contrast to patients with chronic ischemic or non-ischemic cardiomyopathy, patients with RHF often have significantly abnormal afterload (eg, pulmonary hypertension) or valvular heart disease (acquired or congenital pulmonary or tricuspid disease). It is therefore not surprising that the selected therapy should primarily target the cause of RHF. In managing patients with RHF, it is also useful to divide the syndrome into 4 clinical categories: biventricular failure, systemic RV failure, predominant sub-pulmonary RV failure, and hypoplastic RV syndrome. The management of patients with hypoplastic RH is beyond the scope of this review and the reader is referred to the recent consensus statement of Warnes and colleagues.

The physiological goals of RHF treatment include optimization of preload, afterload and contractility. Sodium and fluid restriction and judicious use of diuretics all help optimize RV preload. Clinically, optimal preload may be defined as the preload that results in optimal cardiac output without causing renal dysfunction. Although it is often perceived that patients with RHF require higher levels of filling pressure, the majority of patients may have an optimal preload with normal right atrial pressure (<6 mmHg). Small clinical studies also suggest that resynchronization therapy may be beneficial in selected patients with RHF. As will be discussed, only small studies suggest a beneficial role for beta blockade or ACE inhibitors in RHF; these results have not been confirmed by larger studies. Primary prevention of sudden death using defibrillators is mainly recommended in patients with arrhythmogenic RV dysplasia and tetralogy of Fallot. In the setting of acute RHF, every effort should be made to avoid systemic hypotension, as this could lead to myocardial ischemia and further
Skhiri M et al. Evidence-Based Management of Right Heart Failure

In chronic right heart failure (RHF), the effects of therapy have not been consistently studied across functional class severity (New York Heart Association [NYHA] functional class). Because the prevalence of RHF is relatively small compared to the prevalence of left heart failure (LHF), finding appropriate surrogate end-points has been an important focus of research. Surrogate end-points being considered include exercise capacity, clinical worsening, ventricular remodeling or measures of vascular impedance in pulmonary hypertension.

Evidence Underlying the Management of RHF

Compared to the evidence supporting the management of LHF, the management of RHF is not well supported by randomized controlled trials. Furthermore, clinical trials in patients with RHF have not been powered for mortality endpoints. Among patients with RHF, the evidence is best established for patients with pulmonary arterial hypertension (PAH). In PAH it may, however, be difficult to distinguish whether the beneficial effects of therapy are due to changes in pulmonary vasculature or RV specific effects; we therefore often consider the effects of PAH therapy in the context of the cardiopulmonary unit. In patients with congenital heart disease, the effects of therapy have not been consistently studied across functional class severity (New York Heart Association [NYHA] functional class).

Because the prevalence of RHF is relatively small compared to the prevalence of LHF, finding appropriate surrogate end-points has been an important focus of research. Surrogate end-points being considered include exercise capacity, clinical worsening, ventricular remodeling or measures of vascular impedance in pulmonary hypertension.
General Preventive Measures

Referral to a congenital heart disease or pulmonary hypertension specialist when appropriate is recommended in patients with pulmonary arterial hypertension or complex congenital heart disease. This measure will help avoid any delay in timely intervention such as cardiac surgery, percutaneous closure of a cardiac defect or percutaneous valve replacement or initiation of PAH specific therapy.

Prevention or early recognition of RHF decompensation is key in managing RHF. Factors that may lead to volume overload include non-compliance with sodium (<2 g daily) or fluid restriction, non-compliance with medications or use of nonsteroidal anti-inflammatory drugs or non-dihydropyridine calcium channel blockers. Patients with significant PAH or severe RHF should also be advised against pregnancy, as it is associated with increased maternal and fetal mortality rate. Prevention of infection with influenza and pneumococcal vaccination is also recommended, as is prophylaxis against bacterial endocarditis in patients with mechanical valves, previous infectious endocarditis or in patients with selected congenital heart defects.

Recent studies have shown that supervised cardiac rehabilitation for 8 weeks led to a significant improvement in 6 minute walk test (6MWT) in patients with PAH (mean difference of 111 m...
ETIOLOGY-BASED MANAGEMENT OF RHF, THE MAIN TARGET

Biventricular failure is managed following the guidelines of the AHA/ACC or ESC for managing patients with chronic HF. Patients with biventricular
failure benefit from beta blockade and ACE inhibition or angiotensin receptor blockers. Recent studies have shown that sildenafil may improve pulmonary hemodynamics, exercise capacity and endothelial function in patients with chronic systolic HF (Table 3). Whether patients with left HF and evidence of right heart dysfunction may derive greater benefits from sildenafil still remains to be proven.

In patients with ST elevation myocardial infarction involving the right ventricle, early reperfusion should be achieved as early as possible. Although the RV usually recovers following acute myocardial infarction, reperfusion therapy has also been shown to improve RVEF and reduce the incidence of complete heart block. Maintenance of atrioventricular synchrony, correction of bradycardia and maintenance of hemodynamic stability with appropriate volume loading or inotropic support are also recommended.

In patients with acute hemodynamically compromising pulmonary embolism (systolic blood pressure of ≥40 mmHg from baseline), evidence supports the use of thrombolytic agents (alteplase). Although many clinicians advocate thrombolytic therapy in patients with evidence of RV dilatation and dysfunction without systemic hypotension, the indication has not gained widespread acceptance and remains highly controversial. The controversy arises from the fact that clinical trials did not stratify patients according to RV size and function, although isolated RV dysfunction is a clear prognostic factor of outcome. In patients with chronic thromboembolic disease, pulmonary endarterectomy may decrease pulmonary pressures to near normal and reverse RHF. Because pulmonary endarterectomy may be life saving, pulmonary angiography, usually using computed tomography scan, is a routine part of clinical investigation.

The treatment of PAH has evolved tremendously in the last 20 years. The ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension has recently summarized its recommendations on pulmonary hypertension.
the current management of PAH. The majority of treatments for PAH were approved on the basis of an improvement in 6MWT. Because of the small number of patients with PAH, powering the studies for mortality outcomes will prove to be difficult. Also, more attention is being focused on the effects of therapy on both the pulmonary vasculature and the heart (cardio-pulmonary unit). For example, while both endothelin receptor blockers (bosentan) and sildenafil improve 6MWT, recent studies suggest that sildenafil may also have positive inotropic effects on the RV. Whether these differences will translate in to beneficial long-term effects remains to be proven. Anticoagulation is also recommended in patients with PAH based on several observational studies or sub-analysis of randomized trials (Table 4). Digoxin may lead to clinical improvement, but the evidence favoring its use is based on improvement in acute hemodynamic profile and not long-term effects (Table 5). An interesting recent advance is the demonstration that prostanoid therapy may allow sufficient reversal of pulmonary vascular disease to allow closure of an atrial septal defect.

In patients with tetralogy of Fallot following initial repair, pulmonary valve replacement is recommended in patients with symptomatic pulmonary regurgitation (I, B) or in asymptomatic patients with moderate to severe RV enlargement (IIa, C), moderate to severe RV dysfunction (IIa, C), or moderate to severe tricuspid regurgitation (IIa, C). Other indications include new onset sustained atrial or ventricular arrhythmias or residual significant stenosis (peak RV outflow track gradient >50 mmHg by echocardiography or 70% systemic values; (IIa, C)) or residual ventricular septal defect, with a left-to-right shunt greater than 1.5:1 (IIa, B). Coronary artery anatomy, specifically the possibility of an anomalous anterior descending coronary artery functions as the systemic ventricle. In both these conditions, surgery or intervention is often considered in the presence of significant atrio-ventricular inhibition or beta-blockade in patients with D-TGA, significant or un repaired defects, or conduit stenosis (please refer to the recent guidelines of Warnes and colleagues for more complete information). The benefits of ACE-inhibition or beta-blockade in patients with D-TGA or L-TGA is not well established (Tables 6 and 7). The studies addressing the question are small and underpowered for mortality or clinical outcome. If beta-blockade is given, caution must be used because of the risk of precipitating advanced atrioventricular block (especially in patients with pre-existing sinus or AV nodal dysfunction).

In patients with Ebstein’s anomaly, surgery should be considered in the presence of symptoms with deteriorating exercise capacity, (I, B) cyanosis (oxygen saturation less than 90%) (I, B), paradoxical embolism, (I, B) or progressive RV dilatation or ventricular dysfunction (I, B). The primary operation

### TABLE 4. Warfarin Therapy in Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Characteristics</th>
<th>No.</th>
<th>Design</th>
<th>Main Findingsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuster et al. 1984</td>
<td>Idiopathic PAH</td>
<td>MPAP 64 mmHg; CI 2.2 L/min/m²; TPR 33 WUm²</td>
<td>120</td>
<td>Retrospective, single center, follow up at least 5 years</td>
<td>Beneficial effect: ↑survival on warfarin at 3 years: 48% vs 20%</td>
</tr>
<tr>
<td>Rich et al. 1992</td>
<td>Idiopathic PAH</td>
<td>MPAP 57 mmHg, CI 2.6 L/min/m², PVRI 27 units/m²</td>
<td>64</td>
<td>Sub-study of a prospective CCB trial</td>
<td>Beneficial effect: ↑survival on warfarin at 5 years especially in non responders to CCB challenge: 47% vs 31%</td>
</tr>
<tr>
<td>Frank et al. 1997</td>
<td>Idiopathic or anorexigen induced PAH</td>
<td>NYHA class III &amp; IV, MPAP 49-64 mmHg, PCWP &lt; 8.6 mmHg, CI 1.9-2.4 L/min/m²</td>
<td>173</td>
<td>Two centers, retrospective study, follow-up to 10 years.</td>
<td>Beneficial effect: ↑survival time on warfarin: 7.2 years vs 4.9 year</td>
</tr>
<tr>
<td>Kawut et al. 2005</td>
<td>Idiopathic PAH</td>
<td>MPAP 55 mmHg, CI 1.8 L/min/m²; single center,</td>
<td>84</td>
<td>Retrospective study, follow-up 764 days</td>
<td>Beneficial effect: ↑survival on Warfarin: HR=0.33 [0.12–0.90]</td>
</tr>
</tbody>
</table>

CI indicates cardiac index; CCB, calcium channel blockers; MPAP: mean pulmonary arterial pressure; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; TPR, total pulmonary resistance; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index. Unless otherwise specified, the results refer to statistically significant findings (P<.05). The changes reported refer to relative changes in mean effect size or when indicated by changes in absolute effect size.
EVIDENCE UNDERLYING ACE INHIBITION, BETA-BLOCKADE, DIGOXIN AND HYDRALAZINE THERAPY IN RHF

With the success of medical management of patients with LHF, several researchers have investigated whether therapies proven to be beneficial in LHF may be applied to RHF.68-80 Because most of these studies are underpowered for mortality outcomes and commonly underpowered for exercise capacity, definite conclusions are difficult to make at this time.

A small study supports the use of digoxin therapy in patients with idiopathic pulmonary arterial hypertension.64 In the study of Rich and colleagues, intravenous digoxin therapy produced a modest increase in cardiac output, as well as a significant reduction in circulating norepinephrine level by 15%.

At this time, no evidence clearly supports the use of digoxin therapy in patients with chronic obstructive pulmonary disease and associated RHF.65,66,81 Following initial enthusiasm associated with the use of beta blockade in patients with systemic RV,73,74 a larger randomized controlled trial in pediatric patients with HF did not demonstrate a beneficial trend.71 A multicenter prospective trial on beta blockade in patients with PAH is currently ongoing. In patients with tetralogy of Fallot, no generally consists of closure of any interatrial communications; antiarrhythmia procedures such as surgical division of accessory conduction pathways, cryoablation of atrioventricular node reentry tachycardia, or Maze procedure; and tricuspid valve surgery. The tricuspid valve is repaired when feasible, and tricuspid valve replacement is performed with a mechanical or heterograft bioprosthesis when repair is not feasible or the repair result is not satisfactory. A right reduction atrioplasty is often performed.3

In patients with valvular pulmonary stenosis, percutaneous valvotomy is recommended in asymptomatic patients with a peak instantaneous gradient by Doppler greater than 60 mm Hg or a mean Doppler gradient greater than 40 mm Hg or a symptomatic patient with a peak instantaneous Doppler gradient greater than 50 mm Hg or a mean Doppler gradient greater than 30 mm Hg. The RV usually remodels well after intervention, in the absence of severe RV enlargement.

Recent studies also suggest that patients with flail tricuspid valves may benefit from earlier repair. Messika-Zeitoun and colleagues have demonstrated that flail tricuspid valve is associated with a decreased survival and a high incidence of HF, atrial fibrillation and need for valve replacement.67 At this time, centers with low surgical mortality consider early intervention for asymptomatic patients with flail tricuspid valve.

### TABLE 5. Digoxin Therapy in Right Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Characteristics</th>
<th>No.</th>
<th>Design</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rich et al. 199864</td>
<td>Idiopathic pulmonary arterial hypertension</td>
<td>MPAP 60 mmHg, PCWP 12 mmHg, CO 3.49 L/min</td>
<td>17</td>
<td>Single arm prospective study</td>
<td>Beneficial acute effect: ↑CO by 9%, ↓circulating norepinephrine level by 15%</td>
</tr>
<tr>
<td>Rich et al. 199261</td>
<td>Idiopathic pulmonary arterial hypertension</td>
<td>MPAP 57 mmHg, CI 2.6 L/min/m², PVRI 27 unit/m²</td>
<td>64</td>
<td>Sub-study of a prospective CCB trial</td>
<td>No difference in survival at 5 years</td>
</tr>
<tr>
<td>Kawut et al. 200563</td>
<td>Idiopathic pulmonary arterial hypertension</td>
<td>MPAP 55 mmHg, Peak VO₂ 11.4 ml/kg/min, CI 1.8 L/min/m²</td>
<td>84</td>
<td>Retrospective study. Follow-up 764 days</td>
<td>No difference in survival</td>
</tr>
<tr>
<td>Mathur et al. 198165</td>
<td>Chronic obstructive pulmonary disease</td>
<td>Evidence of RV dysfunction but no history of heart failure</td>
<td>15</td>
<td>Cross-over RCT 8 weeks. Digoxin vs. placebo</td>
<td>No improvement in RVEF in the absence of LV systolic dysfunction</td>
</tr>
<tr>
<td>Brown et al. 198466</td>
<td>Chronic obstructive pulmonary disease</td>
<td>Decreased RVEF and no evidence of CHF</td>
<td>12</td>
<td>Cross-over RCT 2 weeks digoxin vs. placebo</td>
<td>No significant difference in RVEF or exercise duration</td>
</tr>
</tbody>
</table>

CCCB indicates calcium channel blocker; CHF, congestive heart failure; CI, cardiac index; CO, cardiac output; iNO, inhaled nitric oxide; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; RCT, randomized controlled trial; RV, right ventricular; RVEF, right ventricular ejection fraction.

*Unless otherwise specified, the results refer to statistically significant findings (P<.05). The changes reported refer to relative changes in mean effect size or when indicated by changes in absolute effect size.
benefit of the beta-blocker bisoprolol on exercise capacity was demonstrated, although this was only studied in patients with NYHA functional class I or 2.82 Finally in patients with pulmonary hypertension associated with liver disease (porto-pulmonary hypertension), a detrimental effect on hemodynamics was noted in a small study of 10 patients.70 The use of ACE inhibitors or angiotensin receptor blocker was also not associated with any significant beneficial effects on exercise capacity or hemodynamics in patients with systemic RV.75-80 Although the hydralazine and nitrate combination showed beneficial effects in some patients with LHF, the use of hydralazine in PAH was associated with either detrimental effects or less beneficial effects than prostacyclin therapy (Table 8).83-89

NITRIC OXIDE THERAPY AND RHF

Initially, there was a lot of enthusiasm surrounding the use of inhaled nitric oxide (iNO) in patients with RHF or pulmonary hypertension. This was based on the fact that iNO could provide selective pulmonary vasodilatation without causing systemic hypotension or worsening ventilation-perfusion mismatches. This enthusiasm was, however, curbed by the practical difficulties associated with its administration, the development of alternative therapies, and the failure of studies to show consistent benefits of iNO (Table 9). An interesting recent study has, however, showed that iNO could lead to acute hemodynamic improvement when administrated to patients with RV myocardial infarction complicated by cardiogenic shock.90

At this time, iNO is primarily used for acute vasoreactivity testing in PAH, and treatment of patients with acute RHF or severe hypoxemia following lung transplantation (Table 9).49,90-101 Small reports also suggest that iNO may increase left filling pressures and precipitate pulmonary edema in patients with concomitant LHF.92

The role of prophylactic iNO in patients with pulmonary hypertension undergoing cardiac surgery remains controversial. Ongoing studies are investigating the role of inhaled vasodilators such as milrinone or sildenafil in preventing post-operative RHF following cardiac surgery.102,103
expressed in the smooth muscle cells of the coronary arteries), its expression is markedly increased in the hypertrophied RV (as well as in the neonatal RV).59,104 Ongoing multicenter studies are currently underway to assess the effects of sildenafil in patients with diastolic HF.

PHOSPHODIESTERASE 5 INHIBITORS IN PATIENTS WITH RHF OR PULMONARY HYPERTENSION

The use of phosphodiesterase-5 inhibitors in the treatment of PAH has received much attention in the last few years.47-51 PDE5 inhibitors have beneficial effects on pulmonary vascular remodeling with minimal effects on the systemic vasculature (other than the penile circulation). Sildenafil has also been shown to improve RV remodeling and contractility. While expression of phosphodiesterase 5 (PDE5) is minimal in the normal RV (where it is only expressed in the smooth muscle cells of the coronary arteries), its expression is markedly increased in the hypertrophied RV (as well as in the neonatal RV).59,104 Ongoing multicenter studies are currently underway to assess the effects of sildenafil in patients with diastolic HF.

INOTROPIC THERAPY

Inotropic therapy is indicated in patients with acute RHF and signs of low cardiac output. Among the inotopic or vasopressor agents, dobutamine has been the most extensively studied in RHF.105,106

### TABLE 7. Beta Blockade in Patients With Right Heart Failure

| Study | Study Population | Characteristics | No. | Design | Main Findings[^a]
|-------|-----------------|-----------------|-----|--------|---------------------
| Beck-da-Silva et al. 2004[^a] | Biventricular Heart Failure | NYHA II-III, RVEF 31%, LVEF 22% | 30 | Prospective, Bisoprolol for 4 months | Beneficial effect: ↑RVEF by 7.1%^[^b] and ↑LVEF by 7.9%^[^b]
| Quaife et al. 1998[^a] | Biventricular Heart Failure | NYHA II-III, RVEF 27%, LVEF 23% | 22 | RCT. Carvedilol vs placebo for 4 months | Beneficial effect: ↑RVEF by 11%^[^b]
| Provencher et al. 2006[^a] | Porto-pulmonary hypertension | NYHA III, MPAP 52 mmHg, CO 5.24 L/min, 6WMT 338 m | 10 | Prospective, Propranolol or Atenolol | Detrimental effect: ↑cardiac output 28%, ↑6WMT by 79m at one month once beta-blockers withdrawn
| Shaddy et al. 2007[^a] | Congenital heart disease or Left Heart Failure | Dilated CM and systemic RV, Age < 13 yrs, LVEF 27%, NYHA class II & III | 161 | Multicenter RCT, Carvedilol vs Placebo for 8 months | No difference. In patients with systemic LV, a trend towards improvement was noted
| Doughan et al. 2007[^a] | Congenital heart disease | D-TGA (atrial baffle), Adults, RVEF 35%, NYHA class I to III | 60 | Retrospective study. Carvedilol or Metoprolol for 4 months | Beneficial effect: ↓NYHA class especially if pacemaker or initial NYHA class III, Prevents further chamber dilatation
| Josephson et al. 2006[^a] | Congenital heart disease | D-TGA (atrial baffle), NYHA mainly class II, Adults, RV diameter 41.5 mm | 8 | Retrospective study. Median FU of 3 yrs Carvedilol Metoprolol, Sotalol | Beneficial effect: ↓NYHA class in 5 patients
| Giardini et al. 2006[^a] | Congenital heart disease | D-TGA (atrial baffle), L-TGA, Age > 18 yrs, NYHA class II & III, RVEF 34% | 8 | Single arm prospective, Carvedilol for 12 months | Beneficial effect: ↓RVED volume by 6%, ↑RVEF 6%. No change in peak VO2[^c]
| Norozi et al. 2007[^a] | Congenital heart disease | Tetralogy of Fallot, NYHA I and II, Adults, LVEF 57%, CI 3.6 L/min/m² | 33 | RCT, Bisoprolol vs. placebo for 6 months | No difference in peak VO2, RVEF, ventricular volumes, NYHA class

[^6WMT]: indicates 6 minutes walk test; CI, cardiac index; CO, cardiac output; LVEF, left ventricular ejection fraction; MPAP, mean pulmonary arterial pressure; NYHA, New York Heart Association; RCT, randomized controlled trial; RV, right ventricular; RVED, RV end-diastolic volume; RVEF, indicated right ventricular ejection fraction; TGA, transposition of great arteries.

[^a]: Changes in absolute effect size.

[^b]: Unless otherwise specified, the results refer to statistically significant findings (P<.05). The changes reported refer to relative changes in mean effect size.
In RVMI, dobutamine increased cardiac index and stroke volume while maintaining preload. In PAH, dobutamine at doses of 2-5 mcg/kg/min increase cardiac output while decreasing pulmonary vascular resistance. The combination of dobutamine and iNO in pulmonary hypertension has also been shown to increase cardiac index, decrease pulmonary vascular resistance and significantly increase PaO2/FiO2 ratio. Dopamine use is often reserved for hypotensive patients, while milrinone is preferred in the presence of tachyarrhythmias. While epinephrine infusion is commonly used in the intensive care unit, its specific effects in pulmonary hypertension have not been well studied.

Levosimendan is a calcium sensitizer with inotropic properties. Recent studies suggest that levosimendan could improve RV function or pulmonary hemodynamics in patients with biventricular failure or ARDS. Future studies will determine its role in managing patients with acute RHF.

### MAINTENANCE OF SINUS RHYTHM RESYNCHRONIZATION THERAPY

Maintenance of sinus rhythm and heart rate control is important in RHF. Advanced AV block or atrial fibrillation can have profound hemodynamic effects in patients with acute RHF or severe RV dysfunction. In patients with LHF, cardiac resynchronization therapy (CRT) has been shown to improve both survival and exercise capacity and is currently indicated in patients with a QRS>120msec and evidence of LV systolic dysfunction (LVEF<35%). Recent studies also suggest that resynchronization may be beneficial in patients with RHF (Table 10).

### PREVENTION OF SUDDEN DEATH AND DEFIBRILLATOR THERAPY

The mechanisms of sudden death in patients with RHF vary depending on its etiology. Ventricular tachycardia/RV fibrillation,
### TABLE 9. Nitric Oxide in Patients With Right Heart Failure or Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Characteristics</th>
<th>No.</th>
<th>Design</th>
<th>Main Findings*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inglessis et al. 2004</td>
<td>RVMI</td>
<td>MPAP 28 mmHg, PCWP 19 mmHg, CI 1.7 L/min/m², 10 patients intubated</td>
<td>13</td>
<td>Prospective study, iNO and O₂ for 10 minutes</td>
<td>Beneficial effect: ↑CI by 24%, ↓RAP by 2%, ↓MPAP by 13%, ↓PVR by 36%</td>
</tr>
<tr>
<td>Koelling et al. 1998</td>
<td>Biventricular heart failure</td>
<td>MPAP 24 mm Hg, CI 2.3 L/min/m², PCWP 16 mmHg, LVEF 25%</td>
<td>14</td>
<td>Prospective study, iNO during exercise</td>
<td>Beneficial effect: on exercise capacity in selected patients with SPAP &gt;30 mm Hg, LVEDVI &gt;123 mL/m² or RVEF &lt; 35%</td>
</tr>
<tr>
<td>Bocchi et al. 1994</td>
<td>Left heart failure with pulmonary hypertension</td>
<td>NYHA III, MPAP 48 o 89 mmHg, PCWP 25 to 36 mmHg</td>
<td>3</td>
<td>Prospective study, iNO vs. nitroprusside</td>
<td>Detrimental effect: ↑PCWP and pulmonary edema in all patients with iNO</td>
</tr>
<tr>
<td>Morales-Blanhir et al 2004</td>
<td>Pulmonary arterial hypertension</td>
<td>NYHA class II &amp; III, MPAP 50 mmHg, CI 2.2 L/min/m², PCWP 5 mmHg</td>
<td>27</td>
<td>Prospective study, iNO vs. PGI₂ iv followed by oral vasodilator</td>
<td>Beneficial effect: acute vasodilator response with iNO better predicts response to oral agents than PGI₂</td>
</tr>
<tr>
<td>Adhikari et al. 2007</td>
<td>ALI or ARDS</td>
<td>Meta analysis</td>
<td>1237</td>
<td></td>
<td>No beneficial effect. Mortality unchanged</td>
</tr>
<tr>
<td>Rea et al. 2005</td>
<td>Heart and lung transplantation</td>
<td>Systematic review</td>
<td>257</td>
<td>iNO</td>
<td>Beneficial effects in heart transplant. Reduces incidence of RHF, no change in mortality at 30 days</td>
</tr>
<tr>
<td>Khan et al. 2003</td>
<td>Heart or lung transplantation</td>
<td>Early post-op right heart failure, MPAP 32–37 mmHg, CI 2.5–2.6 L/min/m², PaO₂/FIO₂ of 300</td>
<td>25</td>
<td>RT, iNO or PGI₂ for 6 hours each</td>
<td>Beneficial effect: NO: iNO and iPGI₂ had comparable effects on hemodynamics</td>
</tr>
<tr>
<td>Wagner et al. 1997</td>
<td>Right heart failure after LVAD</td>
<td>MPAP &gt;25 mm Hg, RVEF &lt;30%, CI 2.0 L/min/m²</td>
<td>8</td>
<td>Prospective study, iNO</td>
<td>Beneficial effect: ↓PVR by 37.5% ↑CI by 35% Effect more pronounced at 48 hours with ↑RVEF by 20%</td>
</tr>
<tr>
<td>Argenziano et al. 1998</td>
<td>Pulmonary hypertension post LVAD</td>
<td>MPAP 32 mmHg, LVAD flow rate 2.0 L/min/m²</td>
<td>11</td>
<td>RCT- iNO vs. placebo</td>
<td>Beneficial effect: ↓mPAP by 31% ↑LVAD flow index by 25%</td>
</tr>
<tr>
<td>Fattouch et al. 2005</td>
<td>Post MVR with pulmonary hypertension</td>
<td>NYHA III &amp; IV, MPAP 45 mm Hg, PCWP 29 mmHg, CO 4.5 L/min</td>
<td>58</td>
<td>RT, iPGI₂ vs INO vs NTP in the ICU</td>
<td>Beneficial effect: iPGI₂ and iNO ↓mPAP and PVR and ↑ CO. NTP was associated with systemic hypotension in 68%</td>
</tr>
<tr>
<td>Solina et al. 2001</td>
<td>Post CPB with pulmonary hypertension</td>
<td>CI 2.1–2.4 L min⁻¹ m⁻², PVR 287–420 Dyn sec cm⁻¹, RVEF 26–34%</td>
<td>62</td>
<td>RCT, iNO vs. milrinone IV</td>
<td>Beneficial effects of both agents (non-significant difference between agents in terms of hemodynamics)</td>
</tr>
</tbody>
</table>

*Unless otherwise specified, the results refer to statistically significant findings (∗∗P<.05). The changes reported refer to relative changes in mean effect size.

ALI indicates acute lung injury; CI, cardiac index; CO, cardiac output; iNO, inhaled nitric oxide; MPAP, mean pulmonary arterial pressure; NTP, nitroprusside; LAVD, left ventricular assist device; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; PGI₂, prostacyclin; PCWP, pulmonary capillary wedge pressure; post-op- post-operative; RCT, randomized controlled trial; RT, randomized trial; RVEF, right ventricular ejection fraction; SPAP, systolic pulmonary arterial pressure. Although the study of Bocchi et al² had only 3 patients, it was included in the table because it is often referenced.
In patients with advanced refractory RHF, transplantation can be considered after exclusion of all reversible causes and careful consideration of contraindications. In appropriate patients with severe pulmonary vascular disease, heart-lung or double lung transplantation are considered. Because of scarcity of organs, heart-lung transplantation is usually considered only in patients with congenital heart defects and in patients in whom the physician considers recovery of right heart function unlikely. Predictors of persistent RV failure after double lung transplantation have, however, not been well established at this time.

The observation of improved survival of patients with pulmonary hypertension and patent foramen ovale has led to the hypothesis that atrial septostomy, which “decompresses” the RV and increases right to left shunting, could be helpful in severe RV failure. The response to atrial septostomy in pulmonary hypertension is variable. At this time, atrial septostomy should be considered palliative.

In patients with acute RHF refractory to medical treatment, mechanical support of the RV is sometimes used as a bridge to transplantation or a bridge to recovery. The most common indications for RVAD use are severe RV failure after LV assist device, RV failure after heart transplantation or RV failure after massive pulmonary embolism.

### TABLE 10. Resynchronization Therapy in Patients with RHF

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Characteristics</th>
<th>No.</th>
<th>Design</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janousek et al. 2001</td>
<td>Congenital Heart Disease</td>
<td>Children with acute post-operative heart failure with conduction delay</td>
<td>20</td>
<td>Prospective study</td>
<td>Beneficial effects. Improvement in hemodynamics. Improvement in systolic blood pressure</td>
</tr>
<tr>
<td>Dubin et al. 2003</td>
<td>Congenital Heart Disease</td>
<td>Chronic RV dysfunction, RBBB TOF, aortic stenosis after Ross procedure</td>
<td>7</td>
<td>Prospective, Multipacing sites, conductance catheter</td>
<td>Beneficial effect. Atrioventricular augments RV and systemic performance (↑CI by 17±8%, ↑ in RV dP/dt)</td>
</tr>
<tr>
<td>Janousek et al. 2004</td>
<td>Congenital Heart Disease</td>
<td>D-TGA (atrial baffle) L-TGA</td>
<td>8</td>
<td>Prospective</td>
<td>Beneficial effect. ↑RVEF by 9.6%, ↓RVMPI by 7.7%</td>
</tr>
<tr>
<td>Dubin et al. 2005</td>
<td>Congenital Heart Disease and Pediatric</td>
<td>CHD and dilated CMP and congenital atrioventricular block</td>
<td>103</td>
<td>Multicenter Study (22 centers)</td>
<td>Beneficial effects in all 3 groups. Average ↑ in EF 11.9% to 16.1%. Responders had lower baseline EF</td>
</tr>
</tbody>
</table>

CI indicates cardiac index; EF, ejection fraction; RVEF, right ventricular ejection fraction; RVMPI, RV myocardial performance index; TGA, transposition of the great arteries; RBBB, right bundle branch block; RV, right ventricular; TOF, tetralogy of Fallot. Unless otherwise specified, the results refer to statistically significant findings (P<.05). The changes reported refer to relative changes in mean effect size. The changes reported refer to relative changes in mean effect size or when indicated by changes in absolute effect size.
Permanent implantation or “destination therapy” for chronic advanced RV failure has not been studied. Future studies will determine whether mechanical support using axial flow devices could be of benefit in patients with refractory RHF with a contraindication to transplantation.

PERILS AND PITFALLS

Management of RHF may be at the same time simple and complex. In order to optimize patient care, several pitfalls should be avoided. Among them, the most common ones include: a) ordering maximal exercise testing in patients with severe pulmonary vascular disease; b) failure to exclude chronic thromboembolic disease as a cause of pulmonary hypertension; c) delaying referral to a specialized center for appropriate surgical, interventional or medical therapy; d) excessively volume loading a patient with acute RHF; or e) closing an atrial septal defect in a patient with severe pulmonary vascular disease. Caution should also be advised when using inhaled nitric oxide or sildenafil in patients with severe left ventricular filling pressures as increased cardiac output can precipitate pulmonary edema.

EMERGING THERAPIES FOR RHF

In the next few years, several specific therapies for RHF are potentially emerging. Among therapies that improve energy utilization of the heart, metabolic modulators are probably the most promising at this time. Recent experimental studies show that metabolic modulation reverses maladaptive RV remodeling in rats with monocrotaline induced PAH.\(^\text{16,114-117}\) Other potential new therapies include myosin activators, Na/K–ATPase inhibitors, adenosine or vasopressin antagonists or micro-RNA modulators.\(^\text{118}\) An interesting case report also suggests that tricuspid annuloplasty could play a role in managing patients with severe PAH.\(^\text{119}\)

CONCLUSION

RHF is a complex clinical syndrome that presents with lower extremity edema, ascites, decreased exercise tolerance, or arrhythmia. Common causes of RHF include right ventricular myocardial infarction, pulmonary embolism, congenital heart disease, and pulmonary hypertension from a variety of causes. At this time, advances in therapy have mainly been made in treatment of pulmonary arterial hypertension and surgical repair of complex congenital lesions. Ongoing studies will investigate the role of betablockade or cardiac resynchronization therapy in patients with PAH. Emerging new therapies may include metabolic modulators or myosin activators.

ACKNOWLEDGMENTS

We want to acknowledge the educational support of the Vera Moulton Wall Center for Pulmonary Vascular Disease at Stanford as well as the support of the Division of Cardiology of Stanford University.

REFERENCES

11. Jadad AR, Moher D, Klassen TP. Guides for reading and interpreting systematic reviews: II. How did the authors find...
33. Oosterhof T, Tulevski II, Vliegen HW, Spijkerboor AM, Mulder BJ. Effects of volume and/or pressure overload secondary to congenital heart disease (tetralogy of fallot or pulmonary stenosis) on right ventricular function using cardiovascular magnetic resonance and B-type natriuretic peptide levels. Am J Cardiol. 2006;97:1051-5.


