Right Ventricular Function and Failure

Report of a National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure

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Knowledge about the role of the right ventricle in health and disease historically has lagged behind that of the left ventricle. Less muscular, restricted in its role to pumping blood through a single organ, and less frequently or obviously involved than the left ventricle in diseases of epidemic proportions such as myocardial ischemia, cardiomyopathy, or valvulopathy, the right ventricle has generally been considered a mere bystander, a victim of pathological processes affecting the cardiovascular system. Consequently, comparatively little attention has been devoted to how right ventricular dysfunction may be best detected and measured, what specific molecular and cellular mechanisms contribute to maintenance or failure of normal right ventricular function, how right ventricular dysfunction evolves structurally and functionally, or what interventions might best preserve right ventricular function. Nevertheless, even the proportionately limited information related to right ventricular function, its impairment in various disease states, and its impact on the outcome of those diseases suggests that the right ventricle is an important contributor and that further understanding of these issues is of pivotal importance.

For this reason, the National Heart, Lung, and Blood Institute convened a working group charged with delineating in broad terms the current base of scientific and medical understanding about the right ventricle and identifying avenues of investigation likely to meaningfully advance knowledge in a clinically useful direction. The following summary represents the presentations and discussions of this working group.

The right ventricle is affected by and contributes to a number of disease processes, including perhaps most notably pulmonary vascular diseases (cor pulmonale). Other diseases affect the right ventricle in different ways, including global, left ventricular–, or right ventricular–specific cardiomyopathy; right ventricular ischemia or infarction; pulmonary or tricuspid valvular heart disease; and left-to-right shunts.

The Normal Right Ventricle

The right ventricle pumps the same stroke volume as the left ventricle but with ≈25% of the stroke work because of the low resistance of the pulmonary vasculature. Therefore, by virtue of the Laplace relationship, the right ventricle is more thin walled and compliant (Figure 1). The geometry of the chamber is complex, consisting of an inlet (sinus) portion and an outlet (conus) section separated by the crista supraventricularis. Longitudinal shortening is a greater contributor to right ventricular stroke volume than short-axis (circumferential) shortening.1 It is linked to the left ventricle in several ways: by a shared wall (the septum), by mutually encircling epicardial fibers, by attachment of the right ventricular free wall to the anterior and posterior septum, and by sharing the pericardial space. The septum and free wall contribute approximately equally to right ventricular function. The right ventricular free wall blood supply is predominantly from the right coronary artery and receives about equal flow during systole and diastole. The left anterior descending coronary artery supplies the anterior two thirds of the septum, and the posterior descending artery supplies the inferoposterior one third.

The Right Ventricle in Pulmonary Hypertension

The right ventricle is exposed to pressure overload by pulmonary valve stenosis or by chronic pulmonary hyperten-
from any cause (Table 1). An initial adaptive response of myocardial hypertrophy is followed by progressive contractile dysfunction. Chamber dilatation ensues to allow compensatory preload and maintain stroke volume despite reduced fractional shortening. As contractile weakening progresses, clinical evidence of decompensated right ventricular failure occurs, characterized by rising filling pressures, diastolic dysfunction, and diminishing cardiac output, which is compounded by tricuspid regurgitation due to annular dilatation and poor leaflet coaptation. The increased size and pressure overload of the right ventricle also produce diastolic dysfunction of the left ventricle. Thus, the function and size of the right ventricle are not only indicators of the severity and chronicity of pulmonary hypertension but impose an additional cause of symptoms and reduced longevity. Right ventricular function is the most important determinant of longevity in patients with pulmonary arterial hypertension. The specific mechanisms underlying the development of right ventricular failure secondary to pulmonary hypertension are unclear. For example, it is uncertain whether some patients develop right ventricular myocardial ischemia, whether there is microvascular endothelial cell dysfunction, and whether or not myocytes undergo apoptosis. In severe, end-stage pulmonary hypertension, the shape of the right ventricle is changed from the normal conformation, and right ventricular wall stress and right ventricular free wall thickness appear to be inversely related (Figure 2). The mechanism by which a severely dilated “end-stage” right ventricle repairs itself after lung transplantation is also uncertain.

### Table 1. Classification of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension</th>
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<tr>
<td>1.1. Idiopathic (IPAH)</td>
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<tr>
<td>1.2. Familial (FPAH)</td>
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<tr>
<td>1.3. Associated with (APAH):</td>
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<tr>
<td>1.3.1. Collagen vascular disease</td>
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<td>1.3.2. Congenital systemic-to-pulmonary shunts</td>
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<td>1.3.3. Portal hypertension</td>
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<td>1.3.4. HIV infection</td>
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<td>1.3.5. Drugs and toxins</td>
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<tr>
<td>1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher’s disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)</td>
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<tr>
<td>1.4. Associated with significant venous or capillary involvement</td>
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<tr>
<td>1.4.1. Pulmonary veno-occlusive disease (PVOD)</td>
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<tr>
<td>1.4.2. Pulmonary capillary hemangiomatosis (PCH)</td>
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<tr>
<td>1.5. Persistent pulmonary hypertension of the newborn</td>
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<tr>
<td>2. Pulmonary hypertension with left heart disease</td>
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<tr>
<td>2.1. Left-sided atrial or ventricular heart disease</td>
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<tr>
<td>2.2. Left-sided valvular heart disease</td>
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<tr>
<td>3. Pulmonary hypertension associated with lung diseases and/or hypoxemia</td>
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<tr>
<td>3.1. Chronic obstructive pulmonary disease</td>
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<td>3.2. Interstitial lung disease</td>
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<tr>
<td>3.3. Sleep-disordered breathing</td>
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<td>3.4. Alveolar hypoventilation disorders</td>
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<td>3.5. Chronic exposure to high altitude</td>
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<td>3.6. Developmental abnormalities</td>
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<tr>
<td>4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease</td>
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<tr>
<td>4.1. Thromboembolic obstruction of proximal pulmonary arteries</td>
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<tr>
<td>4.2. Thromboembolic obstruction of distal pulmonary arteries</td>
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<tr>
<td>4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)</td>
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<tr>
<td>5. Miscellaneous</td>
</tr>
<tr>
<td>Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)</td>
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left ventricular dilation in a limited pericardial compartment may restrict right ventricular diastolic function. Conversely, right ventricular pressure overload, as may occur with pulmonary hypertensive states, may compromise left ventricular function and lead to coincident evidence of left ventricular failure, such as pulmonary edema or effusion. Furthermore, when the right ventricle fails in the setting of left ventricular failure, it may be unable to maintain the flow volume required to maintain adequate left ventricular preload. Because of the multiple influences affecting right ventricular function due to left ventricular failure, right ventricular status may constitute a “common final pathway” in the progression of congestive heart failure and therefore may be a sensitive indicator of impending decompensation or poor prognosis.

Despite variations in study populations, severity and substrates of disease, and methodologies of assessment, studies demonstrate substantial agreement that evidence of right ventricular dysfunction portends an inferior outcome. Patients with ischemic cardiomyopathy and left ventricular ejection fractions of 18±8% who die during the next 2 years have a worse right ventricular ejection fraction (24±10% by radionuclide ventriculography) than survivors (42±23%). Among patients with an acute myocardial infarction, the presence of a low radionuclide right ventricular ejection fraction (<0.38) plus low left ventricular ejection fraction (<0.30) results in 3 times the 1-year mortality of patients with poor left ventricular function alone.

Patients with myocarditis and poor right ventricular function, defined as a low right ventricular descent (difference between the diastolic and systolic distance from the right ventricle apical endocardium to a perpendicular line through the tricuspid annulus; normal=2±0.2 cm), have a higher likelihood of death or transplantation than those with normal right ventricular function. Indeed, right ventricular dysfunction is the strongest predictor of a negative outcome.

The right ventricular ejection fraction (measured by thermodilution techniques) of patients with idiopathic dilated cardiomyopathy correlates linearly with echocardiographic left ventricular ejection fraction, and, by multivariate analysis of a large number of parameters, only right ventricular ejection fraction and left ventricular ejection fraction are predictors of survival. Survival is also predicted for patients with idiopathic dilated cardiomyopathy by increased diastolic right ventricular chamber area measured echocardiographically, and survival of patients with right ventricular enlargement out of proportion to left ventricular enlargement is poorer. Survival, left ventricular ejection fraction, and symptoms are worse in dilated cardiomyopathy patients with angiographically documented biventricular dysfunction (left ventricular ejection fraction <50%, right ventricular ejection fraction <35%) compared with those with left ventricular dysfunction alone.

In patients with advanced congestive heart failure due to cardiomyopathy or ischemia, right ventricular shortening is the only significant independent associate of survival by multivariate analysis (as opposed to other parameters including left ventricular ejection fraction, cardiac index, and pulmonary resistance). Patients with right ventricular shortening <1.25 cm have a significantly worse actuarial survival over 2 years.
The occurrence of hemodynamic and symptomatic right heart failure under these circumstances suggests that although the circulation can be maintained adequately when the right ventricle is bypassed (as in appropriately selected patients receiving a Fontan procedure), it is more susceptible to deterioration when a defective right ventricle is present. Thus, the enlarged hypocontractile right ventricle appears to play an active role in compromising overall circulatory status. Whether this is due to ventricular interaction, septal involvement, restrictive physiology, or other mechanisms is not established.

The Right Ventricle Is Different From the Left Ventricle

Whereas passive back-pressure, ventricular interdependence, or diffuse disease may account for biventricular dysfunction in most instances of left ventricular failure, recent evidence has emerged that suggests that the ventricles are also categorically different. It is now recognized that the ventricles are also categorically different and that these differences may have implications in the assessment and treatment of patients with predominantly right, left, or biventricular heart failure. For these reasons, right ventricular failure cannot be understood simply by extrapolating data and experience from left ventricular failure.

The Genetic, Molecular, and Cellular Biology of Right Ventricular Development, Function, and Dysfunction

The genetic investigation of cardiac morphogenesis has shown that the right ventricle and the left ventricle originate from different progenitor cells and different sites: The primary heart field gives rise to the atrial chambers and the left ventricle, whereas the cells of the anterior heart field develop into the outflow tract and the right ventricle. The discovery of 2 chamber-restricted basic helix-loop helix transcription factors, HAND1 and HAND2, and studies of knockout mice led to the recognition of chamber-specific gene expression with different transcriptional events leading to right ventricle and left ventricle formation. The transcription factor Bop, as a regulator of right ventricular development, is now recognized to be a transcriptional target of myocyte.
enhancer factor 2C,49 and GATA4 is required for HAND2 expression and right ventricular formation.50 GATA4 regulates cardiac muscle–specific expression of the α-myosin heavy chain gene51 and the gene encoding atrial natriuretic factor.52

The degree of right ventricular hypertrophy in idiopathic pulmonary arterial hypertension, measured as right ventricular wall thickness, is highly variable (0.6 to 1.5 cm),10 and, as in the failing left ventricle, there is evidence for changes of gene expression in the pressure-overloaded failing right ventricle in patients with idiopathic pulmonary arterial hypertension.53 In particular, it appears that there is a recapitulation of the fetal gene pattern with a decrease in the α-myosin heavy chain gene and an increase in the expression of the fetal β-myosin heavy chain.

Clinical experience suggests that some patients with cardiomyopathy or pulmonary arterial hypertension develop right ventricular failure earlier than others as assessed by right heart filling pressures and cardiac output at the time of diagnosis.54 This has suggested that there may be a genotypic difference between patients; some patients develop greater hypertrophy (thicker free wall) of the right ventricle for the same degree of afterload than do others.10 A small cohort study of patients with idiopathic pulmonary arterial hypertension suggested that patients with the angiotensin-converting enzyme DD polymorphism had a normal right atrial pressure and cardiac output, whereas the non-DD patient group demonstrated increased right atrial pressure and decreased cardiac output.55 Whereas it is unlikely that this polymorphism alone can explain differences in degree of right ventricular hypertrophy between patients, this observation has suggested the concept of genetically controlled right ventricular hypertrophy.

Mechanics of Right Ventricular Function
Despite the aforementioned observations, the mechanisms by which left ventricular failure leads to right ventricular dysfunction are incompletely understood. Congestive heart failure adversely affects lung mechanics and gas exchange.56 Pulmonary function abnormalities include a reduction in lung volumes with decreased lung compliance.57,58 Although this restrictive lung physiology is improved somewhat by fluid removal or after heart transplantation, the reduced alveolar-capillary membrane diffusing capacity is not reversible, demonstrating the clinical importance of lung structural remodeling in heart failure.59–61 The lungs from animal models of heart failure as well as from humans with pulmonary venous hypertension demonstrate septal thickening with myofibroblast proliferation and interstitial matrix deposition.62,63 The physical and biological determinants of these changes and their eventual impact on the development of right ventricular failure are currently unknown.

Measurement of Right Ventricular Function
Implicit in the discussion of right ventricular function and dysfunction is the notion that there are reliable means by which to assess these parameters and that there is agreement about what meaningfully defines “function” or “dysfunction.” The measurement of right ventricular function is difficult for many reasons, in part because of the interplay between intrinsic myocardial performance and right ventricular loading conditions. The development of load-independent markers of right ventricular function is a worthwhile goal. Markers of right ventricular dysfunction that have reported implications for clinical deterioration and mortality in heart failure or pulmonary hypertension are shown in Table 2.77–93 The extent to which any of these parameters are useful as outcome measures in clinical research or practice remains unclear.

Treatment of Right Ventricular Dysfunction
Current therapies directed toward pulmonary vasoconstriction, cellular proliferation, and thrombotic factors have improved the quality of life and survival in many patients with severe pulmonary arterial hypertension.61 Likewise, therapies with afterload-reducing agents, β-receptor antagonists, inotropes, and diuretics have improved the functional status and prognosis of patients with left ventricular failure. Moreover, acute responsiveness to pulmonary vasodilators is associated with a better prognosis and survival in patients with advanced heart failure.54,65 Afterload reduction, however, cannot be achieved in many cases, but the increased right ventricular wall thickness and reversal of a fetal gene expression program have not yet been investigated as potential targeted treatments. Chronic intravenous epoprostenol infusion therapy in patients with pulmonary arterial hypertension appears to improve right ventricular function66,67 (although dilation and hypertrophy may not reverse over a 1-year period of observation68), and the effects of the endothelin receptor antagonist bosentan on echocardiographic right ventricular parameters have also suggested a similar improvement in right ventricular function.69 However, the specific myocardial effects of these or other therapies for pulmonary arterial hypertension remain incompletely understood. In addition, right ventricular function, right ventricular–left ventricular interaction, and right ventricular–pulmonary arterial coupling have largely been overlooked as potential targets for investigation or therapy.
Continuous intravenous prostacyclin (epoprostenol) infusion therapy improves survival in idiopathic pulmonary arterial hypertension patients more than in patients with the limited variant of scleroderma-associated pulmonary arterial hypertension. Although the reasons for this discrepancy in treatment outcome are not clear, one possible explanation is the presence of a myocardial global microangiopathy in scleroderma patients.70

**Future Directions**
Given the pivotal involvement of the right ventricle in both common and rare cardiovascular diseases and the paucity of basic knowledge at all levels about its normal and pathological functions, support for further research should be a high priority for investigators and National Institutes of Health funding. Areas of deficient understanding worthy of further exploration include the following issues.

**Measurement**
Although a fair amount of study has been devoted to assessment of right ventricular function, there remains a need to understand how to better define normal parameters of right ventricular function. Critical information is required to determine the most sensitive and specific variables to describe abnormal right ventricular function. It is likely that the definition of function will include parameters of geometry, ejection volume, hypertrophy, dilation, contraction, and oxygen supply to the ventricular wall. A clear picture of these parameters would help in determining which measurements are the best predictors of early right ventricular failure (such as right ventricular wall thickness, muscle perfusion, or metabolic activity). Ideally, a combination of approaches would be used to evaluate right heart function, including imaging techniques (Doppler echocardiography, computed tomography, magnetic resonance imaging, positron emission tomography), implanted continuous monitoring devices, and electrophysiology. Collaboration with the National Institute of Biomedical Imaging and Bioengineering to promote the development of imaging methods to study right ventricular function and dysfunction should be encouraged.

**Distinguishing Characteristics of Right Heart Compared With Left Heart**
Preliminary inquiry suggests that there are distinctions between the ventricles that need to be further evaluated and clarified to understand the differences, similarities, and interplay between the left and right heart. This issue can be addressed with chamber-specific studies in animal models that examine changes in gene expression, protein synthesis, histology, and geometry during development, injury, and stress (exercise and disease).

**Investigation of Mechanism and Role of Hypertrophy**
Although initial right ventricular hypertrophy in response to pressure overload may be adaptive, it is also the seemingly initial step in a remodeling process that is ultimately damaging, perhaps irreversibly so. Attention should be devoted to determining whether right ventricular hypertrophy is good or bad. Research is needed to compare hypertrophy seen in athletes with that seen in patients with diseases such as pulmonary arterial hypertension. Mechanisms of right ventricular hypertrophy and remodeling need to be determined.

**Effect of Pulmonary Disease on Right Ventricular Function**
Few studies address the interaction of right ventricular and pulmonary function. Research is needed to study the complex interaction of the heart and lungs and how changes in one affect the other. Examples of changes include inflammation, stress due to hypoxia or exercise, autoimmune reactions, infarction, and hypertension.

**Models of Right Ventricular Failure**
Researchers must develop reliable, reproducible, and relevant animal models of right ventricular failure. Animal models would be particularly useful in determining factors that initiate right ventricular dysfunction. Models would also help to identify biomarkers and changes in gene expression and protein synthesis associated with right ventricular failure. Valuable information could be obtained from animal models through side-by-side comparisons of changes in the left and right ventricles. Parameters on which to focus would include tissue analysis; gene and protein expression; and markers of oxidative stress, apoptosis, and cell growth. When possible, such analyses should compare tissue from patients with animal models of right heart failure and pulmonary hypertension to address the question of whether data obtained from manipulated animal right ventricles can be extrapolated to right ventricular or interventricular septal biopsy material from the hearts of patients with severe pulmonary hypertension. Animal models will be a necessary component to determine whether right ventricle failure is associated with myocyte apoptosis71–73 or cytokine expression74 (Figure 4).

In addition, data from animal studies suggest that significant differences exist between sexes in the development of right heart failure.75 Studies that further examine gender differences will be important for developing potential new therapeutics and determining whether treatment should be determined by sex.
Translational Research
An emphasis on translational research, particularly studies of human myocardial tissue, is required to determine the important markers of right ventricular function and dysfunction. Studies to identify markers in plasma as well as those in tissue might facilitate prediction of early diagnosis of ventricular dysfunction and may prevent failure. Robust parameters that predict outcome for patients with right heart failure are needed.

Right Ventricular Morphogenesis
The developmental aspects of right heart formation need to be studied to identify mechanisms involved in congenital heart disease and related pulmonary vascular disease.

Targeted Therapy
The development of new therapeutic strategies for right heart failure should be promoted. These new strategies might include cell-based or gene therapy, new drugs, or new combinations of existing drugs.

Awareness
Awareness should be promoted in the pulmonary and cardiology research communities about the lack of knowledge of the right ventricle with well-publicized requests for research proposals. New and established investigators should be encouraged to enter this fruitful area of research.

The consensus of the working group is that the role of the right ventricle in a spectrum of cardiovascular diseases has been relatively neglected proportionate to its central importance. Advancing knowledge through research about the unique genetic, molecular, cellular, and functional characteristics of the right ventricle and their vulnerability to disease will lead to progress in the treatment of cardiomyopathy, pulmonary arterial hypertension, right ventricular ischemic syndromes, and valvular heart disease. The success in such effort requires collaborations between and among clinical and basic investigators from various disciplines, including those in respiratory/pulmonary and cardiovascular fields as well from neuroscientists, immunologists, endocrinologists, and biomedical engineers. Joint meetings of the American Heart Association and the American Thoracic Society would be appropriate venues to promote the importance of understanding the right ventricle and would help to accelerate the gathering of information leading to better treatment and preventative means to reduce morbidity and mortality associated with right heart failure and left heart failure.

Sources of Funding
This workshop was sponsored by the National Institutes of Health, National Heart, Lung, and Blood Institute.

Disclosures
None.

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Circulation. 2006;114:1883-1891
doi: 10.1161/CIRCULATIONAHA.106.632208
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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