REVIEW ARTICLE

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Right Ventricular Failure

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In 1943, in an effort to better understand the role of the right ventricle in health and disease, Isaac Starr and colleagues performed a series of animal experiments in which they severely damaged the right ventricle. When they observed only a minimal increase in peripheral venous congestion, they concluded that "weakness of the right side of the heart…seems less important" in the dynamics of heart failure.[1] A similar conclusion was drawn from the apparent success of the Fontan procedure, which routes venous return directly into the pulmonary circulation, in patients with congenital heart disease. It was later shown that healthy patients who have undergone the Fontan procedure have a 40% decrease in exercise capacity, a finding that speaks to the relevance of the right ventricle even in healthy persons.[2] We also now know that the right ventricle plays a critical pathophysiological and prognostic role in numerous conditions, including left heart failure,[3] pulmonary arterial hypertension,[4] and even severe acute respiratory syndrome coronavirus 2 infection.[5]

During embryonic development, the right ventricle is formed from the secondary heart field into a crescent-shaped, thin-walled structure.[6] It is the most anterior heart chamber, sitting just beneath the sternum. The right ventricle and left ventricle are not distinct structures but rather are integrated anatomically and physiologically through the interventricular septum, with the right ventricle depending on the left ventricle for a substantial portion of its contractile function. This interaction is intensified in the context of right ventricular failure.[6,7] The helical orientation of the myofibrils in the septum produces a primarily longitudinal contractile pattern, whereas the circumferential fibers in the right ventricular free wall contribute a transverse shortening pattern. The latter is less prominent in normal physiology.

Pathophysiology of Right Ventricular Failure

The main determinants of right ventricular function, like those of left ventricular function, are preload, afterload, contractility, and lusitropy. The pathophysiological mechanisms of right ventricular failure can be conceptualized as acute or chronic abnormalities of right ventricular load (preload or afterload) or myocardial function (contractility [inotropy] and active relaxation [lusitropy]), though in clinical states of right ventricular failure, these mechanisms frequently coexist (Fig. 1). A detailed discussion of the pathophysiology of right ventricular failure is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Cellular and Molecular Mechanisms

Pathophysiological processes that initiate or promote right ventricular failure include myocyte hypertrophy, fibrosis, ischemia, neurohormonal activation, inflamma-

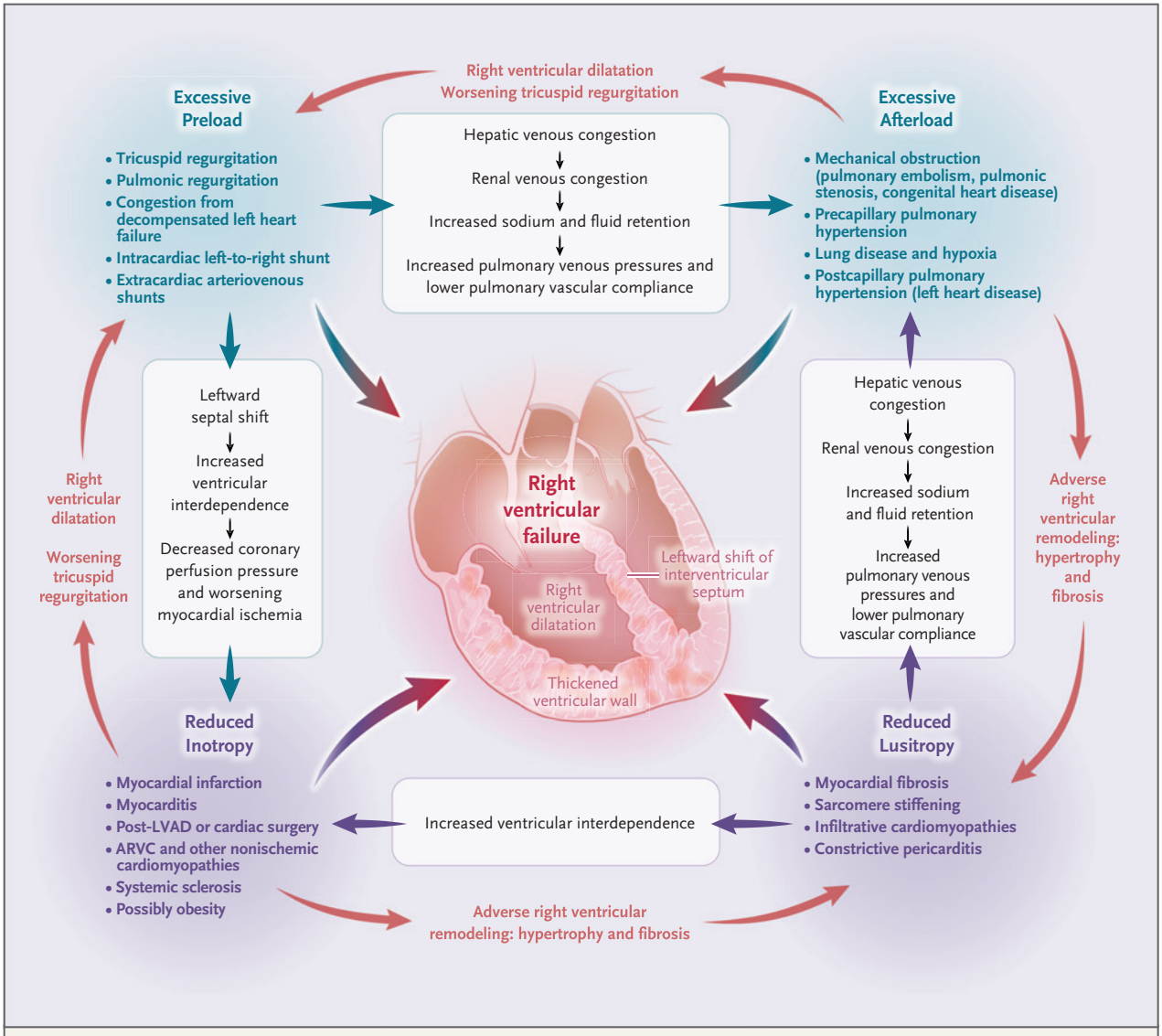


Figure 1. Mechanical Mechanisms of Right Ventricular Failure.

Mechanical mechanisms contributing to right ventricular failure can be conceptualized in four primary categories: excessive preload, excessive afterload, reduced contractility, and reduced lusitropy. These mechanisms frequently coexist and are often cocontributors in states of right ventricular failure. Excessive preload, for example, may concomitantly lead to increased pulmonary venous pressures and resultant increased afterload, through the pathophysiological cascade of hepatic and renal venous congestion, leading to increased sodium and fluid retention. Excessive right ventricular afterload may lead to right ventricular dilatation and worsening of tricuspid regurgitation, giving rise to concomitant preload excess. Excessive preload may lead to contractile impairment through a leftward septal shift, increased ventricular interdependence, and decreased coronary perfusion pressure. Both in isolation and in concert, these mechanical mechanisms may ultimately lead to either acute or chronic right ventricular failure. ARVC denotes arrhythmogenic right ventricular cardiomyopathy, and LVAD left ventricular assist device.

tion, and shifts in metabolic substrates (Fig. 2). (Additional discussion is provided in the Supplementary Appendix.) Most data on molecular mechanisms of right ventricular failure are derived from animal models or clinical studies of pulmonary arterial hypertension. The degree to which these findings apply to other causes of right ventricular failure is unknown.

Chronically increased afterload from any cause results in right ventricular hypertrophy,[9] which is

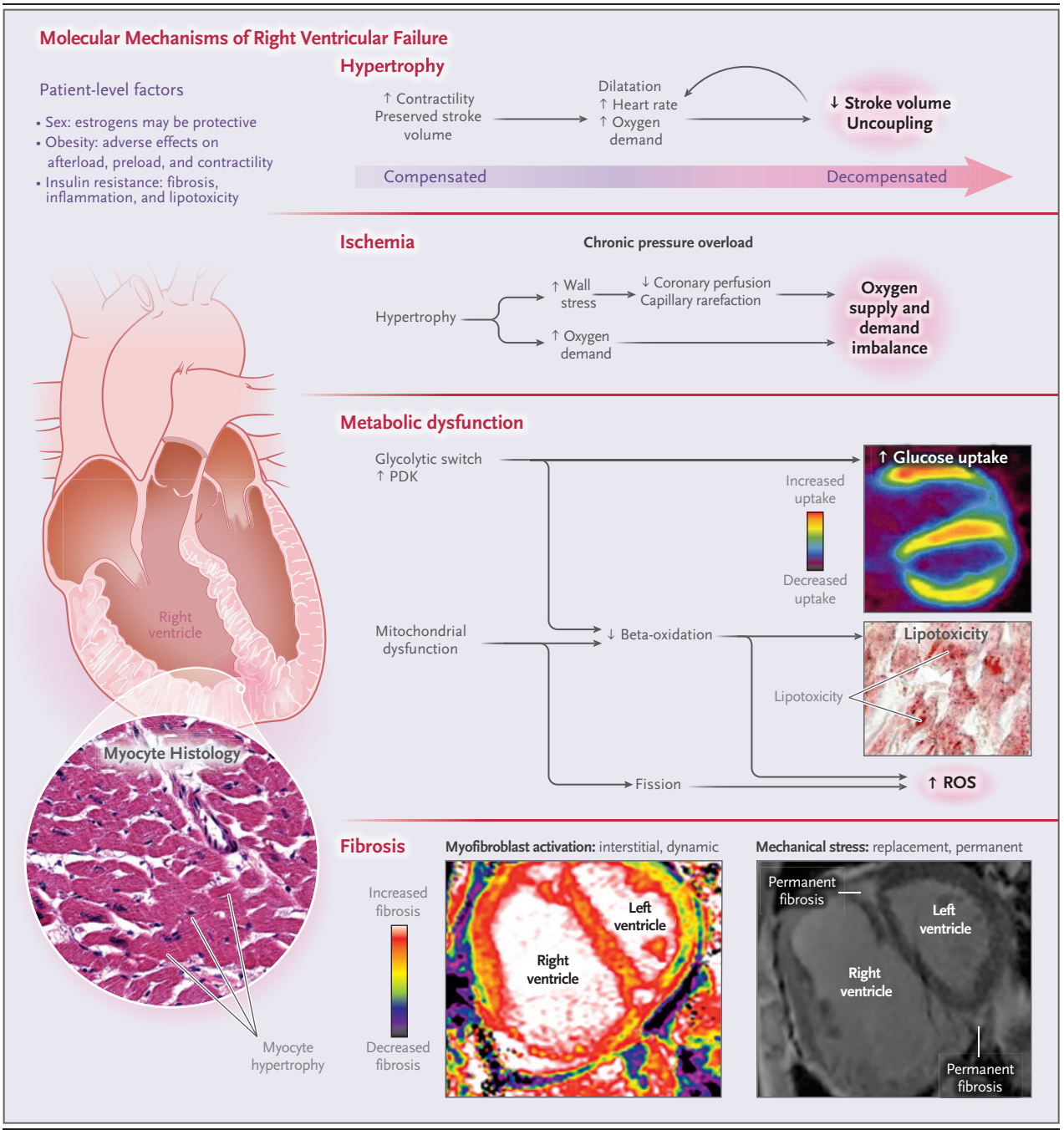
initially adaptive and accompanied by an increase in contractility and preserved stroke volume (homeometric adaptation). These early compensatory mechanisms are achieved in part by neurohormonal activation with increased adrenergic tone. As in left heart failure, neurohormonal activation ultimately becomes maladaptive, characterized by reduced right ventricular beta$_1$-adrenergic receptor density, depletion of tissue adrenergic effectors, and failure of myocyte adenylate cyclase stimulation in response to beta agonists.[10] Over time, as contractility declines or afterload further increases, the right ventricle must dilate to maintain stroke volume (heterometric adaptation). Right ventricular ischemia may result from a mismatch between increased oxygen demand and reduced coronary arterial perfusion due to increased wall stress with hypertrophy and capillary rarefaction.[11] Right ventricular ischemia and reduced right coronary artery flow are reported in patients with pulmonary hypertension and are proportional to right ventricular mass and end-diastolic pressure (i.e., wall stress).[12,13] Eventually, oxygen demand exceeds supply and contractility further declines, resulting in a state of ventriculoarterial uncoupling and right ventricular failure.[14]

Mechanical stress, ischemia, and neurohormonal activation stimulate the production and proliferation of cardiac fibroblast collagen.[15] Early in the disease, increased collagen production may provide protection against right ventricular dilatation. As fibrosis progresses, right ventricular diastolic function and excitation–contraction coupling worsen and contractility is impaired. Right ventricular fibrosis is most prominent at the septal insertion points where mechanical stress is highest but is also observed in the right ventricular free wall. The degree of fibrosis varies according to the cause of pulmonary hypertension, with the highest collagen content observed in patients with systemic sclerosis–associated pulmonary arterial hypertension and lower content observed in those with pulmonary hypertension due to congenital heart disease.[16] The latter observation, along with the persistence of fetal gene isoenzyme expression, may partly explain long-term right ventricular adaptation in patients with congenital heart disease and pulmonary hypertension, as compared with patients in whom pulmonary arterial hypertension is due to other causes.[17] Lusitropic abnormalities occur not only from increased collagen and fibrosis but also from intrinsic stiffening of the right ventricular cardiomyocyte sarcomeres.[18]

In adults, the right ventricle derives energy primarily through fatty acid oxidation, which accounts for 60 to 90% of ATP production. Progressive right ventricular hypertrophy induces a state of relative hypoxia, which activates hypoxia-inducible factor 1 and subsequent up-regulation of glycolytic enzymes and suppression of fatty acid oxidation.[19] Patients with chronic pulmonary hypertension have marked right ventricular glucose uptake, which correlates inversely with right ventricular function and is partially reversed with pulmonary vasodilator therapy. These observations suggest dynamic substrate utilization by the right ventricle, depending on afterload stress and right ventricular contractile compensation.[8] The extent to which observed metabolic substrate shifts provide protection against or contribute to right ventricular failure (i.e., are adaptive or maladaptive) is unclear from clinical and experimental studies (described in the Supplementary Appendix).

Insulin resistance and obesity may be modifiable risk factors for right ventricular dysfunction. Diabetes is associated with worse right ventricular systolic and diastolic function in patients with dilated cardiomyopathy or pulmonary arterial hypertension, and right ventricular remodeling is present in patients with uncomplicated diabetes or prediabetes.[20,21] Potential contributing mechanisms include promotion of myocardial fibrosis, inflammation, microvascular ischemia, and lipotoxicity.

Obesity contributes to right ventricular dysfunction through direct and indirect effects on right ventricular preload, afterload, and contractility. Obese patients with heart failure and preserved ejection fraction, as compared with both nonobese patients with heart failure and preserved ejection fraction and healthy controls, have increased pulmonary pressure, right ventricular dilatation, impaired right ventricular sarcomere function, and more pronounced ventricular interdependence and pericardial constraint, which impair the function of both ventricles.[22,23] Sleep-disordered breathing in obese patients is also a contributing factor. Direct effects of obesity on myocyte function include in-



creased circulating proinflammatory adipokines (and other cytokines) and lipotoxicity from excess myocardial lipid delivery. Mass effects and hypoxia from obesity-associated hypoventilation and sleep apnea increase pulmonary and systemic blood pressures.

DIAGNOSIS AND EVALUATION

The initial evaluation of patients with known or suspected right ventricular failure begins with a detailed medical history taking and thorough physical examination (Table 1). Common (though

Figure 2 (facing page). Molecular Mechanisms of Right Ventricular Failure.

Molecular mechanisms that contribute to right ventricular failure include ischemia, fibrosis, hypertrophy, and metabolic dysfunction, among others. Acute ischemia may result from myocardial infarction, whereas chronic ischemia develops as a result of an imbalance between myocardial oxygen supply and demand, brought about by chronic pressure overload. Chronically elevated afterload results in myocyte hypertrophy, which increases oxygen demand, and reduced perfusion pressure, which decreases oxygen supply. Excessive cardiac fibroblast activation can lead to impaired diastolic function and excitation–contraction coupling, worsening myocardial performance. Interstitial fibrosis can be observed noninvasively using cardiac magnetic resonance imaging quantification of extracellular volume. Higher extracellular volume (red end of scale) indicates more interstitial fibrosis, with normal values typically observed in the green range. Replacement fibrosis is most commonly observed at the septal insertion points in patients with pulmonary hypertension. Myocyte hypertrophy serves initially as a compensatory mechanism. Progressive hypertrophy increases oxygen demand in excess of supply, which ultimately results in right ventricular dilatation, impaired contractility, and decompensation. The right ventricular metabolic substrate utilization in patients with pulmonary arterial hypertension is characterized by an increase in glycolysis and glucose oxidation and a reduction in beta-oxidation. This switch is relatively oxygen-efficient at the cost of lower ATP production. Delivery of fatty acid substrates in excess of mitochondrial oxidative capacity may result in accumulation of toxic lipid species, known as lipotoxicity. In pulmonary arterial hypertension, excess right ventricular mitochondrial fission or fragmentation leads to an imbalanced state of excess fibroblast proliferation and suppressed apoptosis, which may contribute to right ventricular fibrosis. Systemic metabolic dysfunction (obesity and insulin resistance) may be modifiable risk factors for right ventricular failure in susceptible patients. The glucose uptake image is used with permission from Oikawa et al.[8] PDK denotes pyruvate dehydrogenase kinase, and ROS reactive oxygen species.

nonspecific) symptoms include dyspnea, lower-extremity edema, early satiety, abdominal fullness, fatigue, exertional intolerance, and right-upper-quadrant tenderness. Historical features that may suggest right ventricular failure include the presence of coronary artery disease, left heart failure, valvular disease, chronic lung disease, venous thrombosis or embolism, connective tissue disease, and human immunodeficiency virus infection. Relevant features of the social history include tobacco use (potentially indicating lung disease), as well as illicit or prescribed use of an anorexigen. Inquiry about a family history of pulmonary arterial hypertension is important because up to 20% of such cases that are presumed to be idiopathic involve a heritable genetic mutation.[24]

Signs that should raise suspicion of right ventricular failure on physical examination include elevated jugular venous pressure, right ventricular heave on palpation, a prominent pulmonic component of the second heart sound (indicative of pulmonary hypertension), murmur of tricuspid regurgitation, palpable and pulsatile liver (indicative of clinically significant tricuspid regurgitation), hepatojugular reflux, ascites, and lower-extremity edema. Elevated brain natriuretic peptide levels are diagnostically sensitive but not specific and can provide further evidence of right ventricular dysfunction, particularly in the absence of left heart failure. An electrocardiogram (ECG) may show signs of right atrial dilatation, right-axis deviation, or right ventricular hypertrophy.

The etiologic assessment and confirmation of right ventricular failure often require imaging and invasive hemodynamic techniques. The reference standard (though traditionally limited to physiological research) for assessing right ventricular contractility and function relies on pressure–volume relationships and the creation of pressure–volume loops with the use of conductance catheters in the catheterization laboratory.[25] The pressure–volume loop (Fig. 3) represents a single cardiac cycle, with the width of the loop representing stroke volume. A family of pressure–volume loops can be created through acute-load manipulation — most commonly, preload reduction. The ratio of maximal pressure to volume for each loop is determined (end-systolic points), and the slope of a line connecting the end-systolic points represents the end-systolic elastance, a load-independent measure of contractility. Afterload — or more precisely, effective pulmonary arterial elastance — can be estimated as end-systolic pressure over stroke volume.[30] As compared with pulmonary vascular resistance, arterial elastance is a more comprehensive description of afterload because it accounts for both resistive and pulsatile components.[31] The ratio of elastances (end-systolic elastance to

Table 1. Diagnosis and Evaluation of Right Ventricular Failure.*

Diagnostic Tool	Findings
Detailed history	Symptoms of right heart failure: dyspnea, early satiety, abdominal fullness, lower-extremity edema, right-upper-quadrant tenderness, exercise intolerance, fatigue Associated conditions: coronary artery disease, left heart failure or valvular disease, chronic lung disease, venous thrombosis or embolism, connective tissue disease, human immunodeficiency virus infection Social history: tobacco use, illicit drug use, history of illicit or prescribed anorexigen use Family history: pulmonary arterial hypertension, left heart failure, sudden cardiac death, ARVC
Physical examination	Elevated jugular venous pressure, right ventricular heave, loud second component of second heart sound (P2), tricuspid regurgitation murmur, enlarged and pulsatile liver, hepatojugular reflux, ascites, lower-extremity edema
Serum biomarker	Elevated brain natriuretic peptide level
Electrocardiogram	Right atrial dilatation, right ventricular hypertrophy, right-axis deviation
Echocardiogram	Specific right ventricular measurements or findings: TAPSE, TAPSE:PASP ratio, tissue Doppler velocity at lateral tricuspid annulus, fractional area change, right ventricular strain, right ventricular hypertrophy, right atrial size Volumes, ejection fraction (three-dimensional imaging), tricuspid and pulmonary regurgitation, inferior vena cava diameter and collapsibility, leftward displacement or shift of interventricular septum Left heart disease: left ventricular hypertrophy, left atrial size, mitral and aortic valvular disease, left ventricular ejection fraction, left ventricular diastolic dysfunction, intracardiac shunts
Cardiac MRI	Right ventricular volumes (end-systolic and end-diastolic), right ventricular ejection fraction, delayed gadolinium enhancement or fibrosis, right ventricular or right atrial strain, left heart disease, intracardiac shunts, pericardium assessment
Right heart catheterization	RAP and right ventricular end-diastolic pressure, pulmonary-artery pressures (to detect pulmonary hypertension), pulmonary vascular resistance, pulmonary arterial compliance, pulmonary effective arterial elastance, PAWP, estimate of left atrial pressure, cardiac output or index, stroke volume or stroke volume index, pulmonary-artery oxygen saturation, RAP:PAWP ratio, PAPi, possibly measurement of right ventricular reserve with provocation (exercise or inotropes)

* ARVC denotes arrhythmogenic right ventricular cardiomyopathy, MRI magnetic resonance imaging, PAPi pulmonary artery pulsatility index, RAP right atrial pressure, PASP pulmonary-artery systolic pressure, PAWP pulmonary-artery wedge pressure, and TAPSE tricuspid annular plane systolic excursion.

arterial elastance) is therefore a unitless measure of coupling between right ventricular contractility and afterload (so-called right ventricular–pulmonary arterial coupling).

These complex methods have been used to detect subtle right ventricular dysfunction in pulmonary arterial hypertension associated with systemic sclerosis, sex differences in right ventricular function, the effects of therapeutics, and the prognosis in pulmonary hypertension.[28,29,32-35] Although these methods are feasible for research investigations, their clinical applicability is limited by their complexity, invasive nature, and cost. Single-beat methods have been developed (with no requirement for preload manipulation) and have shown good correlation in some studies.[6,29] The feasibility of combining pressure data (on the basis of right heart catheterization or estimates from imaging) and volume data from simultaneous cardiac magnetic resonance imaging (MRI) or three-dimensional echocardiography to construct pressure–volume loops has also been shown.[36] A number of less invasive and clinically available tools can be used to assess right ventricular function.

Patients with suspected right ventricular dysfunction should undergo transthoracic echocardiography, which can provide a rapid assessment of right ventricular size and function and an estimate of pulmonary-artery systolic pressure (PASP) in most patients. Several quantitative measures of right ventricular function are easy to obtain, are reproducible, and have prognostic value, including the tricuspid annular plane systolic excursion (TAPSE), tissue Doppler velocity at the lateral tricuspid annulus, and fractional

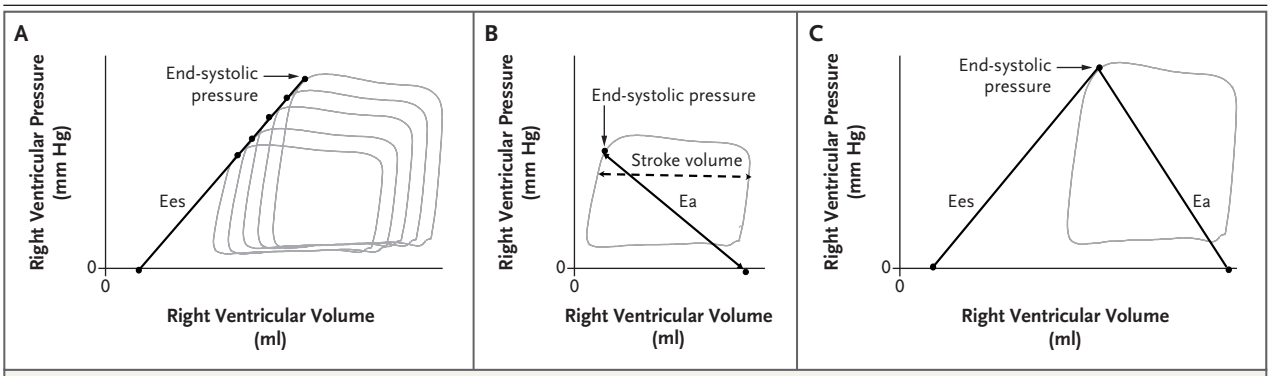


Figure 3. Right Ventricular Pressure–Volume Loops.

A family of pressure–volume loops are created during preload reduction (Panel A). The end-systolic point for each loop (maximal ratio of pressure to volume) and the linear slope through these points represent end-systolic elastance (Ees), a load-independent measure of contractility. Afterload is estimated by calculating the end-systolic pressure and dividing it by the stroke volume (the width of the pressure–volume loop) to determine the so-called effective arterial elastance (Ea) (Panel B). The ratio of Ees to Ea represents coupling between right ventricular contractility and afterload, known as right ventricular–pulmonary arterial (RV-PA) coupling (Panel C). The optimal Ees:Ea ratio, meaning the ratio at which maximal transfer of potential energy from the ventricle to the circulation occurs, is 1.5 to 2.0.[26] In pulmonary hypertension, Ees initially increases to offset the increase in Ea, maintaining RV-PA coupling. Eventually, lack of additional contractile reserve leads to an increase in Ea that is out of proportion to Ees. RV-PA uncoupling is indicated by a ratio below 0.6 to 0.8[26,27] and has been associated with worse outcomes.[28,29]

area change. In addition, echocardiography can be used to calculate the TAPSE:PASP ratio, which has been shown to be at least moderately correlated with the reference standard of right ventricular–pulmonary arterial coupling (Fig. 4A).[37] Right ventricular free-wall longitudinal strain has emerged as a sensitive measure of right ventricular dysfunction, which is prognostic across a wide spectrum of cardiovascular diseases.[38] A dilated or thickened right ventricle and dilated right atrium suggest a chronic state of right ventricular dysfunction. Flattening of the interventricular septum during diastole indicates volume overload, whereas flattening in systole is seen in pressure overload states. Leftward septal displacement can be quantified as the eccentricity index, the ratio of the anteroposterior dimension to the septolateral dimension, with a value of more than 1 indicating right ventricular overload (Fig. 4B).[39] Dilatation of the inferior vena cava without inspiratory collapse indicates elevated right atrial pressure. Finally, echocardiography provides a rapid assessment of left ventricular size, left atrial size, systolic and diastolic function, valve function, and pericardial constraint, which helps narrow the differential diagnosis for the underlying cause of right ventricular failure.

Cardiac MRI may be helpful in the initial evaluation and longitudinal assessment of patients with chronic right ventricular dysfunction, particularly in the case of poor image quality on echocardiography. With the ability to image the right ventricle in multiple planes, cardiac MRI is the reference standard for assessment of right ventricular size, right ventricular ejection fraction, and mass. Right ventricular ejection fraction, stroke volume index,[40] and right ventricular end-systolic volume index are informative measures for prognosis and risk stratification.[41] The ratio of stroke volume to end-systolic volume, a simplified surrogate for right ventricular–pulmonary arterial coupling, is mathematically related to right ventricular ejection fraction but in a nonlinear fashion.[42] This relationship results in a larger physiologic range and greater sensitivity to change, particularly when the right ventricular ejection fraction is mildly to moderately reduced.[43] Another advantage of cardiac MRI over echocardiography is tissue characterization. Contrast-enhanced cardiac MRI allows quantification of right ventricular septal and free-wall fibrosis, which is characterized as either replacement (i.e., permanent scar) or interstitial (dynamic and modifiable). Assessment for right ventricular free-wall morphologic features, motion, and fibrofatty replacement aids the diagnostic evaluation in patients with suspected

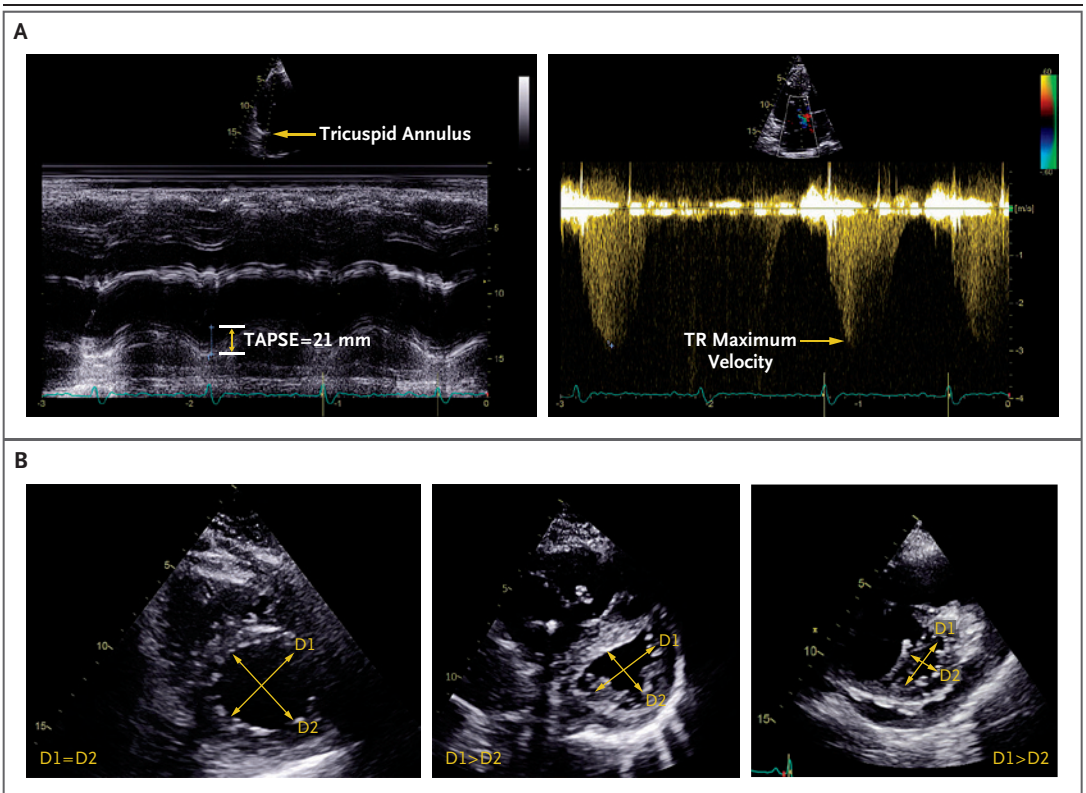


Figure 4. Echocardiographic Measures of Right Ventricular Function.

Tricuspid annular plane systolic excursion (TAPSE), measured by means of M-mode echocardiography, is decreased with impaired right ventricular function (Panel A, left image). The maximal velocity (v) of the tricuspid regurgitation jet is determined from echocardiographic Doppler assessments and is added to right atrial pressure (RAP), estimated during inferior vena cava imaging, to approximate right ventricular systolic pressure (RVSP, calculated with the use of the modified Bernoulli equation: $RVSP = 4v^2 + RAP$) (Panel A, right image). In the absence of right ventricular outflow tract obstruction or pulmonic stenosis, RVSP equals pulmonary-artery systolic pressure (PASP). The ratio of TAPSE to PASP is an estimate of right ventricular–pulmonary arterial coupling. Leftward septal displacement is quantified by means of the eccentricity index, the ratio of the anteroposterior dimension (D1) to the septolateral dimension (D2). If D1 is equal to D2, there is no septal displacement and no evidence of right ventricular overload (Panel B, left image). Two examples of right ventricular overload, in which D1 exceeds D2, are shown, one indicating mild septal displacement and the other indicating severe displacement (Panel B, middle image and right image, respectively).

arrhythmogenic right ventricular cardiomyopathy (ARVC).

Right heart catheterization allows for direct measurement of intracardiac and pulmonary pressures, as well as cardiac output, and is commonly used to estimate right ventricular preload (right atrial pressure or right ventricular end-diastolic pressure) and afterload (pulmonary vascular resistance, pulmonary arterial compliance, and pulmonary arterial elastance). (Definitions are provided in the Supplementary Appendix.) Proper techniques and quality control are critical for ensuring the accuracy of these measurements.[44] On the basis of these assessments, a number of surrogate measures can be calculated to estimate right ventricular function, including the stroke volume and stroke volume index, the ratio of right arterial pressure to pulmonary-artery wedge pressure, the right ventricular stroke work index, and the pulmonary-artery pulsatility index (described in the Supplementary Appendix). In a recent study comparing these hemodynamic right ventricular measures with human right ventricular septal myocyte function, Aslam and colleagues found that the pulmonary-artery pulsatility index was most strongly correlated

with maximal myocyte force generation.[45] However, pressure does not always correlate with intravascular or ventricular volume; thus, pressure-only estimates of preload have important limitations.[46]

There is growing evidence that assessing the right ventricle during provocation with exercise or inotropic stimulation has additive diagnostic and prognostic value.[32,47-49] Right ventricular reserve, the capacity of the ventricle to increase contractility under fixed loading conditions, may be more closely related to right ventricular–pulmonary arterial coupling than are measures assessed under resting conditions. However, the best techniques to assess right ventricular reserve have not yet been determined.[50,51]

DISORDERS OF EXCESSIVE PRELOAD

Tricuspid regurgitation is commonly identified, and its severity is graded by means of echocardiography. Acute tricuspid regurgitation may occur with infectious endocarditis or iatrogenic damage to the tricuspid valve or subvalvular apparatus.[52] A canine model of acute, reversible tricuspid regurgitation showed increased right ventricular filling pressures and a concomitant reduction in cardiac output and aortic blood pressure at the commencement of tricuspid regurgitation.[53] However, acute tricuspid regurgitation, even when severe, is initially well tolerated as long as the right ventricular afterload is normal. Chronic excessive right ventricular preload can occur in the context of right-side (tricuspid or pulmonary) valvular insufficiency, intracardiac left-to-right shunts, or extracardiac arteriovenous shunts. Intracardiac shunts, depending on the location, can usually be detected by means of bubble contrast echocardiography. Systematic oximetric measurements during right heart catheterization (e.g., shunt or oximetric run) may confirm the precise location and quantitate the degree of intracardiac left-to-right shunting. While systemic arteriovenous shunts differ from tricuspid regurgitation and intracardiac shunts in that they lead to reduced systemic vascular resistance and increased total cardiac output, studies have shown that the creation of arteriovenous fistulas or grafts leads to chronic right ventricular dilatation and reduced right ventricular systolic function,[54] both of which are associated with the rate of arteriovenous fistula flow.[55] Flow rates can be estimated by means of ultrasonography or various techniques during right heart catheterization.

DISORDERS OF EXCESSIVE AFTERLOAD

Acute increases in afterload are poorly tolerated by the right ventricle. Acute pulmonary embolus is the classic example, a diagnosis made through a combination of clinical and pretest probability assessment, as well as diagnostic imaging (typically computed tomographic pulmonary angiography or, less commonly, ventilation–perfusion scanning). In addition to right ventricular dilatation or dysfunction and an elevation in the estimated PASP, echocardiography may reveal akinesis of the midright ventricular free wall and hypercontractility at the apex, the so-called McConnell's sign. Acute lung injury diagnosed on the basis of lung imaging may also cause rapid and acute increases in the right ventricular afterload and may be further exacerbated by the impact of positive pressure ventilation (for details, see the discussion in the Supplementary Appendix). Chronic increases in afterload occur with the development of pulmonary hypertension. Echocardiography is the initial screening tool to detect an increase in afterload, as well as its consequences — right ventricular dilatation and dysfunction. Pulmonary hypertension is a hemodynamic diagnosis and is confirmed by right heart catheterization (see the discussion in the Supplementary Appendix). A comprehensive review, including a diagnostic algorithm for pulmonary hypertension, was recently published.[4]

DISORDERS OF CONTRACTILITY

An acute reduction in right ventricular contractility can occur with myocardial infarction or myocarditis or as a result of cardiac surgery. In most patients, the majority of the right ventricle's blood supply comes from the right coronary artery through the right ventricular marginal branches. Thus, proximal right coronary arterial occlusion can substantially compromise right ventricular contractility. In addition to the typical symptoms of myocardial infarction, predominant right ventricular infarcts may be associated with hypotension, a slower heart rate, elevated jugular venous pressure, and clear lung

fields. ECG commonly reveals ST-segment and T-wave changes in the inferior leads. Right-side ECG should be performed when a right ventricular infarct is suspected. Echocardiography can confirm right ventricular involvement but should not preclude rapid coronary angiography when indicated. Isolated right ventricular myocarditis has been reported but occurs more commonly in conjunction with left-side involvement.

Postsurgical right ventricular contractile dysfunction, on the other hand, is common. It is usually manifested as difficulty in weaning the patient from cardiopulmonary bypass, along with low cardiac output and worsening of end-organ dysfunction, though a standard definition is lacking.[56] In patients with left heart failure who are receiving treatment with a left ventricular assist device, acute right ventricular failure is also common and is a leading cause of early complications and death. Postulated mechanisms for reductions in contractility include deleterious changes in right ventricular geometry and septal function, loss of the left ventricular contribution to right ventricular contractility, and potential anchoring of the right ventricular free wall, apex, or both postoperatively.[57] Prediction, mitigation, and management of right ventricular failure in this population remain major unmet needs.

Chronic right ventricular failure due to impaired contractility can occur as part of the spectrum of cardiomyopathy disease states. Left heart failure is the most common cause of right ventricular failure.[58] Although the development of pulmonary hypertension in patients with left heart disease and chronic increases in preload also clearly contribute to right ventricular failure, the same myopathic processes that reduce left ventricular contractility may also affect the right ventricle. Right ventricular involvement is associated with a worse prognosis[59] and is suggested by a combination of clinical manifestations (ascites and edema) and findings on cardiac imaging or right heart catheterization. Though biventricular involvement is increasingly recognized, the genetic disease ARVC may lead to fibrofatty dysplasia of the right ventricle, impaired contractility, and right ventricular failure.[60] The diagnosis of ARVC can be challenging, requiring a high level of clinical suspicion as well as multiple diagnostic tests. The 2010 revised Task Force Criteria provide a framework for diagnosis.[61] Cardiac sarcoidosis may also be manifested as predominant right ventricular dysfunction and may mimic ARVC.[62] Among the disorders associated with pulmonary arterial hypertension, systemic sclerosis is the only one for which there is evidence of depressed sarcomere function, perhaps explaining the clinical outcomes, which are worse than those with idiopathic pulmonary arterial hypertension.[16]

Aside from alteration in load and myocardial function, a special mention of atrial arrhythmias in right ventricular failure is warranted. Atrial fibrillation and right ventricular failure commonly coexist, and atrial fibrillation is associated with reductions in the right atrial emptying fraction and reservoir function, which can exacerbate the pathophysiological features of right ventricular failure.[63,64]

TREATMENT OF RIGHT VENTRICULAR FAILURE

Treatment options for right ventricular failure depend on the primary pathophysiological insult and potential maladaptive compensatory mechanisms, with a focus on optimization of preload, reduction of right ventricular afterload, and augmentation of right ventricular contractility (Table 2). How quickly the insult occurs may account for various responses to treatment measures and may dictate treatment strategies.

IMPORTANCE OF PRELOAD

The optimal preload states in patients with right ventricular failure depend on the physiological cause and tempo of the disease. Patients who are in shock because of an acute increase in right ventricular afterload (due to acute pulmonary embolism) or an acute reduction in contractility (due to a right ventricular infarct) may benefit from volume loading to augment right ventricular stroke volume and increase transpulmonary blood transit. However, the tenet that all patients with acute right ventricular failure require aggressive volume loading is incorrect and may be harmful. In a dog model of acute pulmonary embolism, volume expansion did not increase left ventricular stroke work after a single embolism and actually decreased left ventricular stroke work and left ventricular transmural pressure when the embolism was more extensive.[65] A recent study suggested that patients with inter-

Table 2. Treatment of Right Ventricular Failure.*

Physiological Target and Medications	Nonpharmacologic Therapy	Clinical Application
Preload reduction		
Loop diuretics: furosemide, bumetanide, torsemide Thiazide diuretics for augmentation of response to loop diuretics	Ultrafiltration, atrial septostomy	Beneficial for nearly all causes of chronic right ventricular failure with volume overload If response to diuretics is inadequate, ultrafiltration may be beneficial Atrial septostomy performed for palliation in severe pulmonary arterial hypertension
Afterload reduction		
Calcium-channel blockers: long-acting nifedipine, diltiazem, amlodipine Inhaled vasodilators (continuous): nitric oxide, prostacyclin analogues Endothelin receptor antagonists: bosentan, ambrisentan, macitentan Prostacyclin analogues: epoprostenol, treprostinil, iloprost Phosphodiesterase 5 inhibitors: sildenafil, tadalafil Soluble guanylate cyclase stimulator: riociguat	Mechanical obstruction alleviation, aortopulmonary shunt, lung transplantation	Calcium-channel blockers for vasoreactive pulmonary arterial hypertension (WSPH group 1); should be used only if pulmonary arterial hypertension is idiopathic or drug-associated and vasoreactivity has been shown on right heart catheterization with vasodilator study† Inhaled vasodilators for acute right ventricular failure or cardiogenic shock due to right ventricular failure Endothelin receptor antagonists, phosphodiesterase 5 inhibitors, soluble guanylate cyclase stimulators, and prostacyclin analogues for pulmonary arterial hypertension Inhaled treprostinil for ILD-associated pulmonary hypertension Mechanical obstruction alleviation for chronic thromboembolic pulmonary hypertension, congenital pulmonary vascular obstruction Aortopulmonary shunt for palliation in severe pulmonary arterial hypertension Lung transplantation for severe pulmonary arterial hypertension
Inotropic support		
$Beta_1$-agonists: dobutamine, epinephrine, dopamine Phosphodiesterase 3 inhibitor: milrinone Vasopressors: norepinephrine, vasopressin, phenylephrine Digoxin	NA	RV failure complicated by cardiogenic shock, malperfusion, or hypotension; digoxin may reduce symptoms in patients with chronic RV failure
Mechanical circulatory support		
NA	Percutaneous intracorporeal microaxial pump, extracorporeal RVAD, VA-ECMO, durable ventricular assist device in RVAD configuration, total artificial heart	Intracorporeal microaxial pump, extracorporeal RVAD, and VA-ECMO for right ventricular failure resulting in cardiogenic shock unresponsive to pharmacologic therapy; durable ventricular assist device for intractable right ventricular failure in the absence of severely elevated right ventricular afterload

* ILD denotes interstitial lung disease, NA not applicable, RVAD right ventricular assist device, and VA-ECMO venoarterial extracorporeal membrane oxygenation.

† Pulmonary arterial hypertension is designated as group 1 of five pulmonary hypertension groups in the World Symposium on Pulmonary Hypertension (WSPH) classification. Vasoreactivity is defined as a reduction of mean pulmonary-artery pressure to an absolute value of less than 40 mm Hg and by at least 10 mm Hg while cardiac output is maintained or increased.

mediate-risk pulmonary embolism who were randomly assigned to receive a single dose of furosemide were more likely than those who received placebo to meet the combined end point of normalization of the simplified Pulmonary Embolism Severity Index and absence of oliguria.[66]

Patients with right ventricular infarction have a variable response to volume loading. Patients who initially have relative volume depletion and right ventricular infarction are likely to benefit from volume loading. However, volume loading in patients with normal intravascular volume may compromise cardiac output through increased pericardial constraint and a decrease in the left ventricular transmural filling pressure.[67-69]

Invasive hemodynamic monitoring may be beneficial to assess the response to preload alteration in such patients. Those with chronic right ventricular failure benefit from volume removal and decongestion. Normalization of the preload can reduce tricuspid valve annular dilatation and tricuspid regurgitation, right ventricular wall stress, and septal deformation.[70] Volume reduction is most commonly accomplished with intravenous diuretics, though ultrafiltration may be necessary in some cases. New therapies are also being developed to specifically limit venous return in patients with heart failure.[71]

AFTERLOAD REDUCTION

For patients with elevated right ventricular afterload and right ventricular failure, reducing afterload is beneficial. The effect in a patient with acutely increased right ventricular afterload (e.g., as a result of thrombectomy or thrombolysis for acute pulmonary embolism) can be dramatic. For patients with chronically elevated right ventricular afterload and right ventricular failure, afterload reduction can also be therapeutic. However, differences in the specific cause of elevated right ventricular afterload may dictate the relative benefit of afterload-reducing therapies across disease states.

In patients with pulmonary arterial hypertension, clinical trials have established the long-term benefit of pharmacotherapy targeted toward afterload reduction. Pharmacologic pulmonary vasodilator therapy currently focuses on three pathways: endothelin antagonists, augmented signaling in the prostacyclin pathway, and the nitric oxide pathway.[4] Up-front combination therapy is now the standard of care, and increasingly aggressive afterload reduction targets are being considered in patients with right ventricular dysfunction.[4,72-74] Several therapies targeting new pathways also appear to be promising.[75] For pulmonary hypertension due to lung disease, a recent clinical trial showed improved exercise capacity in patients treated with inhaled treprostinil.[76] In patients with pulmonary hypertension due to chronic thromboembolic disease, surgical pulmonary endarterectomy or (in inoperable patients) percutaneous balloon pulmonary angioplasty should be considered, alongside anticoagulation therapy.[77] Adjunctive pharmacologic therapies aimed at afterload reduction are also used.[74] For patients with acute right ventricular failure and chronically elevated precapillary right ventricular afterload, inhaled pulmonary vasodilators (nitric oxide or epoprostenol) can provide immediate improvement. For intractable right ventricular failure in this clinical context, lung or heart–lung transplantation may be considered in selected patients.[74,78] Referral to pulmonary hypertension centers of excellence is recommended.

Direct pulmonary vasodilators have largely not proved beneficial in patients with pulmonary hypertension due to left heart disease, may not provide the desired reduction in afterload, and may even be harmful.[74,79-82] Nevertheless, use of pulmonary vasodilators remains common, with one survey showing that 77% of centers use these medications.[83] The Sildenafil for Improving Outcomes after Valvular Correction (SIOVAC) study showed that in patients with persistent pulmonary hypertension after correction of left-side valvular disease, sildenafil led to outcomes that were worse than those with placebo.[80] In most of these studies, the study population was not enriched with patients who had high afterload or clinically significant right ventricular failure.

Reduction of right ventricular afterload in patients with left heart disease and persistent pulmonary hypertension is best achieved through optimization of guideline-directed medical therapy and normalization of left-heart filling pressures. Reduction of left atrial pressure may both increase pulmonary vascular compliance and reduce pulmonary vascular resistance.[84] Reduction of pulmonary pressure and pulmonary vascular resistance after normalization of left atrial pressure has also been shown in studies evaluating the administration of systemic vasodilators such as nitroprusside, implantation of ventricular assist devices, and heart transplantation. Thus, volume removal in patients who have hypervolemia with right ventricular failure and left heart disease will improve right ventricular afterload, as well as preload.

Finally, given the high prevalence of sleep-disordered breathing among patients with pulmonary hypertension (including pulmonary arterial hypertension), both diagnosis and treatment are important, with opportunities to alleviate associated hypoxemia, reduce afterload, and perhaps limit right ventricular ischemia.[85]

AUGMENTATION OF CONTRACTILITY

Initial efforts should focus on addressing the underlying cause of disease while augmenting right ventricular contractility to support cardiac output. Urgent reperfusion therapy is warranted in patients with acute right ventricular myocardial infarction.[86] For patients with certain types of inflammatory heart disease and right ventricular failure, immunosuppression may be beneficial. While the underlying cause is being determined, inotropic or vasodilator support may be necessary to maintain cardiac output. Dobutamine increases cardiac output and stroke volume in patients with right ventricular myocardial infarction[68] and those with pulmonary hypertension.[87] Milrinone may be used, with careful attention to avoid excess systemic vasodilatation and hypotension. The latter may lead to right ventricular ischemia and reduction in left ventricular contractility. The evidence for using digoxin in patients with right ventricular failure is mixed.

For patients with acutely decompensated right ventricular failure and shock who do not have a response to pharmacologic therapy, there has been a recent proliferation of temporary mechanical support devices to help augment blood flow from the systemic to pulmonary circulation.[88] These support devices have been studied predominantly in patients with concomitant left heart failure. In patients with severe pulmonary arterial hypertension, a temporary isolated right ventricular assist device should not be used, since it may confer a predisposition to pulmonary hemorrhage. Extracorporeal membrane oxygenation may be used in severe cases. Despite the use of aggressive pharmacotherapy, mechanical circulatory support, or both, right ventricular failure may prove intractable and lead to irrevocable end-organ dysfunction and death. In patients with persistent right ventricular failure and no curative options, palliative care with a focus on symptom relief and on addressing the goals of care should be instituted early and in parallel with pharmacologic therapy.[89]

FUTURE DIRECTIONS AND CONCLUSIONS

Although clinicians are now aware of the importance of the right ventricle in health and disease, a number of challenges remain.[90] Assessment of right ventricular function remains challenging and imperfect; better surrogates for right ventricular–pulmonary arterial coupling are needed, as are ways to identify the at-risk right ventricle. Many long-term therapies rely solely on load amelioration, and therapeutics that directly target right ventricular contractility and lusitropy are needed. Finally, the right ventricle should be considered in clinical trial design, in some cases as part of the inclusion criteria and in other cases as part of the clinical end points and therapeutic response stratification.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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