Right Ventricular Function in Cardiovascular Disease, Part I

Anatomy, Physiology, Aging, and Functional Assessment of the Right Ventricle

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In 1616, Sir William Harvey was the first to describe the importance of right ventricular (RV) function in his seminal treatise, *De Motu Cordis*: "Thus the right ventricle may be said to be made for the sake of transmitting blood through the lungs, not for nourishing them."[1,2] For many years that followed, emphasis in cardiology was placed on left ventricular (LV) physiology, overshadowing the study of the RV. In the first half of the 20th century, the study of RV function was limited to a small group of investigators who were intrigued by the hypothesis that human circulation could function adequately without RV contractile function.[3] Their studies, however, were based on an open pericardial dog model, which failed to take into account the complex nature of ventricular interaction. In the early 1950s through the 1970s, cardiac surgeons recognized the importance of right-sided function as they evaluated procedures to palliate right-heart hypoplasia. Since then, the importance of RV function has been recognized in heart failure, RV myocardial infarction, congenital heart disease and pulmonary hypertension. More recently, advances in echocardiography and magnetic resonance imaging have created new opportunities for the study of RV anatomy and physiology.

The goal of the present review is to offer a clinical perspective on RV structure and function. In the first part, we discuss the anatomy, physiology, aging, and assessment of the RV. In the second part, we discuss the pathophysiology, clinical importance, and management of RV failure.

Anatomy of the RV

Macroscopic Anatomy of the RV

In the normal heart, the RV is the most anteriorly situated cardiac chamber and lies immediately behind the sternum. In the absence of transposition of great arteries, the RV is delimited by the annulus of the tricuspid valve and by the pulmonary valve. As suggested by Goor and Lillehi,[4] the RV can be described in terms of 3 components: (1) the inlet, which consists of the tricuspid valve, chordae tendineae, and papillary muscles; (2) the trabeculated apical myocardium; and (3) the infundibulum, or conus, which corresponds to the smooth myocardial outflow region[4,5] (Figure 1). In the study of congenital heart disease, this division seems to be more practical than the traditional division of the RV into sinus and conus components.[5] Additionally, the RV can also be divided into anterior, lateral, and inferior walls, as well as basal, mid, and apical sections.[6]

Three prominent muscular bands are present in the RV: the parietal band, the septomarginal band, and the moderator band. The parietal band and the infundibular septum make up the crista supraventricularis.[7] The septomarginal band extends inferiorly and becomes continuous with the moderator band, which attaches to the anterior papillary muscle.[7] When abnormally formed or hypertrophied, the septomarginal band can divide the ventricle into 2 chambers (double-chambered RV).[5] Another important characteristic of the RV is the presence of a ventriculoinfundibular fold that separates the tricuspid and pulmonary valves. In contrast, in the LV, the aortic and mitral valves are in fibrous continuity (Figure 1).

The shape of the RV is complex. In contrast to the ellipsoidal shape of the LV, the RV appears triangular when viewed from the side and crescent shaped when viewed in cross section.[6] The shape of the RV is also influenced by the position of the interventricular septum. Under normal loading and electrical conditions, the septum is concave toward the LV in both systole and diastole.[6] In the mature child and adult, the volume of the RV is larger than the volume of the LV, whereas RV mass is approximately one sixth that of the LV.[8]

Myofiber Architecture of the RV

The ventricles are not composed of a single muscle layer but rather of multiple layers that form a 3-dimensional (3D) network of fibers.[5] As described by Ho and Nihoyannopoulos,[5] the RV wall is mainly composed of superficial and deep muscle layers. The fibers of the superficial layer are arranged more or less circumferentially in a direction that is parallel to the atrioventricular (AV) groove (Figure 1).[5,9] These fibers turn obliquely toward the cardiac apex on the sternocostal aspect and continue into the superficial myofibers of the

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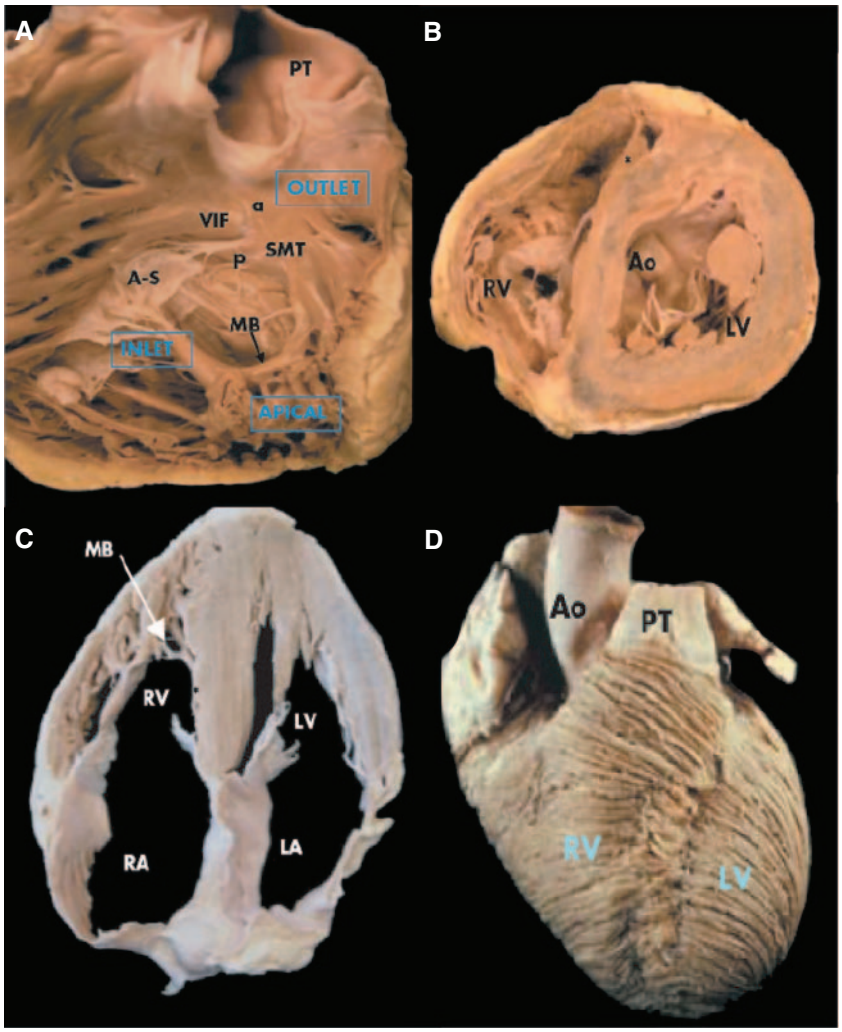

Figure 1. A, The inlet, trabeculated apical myocardium and infundibulum of the RV. The tricuspid and pulmonary valves are separated by the ventriculoinfundibular fold (VIF). B, Short-axis plane of the RV demonstrating its crescentic shape. C, The 4-chamber anatomic plane of the heart showing the moderator band (MB) and the more apical insertion of the tricuspid valve. D, Superficial muscle layer of the RV (dissection by Damian Sanchez-Quintana, University of Extremadura, Spain). SMT indicates septomarginal trabeculation with its anterior (a) and posterior (p) arm; A-S, anterosuperior leaflet of the tricuspid valve; PT, pulmonary trunk; Ao, aorta; RA, right atrium; and LA, left atrium. Reproduced from Ho and Nihoyannopoulos[5] with permission from the publisher. Copyright © 2006, BMJ Publishing Group Ltd.

LV.[5,9] The deep muscle fibers of the RV are longitudinally aligned base to apex. In contrast to the RV, the LV contains obliquely oriented myofibers superficially, longitudinally oriented myofibers in the subendocardium, and predominantly circular fibers in between. This arrangement contributes to the more complex movement of the LV, which includes torsion, translation, rotation, and thickening.[5,9]

The continuity between the muscle fibers of the RV and LV functionally binds the ventricles together and represents the anatomic basis of free ventricular wall traction caused by LV contraction. This continuity also contributes, along with the interventricular septum and pericardium, to ventricular interdependence.[9]

Distinguishing Anatomic Features of the RV

Although the RV is usually located on the right side of the heart and connects with the pulmonary circulation, the anatomic RV is defined by its structure rather than by its position or connections. The morphological features that best differentiate anatomic RV, LV, or indeterminate ventricle include the following: (1) the more apical hinge line of the septal leaflet of the tricuspid valve relative to the anterior leaflet of the mitral valve; (2) the presence of a moderator band; (3) the presence of more than 3 papillary muscles; (4) the trileaflet configuration of the tricuspid valve with septal papillary attachments; and (5) the presence of coarse trabeculations.[5,7] Prominent trabeculations in the systemic ventricle can also be seen in congenitally corrected transposition of great arteries (anatomic RV) or in noncompaction of the LV.

Physiology

The primary function of the RV is to receive systemic venous return and to pump it into the pulmonary arteries. Under normal circumstances, the RV is connected in series with the LV and is, therefore, obligated to pump on average the same effective stroke volume.

Mechanical Aspects of Ventricular Contraction

RV contraction is sequential, starting with the contraction of the inlet and trabeculated myocardium and ending with the contraction of the infundibulum (approximately 25 to 50 ms apart).[9] Contraction of the infundibulum is of longer duration than contraction of the inflow region.[9]

The RV contracts by 3 separate mechanisms: (1) inward movement of the free wall, which produces a bellows effect; (2) contraction of the longitudinal fibers, which shortens the long axis and draws the tricuspid annulus toward the apex; and (3) traction on the free wall at the points of attachment

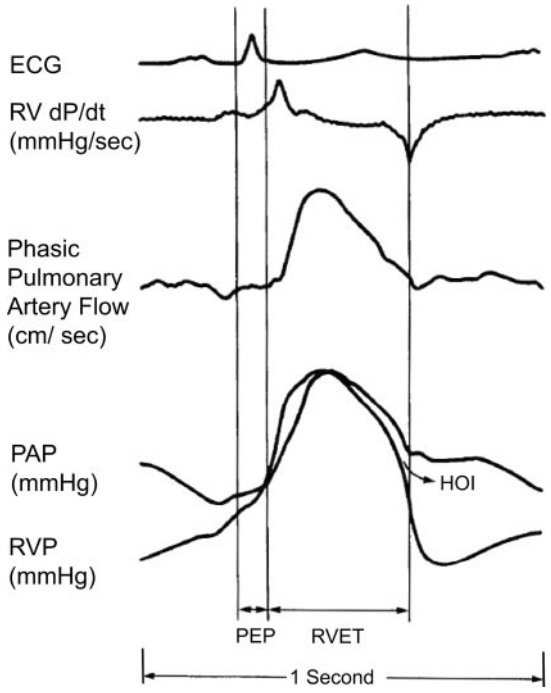

Figure 2. Simultaneously recorded ECG, RV analog signal of pressure development (dP/dt), phasic pulmonary artery flow, pulmonary artery pressure (PAP), and RV pressure (RVP) in the human subject. PEP indicates preejection period; RVET, RV ejection time; and HOI, hangout interval. Reproduced from Dell'Italia and Walsh,[12] copyright © 1988, with permission from Elsevier.

secondary to LV contraction.[6] Shortening of the RV is greater longitudinally than radially.[10] In contrast to the LV, twisting and rotational movements do not contribute significantly to RV contraction. Moreover, because of the higher surface-to-volume ratio of the RV, a smaller inward motion is required to eject the same stroke volume.[6]

RV Hemodynamics

Under normal conditions, the RV is coupled with a low-impedance, highly distensible pulmonary vascular system. Compared with the systemic circulation, pulmonary circulation has a much lower vascular resistance, greater pulmonary artery distensibility, and a lower peripheral pulse wave reflection coefficient.[9]

Under normal conditions, right-sided pressures are significantly lower than comparable left-sided pressures.[11] RV pressure tracings show an early peaking and a rapidly declining pressure in contrast to the rounded contour of LV pressure tracing (Figure 2).[12] RV isovolumic contraction time is shorter because RV systolic pressure rapidly exceeds the low pulmonary artery diastolic pressure. A careful study of hemodynamic tracings and flow dynamics also reveals that end-systolic flow may continue in the presence of a negative ventricular-arterial pressure gradient (Figure 2).[9,12] This interval, which is referred to as the hangout interval, is most likely explained by the momentum of blood in the outflow tract.[12]

Cardiodynamics

RV systolic function is a reflection of contractility, afterload, and preload. RV performance is also influenced by heart

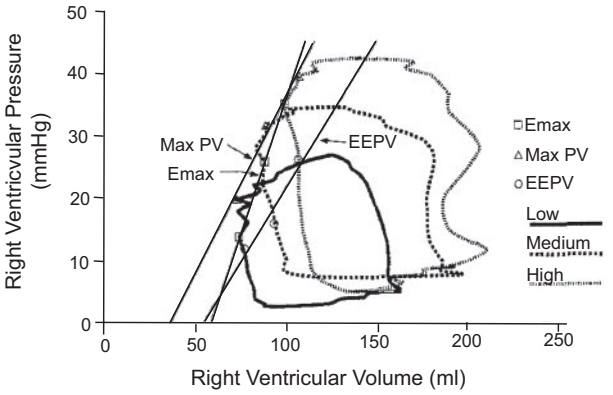

Figure 3. Pressure–volume loops of the RV under different loading conditions. The slope of maximum time-varying elastance (Emax), maximum pressure-volume ratio (Max PV), and end-ejection pressure/volume (EEPV) are displayed on the graph. Reproduced from Dell'Italia and Walsh,[20] copyright © 1988, with permission from the European Society of Cardiology.

rhythm, synchrony of ventricular contraction, RV force-interval relationship, and ventricular interdependence.[13–16] Significant valvular regurgitation or shunt physiology should always be considered because they can decrease effective cardiac output.[9]

The complex relationship between RV contractility, preload, and afterload can be better understood with the help of pressure-volume loops. Pressure-volume loops depict instantaneous pressure-volume curves under different loading conditions. For the LV, Suga et al[17] showed that the end-systolic pressure-volume relationship can be approximated by a linear relationship. The slope of this relationship is referred to as ventricular elastance. Because of its relative load independence, many investigators consider ventricular elastance as the most reliable index of contractility.[18]

Interestingly, despite having markedly different ventricular geometry and hemodynamics, many studies showed that the RV also follows a time-varying elastance model (Figure 3).[19,20] Because of the different shape of RV pressure-volume curves, maximal RV elastance better reflects RV contractility than does the end-systolic elastance commonly used in LV pressure-volume interpretation.[20] On the basis of the study by Dell'Italia and Walsh,[20] the normal maximal RV elastance is 1.30±0.84 mm Hg/mL. Although maximal RV elastance is the most reliable index of RV contractility, some studies have outlined limitations in the RV time-elastance model, such as nonlinearity, variability in slope values, and afterload dependency.[21]

RV afterload represents the load that the RV has to overcome during ejection. Compared with the LV, the RV demonstrates a heightened sensitivity to afterload change (Figure 4).[22,23] Although in clinical practice, pulmonary vascular resistance (PVR) is the most commonly used index of afterload, PVR may not reflect the complex nature of ventricular afterload. A more complete model would ideally take into account the static and dynamic components of pulmonary vascular impedance as well as potential valvular or intracavitary resistive components.[9]

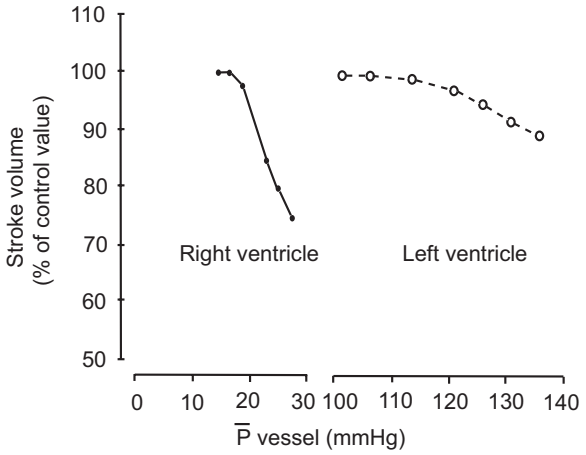

Figure 4. The response of the RV and LV to experimental increase in afterload. Reproduced from MacNee[22] with permission from the publisher. Copyright © 1994, the American Thoracic Society.

RV preload represents the load present before contraction. Within physiological limits, an increase in RV preload improves myocardial contraction on the basis of the Frank-Starling mechanism. Beyond the physiological range, excessive RV volume loading can compress the LV and impair global ventricular function through the mechanism of ventricular interdependence.[23] Compared with LV filling, RV filling normally starts before and finishes after. RV isovolumic relaxation time is shorter, and RV filling velocities (E and A) and the E/A ratio are lower. The respiratory variations in RV filling velocities are, however, more pronounced.[6,24] Many factors influence RV filling, including intravascular volume status, ventricular relaxation, ventricular chamber compliance, heart rate, passive and active atrial characteristics, LV filling, and pericardial constraint.[25] The filling period is also an important determinant of ventricular preload and function. As demonstrated by Dell'Italia,[13] the RV follows a force-interval relationship in which stroke volume increases above baseline after longer filling periods, as seen in postextrasystolic beats. On the basis of the sarcomere length-pressure curve relationship, RV compliance is believed to be greater than LV compliance.[26,27] Also, in general, the pericardium imposes greater constraint on the thinner, more compliant, low-pressure RV.[9]

Heart Rhythm and Dyssynchrony

Maintenance of sinus rhythm and AV synchrony is especially important in the presence of RV dysfunction. For example, atrial fibrillation or complete AV block are poorly tolerated in acute RV myocardial infarction, acute pulmonary emboli, or chronic RV failure.[14]

RV dyssynchrony refers to the concept of suboptimal coordination of RV mechanical function. RV dyssynchrony could potentially lead to reduced cardiac output or increased filling pressures. The effects of "resynchronization therapy" in patients with RV failure and congenital heart disease have been assessed recently in a multicenter international study (n=103).[28] Dubin and colleagues[28] demonstrated that resynchronization therapy was associated with improvement in RV ejection fraction (RVEF) in patients with congenital heart disease with either systemic or pulmonic RV.

Ventricular Interdependence

Ventricular interdependence refers to the concept that the size, shape, and compliance of 1 ventricle may affect the size, shape, and pressure-volume relationship of the other ventricle through direct mechanical interactions.[16] Although always present, ventricular interdependence is most apparent with changes in loading conditions such as those seen with respiration or sudden postural changes.[16] Ventricular interdependence plays an essential part in the pathophysiology of RV dysfunction.

Systolic ventricular interdependence is mediated mainly through the interventricular septum. The pericardium may not be as important for systolic ventricular interdependence as it is for diastolic ventricular interdependence.[15,16] Experimental animal studies showed that approximately 20% to 40% of RV systolic pressure and volume outflow results from LV contraction.[16] Moreover, in the presence of scarring of the RV or replacement with a noncontractile patch, the septum is able to maintain circulatory stability as long as the RV is not dilated.[29]

The evidence for diastolic ventricular interdependence is well established and based on many experimental and clinical studies.[16,30] In acute RV pressure- or volume-overload states, dilatation of the RV shifts the interventricular septum toward the left, alters LV geometry, and increases pericardial constraint. As a consequence, the LV diastolic pressure-volume curve shifts upward (decreased distensibility), which potentially leads to a decreased LV preload, an increased LV end-diastolic pressure (usually a mild increase), or low cardiac output states. Acute RV dilatation has also been shown to lead to a decrease in LV elastance.[9,16] Conversely, LV volume or pressure overload has also been shown to shift upward the RV diastolic pressure-volume relationship and to redistribute RV filling into late diastole.[30,31]

Perfusion of the RV

The blood supply of the RV varies according to the dominance of the coronary system. In a right-dominant system, which is found in ≈80% of the population, the right coronary artery supplies most of the RV.[9,32] The lateral wall of the RV is supplied by the marginal branches of the RV, whereas the posterior wall and the inferoseptal region are supplied by the posterior descending artery. The anterior wall of the RV and the anteroseptal region are supplied by branches of the left anterior descending artery. The infundibulum derives its supply from the conal artery, which has a separate ostial origin in 30% of cases. The separate ostium explains the preservation of infundibular contraction in the presence of proximal right coronary occlusion.[9,32]

In the absence of severe RV hypertrophy or pressure overload, proximal right coronary artery flow occurs during both systole and diastole.[33] However, beyond the RV marginal branches, diastolic coronary blood flow predominates.[7] The relative resistance of the RV to irreversible ischemic injury may be explained by (1) its lower oxygen consumption, (2) its more extensive collateral system, especially from

Table 1. Comparison of Normal RV and LV Structure and Function

Characteristics	RV	LV
Structure	Inflow region, trabeculated myocardium, infundibulum	Inflow region and myocardium, no infundibulum
Shape	From the side: triangular[9] cross section: crescentic	Elliptic[9]
End-diastolic volume, mL/m^2	75±13 (49–101)[8]	66±12 (44–89)[8]
Mass, g/m^2	26±5 (17–34)[8]	87±12 (64–109)[8]
Thickness of ventricular wall, mm	2 to 5[5,6]	7 to 11[6]
Ventricular pressures, mm Hg	25/4 [(15–30)/(1–7)][11]	130/8 [(90–140)/(5–12)][11]
RVEF, %	61±7 (47–76)[8]	67±5 (57–78)[8]
	>40–45*	>50*
Ventricular elastance (Emax), mm Hg/mL	1.30±0.84[20]	5.48±1.23[18]
Compliance at end diastole, mm Hg^{-1}	Higher compliance than LV[26]†	5.0±0.52×10^{-2}[27]
Filling profiles	Starts earlier and finishes later ↑ lower filling velocities[6]	Starts later and finishes[6] earlier, higher filling velocities
PVR vs SVR, dyne · s · cm^{-5}	70 (20–130)[11]	1100 (700–1600)[11]
Stroke work index, g/m^2 per beat	8±2 (1/6 of LV stroke work)[9]	50±20[11]
Exercise reserve	↑ RVEF ≥5%[9]	↑ LVEF ≥5%[37]
Resistance to ischemia	Greater resistance to ischemia[9]	More susceptible to ischemia[9]
Adaptation to disease state	Better adaptation to volume overload states[9]	Better adaptation to pressure overload states[9]

PVR indicates pulmonary vascular resistance; SVR, systemic vascular resistance; and ↑, increase.
*Lower range of normal RV function used in clinical practice; lower value of normal described with radionuclide angiography.
†Mainly based on sarcomere length–pressure curve relationship, limited data on end-diastolic passive compliance in humans.

the moderator band artery, a branch of the first septal perforator that originates from the left anterior descending coronary artery, and (3) its ability to increase oxygen extraction.[34]

Regulation of RV Function

The mechanisms that can acutely regulate RV as well as LV function include heart rate, the Frank-Starling mechanism and the autonomic nervous system. The autonomic nervous system has a differential effect on the inflow and outflow region of the RV. In fact, weak vagal stimulation, which causes bradycardia, prolongs the normal sequence of activation, whereas sympathetic stimulation may abolish the usual delay or even reverse the sequence of contraction in these 2 regions of the RV.[9] The inflow and outflow regions may also differ in their response to sympathetic activation or inotropic stimulation; animal and human studies have suggested that the inotropic response of the infundibulum may be greater than that of the inflow tract.[35,36] As will be discussed in the second part of this series, numerous studies also describe the role of the renin-angiotensin-aldosterone system, natriuretic peptides, the endothelin system, tumor necrosis factor, and inflammation in patients with RV dysfunction. Table 1 summarizes important anatomic and physiological characteristics of the RV.[5,6,8,9,11,18,20,26,27,37]

Embryology and Aging

A basic understanding of embryology is helpful in the study of cardiovascular and congenital heart disease. The RV and RV outflow tract are derived from the anterior heart field, whereas the LV and the atrial chambers are derived from the primary heart field.[38] Transcription factors such as HAND1 and HAND2 appear to play an important role in chamber-specific heart formation.[39] The sinus part of the RV is derived from the ventricular portion of the primitive cardiac tube, whereas the infundibulum is derived from the conus cordis. In the anatomic LV, subaortic conal absorption occurs, which explains the absence of an infundibular component as well as mitral-aortic continuity.[9] Under normal conditions, the dextroventricular loop positions the anatomic RV to the right and the anatomic LV to the left. The complex spiral development of the outflow tracts explains the characteristic "crisscross" relationship between right and left outflow tracts, with the RV outflow tract being located anteriorly and to the left of the LV outflow tract.[6,7]

The RV undergoes significant changes with aging, especially after birth and during infancy. In the fetus, cardiovascular physiology is characterized by a high-resistance pulmonary circulation; a low-resistance systemic circulation; a large, nonrestrictive ductus arteriosus; right-to-left flow across the foramen ovale; equal pulmonary arterial and aortic pressure; and hypoxemia.[40–42] RV and LV free-wall thickness and force development are equal throughout fetal life, and the interventricular septum is midline and flat throughout the cardiac cycle.[40–42] After birth and in infancy, RV hypertrophy regresses, and the heart remodels to the typical postnatal heart with a crescent-shaped RV and an elliptic LV. With aging, several changes occur in the RV and the pulmonary vascular system. The pulmonary artery pressure and vascular resistance mildly increase with normal aging, most probably secondary to an increase in arterial stiffness of the pulmonary vasculature.[43,44] RVEF remains relatively well

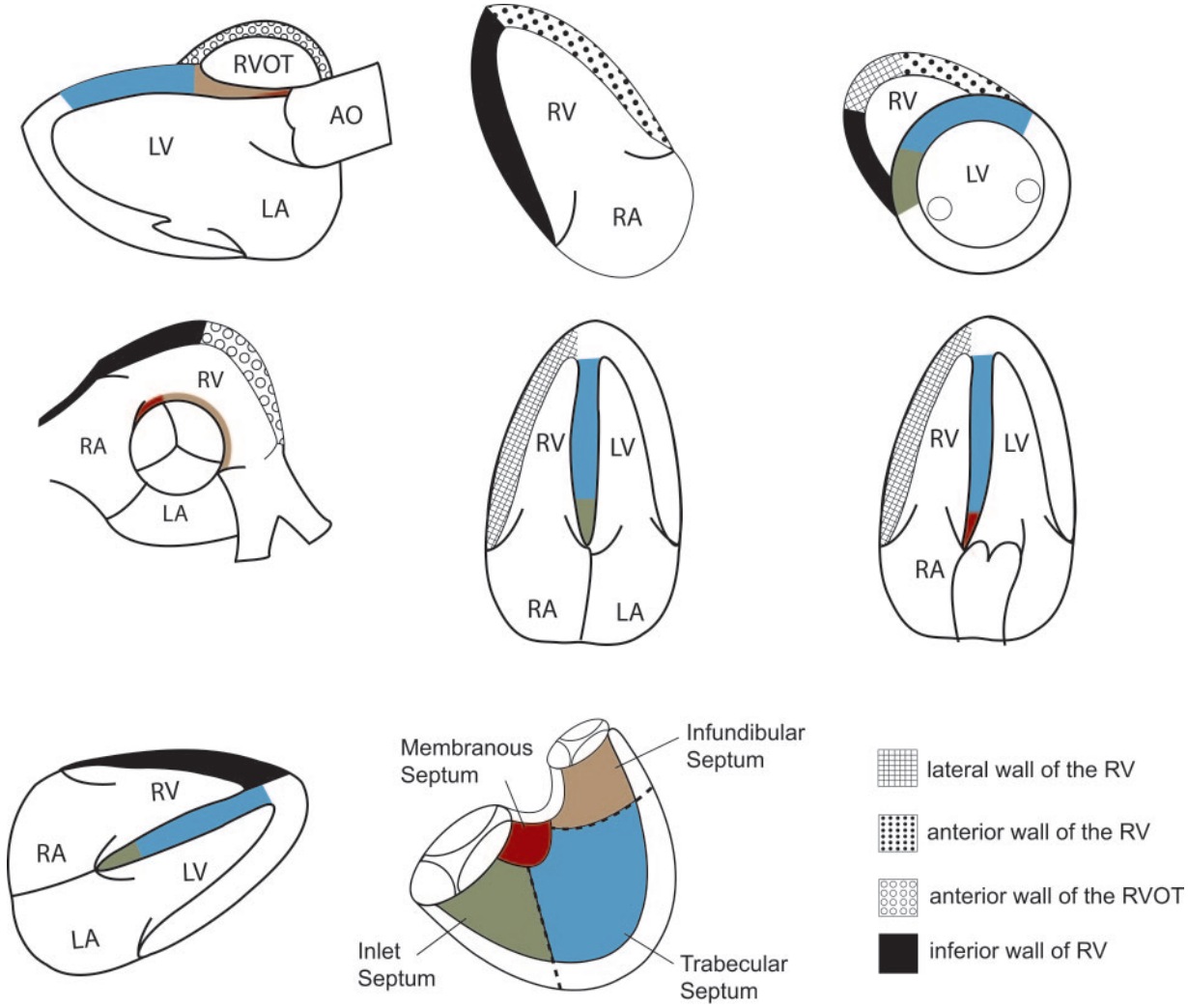

Figure 5. Segmental anatomy of the RV as shown in representative echocardiographic views. The colors indicate the different subdivisions of the interventricular septum. RVOT indicates RV outflow tract; AO, aorta; LA, left atrium; and RA, right atrium. Adapted from Weyman[6] with permission from the publisher. Copyright © 1994, Lippincott Williams & Wilkins.

preserved with aging, as does LV ejection fraction. RV diastolic function changes with time. Doppler indices, reflective of flow pattern, demonstrate a reduced early RV diastolic filling, increased late filling, and reduced myocardial diastolic velocities.[45] These changes are analogous to changes in LV diastolic filling profiles. Changes in RV systolic reserve with exercise have not been well studied but most likely parallel the small decline seen in LV systolic reserve.[46]

Assessment of the RV

Overview of RV Assessment

Evaluation of RV structure and function in patients with cardiopulmonary disorders is an essential component of clinical management. Although there have been significant improvements in cardiac imaging, many factors contribute to the challenges of RV assessment. These include (1) the complex geometry of the RV; (2) the limited definition of RV endocardial surface caused by the heavily trabeculated myocardium; (3) the retrosternal position of the RV, which can limit echocardiographic imaging windows; and (4) the marked load dependence of indices of RV function.[6]

The RV can be studied with many imaging and functional modalities. In clinical practice, echocardiography is the mainstay of evaluation of RV structure and function. Compared with other modalities, it offers the advantages of versatility and availability. Also, Doppler-derived indices of RV function, such as the myocardial performance index and tricuspid annular isovolumic acceleration (IVA), are emerging as promising parameters of RV function. Figure 5 summarizes the segmental anatomy of the RV in different echocardiographic views.[6] Cardiac magnetic resonance imaging (MRI) is increasingly used as a standard tool in the evaluation of RV structure and function. MRI is the most accurate method for assessing RV volume. With careful attention to detail, diastolic and systolic volumes can be determined and used to calculate ejection fraction. In addition, MRI flow studies are used to estimate forward flow through semilunar valves and AV valves, which allows accurate calculation of regurgitant fractions, cardiac output, and shunt fraction. In the future, MRI could also have a potential role in assessing the physiological characteristics of pulmonary arterial flow. Radionuclide-based techniques provide reliable and geomet-

rically independent assessments of RVEF. Radionuclide-based time activity curves are also useful in the quantification of shunts. Cardiac catheterization provides direct hemodynamic data and allows accurate assessment of pulmonary vascular resistance. Pulmonary angiography and coronary angiography can further delineate important anatomic and functional characteristics. Compared with CT angiography, pulmonary angiography may be limited in its assessment of proximal lamination but has a relative benefit in assessing distal obstruction. Analysis of RV function by pressure-volume loops is useful because it quantifies various determinants of RV function such as RV elastance, dP/dt, ventricular compliance, stroke work, and preload recruitable stroke work. Currently, the conductance catheter is the most frequently used method to construct pressure-volume loops. This catheter contains a high-fidelity pressure sensor and up to 12 electrodes to measure RV electrical conductance, from which instantaneous RV chamber volume is determined.[47] Compared with LV conductance studies, RV conductance studies are technically more challenging because of the difficulty in obtaining reliable ventricular volumes.

Assessment of RV Structure

A change in RV shape and volume can be the first sign of RV dysfunction, pressure or volume overload, or arrhythmogenic RV dysplasia. A comprehensive assessment of RV structure should include the study of (1) RV volume, (2) RV shape and internal architecture, (3) RV hypertrophy and mass, (4) tissue characterization, and (5) assessment for potential masses (Table 2).[6,8,48–50]

To be accurate, volume assessment should always take into account the complex shape of the RV. Furthermore, the infundibulum should be included in the volume measurement because it can account for as much as 25% to 30% of RV volume.[51] The simplest and most routinely used method for assessing RV volume includes linear dimensions and areas obtained from single tomographic echocardiographic planes. The best correlations between single-plane measurements and RV volumes have been obtained with the maximal short-axis dimension and the planimetered RV area (in the 4-chamber view).[6] Significant overlap has been noted, however, between normal and volume-overloaded conditions, especially for mild to moderate enlargement.[6] In an effort to be more accurate, different approaches have been sought to directly measure RV volume. These include the area-length method and Simpson's rule approach. In 2-dimensional echocardiography, numerous studies showed that the area-length method that uses an ellipsoid or pyramidal model correlates better with RV volume than Simpson's rule.[6] The main difficulty seen with the application of Simpson's rule to 2-dimensional echocardiographic images is obtaining 2 appropriate orthogonal views with a common long axis. Three-dimensional echocardiography is a promising technique that could lead to more accurate assessment of RV volume. However, visualization of the anterior wall and inclusion of the infundibulum in a simple model remain difficult, which explains the variable correlations with MRI and cast models.[6,51,52] MRI is considered the most reliable method for measuring RV volumes. By acquiring parallel and contiguous tomographic images with high temporal resolution, MRI obviates the need for geometric assumptions. Volume is then calculated by summing the volume of each slice with Simpson's rule.

Table 2. Structural Characteristics of the RV

Feature	Criteria (Reference)	Interpretation
Dilatation	Volume >101 mL/m^2[8]	Volume overload
	RV max SAX >43 mm[6]	Pressure overload
	RVEDA/LVEDA >2/3[6]	Intrinsic myocardial disease
D-shaped LV	Eccentricity index >1[49]*	RV pressure or volume overload
		Diastolic D-shape LV suggests volume overload
		Systolic D-shape LV suggests pressure overload
Hypertrophy	Mass >35 g/m^2[8]	Pressure-overloaded RV
	RV inferior wall >5 mm[6]	Hypertrophic cardiomyopathy, infiltrative disease; exclude double-chambered RV
Aneurysm	Localized RV dilatation[6]	ARVD; RVMI; localized absence of pericardium
TV septal insertion	Septal insertion >1 cm or 8 mm/m^2[50]	Consider Ebstein's anomaly
Delayed enhancement	Area of delayed contrast uptake and washout in MRI	Suggests myocardial fibrosis
Fatty infiltration	High-intensity signal on MRI	Consider ARVD

RV max SAX indicates RV maximal short-axis diameter; RVEDA/LVEDA, ratio of RV to LV end-diastolic area; ARVD, arrhythmogenic RV dysplasia; RVMI, RV myocardial infarction; and TV, tricuspid valve.

*The eccentricity index measures the degree of septal displacement and is defined as the ratio of the minor axis diameter of the LV parallel to the septum to that perpendicular to it.

Assessment of RV Function

The load dependence of many of the indices of RV function and the difficulty in constructing and analyzing RV pressure-volume loops render the study of RV function particularly challenging. In this section, we will review noninvasive and invasive indices of contractility, preload, and afterload in the context of clinical practice.

Selected Indices of RV Contractility

An ideal index of contractility should be independent of afterload and preload, sensitive to change in inotropy, independent of heart size and mass, easy and safe to apply, and proven to be useful in the clinical setting.[53] In clinical practice, RVEF is the most commonly used index of RV contractility. Although widely accepted, RVEF is highly dependent on loading conditions and may not adequately reflect contractility. Because the RV chamber is larger than the LV chamber, RVEF is, under normal conditions, lower than LV ejection fraction. The normal range of RVEF varies between 40% and 76% depending on the methodology used. MRI is the most accurate method for measuring RVEF. According to Lorenz and colleagues,[8] the normal value of RVEF is 61±7%, ranging from 47% to 76%. RV images can be acquired in the short-axis or axial direction. Alfakih and colleagues[54] demonstrated that the axial orientation resulted

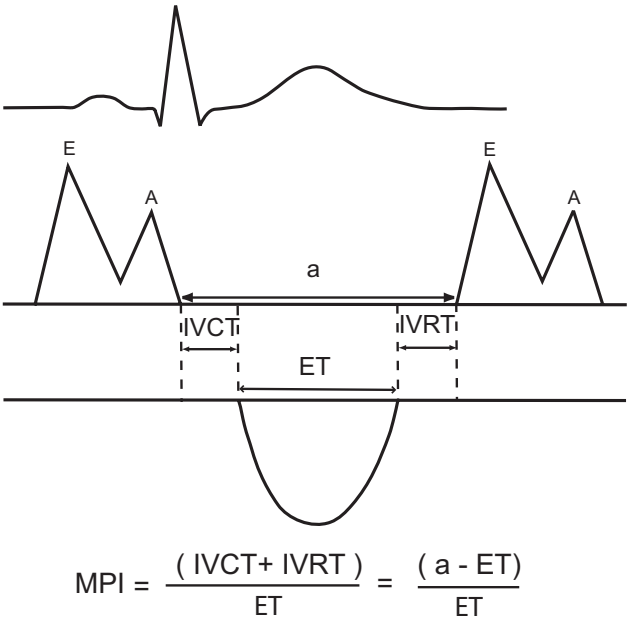

Figure 6. The RV myocardial performance index (MPI). E indicates the rapid filling velocity; A, atrial filling velocity; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; and ET, ejection time.

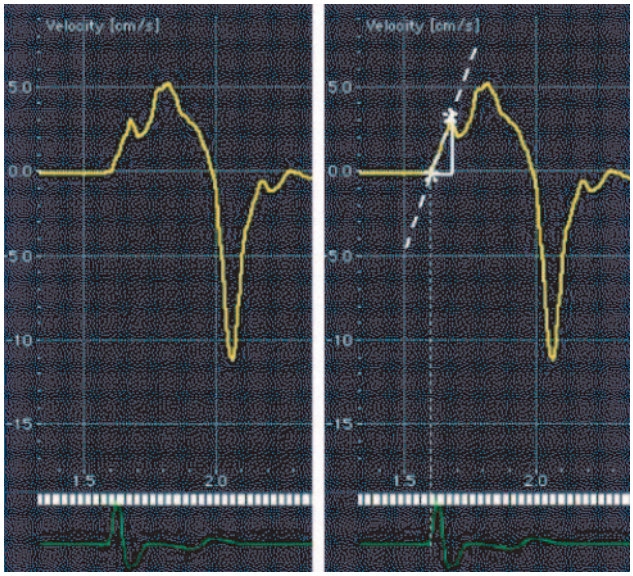

Figure 7. Tissue Doppler echocardiography spectral curve at the level of the tricuspid annulus. The isovolumic myocardial acceleration is calculated as the difference between baseline and peak velocity (stars) during isovolumic contraction divided by their time interval. Reproduced from Vogel et al[64] with permission from the publisher. Copyright © 2004, the American College of Cardiology Foundation.

in a better intraobserver and interobserver reproducibility than the short-axis orientation. The lower limit of radionuclide-derived normal RVEF ranges from 40% to 45%.[55] Radionuclide angiography can be completed with either first-pass or equilibrium techniques. Both techniques have the advantage of being independent of geometric assumption and have been validated extensively. The first-pass technique has the disadvantage of having a lower count density, whereas the equilibrium technique has difficulty separating the right atrium from the RV.[55] Echocardiography is less accurate than the 2 previously mentioned methods. Two-dimensional assessment of RVEF with Simpson's rule and the area-length method showed moderate correlation with radionuclide- or MRI-derived RVEF (correlations ranging from 0.65 to 0.80).[6] In the clinical setting, 3D echocardiography has also shown variable correlations with RVEF. Difficulties that still need to be overcome include delineation of the anterior wall and identification of the infundibular plane. RV fractional area change represents the ratio of systolic area change to diastolic RV area. It is measured in the 4-chamber view and can be incorporated systematically into the basic echocardiographic study. In end-stage pulmonary disease, a good correlation has been reported between RV fractional area change and RVEF.[56]

Tricuspid annular plane systolic excursion is another useful quantitative measurement of RV systolic performance. This method reflects the longitudinal systolic excursion of the lateral tricuspid valve annulus toward the apex. It is usually measured with M-mode imaging in the 4-chamber view.[57] Studies showed moderate correlation between tricuspid annular plane systolic excursion and RVEF measured by radionuclide angiography.[58]

RV myocardial performance index, which is the ratio of isovolumic time intervals to ventricular ejection time, has been described as a nongeometric index of global ventricular function (Figure 6).[59] RV myocardial performance index appears to be relatively independent of preload, afterload, and heart rate and has been useful in assessing patients with congenital heart disease and pulmonary hypertension.[60–62] The normal value of this index is 0.28 ± 0.04, and it usually increases in the presence of RV systolic or diastolic dysfunction. Recently, Yoshifuku and colleagues[62] described pseudonormalized values in acute and severe RV myocardial infarction, which can probably be explained by a decrease in isovolumic contraction time associated with an acute increase in RV diastolic pressure.

Tissue Doppler imaging, which measures myocardial velocities, also allows quantitative assessment of RV systolic function. Systolic tissue Doppler signal of the tricuspid annulus (St) has been studied as an index of RV function in patients with heart failure. Peak systolic values <11.5 cm/s identified the presence of ventricular systolic dysfunction (RVEF $<50\%$) with a sensitivity and specificity of 90% and 85%, respectively.[63]

IVA represents a new tissue Doppler–derived parameter of systolic performance. It is calculated by dividing the maximal isovolumic myocardial velocity by the time to peak velocity: IVA=maximum velocity/time to peak (Figure 7).[64] Vogel and colleagues studied the value of myocardial IVA in a closed-chest animal model during modulation of preload, afterload, contractility, and heart rate. Their study showed that IVA reflects RV myocardial contractile function and is less affected by preload and afterload within a physiological range than either the maximum first derivative of RV pressure development (dP/dt max) or ventricular elastance.[64] Two clinical studies confirmed its value in congenital heart disease, ie, after repair of tetralogy of Fallot and in transposition

Table 3. Selected Indices of RV Contractility

Functional Parameters	Normal Value	Load Dependence*	Clinical Utility
RVEF, %	61±7% (47%–76%)[8]	+ + +	Clinical validation, wide acceptance
	>40%–45%		Prognostic value in cardiopulmonary disorders[9]
RVFAC, %	>32%[48]	+ + +	Good correlation with RVEF
			Prognostic value in MI and bypass surgery[48]
TAPSE, mm	>15[48]	+ + +	Simple measure not limited by endocardial border recognition: Good correlation with RVEF
Sm annular, cm/s	>12[63]	+ + +	Good sensitivity and specificity for RVEF <50%[63]
Strain	Basal: 19±6[68]	+ + +	Correlates with stroke volume[69,70]
	Mid: 27±6		
	Apical: 32±6		
Strain rate, s^{-1}	Basal: 1.50±0.41[68]	+ +	Correlates with contractility[69,70]
	Mid: 1.72±0.27		
	Apical: 2.04±0.41		
RVMPI	0.28±0.04[59]	+ +	Global nongeometric index of systolic and diastolic function, prognostic value PH, CHD[60–62]
dP/dt max, mm Hg/s	100–250[9]	+ +	Not a reliable index of contractility[66]
			More useful in assessing directional change when preload accounted for
IVA, m/s^2	1.4±0.5[64]	+	Promising new noninvasive index of contractility, studies in CHD[64,65]
Maximal RV elastance, mm Hg/mL	1.30±0.84[20]	+	Most reliable index of contractility[9]

RVFAC indicates RV fractional area change; MI, myocardial infarction; TAPSE, tricuspid annular plane systolic excursion; Sm, tissue Doppler maximal systolic velocity at the tricuspid annulus; RVMPI, RV myocardial performance index; PH, pulmonary hypertension; and CHD, congenital heart disease.

*Should be viewed as a general indication of load dependence.

of the great arteries.[64,65] Further validation of this new index is being actively pursued.

dP/dt max is also used as an index of RV contractility. As demonstrated by numerous studies, RV dP/dt max is significantly affected by loading conditions and cannot be used as a reliable index of contractility.[66] It may, however, be useful in assessing directional change in response to therapy.

As discussed earlier, maximum ventricular elastance is considered by many investigators as the best index of contractility.[20] Because conductance catheterization is invasive and time consuming, it is predominantly used as a research tool for assessment of ventricular function.[65] More recently, single-beat estimation of RV elastance with the maximal pressure of isovolumic beat has been validated in the clinical setting. This method could potentially simplify the measure of ventricular elastance.[67] Table 3 compares different indices of RV systolic function.[8,9,20,48,59–70]

Patterns of RV Segmental Dysfunction

In pulmonary embolism, McConnell and colleagues[71] described a distinct pattern of RV dysfunction, characterized by severe hypokinesia of the RV mid free wall, with normal contraction of the apical segment. Compared with several other conditions, the finding showed a sensitivity of 77% and a specificity of 94% for pulmonary embolism. Recently, Casazza and colleagues[72] also recognized this pattern of ventricular dysfunction in patients with acute RV myocardial infarction.

In RV myocardial infarction, the pattern of segmental dysfunction depends on the culprit artery. With involvement of the right coronary artery proximal to the marginal branches (in a right-dominant coronary system), segmental hypokinesia is seen in the lateral and inferior wall. With involvement of the posterior descending artery, hypokinesia is usually limited to the inferior segments. In anterior myocardial infarction involving the left anterior descending coronary artery, RV hypokinesia is usually limited to the anterior wall.

In patients with arrhythmogenic RV dysplasia who meet the Task Force diagnostic criteria for this condition, Yoerger and colleagues[73] showed that RV enlargement and decreased RV function occur frequently. Regional wall-motion abnormalities occurred in 79% of probands; the apex (72%) and the anterior wall (70%) were the most common sites of these abnormalities.[73]

RV Diastolic Parameters and Estimation of Preload

Because RV diastole is composed of many phases, it cannot be described by a single parameter. The different parameters used in the study of RV diastole include (1) RV end-diastolic or right atrial pressures, (2) RV volume, (3) RV filling profiles, (4) relaxation-phase indices (dP/dt minimum and the time constant of isovolumic pressure decay), and (5) passive chamber characteristics such as compliance (Table 4).[11,25,48,74–77]

Right atrial pressure or RV end-diastolic pressure can be measured directly during right-heart catheterization or estimated noninvasively by assessing inferior vena cava diameter and collapse index.[48] The annular tricuspid E/e ratio and annular tissue Doppler relaxation time have also shown moderate correlation with right atrial pressure.[78] Assessment of RV preload is

Table 4. Selected Indices of RV Function

Index	Normal Values	Clinical Utility-Comment
Diastolic parameters		
Pressures, mm Hg	RAmean: 3 (1–5)[11] RVEDP: 4 (1–7)	High values suggest diastolic dysfunction
Inferior vena cava	≤1.7 cm, CI ≥50%[48]	Estimates RA pressure: (mm Hg)* IVC ≤1.7 cm, CI ≥50%: 0–5 IVC >1.7 cm, CI ≥50%: 6–10 IVC >1.7 cm, CI <50%: 10–15 IVC >1.7 cm, fixed: ≥15
Diastolic E/A velocity ratio	1.50±0.3[25]	RV diastolic profiles have not been well correlated with chamber compliance or ventricular pressures; E/A >2 and DT <160 ms suggest restrictive physiology
E deceleration time, ms	198±23[25]	
Hepatic vein S/D velocity ratio	>1 in sinus rhythm[74] <1 in AF	Reversal of systolic flow seen in severe diastolic dysfunction or severe TR
Diastolic pulmonary flow	Absent	Presence suggests "restrictive" physiology in TOF[75]
End-diastolic compliance	not well defined	Limited data available in humans
Ventricular interdependence		
Respiratory variation in E velocity	Tricuspid: ≤15% inspiratory ↑ Mitral: ≤10% inspiratory ↓[76]	Increased respiratory variations seen in constriction (TΔ ≥40%, MΔ ≥25%) or tamponade (TΔ ≥80%, MΔ ≥40%)[76]
Valvular function		
Tricuspid regurgitation	<1/4	VC >7 mm and hepatic vein S reversal in severe TR[77]
Tricuspid valve gradient, mean, mm Hg	<2	Gradient >5 mm Hg and area <1 cm^2 in severe TS[77]
Pulmonary regurgitation	<1/4	RF >40% suggests severe PR[77]; PHT ≤100 ms in moderate-severe PR (TOF)
Pulmonary peak gradient, mm Hg	Maximal gradient <25 (upper limit of normal)	Maximal gradient 50–80 mm Hg suggests moderate PS and peak gradient >80 mm Hg suggests severe PS[77]

RAmean indicates mean right atrial pressure; RVEDP, RV end-diastolic pressure; IVC, inferior vena cava; CI, collapse index; RA, right atrial; E, rapid filling velocity of the RV; A, end-diastolic ventricular filling corresponding to the atrial contraction; DT, deceleration time; S/D, systolic to diastolic ratio of hepatic vein flow; AF, atrial fibrillation; TR, tricuspid regurgitation; TOF, tetralogy of Fallot; T, tricuspid; M, mitral; VC, venae contracta; TVG, tricuspid valve gradient; TS, tricuspid stenosis; PR, pulmonary regurgitation; RF, regurgitant fraction; PHT, pressure half-time; and PS, pulmonary stenosis.

*Athletes can have a dilated IVC without increased pressure. There exists variability in IVC size thresholds used in the literature.

more challenging. Although RV volume usually represents a reliable index of preload, RV volume may not always reflect sarcomeric length or predict response to fluid therapy.[20] Also, although right atrial pressure and RV end-diastolic pressure are often used as surrogates for RV preload, many studies showed that pressure and volume are not linearly related. More recently, in the intensive care setting, dynamic respiratory changes in right atrial pressure and dynamic changes in arterial pulse pressure have been shown to be better markers of fluid responsiveness than catheter-derived RV end-diastolic volume or absolute values of pressures.[79]

RV chamber compliance or stiffness has not been studied extensively in humans owing to the difficulty in obtaining accurate and simultaneous estimation of RV volume. Therefore, correlations between RV filling profiles and chamber characteristics are not well established. In tetralogy of Fallot, however, diastolic pulmonary flow during atrial systole has been described as indicating decreased ventricular compliance or restrictive physiology.[75] The time constant of isovolumic pressure decay and dP/dt minimum have been shown to have marked load dependence and are not used routinely in the study of ventricular diastology.[80]

Assessment of RV Afterload

Pulmonary vascular resistance is the most commonly used index of RV afterload in clinical practice; however, a more complete understanding of afterload should take into account resistive, capacitive, inertial, and pulse-reflection properties of the pulmonary vasculature, as well as potential outflow or ventricular resistive component.[9] Models of the pulmonary vasculature that integrate passive and dynamic components of vascular impedance are being actively investigated.

Assessment of Ventricular Interdependence

Assessment of ventricular interdependence is helpful in differentiating restrictive from constrictive physiology, both of which can present with right-sided heart failure. Ventricular interdependence may be clinically assessed by considering (1) the degree of reciprocal respiratory change in ventricular filling profiles, (2) ventricular coupling (in dimension or pressure), or (3) abnormal septal motions. In assessing ventricular interdependence, it is also important to consider the effects of ventricular dysfunction on the pressure-volume relationship and function of the other ventricle.

Strain and Strain Rate Analysis

Strain is defined as the degree of deformation of an object, whereas strain rate represents the speed at which strain occurs.[81] In echocardiography, RV longitudinal strain can be assessed reliably from apical views, whereas radial strain is difficult and is hampered by near-field artifacts and extremely small computational distance. Theoretically, MRI could provide highly reproducible data on RV myocardial deformation not only in the longitudinal and radial directions but also in the circumferential direction. At this moment, however, few data are available on RV MRI strain. In mathematical models and in experimental studies, longitudinal strain appears to correlate best with changes in stroke volume, whereas longitudinal strain rate is more related to local contractile function and appears to be more independent of loading.[70]

Evaluation of RV Dyssynchrony

The study of RV dyssynchrony is in its early stages, but several groups are currently investigating specific ECG (QRS duration) and mechanical criteria of RV dyssynchrony. Echocardiographic indices of dyssynchrony are assessed by measuring time delay in mechanical activity between segments. At this time, areas that can be assessed by tissue Doppler imaging are limited to the septum-RV free wall. MRI could theoretically have the advantage of assessing 3D indices of dyssynchrony.

Cardiac Rhythm and the RV

Cardiac rhythm plays an essential role in RV function. Atrial fibrillation can severely compromise RV function. In addition, ventricular tachycardia can originate from the RV in a variety of disorders, such as arrhythmogenic RV dysplasia, RV myocardial infarction, left bundle-branch block, idiopathic ventricular tachycardia, or after surgical repair of congenital disease.[82] Although ventricular tachycardia that arises from the RV usually has a left bundle-branch block morphology, most ventricular tachycardia with this morphology arises from a paraseptal LV location.[82]

Cardiac Markers

Recent studies showed that serum levels of B-type natriuretic peptide may be useful in diagnosing RV failure associated with pulmonary hypertension, congenital heart disease, or pulmonary disease.[83–85] In pulmonary arterial hypertension, an elevated B-type natriuretic peptide level at baseline (>150 pg/mL) and follow-up (>180 pg/mL) has been associated with worse survival.[83] Elevated troponin levels have also been associated with worse outcome in pulmonary embolism and pulmonary hypertension.[86,87]

Conclusion and Future Directions

A proper understanding of RV physiology requires knowledge of ventricular contractility, preload, and afterload, as well as ventricular interdependence and pericardial constraint. Because of its complex shape and marked load dependence, the study of the RV remains challenging. New and promising noninvasive indices of contractility include tissue Doppler IVA and RV myocardial performance index. In the future, advances in cardiac imaging are expected in the field of 3D echocardiography, strain imaging, diffusion tensor MRI imaging, and tissue characterization. These could lead to the discovery of new noninvasive indices of contractility and chamber compliance and to a better understanding of ventricular remodeling.

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Disclosures

None.

References

1. Harvey W. *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus.* 1628.
2. Goldstein J. The right ventricle: what's right and what's wrong. *Coron Artery Dis*. 2005;16:1–3.
3. Lee FA. Hemodynamics of the right ventricle in normal and disease states. *Cardiol Clin*. 1992;10:59–67.
4. Goor DA, Lillehei CW. Congenital malformations of the heart. In: Goor DA, Lillehei CW. *Congenital Malformations of the Heart: Embryology, Anatomy, and Operative Considerations.* 1st ed. New York, NY: Grune & Stratton; 1975:1–37.
5. Ho SY, Nihoyannopoulos P. Anatomy, echocardiography, and normal right ventricular dimensions. *Heart*. 2006;92(suppl 1):i2–i13.
6. Jiang L. Right ventricle. In: Weyman AE, ed. *Principle and Practice of Echocardiography.* Baltimore, Md: Lippincott Williams & Wilkins; 1994:901–921.
7. Farb A, Burke AP, Virmani R. Anatomy and pathology of the right ventricle (including acquired tricuspid and pulmonic valve disease). *Cardiol Clin*. 1992;10:1–21.
8. Lorenz CH, Walker ES, Morgan VL, Klein SS, Graham TP Jr. Normal human right and left ventricular mass, systolic function, and gender differences by cine magnetic resonance imaging. *J Cardiovasc Magn Reson*. 1999;1:7–21.
9. Dell'Italia LJ. The right ventricle: anatomy, physiology, and clinical importance. *Curr Probl Cardiol*. 1991;16:653–720.
10. Petitjean C, Rougon N, Cluzel P. Assessment of myocardial function: a review of quantification methods and results using tagged MRI. *J Cardiovasc Magn Reson*. 2005;7:501–516.
11. Davidson C, Bonow R. Cardiac catheterization. In: Zipes D, Libby P, Bonow R, Braunwald E, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* 7th ed. Philadelphia, Pa: Elsevier; 2005: chap ll.
12. Dell'Italia LJ, Walsh RA. Acute determinants of the hangout interval in the pulmonary circulation. *Am Heart J*. 1988;116:1289–1297.
13. Dell'Italia LJ. Mechanism of postextrasystolic potentiation in the right ventricle. *Am J Cardiol*. 1990;65:736–741.
14. Goldstein JA, Barzilai B, Rosamond TL, Eisenberg PR, Jaffe AS. Determinants of hemodynamic compromise with severe right ventricular infarction. *Circulation*. 1990;82:359–368.
15. Feneley MP, Gavaghan TP, Baron DW, Branson JA, Roy PR, Morgan JJ. Contribution of left ventricular contraction to the generation of right ventricular systolic pressure in the human heart. *Circulation*. 1985;71: 473–480.
16. Santamore WP, Dell'Italia LJ. Ventricular interdependence: significant left ventricular contributions to right ventricular systolic function. *Prog Cardiovasc Dis*. 1998;40:289–308.
17. Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res*. 1973;32:314–322.
18. Starling MR, Walsh RA, Dell'Italia LJ, Mancini GB, Lasher JC, Lancaster JL. The relationship of various measures of end-systole to left ventricular maximum time-varying elastance in man. *Circulation*. 1987; 76:32–43.
19. Brown KA, Ditchey RV. Human right ventricular end-systolic pressure-volume relation defined by maximal elastance. *Circulation*. 1988;78: 81–91.

20. Dell'Italia LJ, Walsh RA. Application of a time varying elastance model to right ventricular performance in man. *Cardiovasc Res*. 1988;22:864–874.
21. Kass DA, Maughan WL. From "Emax" to pressure-volume relations: a broader view. *Circulation*. 1988;77:1203–1212.
22. MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease: part one. *Am J Respir Crit Care Med*. 1994;150:833–852.
23. Chin KM, Kim NH, Rubin LJ. The right ventricle in pulmonary hypertension. *Coron Artery Dis*. 2005;16:13–18.
24. Yu CM, Sanderson JE, Chan S, Yeung L, Hung YT, Woo KS. Right ventricular diastolic dysfunction in heart failure. *Circulation*. 1996;93:1509–1514.
25. Burgess MI, Mogulkoc N, Bright-Thomas RJ, Bishop P, Egan JJ, Ray SG. Comparison of echocardiographic markers of right ventricular function in determining prognosis in chronic pulmonary disease. *J Am Soc Echocardiogr*. 2002;15:633–639.
26. Leyton RA, Sonnenblick EH. The sarcomere as the basis of Starling's law of the heart in the left and right ventricles. *Methods Achiev Exp Pathol*. 1971;5:22–59.
27. Gaasch WH, Cole JS, Quinones MA, Alexander JK. Dynamic determinants of left ventricular diastolic pressure-volume relations in man. *Circulation*. 1975;51:317–323.
28. Dubin AM, Janousek J, Rhee E, Strieper MJ, Cecchin F, Law IH, Shannon KM, Temple J, Rosenthal E, Zimmerman FJ, Davis A, Karpawich PP, Al AA, Vetter VL, Kertesz NJ, Shah M, Snyder C, Stephenson E, Emmel M, Sanatani S, Kanter R, Batra A, Collins KK. Resynchronization therapy in pediatric and congenital heart disease patients: an international multicenter study. *J Am Coll Cardiol*. 2005;46:2277–2283.
29. Hoffman D, Sisto D, Frater RW, Nikolic SD. Left-to-right ventricular interaction with a noncontracting right ventricle. *J Thorac Cardiovasc Surg*. 1994;107:1496–1502.
30. Taylor RR, Covell JW, Sonnenblick EH, Ross J Jr. Dependence of ventricular distensibility on filling of the opposite ventricle. *Am J Physiol*. 1967;213:711–718.
31. Efthimiadis GK, Parharidis GE, Gemitzis KD, Nouskas IG, Karvounis HI, Styliadis IK, Louridas GE. Doppler echocardiographic evaluation of right ventricular diastolic function in isolated valvular aortic stenosis. *J Heart Valve Dis*. 1999;8:261–269.
32. Brown GF. Vascular pattern of myocardium of right ventricle of human heart. *Br Heart J*. 1968;30:679–686.
33. Kinch JW, Ryan TJ. Right ventricular infarction. *N Engl J Med*. 1994;330:1211–1217.
34. Haupt HM, Hutchins GM, Moore GW. Right ventricular infarction: role of the moderator band artery in determining infarct size. *Circulation*. 1983;67:1268–1272.
35. Heerdt PM, Pleimann BE. The dose-dependent effects of halothane on right ventricular contraction pattern and regional inotropy in swine. *Anesth Analg*. 1996;82:1152–1158.
36. Denault AY, Chaput M, Couture P, Hebert Y, Haddad F, Tardif JC. Dynamic right ventricular outflow tract obstruction in cardiac surgery. *J Thorac Cardiovasc Surg*. 2006;132:43–49.
37. Mao S, Budoff MJ, Oudiz RJ, Bakhsheshi H, Wang S, Brundage BH. Effect of exercise on left and right ventricular ejection fraction and wall motion. *Int J Cardiol*. 1999;71:23–31.
38. Zaffran S, Kelly RG, Meilhac SM, Buckingham ME, Brown NA. Right ventricular myocardium derives from the anterior heart field. *Circ Res*. 2004;95:261–268.
39. McFadden DG, Barbosa AC, Richardson JA, Schneider MD, Srivastava D, Olson EN. The Hand1 and Hand2 transcription factors regulate expansion of the embryonic cardiac ventricles in a gene dosage-dependent manner. *Development*. 2005;132:189–201.
40. Hopkins WE, Waggoner AD. Severe pulmonary hypertension without right ventricular failure: the unique hearts of patients with Eisenmenger syndrome. *Am J Cardiol*. 2002;89:34–38.
41. Rudolph AM. The changes in the circulation after birth: their importance in congenital heart disease. *Circulation*. 1970;41:343–359.
42. Rudolph AM. The fetal circulation and its adjustments after birth in congenital heart disease. *UCLA Forum Med Sci*. 1970;10:105–118.
43. Davidson WR Jr, Fee EC. Influence of aging on pulmonary hemodynamics in a population free of coronary artery disease. *Am J Cardiol*. 1990;65:1454–1458.
44. Dib JC, Abergel E, Rovani C, Raffoul H, Diebold B. The age of the patient should be taken into account when interpreting Doppler assessed pulmonary artery pressures. *J Am Soc Echocardiogr*. 1997;10:72–73.
45. Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Taliercio CP, Taylor CL, Bailey KR, Seward JB. Age-related prevalence of valvular regurgitation in normal subjects: a comprehensive color flow examination of 118 volunteers. *J Am Soc Echocardiogr*. 1990;3:54–63.
46. Jones NL, Killian KJ. Exercise limitation in health and disease. *N Engl J Med*. 2000;343:632–641.
47. Bleeker GB, Steendijk P, Holman ER, Yu CM, Breithardt OA, Kaandorp TA, Schalij MJ, van der Wall EE, Nihoyannopoulos P, Bax JJ. Assessing right ventricular function: the role of echocardiography and complementary technologies. *Heart*. 2006;92(suppl 1):i19–i26.
48. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
49. Ryan T, Petrovic O, Dillon JC, Feigenbaum H, Conley MJ, Armstrong WF. An echocardiographic index for separation of right ventricular volume and pressure overload. *J Am Coll Cardiol*. 1985;5:918–927.
50. Ports TA, Silverman NH, Schiller NB. Two-dimensional echocardiographic assessment of Ebstein's anomaly. *Circulation*. 1978;58:336–343.
51. Nesser HJ, Tkalec W, Patel AR, Masani ND, Niel J, Markt B, Pandian NG. Quantitation of right ventricular volumes and ejection fraction by three-dimensional echocardiography in patients: comparison with magnetic resonance imaging and radionuclide ventriculography. *Echocardiography*. 2006;23:666–680.
52. Kjaergaard J, Petersen CL, Kjaer A, Schaadt BK, Oh JK, Hassager C. Evaluation of right ventricular volume and function by 2D and 3D echocardiography compared to MRI. *Eur J Echocardiogr*. 2006;7:430–438.
53. Carabello BA. Evolution of the study of left ventricular function: everything old is new again. *Circulation*. 2002;105:2701–2703.
54. Alfakih K, Plein S, Bloomer T, Jones T, Ridgway J, Sivananthan M. Comparison of right ventricular volume measurements between axial and short axis orientation using steady-state free precession magnetic resonance imaging. *J Magn Reson Imaging*. 2003;18:25–32.
55. Jain D, Zaret BL. Assessment of right ventricular function: role of nuclear imaging techniques. *Cardiol Clin*. 1992;10:23–39.
56. Schenk P, Globits S, Koller J, Brunner C, Artemiou O, Klepetko W, Burghuber OC. Accuracy of echocardiographic right ventricular parameters in patients with different end-stage lung diseases prior to lung transplantation. *J Heart Lung Transplant*. 2000;19:145–154.
57. Hammarstrom E, Wranne B, Pinto FJ, Puryear J, Popp RL. Tricuspid annular motion. *J Am Soc Echocardiogr*. 1991;4:131–139.
58. Ueti OM, Camargo EE, Ueti AA, de Lima-Filho EC, Nogueira EA. Assessment of right ventricular function with Doppler echocardiographic indices derived from tricuspid annular motion: comparison with radionuclide angiography. *Heart*. 2002;88:244–248.
59. Tei C, Dujardin KS, Hodge DO, Bailey KR, McGoon MD, Tajik AJ, Seward SB. Doppler echocardiographic index for assessment of global right ventricular function. *J Am Soc Echocardiogr*. 1996;9:838–847.
60. Eidem BW, Tei C, O'Leary PW, Cetta F, Seward JB. Nongeometric quantitative assessment of right and left ventricular function: myocardial performance index in normal children and patients with Ebstein anomaly. *J Am Soc Echocardiogr*. 1998;11:849–856.
61. Yeo TC, Dujardin KS, Tei C, Mahoney DW, McGoon MD, Seward JB. Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. *Am J Cardiol*. 1998;81:1157–1161.
62. Yoshifuku S, Otsuji Y, Takasaki K, Yuge K, Kisanuki A, Toyonaga K, Lee S, Murayama T, Nakashima H, Kumanohoso T, Minagoe S, Tei C. Pseudonormalized Doppler total ejection isovolume (Tei) index in patients with right ventricular acute myocardial infarction. *Am J Cardiol*. 2003;91:527–531.
63. Meluzin J, Spinarova L, Bakala J, Toman J, Krejci J, Hude P, Kara T, Soucek M. Pulsed Doppler tissue imaging of the velocity of tricuspid annular systolic motion: a new, rapid, and non-invasive method of evaluating right ventricular systolic function. *Eur Heart J*. 2001;22:340–348.
64. Vogel M, Derrick G, White PA, Cullen S, Aichner H, Deanfield J, Redington AN. Systemic ventricular function in patients with transpo-

sition of the great arteries after atrial repair: a tissue Doppler and conductance catheter study. *J Am Coll Cardiol*. 2004;43:100–106.
65. Vogel M, Schmidt MR, Kristiansen SB, Cheung M, White PA, Sorensen K, Redington AN. Validation of myocardial acceleration during isovolumic contraction as a novel noninvasive index of right ventricular contractility: comparison with ventricular pressure-volume relations in an animal model. *Circulation*. 2002;105:1693–1699.
66. Stein PD, Sabbah HN, Anbe DT, Marzilli M. Performance of the failing and nonfailing right ventricle of patients with pulmonary hypertension. *Am J Cardiol*. 1979;44:1050–1055.
67. Brimioulle S, Wauthy P, Ewalenko P, Rondelet B, Vermeulen F, Kerbaul F, Naeije R. Single-beat estimation of right ventricular end-systolic pressure-volume relationship. *Am J Physiol Heart Circ Physiol*. 2003; 284:H1625–H1630.
68. Kowalski M, Kukulski T, Jamal F, D'hooge J, Weidemann F, Rademakers F, Bijnens B, Hatle L, Sutherland GR. Can natural strain and strain rate quantify regional myocardial deformation? A study in healthy subjects. *Ultrasound Med Biol*. 2001;27:1087–1097.
69. Weidemann F, Jamal F, Sutherland GR, Claus P, Kowalski M, Hatle L, De SI, Bijnens B, Rademakers FE. Myocardial function defined by strain rate and strain during alterations in inotropic states and heart rate. *Am J Physiol Heart Circ Physiol*. 2002;283:H792–H799.
70. Jamal F, Bergerot C, Argaud L, Loufouat J, Ovize M. Longitudinal strain quantitates regional right ventricular contractile function. *Am J Physiol Heart Circ Physiol*. 2003;285:H2842–H2847.
71. McConnell MV, Solomon SD, Rayan ME, Come PC, Goldhaber SZ, Lee RT. Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. *Am J Cardiol*. 1996;78:469–473.
72. Casazza F, Bongarzoni A, Capozi A, Agostoni O. Regional right ventricular dysfunction in acute pulmonary embolism and right ventricular infarction. *Eur J Echocardiogr*. 2005;6:11–14.
73. Yoerger DM, Marcus F, Sherrill D, Calkins H, Towbin JA, Zareba W, Picard MH. Echocardiographic findings in patients meeting task force criteria for arrhythmogenic right ventricular dysplasia: new insights from the Multidisciplinary Study of Right Ventricular Dysplasia. *J Am Coll Cardiol*. 2005;45:860–865.
74. Appleton CP, Hatle LK, Popp RL. Superior vena cava and hepatic vein Doppler echocardiography in healthy adults. *J Am Coll Cardiol*. 1987; 10:1032–1039.
75. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot: QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation*. 1995;92:231–237.
76. Oh JK, Hatle LK, Seward JB, Danielson GK, Schaff HV, Reeder GS, Tajik AJ. Diagnostic role of Doppler echocardiography in constrictive pericarditis. *J Am Coll Cardiol*. 1994;23:154–162.
77. Bonow RO, Carabello BA, Kanu C, de Leon A Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons [published correction appears in *Circulation*. 2007;115:e409]. *Circulation*. 2006;114:e84–e231.
78. Abbas A, Lester S, Moreno FC, Srivathsan K, Fortuin D, Appleton C. Noninvasive assessment of right atrial pressure using Doppler tissue imaging. *J Am Soc Echocardiogr*. 2004;17:1155–1160.
79. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest*. 2002;121:2000–2008.
80. Leeuwenburgh BP, Steendijk P, Helbing WA, Baan J. Indexes of diastolic RV function: load dependence and changes after chronic RV pressure overload in lambs. *Am J Physiol Heart Circ Physiol*. 2002;282: H1350–H1358.
81. D'hooge J, Heimdal A, Jamal F, Kukulski T, Bijnens B, Rademakers F, Hatle L, Suetens P, Sutherland GR. Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. *Eur J Echocardiogr*. 2000;1:154–170.
82. Hoch DH, Rosenfeld LE. Tachycardias of right ventricular origin. *Cardiol Clin*. 1992;10:151–164.
83. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N, Miyatake K, Kangawa K. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation*. 2000;22;102: 865–870.
84. Yap LB, Mukerjee D, Timms PM, Ashrafian H, Coghlan JG. Natriuretic peptides, respiratory disease, and the right heart. *Chest*. 2004;126: 1330–1336.
85. Oosterhof T, Tulevski II, Vliegen HW, Spijkerboer 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;1;97:1051–1055.
86. Konstantinides S, Geibel A, Olschewski M, Kasper W, Hruska N, Jackle S, Binder L. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. *Circulation*. 2002;106: 1263–1268.
87. Torbicki A, Kurzyna M, Kuca P, Fijalkowska A, Sikora J, Florczyk M, Pruszczyk P, Burakowski J, Wawrzynska L. Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension. *Circulation*. 2003;108:844–848.

KEY WORDS: imaging ■ heart failure ■ ventricles ■ aging ■ contractility ■ echocardiography ■ physiology

Right Ventricular Function in Cardiovascular Disease, Part II

Pathophysiology, Clinical Importance, and Management of Right Ventricular Failure

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

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

Definitions

RV failure is a complex clinical syndrome that can result from any structural or functional cardiovascular disorder that impairs the ability of the RV to fill or to eject blood. The cardinal clinical manifestations of RV failure are (1) fluid retention, which may lead to peripheral edema, ascites, and anasarca; (2) decreased systolic reserve or low cardiac output, which may lead to exercise intolerance and fatigue; or (3) atrial or ventricular arrhythmias. RV dysfunction, on the other hand, refers to abnormalities of filling or contraction without reference to signs or symptoms of HF. Many indexes can be used to describe RV dysfunction. Among them, RV ejection fraction (RVEF) is the most commonly used index of RV function even though it is a highly load-dependent index of contractility (Table 1).

Pathophysiology

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

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

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

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

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

Table 2. Mechanisms and Specific Causes of Right Heart Failure

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

RA indicates right atrium.

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

In contrast to volume-overload states, moderate to severe acquired PH in the adult often leads to RV dilatation and failure.[9] Pressure overload of the RV also may lead to RV ischemia, which may further aggravate ventricular dysfunction.[9] Compared with volume-overload states, histological changes are more pronounced in RV pressure-overload states as demonstrated by the increased density of myocardial connective tissue seen in both animal and human studies.[10,11] In acute pressure-overload states such as pulmonary embolism (PE), an adult with a previously normal RV is incapable of acutely generating a mean pulmonary artery pressure >40 mm Hg, and RV failure occurs early in the presence of a significant embolic burden.[12] In most patients with idiopathic PAH, progressive RV dilatation and RV dysfunction occur. Clinical experience suggests, however, that some patients with PH develop RV failure earlier than others with the same degree of pulmonary pressure. Altered gene expression and neurohormonal activation may partially account for these differences.[5] Recent studies showed that in some patients with idiopathic PAH, expression and recapitulation of the fetal gene pattern occur as demonstrated by the decreased expression of the α-myosin heavy chain gene and the increased expression of the fetal β-myosin heavy chain.[5] An association between angiotensin-converting enzyme DD polymorphism and RV adaptation in PAH also has been suggested recently by some investigators.[13]

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

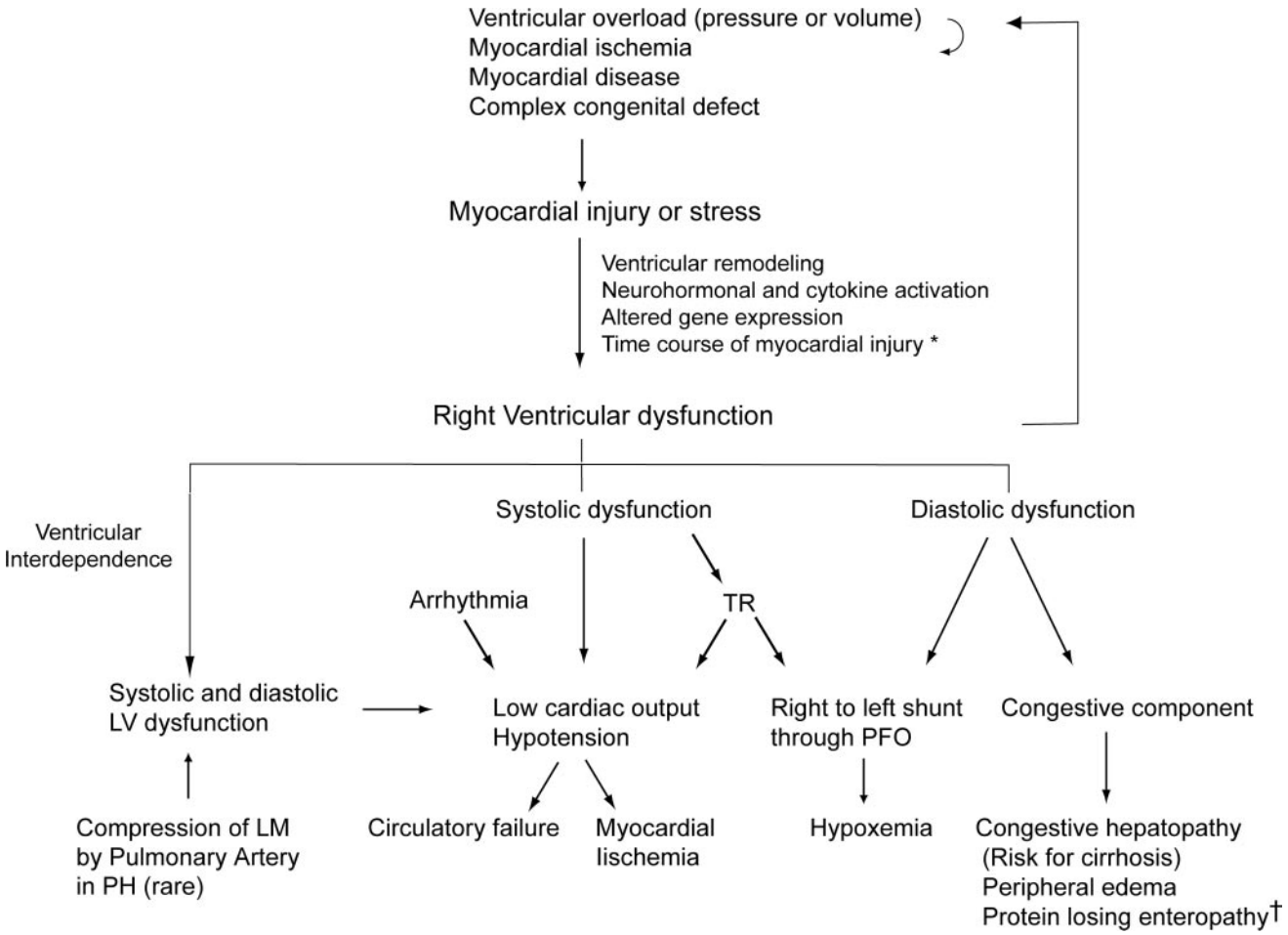

Figure 1. Pathophysiology of RV failure. *The time course (acute or chronic) and time of onset of the disease process (newborn, pediatric, or adult years) also influence RV adaptation to disease. Neurohormonal activation and altered gene expression modulate the development of RV dysfunction (Figure 2).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

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

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

Neurohormonal and Cytokine Activation

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

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

The renin-angiotensin-aldosterone system plays an important role in the pathophysiology of left HF.[22] Many studies also suggest its importance in RV failure. In a rabbit model of RV failure induced by pulmonary artery banding, Rouleau and colleagues[23] demonstrated that RV pressure overload led to a loss of responsiveness to the inotropic effects of angiotensin II and to an uncoupling of angiotensin 1 receptors to downstream signaling pathways. In patients with cor pulmonale, activation of the renin-angiotensin-aldosterone system also may contribute to fluid retention and ventricular remodeling.[16]

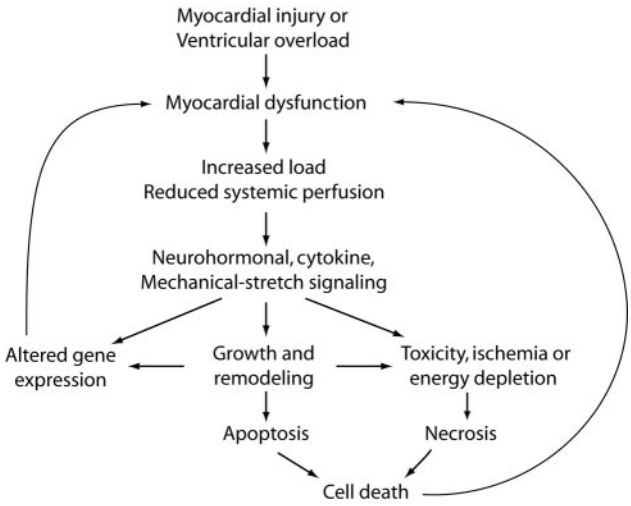

Figure 2. Postulated interactions between ventricular remodeling, neurohormonal and cytokine activation, and gene expression in the setting of RV failure. Adapted from Voelkel et al[5] with permission from the publisher. Copyright © 2006, the American Heart Association.

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

Atrial natriuretic peptide and B-type natriuretic peptide are 2 natriuretic peptides of cardiac origin. B-type natriuretic peptide levels may increase in RV pressure- or volume-overload states such as PH, cor pulmonale, PE, and selected CHD.[18,19] Elevated B-type natriuretic peptide levels also are associated with an increased risk of mortality in patients with idiopathic PAH.[18]

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

Hemodynamic and Systemic Consequences of RV Failure

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

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

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

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

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

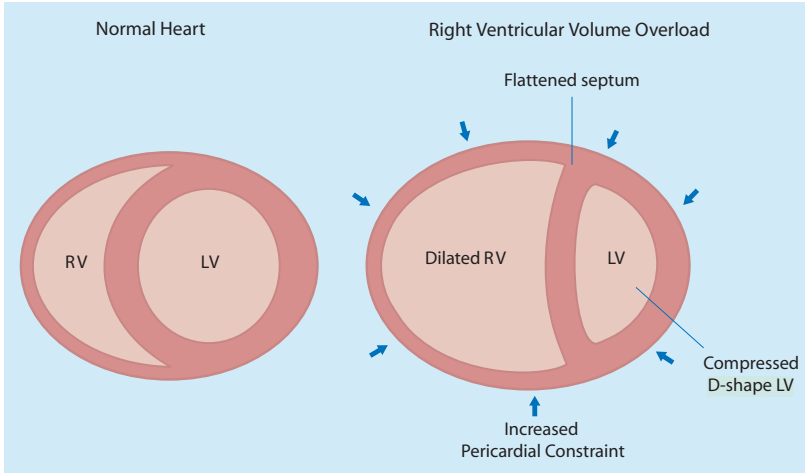

Figure 3. Ventricular interdependence in RV failure. Dilatation of the RV shifts the interventricular septum toward the left, changing LV geometry. Acute RV distension also may lead to an increase in pericardial constraint (arrows). These changes may contribute to low cardiac output state by decreasing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

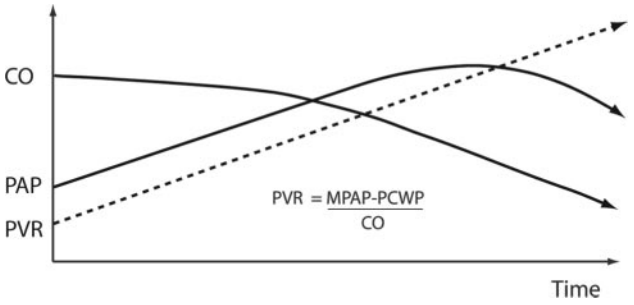

Figure 4. Hemodynamics in progressive pulmonary vascular disease. A decrease in pulmonary arterial pressure (PAP) in patients with PH may be a sign of low cardiac output (CO) and severe RV failure. PVR indicates pulmonary vascular resistance; PCWP, pulmonary artery capillary wedge pressure; and MPAP,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

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

Arrhythmias and Sudden Death in RV Disease

Atrial tachyarrhythmias are the most common arrhythmias encountered in patients with RV failure. In the setting of acute RV failure or severe RV dysfunction, atrial tachyarrhythmias often lead to hemodynamic instability. Many studies have demonstrated that atrial flutter or atrial fibrillation is associated with an increased risk of morbidity or mortality in patients with RVMI, PH, and CHD.[15,29–31] Right atrial dilatation and remodeling and postsurgical scars within the atria, as in postoperative CHD, represent important substrates for atrial flutter.[30,31]

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

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

Stages of RV Failure and Prognostic Factors

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

Table 3. Arrhythmias in Acquired RV Disease and CHD

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

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

*CHD with primary LV or valvular disease.

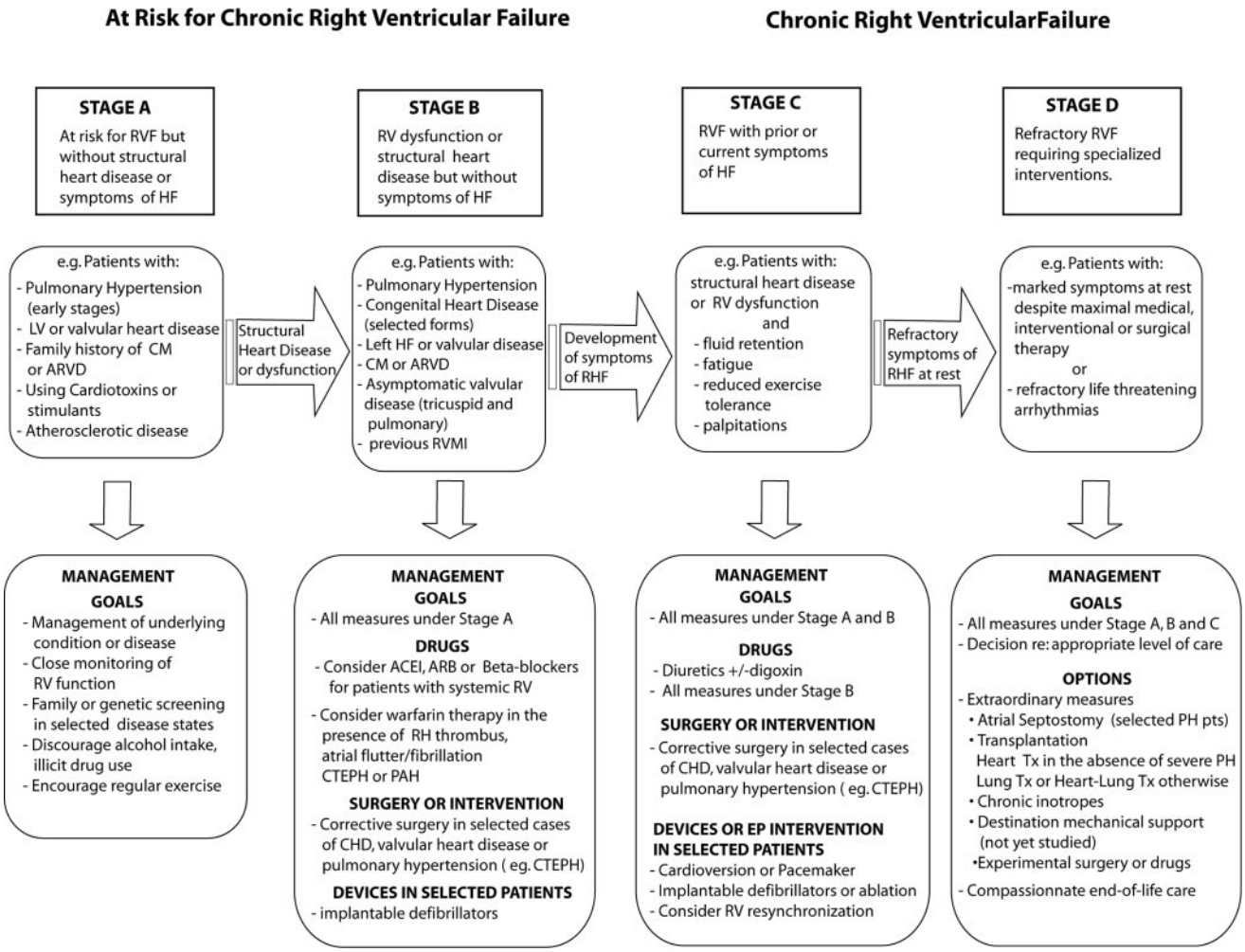

Figure 5. Stages and management of chronic RV failure. The management of chronic RV failure should always be tailored to its underlying cause. ARVD indicates arrhythmogenic RV dysplasia; RH, right heart; CM, cardiomyopathy; CETPH, chronic thromboembolic pulmonary hypertension; and Tx, transplantation.

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

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

Clinical Importance of RV Function

Heart Failure

RV dysfunction in left HF may occur in both ischemic and nonischemic cardiomyopathy. RV dysfunction in HF may be secondary to pulmonary venous hypertension, intrinsic myocardial involvement, ventricular interdependence, neurohormonal interactions, or myocardial ischemia. RV dysfunction appears to be more common in nonischemic cardiomyopathy than in ischemic cardiomyopathy and more closely parallels LV dysfunction.[37]

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

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

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

Study	Population	NYHA Class (%)	n	RV Dysfunction Criteria	Main Findings (Significant Findings)
Polak et al,[42] 1983	CAD	II–IV	34	RVEF <35%	23% survival (RVD) vs 71% survival at 2 y
Di Salvo et al,[39] 1995	CAD, IDC	III–IV	67	RVEF <35%	RVD and % Vo_2-independent predictors of survival at 2 y
De Groote et al,[38] 1998	CAD, IDC	II–III	205	RVEF <35%	RVD, maximal Vo_2, NYHA-independent predictors of survival at 2 y
Ghio et al,[41] 2001	CAD, IDC	III–IV (70)	377	RVEF <35%	Incremental value of PAP and RV function in predicting event-free survival
Sun et al,[44] 1997	IDC	III–IV (74)	100	RV area/LV area >0.5	RV enlargement independent predictor of survival
Meluzin et al,[43] 2005	CAD, IDC	II–IV	140	RVMPI >1.20, IVA <2.52 cm/s, TAV <10.8 cm/s	RVMPI and TDI indexes were predictive of mortality or event-free survival

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

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

RV Myocardial Infarction

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

Valvular Heart Disease

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

In chronic severe mitral regurgitation, significant PH at rest (>50 mm Hg) may occur in almost half of the patients, leading to RV dysfunction first during exercise and ultimately at rest.[52,53] In unoperated patients, subnormal RVEF at rest is associated with decreased exercise tolerance, complex arrhythmias, and mortality.[53] Decreased RV systolic reserve in asymptomatic patients is associated with an increased risk of progression to HF.[53]. In patients undergoing mitral valve surgery, Wencker and colleagues[54] demonstrated in a small prospective study that preoperative RVEF ≤20% predicted late postoperative deaths.

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

Arrhythmogenic RV Dysplasia and Uhl's Anomaly

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

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

Congenital Heart Disease

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

circulation (systemic RV). RV failure is common in CHD and is closely related to patient outcome.[7]

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

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

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

RV outflow tract obstruction may occur in a number of congenital abnormalities, including pulmonary valve stenosis, double-chambered RV, infundibular hypertrophy, or dynamic obstruction of the RV outflow tract. The RV usually adapts well to pulmonary valve stenosis even when severe. In patients with moderate to severe pulmonary valve stenosis, symptoms are unusual during childhood and adolescence.[7] In adults, symptoms of fatigue and dyspnea usually reflect the inability to increase cardiac output with exercise. Eventually, long-standing untreated severe obstruction may lead to RV failure and tricuspid regurgitation.[7]

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

Idiopathic PAH

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

Thromboembolic Disease

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

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

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

Chronic Pulmonary Disease

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

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

Acute Respiratory Distress Syndrome

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

Sepsis

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

Cardiac Surgery

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

Severe RV failure after cardiac surgery occurs in ≈0.1% of patients and is associated with high mortality rates.[75] Severe RV failure may occur after coronary artery bypass surgery, valve replacement, heart transplantation, and LV assist device placement. Factors involved in the pathophysiology of RV failure in cardiac surgery include RV ischemia, PH, reperfusion lung injury, pulmonary emboli, sepsis, and acute unloading of the LV after insertion of an LV assist device.[75]

Management of RV Failure

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

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

General Measures

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

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

Management Based on the Cause of RV Failure

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

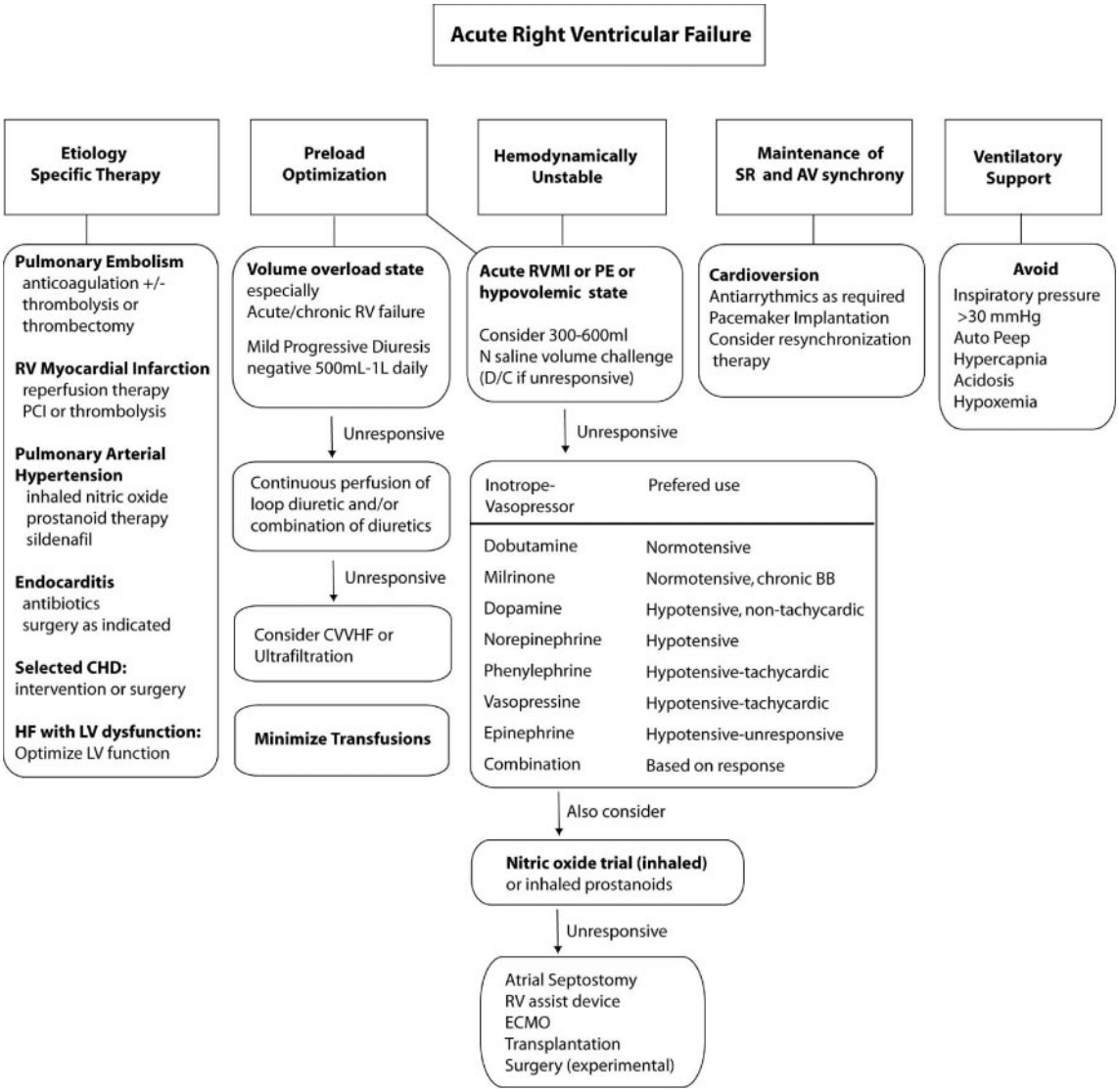

Figure 6. Management of acute RV failure. Hemodynamic instability is defined by hypotension or signs of low cardiac output (eg, renal failure). SR indicates sinus rhythm; PCI, percutaneous coronary intervention; AV, atrioventricular; ECMO, extracorporal membrane oxygenation; and CVVHF, continuous venovenous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

receptor antagonists. All 3 therapies have led to a significant, although relatively modest, improvement in exercise capacity in patients with PAH.[52] In the acutely decompensated PAH, inhaled nitric oxide, intravenous or inhaled epoprostenol, iloprost, and inotropic support are the most useful agents (Figure 6). In the presence of pulmonary venous hypertension or in patients with HF with biventricular dysfunction, treatment should be directed at optimizing HF management and fluid retention. In patients with PH secondary to various causes of parenchymal lung disease and/or hypoxemia, primary therapy consists of treating the underlying cause of hypoxemia and ventilatory or oxygen support as required. These patients usually do not benefit from treatment with pulmonary vasodilators. In patients with thromboembolic disease, therapy consists of anticoagulation. Thrombolysis or thrombectomy is considered in the presence of hemodynamically unstable patients. The use of thrombolysis in patients with RV dysfunction without shock is still controversial.[65,66] Pulmonary endarterectomy may be lifesaving in patients with CTEPH.[67]

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

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

Optimization of Preload

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

Optimization of RV Afterload

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

Optimization of Contractility

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

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

Maintenance of Sinus Rhythm

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

Resynchronization of the RV

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

Prevention of Sudden Death

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

Anticoagulation

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

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

Neurohormonal Modulation of RV Failure: Angiotensin-Converting Enzyme Inhibitors and β-Blockers

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

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

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

Supplemental Oxygen Therapy and Ventilation

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

Atrial Septostomy

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

Transplantation

Transplantation may be considered in selected patients with advanced refractory RV failure. Originally, it was believed that patients with advanced RV failure secondary to PH could be candidates only for heart-lung transplantation. However, because of the scarcity of organs, lung transplantation has been tried and has been successful in many patients.[52] Survival in PAH patients who undergo lung transplantation is ≈65% to 75% at 1 year.[96] Predictors of persistent RV failure after lung transplantation have not been well characterized at this time. Patients with complex CHD with PH should be considered candidates for heart-lung transplantation. Patients with refractory RV failure associated with left HF or patients with arrhythmogenic RV dysplasia and refractory tachyarrhythmias may be considered for heart transplantation in the absence of severe PH.

RV Assist Device

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

Conclusions

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

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None.

References

1. Dell'Italia LJ. The right ventricle: anatomy, physiology, and clinical importance. *Curr Probl Cardiol*. 1991;16:653–720.
2. Goldstein JA, Vlahakes GJ, Verrier ED, Schiller NB, Tyberg JV, Ports TA, Parmley WW, Chatterjee K. The role of right ventricular systolic dysfunction and elevated intrapericardial pressure in the genesis of low output in experimental right ventricular infarction. *Circulation*. 1982;65:513–522.
3. Kagan A. Dynamic responses of the right ventricle following extensive damage by cauterization. *Circulation*. 1952;5:816–823.
4. Mehta SR, Eikelboom JW, Natarajan MK, Diaz R, Yi C, Gibbons RJ, Yusuf S. Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. *J Am Coll Cardiol*. 2001;37:37–43.
5. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, Dupuis J, Long CS, Rubin LJ, Smart FW, Suzuki YJ, Gladwin M, Denholm EM, Gail DB. 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. *Circulation*. 2006; 114:1883–1891.
6. Simonneau G, Galie N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M, Rich S, Fishman A. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2004;43: 5S–12S.
7. Davlouros PA, Niwa K, Webb G, Gatzoulis MA. The right ventricle in congenital heart disease. *Heart*. 2006;92(suppl 1):i27–i38.
8. Messika-Zeitoun D, Thomson H, Bellamy M, Scott C, Tribouilloy C, Dearani J, Tajik AJ, Schaff H, Enriquez-Sarano M. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. *J Thorac Cardiovasc Surg*. 2004;128:296–302.
9. Chin KM, Kim NH, Rubin LJ. The right ventricle in pulmonary hypertension. *Coron Artery Dis*. 2005;16:13–18.
10. Marino TA, Kent RL, Uboh CE, Fernandez E, Thompson EW, Cooper G. Structural analysis of pressure versus volume overload hypertrophy of cat right ventricle. *Am J Physiol*. 1985;249:H371–H379.
11. Kasimir MT, Seebacher G, Jaksch P, Winkler G, Schmid K, Marta GM, Simon P, Klepetko W. Reverse cardiac remodelling in patients with primary pulmonary hypertension after isolated lung transplantation. *Eur J Cardiothorac Surg*. 2004;26:776–781.
12. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*. 1999;353:1386–1389.
13. Abraham WT, Raynolds MV, Badesch DB, Wynne KM, Groves BM, Roden RL, Robertson AD, Lowes BD, Zisman LS, Voelkel NF, Bristow MR, Perryman MB. Angiotensin-converting enzyme DD genotype in patients with primary pulmonary hypertension: increased frequency and association with preserved haemodynamics. *J Renin Angiotensin Aldosterone Syst*. 2003;4:27–30.
14. Hopkins WE, Waggoner AD. Severe pulmonary hypertension without right ventricular failure: the unique hearts of patients with Eisenmenger syndrome. *Am J Cardiol*. 2002;89:34–38.
15. O'Rourke RA, Dell'Italia LJ. Diagnosis and management of right ventricular myocardial infarction. *Curr Probl Cardiol*. 2004;29:6–47.
16. Kiely DG, Cargill RI, Lipworth BJ. Angiotensin II receptor blockade and effects on pulmonary hemodynamics and hypoxic pulmonary vasoconstriction in humans. *Chest*. 1996;110:698–703.
17. Mulder P, Richard V, Derumeaux G, Hogie M, Henry JP, Lallemand F, Compagnon P, Mace B, Comoy E, Letac B, Thuillez C. Role of endogenous endothelin in chronic heart failure: effect of long-term treatment with an endothelin antagonist on survival, hemodynamics, and cardiac remodeling. *Circulation*. 1997;96:1976–1982.
18. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N, Miyatake K, Kangawa K. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation*. 2000;102: 865–870.
19. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, Coats AJ, Anker SD, Gatzoulis MA. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation.* 2002; 106:92–99.
20. Fan TH, Liang CS, Kawashima S, Banerjee SP. Alterations in cardiac beta-adrenoceptor responsiveness and adenylate cyclase system by congestive heart failure in dogs. *Eur J Pharmacol*. 1987;140:123–132.
21. Nootens M, Kaufmann E, Rector T, Toher C, Judd D, Francis GS, Rich S. Neurohormonal activation in patients with right ventricular failure from pulmonary hypertension: relation to hemodynamic variables and endothelin levels. *J Am Coll Cardiol*. 1995;26:1581–1585.
22. Weber KT. Aldosterone in congestive heart failure. *N Engl J Med*. 2001;345:1689–1697.
23. Rouleau JL, Kapuku G, Pelletier S, Gosselin H, Adam A, Gagnon C, Lambert C, Meloche S. Cardioprotective effects of ramipril and losartan in right ventricular pressure overload in the rabbit: importance of kinins and influence on angiotensin II type 1 receptor signaling pathway. *Circulation*. 2001;104:939–944.
24. Ueno M, Miyauchi T, Sakai S, Kobayashi T, Goto K, Yamaguchi I. Effects of physiological or pathological pressure load in vivo on myocardial expression of ET-1 and receptors. *Am J Physiol*. 1999;277: R1321–R1330.
25. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, Badesch DB, Roux S, Rainisio M, Bodin F, Rubin LJ. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet*. 2001;358: 1119–1123.
26. Rich S, McLaughlin VV. Endothelin receptor blockers in cardiovascular disease. *Circulation*. 2003;108:2184–2190.
27. Sharma R, Bolger AP, Li W, Davlouros PA, Volk HD, Poole-Wilson PA, Coats AJ, Gatzoulis MA, Anker SD. Elevated circulating levels of inflammatory cytokines and bacterial endotoxin in adults with congenital heart disease. *Am J Cardiol*. 2003;92:188–193.
28. Feldt RH, Driscoll DJ, Offord KP, Cha RH, Perrault J, Schaff HV, Puga FJ, Danielson GK. Protein-losing enteropathy after the Fontan operation. *J Thorac Cardiovasc Surg*. 1996;112:672–680.
29. Goldstein JA, Harada A, Yagi Y, Barzilai B, Cox JL. Hemodynamic importance of systolic ventricular interaction, augmented right atrial contractility and atrioventricular synchrony in acute right ventricular dysfunction. *J Am Coll Cardiol*. 1990;16:181–189.
30. Tongers J, Schwerdtfeger B, Klein G, Kempf T, Schaefer A, Knapp JM, Niehaus M, Korte T, Hoeper MM. Incidence and clinical relevance of supraventricular tachyarrhythmias in pulmonary hypertension. *Am Heart J*. 2007;153:127–132.
31. Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. *Circulation*. 2007;115:534–545.
32. Hoch DH, Rosenfeld LE. Tachycardias of right ventricular origin. *Cardiol Clin*. 1992;10:151–164.
33. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med*. 1991;115:343–349.
34. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation*. 2005;112:828–835.
35. Wensel R, Opitz CF, Anker SD, Winkler J, Hoffken G, Kleber FX, Sharma R, Hummel M, Hetzer R, Ewert R. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation*. 2002;106:319–324.
36. Nagaya N, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Nakanishi N, Yamagishi M, Kunieda T, Miyatake K. Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. *Am J Respir Crit Care Med*. 1999;160:487–492.
37. Juilliere Y, Barbier G, Feldmann L, Grentzinger A, Danchin N, Cherrier F. Additional predictive value of both left and right ventricular ejection fractions on long-term survival in idiopathic dilated cardiomyopathy. *Eur Heart J*. 1997;18:276–280.
38. de Groote P, Millaire A, Foucher-Hossein C, Nugue O, Marchandise X, Ducloux G, Lablanche JM. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. *J Am Coll Cardiol*. 1998;32:948–954.
39. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. *J Am Coll Cardiol*. 1995;25:1143–1153.
40. Gavazzi A, Berzuini C, Campana C, Inserra C, Ponzetta M, Sebastiani R, Ghio S, Recusani F. Value of right ventricular ejection fraction in predicting short-term prognosis of patients with severe chronic heart failure. *J Heart Lung Transplant*. 1997;16:774–785.
41. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Recusani F, Tavazzi L. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol*. 2001;37: 183–188.
42. Polak JF, Holman BL, Wynne J, Colucci WS. Right ventricular ejection fraction: an indicator of increased mortality in patients with congestive heart failure associated with coronary artery disease. *J Am Coll Cardiol*. 1983;2:217–224.
43. Meluzin J, Spinarova L, Hude P, Krejci J, Kincl V, Panovsky R, Dusek L. Prognostic importance of various echocardiographic right ventricular functional parameters in patients with symptomatic heart failure. *J Am Soc Echocardiogr*. 2005;18:435–444.
44. Sun JP, James KB, Yang XS, Solankhi N, Shah MS, Arheart KL, Thomas JD, Stewart WJ. Comparison of mortality rates and progression of left ventricular dysfunction in patients with idiopathic dilated cardiomyopathy and dilated versus nondilated right ventricular cavities. *Am J Cardiol*. 1997;80:1583–1587.
45. Mendes LA, Dec GW, Picard MH, Palacios IF, Newell J, Davidoff R. Right ventricular dysfunction: an independent predictor of adverse outcome in patients with myocarditis. *Am Heart J*. 1994;128:301–307.

46. Baker BJ, Wilen MM, Boyd CM, Dinh H, Franciosa JA. Relation of right ventricular ejection fraction to exercise capacity in chronic left ventricular failure. *Am J Cardiol*. 1984;54:596–599.
47. Clark AL, Swan JW, Laney R, Connelly M, Somerville J, Coats AJ. The role of right and left ventricular function in the ventilatory response to exercise in chronic heart failure. *Circulation*. 1994;89:2062–2069.
48. Yu HC, Sanderson JE. Different prognostic significance of right and left ventricular diastolic dysfunction in heart failure. *Clin Cardiol*. 1999;22: 504–512.
49. Wroblewski E, James F, Spann JF, Bove AA. Right ventricular performance in mitral stenosis. *Am J Cardiol*. 1981;47:51–55.
50. Lewis BM, Gorlin R, Houssay HE, Haynes FW, Dexter L. Clinical and physiological correlations in patients with mitral stenosis, V. *Am Heart J*. 1952;43.
51. Ward C, Hancock BW. Extreme pulmonary hypertension caused by mitral valve disease. Natural history and results of surgery. *Br Heart J*. 1975;37:74–78.
52. McLaughlin VV, Rich S. Pulmonary hypertension. *Curr Probl Cardiol*. 2004;29:575–634.
53. Borer JS, Bonow RO. Contemporary approach to aortic and mitral regurgitation. *Circulation*. 2003;108:2432–2438.
54. Wencker D, Borer JS, Hochreiter C, Devereux RB, Roman MJ, Kligfield P, Supino P, Krieger K, Isom OW. Preoperative predictors of late postoperative outcome among patients with nonischemic mitral regurgitation with "high risk" descriptors and comparison with unoperated patients. *Cardiology*. 2000;93:37–42.
55. Boldt J, Zickmann B, Ballesteros M, Dapper F, Hempelmann G. Right ventricular function in patients with aortic stenosis undergoing aortic valve replacement. *J Cardiothorac Vasc Anesth*. 1992;6:287–291.
56. Haddad F, Denault AY, Couture P, Cartier R, Pellerin M, Levesque S, Lambert J, Tardif JC. Right ventricular myocardial performance index predicts perioperative mortality or circulatory failure in high-risk valvular surgery. *J Am Soc Echocardiogr*. 2007;20:1065–1072.
57. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circulation*. 2004;110:1879–1884.
58. Webb G, Gatzoulis MA. Atrial septal defects in the adult: recent progress and overview. *Circulation*. 2006;114:1645–1653.
59. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. *Am J Cardiol*. 2005;95:779–782.
60. Cullen S, Shore D, Redington A. Characterization of right ventricular diastolic performance after complete repair of tetralogy of Fallot: restrictive physiology predicts slow postoperative recovery. *Circulation*. 1995;91:1782–1789.
61. Gatzoulis MA, Clark AL, Cullen S, Newman CG, Redington AN. Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot: restrictive physiology predicts superior exercise performance. *Circulation*. 1995;91:1775–1781.
62. Warnes CA. Transposition of the great arteries. *Circulation*. 2006;114: 2699–2709.
63. Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W, Ettinger NA, Hill NS, Summer WR, de Boisblanc B, Schwartz T, Koch G, Clayton LM, Jobsis MM, Crow JW, Long W. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol*. 2002;39:1214–1219.
64. Yeo TC, Dujardin KS, Tei C, Mahoney DW, McGoon MD, Seward JB. Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. *Am J Cardiol*. 1998;81:1157–1161.
65. Hamel E, Pacouret G, Vincentelli D, Forissier JF, Peycher P, Pottier JM, Charbonnier B. Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: results from a 128-patient monocenter registry. *Chest*. 2001;120:120–125.
66. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med*. 2002;347:1143–1150.
67. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. *Circulation*. 2006;113:2011–2020.
68. MacNee W, Skwarski KM. Right-heat failure and cor pulmonale. In: Crawford MH, DiMarco JP, Paulus WJ, eds. *Cardiology*. 2nd ed. St Louis, Mo: Mosby; 2004:1017.
69. Burgess MI, Mogulkoc N, Bright-Thomas RJ, Bishop P, Egan JJ, Ray SG. Comparison of echocardiographic markers of right ventricular function in determining prognosis in chronic pulmonary disease. *J Am Soc Echocardiogr*. 2002;15:633–639.
70. Vieillard-Baron A, Jardin F. Why protect the right ventricle in patients with acute respiratory distress syndrome? *Curr Opin Crit Care*. 2003;9: 15–21.
71. Maeder M, Fehr T, Rickli H, Ammann P. Sepsis-associated myocardial dysfunction: diagnostic and prognostic impact of cardiac troponins and natriuretic peptides. *Chest*. 2006;129:1349–1366.
72. Parker MM, McCarthy KE, Ognibene FP, Parrillo JE. Right ventricular dysfunction and dilatation, similar to left ventricular changes, characterize the cardiac depression of septic shock in humans. *Chest*. 1990;97: 126–131.
73. Maslow AD, Regan MM, Panzica P, Heindel S, Mashikian J, Comunale ME. Precardiopulmonary bypass right ventricular function is associated with poor outcome after coronary artery bypass grafting in patients with severe left ventricular systolic dysfunction. *Anesth Analg*. 2002;95: 1507–1518.
74. Reichert CL, Visser CA, van den Brink RB, Koolen JJ, van Wezel HB, Moulijn AC, Dunning AJ. Prognostic value of biventricular function in hypotensive patients after cardiac surgery as assessed by transesophageal echocardiography. *J Cardiothorac Vasc Anesth*. 1992;6:429–432.
75. Kaul TK, Fields BL. Postoperative acute refractory right ventricular failure: incidence, pathogenesis, management and prognosis. *Cardiovasc Surg*. 2000;8:1–9.
76. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, Meyer FJ, Karger G, Buss J, Juenger J, Holzapfel N, Opitz C, Winkler J, Herth FF, Wilkens H, Katus HA, Olschewski H, Grunig E. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation*. 2006; 114:1482–1489.
77. Bowers TR, O'Neill WW, Grines C, Pica MC, Safian RD, Goldstein JA. Effect of reperfusion on biventricular function and survival after right ventricular infarction. *N Engl J Med*. 1998;338:933–940.
78. Landzberg MJ. Congenital heart disease associated pulmonary arterial hypertension. *Clin Chest Med*. 2007;28:243–253.
79. Steele PM, Fuster V, Cohen M, Ritter DG, McGoon DC. Isolated atrial septal defect with pulmonary vascular obstructive disease: long-term follow-up and prediction of outcome after surgical correction. *Circulation*. 1987;76: 1037–1042.
80. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest*. 2002;121:2000–2008.
81. Piazza G, Goldhaber SZ. The acutely decompensated right ventricle: pathways for diagnosis and management. *Chest*. 2005;128:1836–1852.
82. Gould S, Cimino MJ, Gerber DR. Packed red blood cell transfusion in the intensive care unit: limitations and consequences. *Am J Crit Care*. 2007; 16:39–48.
83. Inglessis I, Shin JT, Lepore JJ, Palacios IF, Zapol WM, Bloch KD, Semigran MJ. Hemodynamic effects of inhaled nitric oxide in right ventricular myocardial infarction and cardiogenic shock. *J Am Coll Cardiol*. 2004;44:793–798.
84. Dell'Italia LJ, Starling MR, Blumhardt R, Lasher JC, O'Rourke RA. Comparative effects of volume loading, dobutamine, and nitroprusside in patients with predominant right ventricular infarction. *Circulation*. 1985; 72:1327–1335.
85. Vizza CD, Rocca GD, Roma AD, Iacoboni C, Pierconti F, Venuta F, Rendina E, Schmid G, Pietropaoli P, Fedele F. Acute hemodynamic effects of inhaled nitric oxide, dobutamine and a combination of the two in patients with mild to moderate secondary pulmonary hypertension. *Crit Care*. 2001;5:355–361.
86. Rich S, Seidlitz M, Dodin E, Osimani D, Judd D, Genthner D, McLaughlin V, Francis G. The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. *Chest*. 1998;114:787–792.
87. Mathur PN, Powles P, Pugsley SO, McEwan MP, Campbell EJ. Effect of digoxin on right ventricular function in severe chronic airflow obstruction: a controlled clinical trial. *Ann Intern Med*. 1981;95: 283–288.
88. Dubin AM, Janousek J, Rhee E, Strieper MJ, Cecchin F, Law IH, Shannon KM, Temple J, Rosenthal E, Zimmerman FJ, Davis A, Karpawich PP, Al Ahmad A, Vetter VL, Kertesz NJ, Shah M, Snyder C, Stephenson E, Emmel M, Sanatani S, Kanter R, Batra A, Collins KK. Resynchronization therapy in pediatric and congenital heart disease patients: an international multicenter study. *J Am Coll Cardiol*. 2005;46: 2277–2283.

89. Dubin AM, Feinstein JA, Reddy VM, Hanley FL, Van Hare GF, Rosenthal DN. Electrical resynchronization: a novel therapy for the failing right ventricle. *Circulation*. 2003;107:2287–2289.
90. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot: QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation*. 1995;92:231–237.
91. Massie B, Kramer BL, Topic N, Henderson SG. Hemodynamic and radionuclide effects of acute captopril therapy for heart failure: changes in left and right ventricular volumes and function at rest and during exercise. *Circulation*. 1982;65:1374–1381.
92. Quaife RA, Christian PE, Gilbert EM, Datz FL, Volkman K, Bristow MR. Effects of carvedilol on right ventricular function in chronic heart failure. *Am J Cardiol*. 1998;81:247–250.
93. Dore A, Houde C, Chan KL, Ducharme A, Khairy P, Juneau M, Marcotte F, Mercier LA. Angiotensin receptor blockade and exercise capacity in adults with systemic right ventricles: a multicenter, randomized, placebo-controlled clinical trial. *Circulation*. 2005;112:2411–2416.
94. Provencher S, Herve P, Jais X, Lebrec D, Humbert M, Simonneau G, Sitbon O. Deleterious effects of beta-blockers on exercise capacity and hemodynamics in patients with portopulmonary hypertension. *Gastroenterology*. 2006;130:120–126.
95. Sandoval J, Gaspar J, Pulido T, Bautista E, Martinez-Guerra ML, Zeballos M, Palomar A, Gomez A. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension: a therapeutic alternative for patients nonresponsive to vasodilator treatment. *J Am Coll Cardiol*. 1998;32:297–304.
96. Mendeloff EN, Meyers BF, Sundt TM, Guthrie TJ, Sweet SC, de la Morena M, Shapiro S, Balzer DT, Trulock EP, Lynch JP, Pasque MK, Cooper JD, Huddleston CB, Patterson GA. Lung transplantation for pulmonary vascular disease. *Ann Thorac Surg*. 2002;73:209–217.

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