Biomechanics of the right ventricle in health and disease (2013 Grover Conference series)

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Abstract: Right ventricular (RV) function is a major determinant of the symptomatology and outcome in pulmonary hypertension. The normal RV is a thin-walled flow generator able to accommodate large changes in venous return but unable to maintain flow output in the presence of a brisk increase in pulmonary artery pressure. The RV chronically exposed to pulmonary hypertension undergoes hypertrophic changes and an increase in contractility, allowing for preserved flow output in response to peripheral demand. Failure of systolic function adaptation (homeometric adaptation, described by Anrep's law of the heart) results in increased dimensions (heterometric adaptation; Starling's law of the heart), with a negative effect on diastolic ventricular interactions, limitation of exercise capacity, and vascular congestion. Ventricular function is described by pressure-volume relationships. The gold standard of systolic function is maximum elastance (E_{max}), or the maximal value of the ratio of pressure to volume. This value is not immediately sensitive to changes in loading conditions. The gold standard of afterload is arterial elastance (E_a), defined by the ratio of pressure at E_{max} to stroke volume. The optimal coupling of ventricular function to the arterial circulation occurs at an E_{max}/E_a ratio between 1.5 and 2. Patients with severe pulmonary hypertension present with an increased E_{max}, a trend toward decreased E_{max}/E_a, and increased RV dimensions, along with progression of the pulmonary vascular disease, systemic factors, and left ventricular function. The molecular mechanisms of RV systolic failure are currently being investigated. It is important to refer biological findings to sound measurements of function. Surrogates for E_{max} and E_a are being developed through bedside imaging techniques.

Keywords: right ventricle, pulmonary hypertension, preload, afterload, maximum elastance, end-systolic elastance, arterial elastance.

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One must inquire how increasing pulmonary vascular resistance results in impaired right ventricular function.
—J. T. Reeves, 1989[1]

In 1988, Jack Reeves and his colleagues noted that pulmonary hypertension is a common complication of cardiac and pulmonary diseases, that associated alterations in right ventricular (RV) function cause symptoms and limit survival, and that, paradoxically, research in this area had been relatively scarce.[1] Accordingly, they called for more studies to improve the understanding of RV failure in health and disease. Twenty-five years later, there has been significant progress, but our present knowledge remains incomplete, and calls for more research have been repeated.[2,3]

The right ventricle (RV) in mammals and birds is a thin-walled flow generator, designed to accommodate the entire systemic venous return undergoing gas exchange in the pulmonary circulation, which is a separate high-flow, low-pressure system.[4] The pulmonary vascular pressures at rest and at mild levels of exercise are so low that a mean systemic filling pressure in the range of 10–15 mmHg is sufficient to drive the venous return through the pulmonary circulation to the left heart without the assistance of RV pumping. In 1943, Starr and his colleagues[5] showed that ablation of the RV in dogs is compatible with life with little change in pulmonary venous pressure. In 1971, Fontan and Baudet[6] introduced the first cavopulmonary anastomosis bypassing the RV as a palliative intervention for car-

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diac malformations. Patients with the so-called Fontan circulation may enjoy a near-normal sedentary life for several decades but rapidly deteriorate in case of increased pulmonary artery pressure (P_{pa}), for example, with altitude exposure or when the left ventricular (LV) filling pressure increases.[7]

The structure of the RV is not adequate to cope with a brisk increase in pulmonary vascular resistance (PVR) produced, for example, by pulmonary arterial constriction to mimic massive pulmonary embolism.[8] However, if given time, the RV is able to adapt to a progressive increase in PVR by increasing contractility and remodeling, basically much like the left ventricle (LV).[9] Beat-to-beat changes in preload or afterload are accompanied by a heterometric dimension adaptation described by Starling's law of the heart. Sustained changes in load are associated with a homeometric contractility adaptation described by Anrep's law of the heart.

In 1912, Gleb Vassilevitch von Anrep,[10] who was active at that time in Pavlov's laboratory in St. Petersburg, reported on the rapid increase in LV contractility in response to aortic constriction. Von Anrep was sent by Pavlov to London to work, under Starling's supervision, on the humoral control of digestion. He soon observed the rapid switch from the heterometric to the homeometric adaptation to loading in Starling's heart-lung preparation. Thus, after an acute increase in venous return or systemic vascular resistance, the heart initially dilates, allowing for increased or maintained stroke volume (SV), respectively, but after a few minutes the cardiac dimensions are back to baseline values in spite of persistently increased loading, indicating increased contractility. Starling thought that much of this observation was related to rapid deterioration of the experimental preparation. Later studies confirmed the predominant role of the homeometric, or systolic function, adaptation within the first few minutes after an acute increase in either preload or afterload.[11] This is illustrated by a 10-minute recording of RV volumes after the acute increase in venous return in Figure 1.

Whether the time course of systolic function adaptation to afterload is the same for the RV and the LV is not known. Comparisons between studies are difficult because of the differences in ventricular structure and relative changes in arterial pressure. Contractility responses to increased afterload may depend on the volume status or on systemic disease components. Ventricular hypertrophy occurs, which increases the contractile force and decreases wall tension, but the time course, pathobiology, and contribution to preserved contractility are not well understood. When loading conditions become excessive and prolonged, the homeometric adaptation eventually fails, and Starling's heterometric adaptation comes again into play, at the price of increased dimensions and filling pressures.[9]

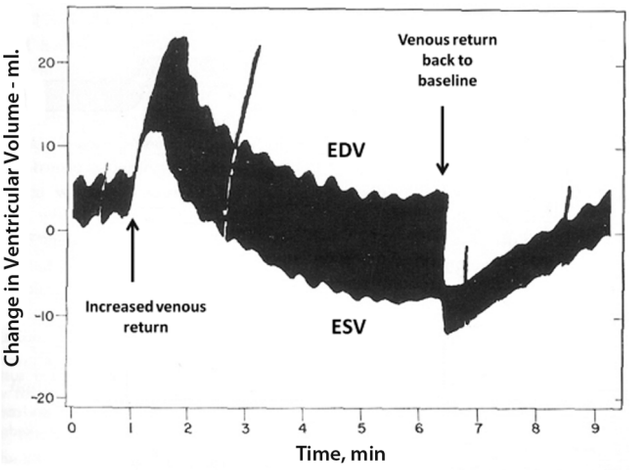

Figure 1. Time-course of right ventricular volume changes after a brisk increase in venous return. The initial heterometric adaptation is followed by a homeometric adaptation, allowing for a return to the initial end-diastolic volume (EDV) with decreased end-systolic volume (ESV) and increased stroke volume. Reproduced from Rosenblueth et al.[11] with permission.

Accordingly, RV failure can be defined by a dyspnea-fatigue syndrome with eventual systemic congestion, caused by the inability of the RV to maintain flow output using Anrep's homeometric adaptation, in response to metabolic demand, without the use of Starling's heterometric adaptation.[9] In this definition, cardiac output is not necessarily low but is low relative to oxygen uptake or aerobic exercise capacity, and vascular congestion is implicit.

SYSTOLIC FUNCTION

The gold-standard measurement of cardiac contractility in an intact being is the maximal elastance (E_{max}), or the maximum value of the ratio of ventricular pressure to volume during the cardiac cycle.[9] LV E_{max} coincides with end systole and is thus equal to the ratio of end-systolic pressure (ESP) to end-systolic volume (ESV). End-systolic elastance (E_{es}) is measured at the upper left corner of a square-shaped pressure-volume loop.[12] Because of low pulmonary vascular impedance, the normal RV pressure-volume loop has a triangular shape, and E_{max} occurs before the end of ejection, or end systole. However, a satisfactory definition of E_{max} can be obtained by the generation of a family of pressure-volume loops at decreasing venous return, as illustrated in Figure 2.[13] Thus, in spite of embryological and structural differences, the "laws of the heart" apply similarly to the RV and the LV.

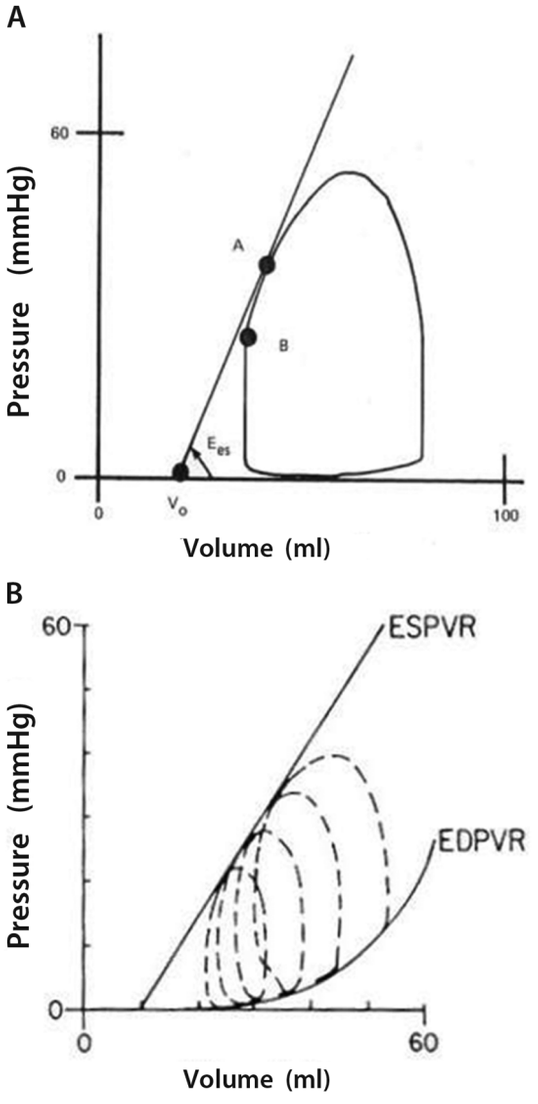

Figure 2. *A*, A normal right ventricular pressure-volume loop is of triangular shape, with maximum elastance (or E_{es}, point A) occurring before the end of systole (point B). *B*, A decrease in venous return allows for the recording of a family of right ventricular pressure-volume loops and the use of end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR) to define systolic and diastolic function. Reproduced from Maughan et al.[13] with permission.

Instantaneous measurements of RV volumes are difficult at the bedside, and so are manipulations of venous return. This is why single-beat methods have been developed, initially for the LV[14] and then for the RV.[15] The single-beat method relies on a maximum-pressure (P_{max}) calculation from a nonlinear extrapolation of the early and late portions of an RV pressure curve, an integration of pulmonary flow, and synchronization of the signals. The E_{max} is estimated from the slope of a tangent from P_{max} to the pressure-volume curve (Figure 3). It is important to note that this graphic analysis uses relative changes in volume and thus does not require measurement of absolute volumes. This is acceptable because E_{max} is essentially preload, or end-diastolic volume (EDV), independent.[9] On the other hand, excellent agreement between P_{max} measured

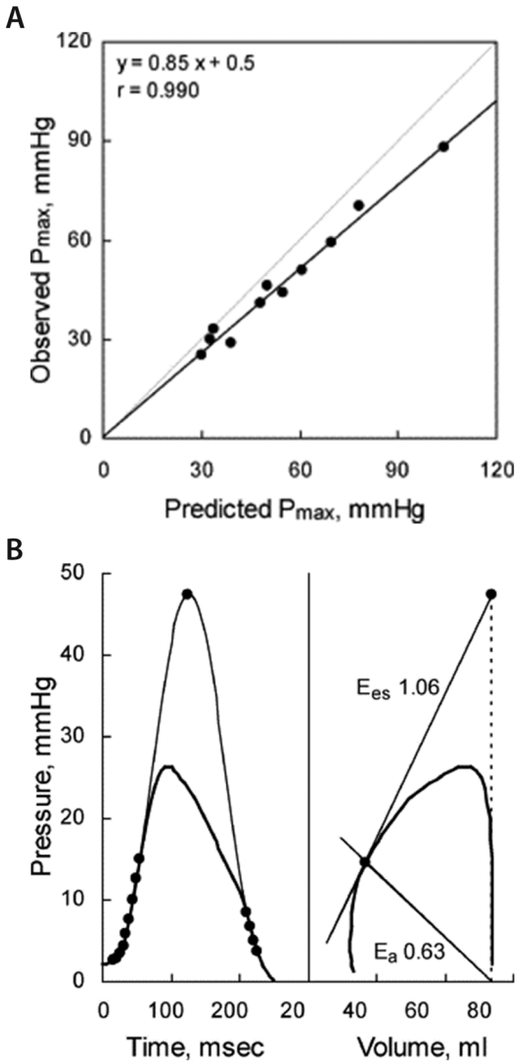

Figure 3. Single-beat method for measurement of right ventriculo-arterial coupling in an anesthetized dog. *A*, Good agreement between directly measured maximum right ventricular (RV) pressure (P_{max}) when the pulmonary arterial trunk is clamped during one heart beat (black line) and extrapolated P_{max} (gray line). The slightly lower observed P_{max} is explained by the proximal pulmonary arterial compliance. *B*, P_{max} is calculated from early and late portions of the RV pressure curve, end-systolic elastance (E_{es}) or arterial elastance (E_a) graphically determined from P_{max}, and relative changes in volume and pressure during systole. Reproduced from Brimioulle et al.[15] with permission.

directly by clamping the main pulmonary artery for one beat and P_{max} estimated by simple sinusoidal extrapolation of early and late portions of the RV pressure curve has been demonstrated in a large-animal experimental preparation.[15]

Single-beat measurements of RV E_{max} have been reported in patients with pulmonary arterial hypertension (PAH), using fluid-filled catheters and magnetic resonance imaging (MRI),[16] and in a patient with a congenitally corrected transposition of the great arteries and a systemic RV, using high-fidelity micromanometer-tipped catheters and transonic measurements of pulmonary flow.[17] Measurements of RV E_{max} have also been reported in idiopathic and systemic sclerosis–associated PAH, using conductance catheter methodology for instantaneous high-fidelity pressure and volume determinations.[18] In that study, the Valsalva maneuver was validated against inferior vena cava occlusion in order to decrease venous return for the definition of E_{max} by a family of pressure-volume loops.[18] These limited reports confirm the importance of systolic function adaptation to afterload previously demonstrated in various animal species[19] or experimental models of acute[15,20,21] or chronic[22-26] pulmonary hypertension.

COUPLING OF SYSTOLIC FUNCTION TO AFTERLOAD

Afterload can be defined by the maximum ventricular wall stress or by arterial hydraulic load.[27,28] Wall stress is approximated by the maximum value of the product of volume and pressure divided by wall thickness. This is a transposition of Laplace's law for spheric structures and thus is problematic for the RV because of considerable regional variations in RV internal radius.[27] Hydraulic load calculations require instantaneous measurements of arterial pressure and flow and spectral analysis to derive arterial impedance calculations.[28] A more straightforward approach is to derive arterial elastance (E_a) as it is "seen" by the ventricle, and thus graphically determined on a pressure-volume loop, by dividing pressure at E_{max} by SV.[9] Because contractility is homeometrically adjusted to afterload, its adequacy is best evaluated as a ratio of E_{max} to E_a, which defines RV-arterial coupling. The optimal mechanical coupling occurs when the ratio of E_{max} to E_a is equal to 1. The optimal energy transfer from the RV to the pulmonary circulation occurs at E_{max}/E_a ratios of 1.5–2.[9]

RV-arterial coupling measured with the E_{max}/E_a ratio has been investigated in models of pulmonary hypertension with and without RV failure and in models with persistent RV failure after transient pulmonary artery banding (to mimic a pulmonary hypertensive crisis) and pharmacological interventions. The results are summarized in Tables 1 and 2. The acute hypoxia-induced increase in PVR was associated with preserved RV-arterial coupling because of increased RV contractility.[15,19,29-31] The adapted increase in RV contractility with preserved RV-arterial coupling was also reported in pulmonary hypertension following either microembolism or pulmonary arterial banding.[19] Endotoxic shock–induced increase in PVR was associated with early preservation of RV-arterial coupling but deterioration as soon as 1 hour after the initial insult because of an unsustained adaptive increase in contractility.[21] Chronic aortopulmonary shunting as a model of persistent ductus arteriosus in growing piglets was associated with preserved RV-arterial coupling after 3 months,[24,37] but with uncoupling after 6

Table 1. Right ventricular–arterial coupling in experimental models of pulmonary hypertension

Model	Animal	E_{max}	E_a	E_{max}/E_a	Reference(s)
Hypoxia	Dog, goat, pig	Increase	Increase	No change	15, 19, 29–31
Monocrotaline	Rat	Increase	Increase	Decrease	25
Sepsis, early	Pig	Increase	Increase	No change	21
Sepsis, late	Pig	No change	Increase	Decrease	21
Embolism	Dog, goat, pig	Increase	Increase	No change	19
PA banding	Dog, goat, pig	Increase	Increase	No change	19
AP shunting, 3 months	Pig	Increase	Increase	No change	24
AP shunting, 6 months	Pig	Decrease	Increase	Decrease	25
RVF on PA banding	Dog, pig	Decrease	Increase	Decrease	32–35
Chronic heart failure	Dog	No change	Increase	Decrease	36

Note: E_{max}: maximum right ventricular elastance; E_a: pulmonary arterial elastance; PA: pulmonary artery; AP; aortopulmonary; RVF: right ventricular failure.

Table 2. Effects of pharmacological intervention in experimental pulmonary hypertension

Model	Drug	E_{max}	E_a	E_{max}/E_a	Reference(s)
Hypoxia	Dobutamine	Increase	No change	Increase	15
RHF on PA banding	Dobutamine	Increase	Decrease or no change	Increase	32, 33
RHF on PA banding	Levosimendan	Increase	Decrease	Increase	33, 35
RHF on PA banding	Norepinephrine	Increase	No change	Increase	32
Chronic heart failure	Milrinone	Increase	No change	Increase	36
Chronic heart failure	Nitroprusside	No change	No change	No change	36
Chronic heart failure	Nitric oxide	No change	No change	No change	36
Hypoxia	Propranolol	Decrease	Increase	Decrease	15
Monocrotaline	Bisoprolol	Increase	No change	Increase	26
AP shunting, 3 months	Epoprostenol	No change	Decrease	Increase	37
RHF on PA banding	Epoprostenol	No change	Decrease	Increase	34
Hypoxia	Sildenafil	No change	Decrease	Increase	30
Monocrotaline	Sildenafil	Increase	Decrease	Increase	38
Hypoxia	Isoflurane	Decrease	Increase	Decrease	29

Note: E_{max}: maximum right ventricular elastance; E_a: pulmonary arterial elastance; RHF: right heart failure.

months because of RV systolic function failure.[25] Persistent RV failure after tight transient pulmonary arterial ensnarement was characterized by a profound RV-arterial uncoupling because of a persistent decrease in contractility and a reactive increase in PVR.[32-35] Monocrotaline-induced pulmonary hypertension was associated with RV-arterial uncoupling because of an insufficient increase in contractility to match increased afterload.[26] Mild pulmonary hypertension in heart failure induced by several weeks of overpacing as a model of tachycardiomyopathy was associated with RV-arterial uncoupling by absence of adapted increase in RV contractility.[36] Altogether, these studies support the notion of RV systolic function adaptation to increased afterload in various models of pulmonary hypertension, but with RV-arterial uncoupling in the context of inflammation (endotoxemia, monocrotaline), long-term increase in PVR, or left heart failure.

Low-dose dobutamine increased RV-arterial coupling by an inotropic effect without[15,33] or with[32] a decreased afterload. Low-dose norepinephrine improved RV-arterial coupling through an exclusive positive inotropic effect that was, however, less pronounced than that with low-dose dobutamine.[32] Acute administration of propranolol caused deterioration of RV-arterial coupling through combined negative inotropy and pulmonary vasoconstriction during an acute hypoxic exposure.[15] Chronic administration of bisoprolol improved RV-arterial coupling by an improved contractility in monocrotaline-induced pulmonary hypertension.[26] Acute administration of epoprostenol or inhaled nitric oxide (NO) improved RV-arterial coupling through selective pulmonary vasodilating effects in overcirculation-induced pulmonary hypertension.[37] Acute epoprostenol administration partially restored RV-arterial coupling through an exclusive pulmonary vascular effect in pulmonary banding–induced persistent RV failure[34] or was associated with maintained RV-arterial coupling because of decreased contractility in proportion to decreased PVR in hypoxia.[31] Levosimendan improved RV-arterial coupling through combined inotropy and vasodilation in pulmonary banding–induced persistent RV failure.[33,35] Sildenafil improved RV-arterial coupling in acute hypoxic pulmonary hypertension because of pulmonary vasodilating effects,[30] but it improved coupling because of a positive inotropic effect in monocrotaline-induced pulmonary hypertension.[38] Bosentan had no intrinsic effect on contractility in pulmonary hypertension after 3 months of aortopulmonary shunting.[24] Milrinone improved RV-arterial coupling by an improved contractility in tachycardia-induced congestive heart failure with mild pulmonary hypertension, while nitroprusside or inhaled NO had no effect in this model.[36] Isoflurane and enflurane caused deterioration of RV-arterial coupling because of combined decrease in contractility and increase in PVR.[29]

Measurements of E_{max} and E_a have been reported in patients with pulmonary hypertension. These results are summarized in Table 3. The reported profile was that of increased RV contractility in the face of increased PVR

Table 3. Right ventriculoarterial coupling in patients with pulmonary arterial hypertension

Diagnosis	E_{max}	E_a	E_{max}/E_a	Reference
IPAH	Increase	Increase	Decrease	16
CCTGA	Increase	Increase	Decrease	17
IPAH	Increase	Increase	No change	18
SSc-PAH	Increase	Increase	Decrease	18

Note: E_{max}: maximum right ventricular elastance; E_a: pulmonary arterial elastance; IPAH: idiopathic pulmonary arterial hypertension; CCTGA: congenitally corrected transposition of the great arteries (systemic right ventricle); SSc-PAH: systemic sclerosis–associated pulmonary arterial hypertension.

with or without preservation of the E_{max}/E_a ratio in patients with idiopathic PAH (Figure 4).[16,18] Insufficient increase in contractility to preserve RV-arterial coupling was observed in a patient with a systemic RV in the context of a congenitally corrected transposition of the great arteries[17] and in patients with systemic sclerosis–associated PAH.[18]

Thus, it appears that RV-arterial coupling tends to be maintained by an adaptive increase in E_{max} in models such as hypoxic exposure or a few months of aortopulmonary shunting associated with only moderate increase in P_{pa}. Prolonged mechanical stress, such as with 6 months of overcirculation in piglets or altered LV function after several weeks of overpacing-induced tachycardia in dogs, may cause uncoupling of the RV from the pulmonary circulation, with variable Starling's mechanism, or increased EDV. Monocrotaline has extrapulmonary toxic effects and causes an inflammatory pulmonary vascular disease.[39] This is associated with altered RV systolic function adaptation and leads to increased RV volumes. A general trend in reported studies is that increased pulmonary arterial obstruction, such as pulmonary stenosis or pulmonary artery banding, allows for better and more prolonged preservation of RV-arterial coupling when compared to conditions where the PVR is increased because of pulmonary vascular diseases.[3,40] It has to be added that Starling's mechanism may contribute to RV systolic function adaptation in any model, depending on the volume status and the contribution of preload to afterload-induced changes, with volume overload as a cause of enhanced RV hypertrophy.[41]

In patients with idiopathic PAH, RV-arterial coupling may be preserved with no increase in RV volume for a while, but the presence of systemic disease, such as systemic sclerosis, may be a cause of earlier RV failure.[18] The determinants of long-term preservation of RV-arterial coupling in patients with severe pulmonary hypertension or a systemic RV are not known. The pathobiologic events leading to RV-arterial uncoupling and increased RV volumes remain to be identified. Knowing the signaling pathways responsible for maintained RV function in the presence of severely increased afterload may offer interesting therapeutic perspective.[3]

The current understanding of the pathophysiology of RV failure involves neurohumoral activation, expression of inflammatory mediators, apoptosis, capillary loss, oxidative stress, and metabolic shifts, with variable fibrosis and hypertrophy.[3,42] The exact sequence of events and interactions is being explored, and each has still to be referred to sound measurements of function, as illustrated in recent studies that showed inflammation and apoptosis to be correlated with decreased E_{max}/E_a in acute[43] as well as chronic[25,44] models of RV failure as a universal relationship (Figure 5).

SIMPLIFIED METHODS FOR THE MEASUREMENT OF RV-ARTERIAL COUPLING

Volume measurements

A ratio of elastances can be simplified to a ratio of volumes, provided that ESV is measured at the point of E_{max} and not at the end of RV ejection. Pressure-volume relationships obtained for the LV after the Mustard procedure connect-

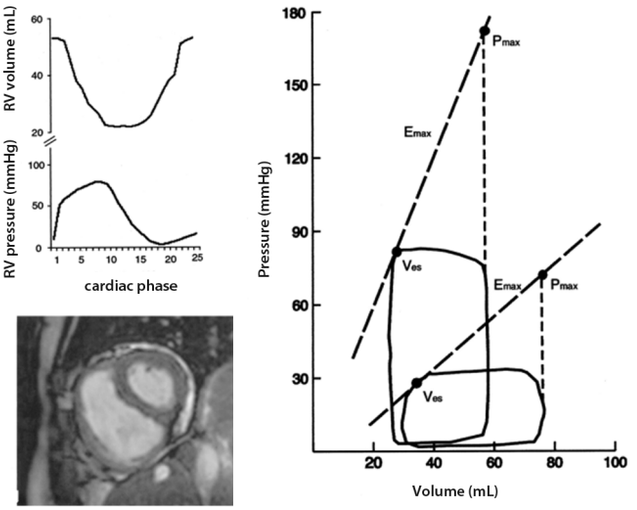

Figure 4. Right ventricular (RV) pressure-volume loops with calculated maximal RV pressure (P_{max}), maximal elastance (E_{max}), and arterial elastance (E_a) in a normal subject and in a patient with pulmonary arterial hypertension (PAH). *Left*, source volume and pressure signals of the PAH patient (*top*) and a magnetic resonance image of the normal control (*bottom*). *Right*, pulmonary hypertension was associated with a marked increase in pressures and E_a, accompanied by an increase in E_{max}. The normal subject had an E_{max}/E_a ratio of 2. The E_{max}/E_a ratio was decreased to 1 in the PAH patient. V_{es}: end-systolic volume. Reproduced from Kuehne et al.[16] with permission.

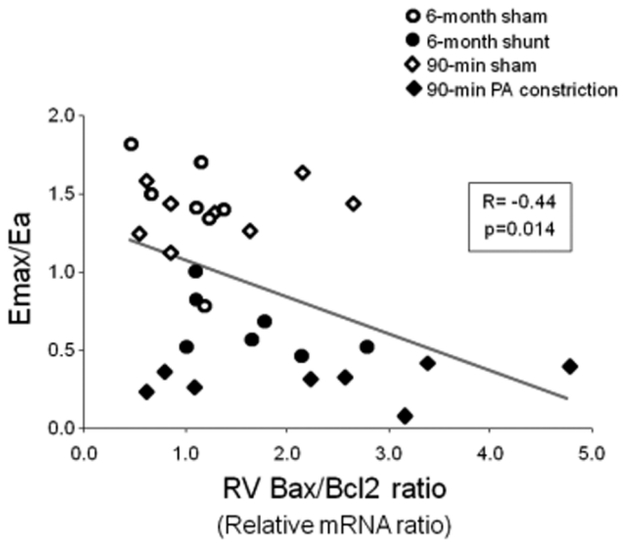

Figure 5. Decreased right ventricular (RV) maximum elastance/arterial elastance (E_{max}/E_a) ratio correlated with the Bax/Bcl2 ratio indicating activation of apoptosis as a universal mechanism in models of acute or chronic RV failure. Data from Rondelet et al.[25] and Dewachter et al.[43] PA: pulmonary artery; mRNA: messenger RNA.

ing the LV to the pulmonary circulation are indistinguishable from the normal triangular shape of the RV, while the overall shape of the pressure-volume loop of the systemic RV resembles that of the normal LV.[45] Thus, the discrepancy between E_{es} and E_{max} may increase with ventricular unloading.

Sanz and colleagues[46] measured ESV and SV by MRI in a large group of patients with pulmonary hypertension and showed that the SV/ESV ratio is initially preserved and then decreases with increasing severity of pulmonary hypertension. This result calls for further evaluation of the functional and prognostic relevance of SV/ESV. It can be reasoned that the SV/ESV ratio includes information about the RV ejection fraction (EF), or SV/EDV ratio,[27] but in a less preload-dependent manner. A recent study reported on the negative effect on outcome of decreased RVEF in spite of a targeted therapy-associated decrease of PVR in patients with PAH.[47] Systemic vasodilating effects of targeted therapies in PAH may increase venous return and increase EDV, which decreases EF if SV remains essentially unchanged, while an increase in cardiac output may decrease PVR without any change in the functional state of the pulmonary circulation.[48] The SV/ESV ratio as a measure of RV-arterial coupling could clarify these confounding effects of changes in preload.

Current progress in echocardiography makes accurate measurements of the pulmonary circulation and RV function possible,[49,50] even though the precision of this approach may remain an issue for individual decision making based on cut-off values.[51] Advances in 3-dimensional echocardiography now offer the perspective of easier bedside measurements of RV volumes,[52] and thus of EF or SV/ESV, for the evaluation of RV-arterial coupling.

Pressure measurements

Another simplified approach for the measurement of RV-arterial coupling, introduced by Trip and colleagues,[53] relies on a P_{max} calculated from an RV pressure curve (which is easily obtained during right heart catheterization), mean P_{pa} (mP_{pa}) taken as a surrogate for ESP, and RV volume measurements by MRI. These authors calculated E_{max} as $(P_{max} - mP_{pa})/(EDV - ESV)$ and E_{max} at $V_0 = 0$ as mP_{pa}/ESV (Figure 6); V_0 is the extrapolated volume intercept of the linear best fit of a multipoint E_{max} pressure-volume relationship. The results showed that mP_{pa}/ESV was lower than $(P_{max} - mP_{pa})/SV$, on average about half the value, while V_0 ranged from −8 to 171 mL and was correlated with EDV and ESV. From this the authors concluded that V_0 is dependent on RV dilatation and thus that the estimated E_{max} may be more preload dependent than previously assumed. This is possible, although a more likely explanation is the uncertainties of extrapolation from linear fits of relationships that have been demonstrated to be curvilinear,[54] as illustrated in Figure 7. The E_{es} is best determined by interpolation of pressure-volume coordinates,[54] with further tightening by a correction for EDV.[9,18] Further uncer-

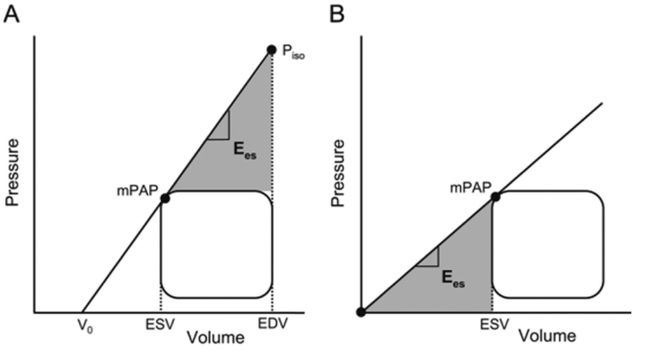

Figure 6. Simplified pressure method for the determination of right ventricular (RV) maximum elastance/arterial elastance (E_{es}/E_a) ratio. E_{max} is calculated as $(P_{max} - mPAP)/(EDV - ESV)$ in *A* and as $mPAP/ESV$ in *B*. A positive V_0 is associated with a higher estimated E_{max}. mPAP: mean pulmonary artery pressure; P_{max}: maximum RV pressure; ESV: end-systolic volume; EDV: end-diastolic volume; V_0: ventricular volume at zero pressure. Reproduced from Trip et al.[53] with permission.

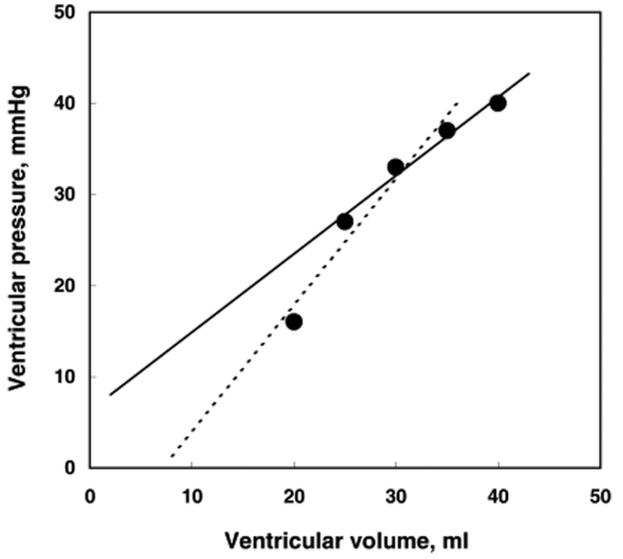

Figure 7. Linear extrapolation from slightly curvilinear end-systolic pressure-volume relationships may lead to markedly different pressure or volume intercepts. In this series of 5 pressure-volume coordinates, omission of the highest or the lowest pressure point changes the zero-pressure volume intercept from a negative to a positive value.

tainty is related to the use of the mP_{pa}/SV ratio or the slope of (P_{max} − mP_{pa})/SV as a surrogate for an E_{max} determination from single- or (better) multiple-beat pressure-volume relationships. Extrapolations amplify errors that are made by the use of surrogate pressures and volumes.

ALTERNATIVE METHODS TO EVALUATE RV-ARTERIAL COUPLING

The pump function graph

The coupling of RV function to the pulmonary circulation can also be described by pump function curves relating the mean RV pressure to SV.[55] A pump function graph is built from measurements of the mean RV pressure and SV, a calculated P_{max} at zero SV, and a parabolic extrapolation to a zero-pressure SV (Figure 8). In this representation, an increase in preload shifts the curve to greater SV with no change in shape, while an increased contractility leads to a higher P_{max} with no change in maximum SV. This analysis helps us understand that at a high PVR a fall in pressure markedly increases SV while at a low PVR the pressure is more affected than the SV.[27] The pump function graph has been used to explain more severe RV failure at any level of mP_{pa} in systemic sclerosis.[56] This was later confirmed by E_{max}/E_a determinations.[18] The limitations of the pump function graph are in its sensitivity to changes in preload and, as mentioned above, to the use of mean RV pressure or mP_{pa} as surrogates for the RV pressure at E_{max}.

The contractile reserve

Systolic function adaptation to afterload can also be tested dynamically to determine the contractile reserve, or the capacity to increase contractility at a given level of loading. Contractile or ventricular reserve determined with exercise or pharmacological stress tests (typically an infusion of dobutamine) has been shown to be a strong predictor of outcome in heart failure.[57] The evaluation of the RV contractile reserve has not been reported in patients with pulmonary hypertension. In rats with pulmonary arterial banding, E_{max} was shown to increase to the same extent in response to 2.5 μg/kg/min of dobutamine, as in controls, suggesting preserved systolic function in this pulmonary hypertension model.[23]

A more straightforward, noninvasive approach was recently introduced by Grünig and his colleagues.[58] These authors simply used Doppler echocardiography to measure RV systolic pressure from the maximum velocity of tricuspid regurgitation at rest and at exercise, and they showed, in 124 patients with either PAH or chronic thromboembolic pulmonary hypertension, that an exercise-induced increase by more 30 mmHg was a strong predictor of exercise capacity and survival (Figure 9). Further studies will be necessary to explore improved indices of RV contractile

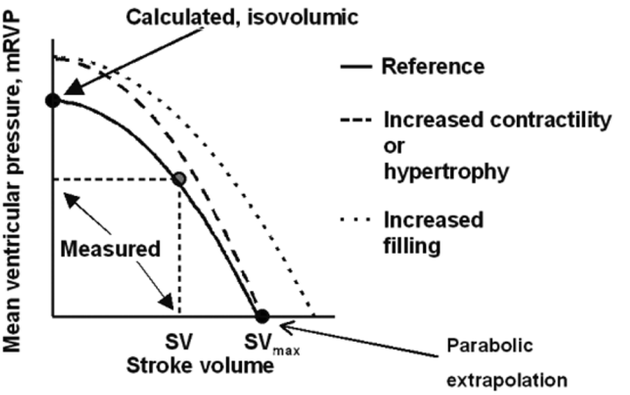

Figure 8. Pump function curve defined by mean right ventricular pressure as a function of stroke volume (SV). The zero-SV point is calculated from a maximum-pressure determination (see Figure 3). The zero-pressure point results from a parabolic extrapolation from measured and zero-SV points. Increased preload shifts the curve in parallel to higher SV. Increased contractility increases pressure generated at any given value of SV, but in proportion to decreased SV. Reproduced from Elzinga and Westerhof[55] with permission.

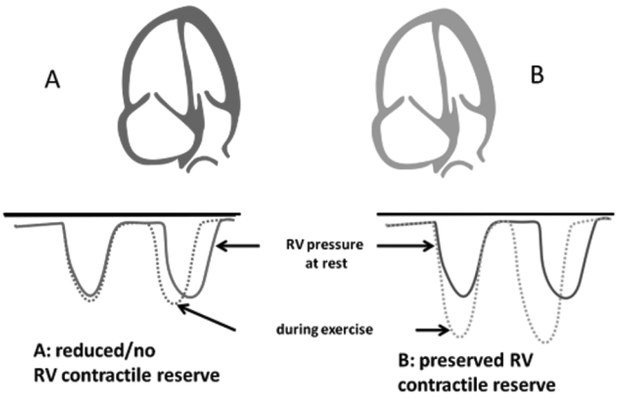

Figure 9. Right ventricular contractile reserve defined by exercise-induced increase in the systolic pressure. Reproduced from Grünig et al.[58] with permission. A color version of this figure is available online.

reserve by incorporating volume measurements and ESP determinations, because this is now becoming possible through noninvasive bedside methodology.

SURROGATE MEASUREMENTS OF RV-ARTERIAL COUPLING

RV systolic function can be estimated by a series of invasive and noninvasive measurements that are easily available in daily clinical practice. Right heart catheterization allows measurements of P_{pa}, right atrial pressure, and cardiac output (Fick or thermodilution) and thus calculations of RV function curves, such as cardiac output or stroke work, as functions of right atrial pressure. The limitations of these invasive measurements are the absence of RV volume measurements needed for EF calculations or estimations of preload and the insufficient definition of afterload by PVR. Imaging techniques such as MRI or 3-dimensional echocardiography allow the measurements of RV volumes, and thus EF and ESP/ESV ratios, as an estimation of RV contractility. The limitation of imaging is the absence of direct pressure measurements.

A series of imaging-derived indices of RV systolic function have been shown to be related to the functional state and prognosis of patients with severe pulmonary hypertension: MRI-determined EF, Doppler echocardiography of fractional area change (a surrogate for EF), tricuspid annual plane systolic excursion, and tissue Doppler imaging of the tricuspid annulus systolic velocity S wave and isovolumic acceleration (IVA) or maximum isovolumic velocity (IVV), strain or strain rate.[49,50] Isovolumic phase indices, such as the IVA or IVV, are probably less preload dependent, and as such are the closest estimates of E_{max} measurements.[59,60]

DIASTOLIC FUNCTION

This review has focused on RV systolic function and RV-arterial coupling as the essential biomechanical mechanisms of ventricular function adaptation to increased afterload. However, a Starling mechanism may contribute at any stage of disease progression, depending on the rate of progression, a more or less inflammatory nature of pulmonary hypertension, and any systemic condition affecting cardiac function. There is thus interest in taking into account diastolic function in the RV adaptation to pulmonary hypertension.

Diastolic function is described by a diastolic elastance curve determined by a family of pressure-volume loops at variable loading. This function is curvilinear and therefore impossible to summarize as a single number. Several formulas have been proposed, but none has made it yet to clinical studies.[27] A series of surrogate measurements of diastolic function are provided by Doppler echocardiography: isovolumic relaxation time and a decreased ratio of transmitral E and A waves or mitral annulus tissue Doppler imaging E′/A′ waves, increased right atrial or RV surface areas on apical 4-chamber views, altered eccentricity index on a parasternal short-axis view, estimates of right atrial pressure from RV diastolic function indices or inferior vena cava dimensions, pericardial effusion, and the so-called Tei index, which is the ratio of isovolumic time intervals to ventricular ejection time and thus integrates diastolic and systolic function.[49,50]

VENTRICULAR INTERACTION

RV function has to be understood in the light of its direct and indirect interactions with LV function.[1] Direct interaction, or ventricular interdependence, is defined as the forces that are transmitted from one ventricle to the other through the myocardium and pericardium, independent of neural, humoral, or circulatory effects.[61] Diastolic ventricular interaction refers to the competition for space within the indistensible pericardium when the RV dilates, which alters LV filling and may be a cause of inadequate cardiac output response to metabolic demand. Right heart catheterization and imaging studies have shown that in patients with severe pulmonary hypertension, pulmonary artery wedge pressure and LV peak filling rate are altered in proportion to decreased RVEF.[62] Systolic interaction refers to positive interactions between RV and LV contractions. It can be shown experimentally that aortic constric-

tion markedly improves RV function in animals with pulmonary arterial banding.[63] This is explained by a mechanical entrainment effect but also by LV systolic function determining systemic blood pressure, which is an essential determinant of RV coronary perfusion. Increased RV filling pressures and excessive decrease in blood pressure may be causes of RV ischemia and decreased contractility.[1] An additional cause of negative ventricular interaction disclosed by imaging studies is asynchrony, which has been shown to develop in parallel to increased P_{pa} and contributes to altered RV systolic function and LV underfilling.[64]

LIMITATIONS AND PERSPECTIVES

Measurements of systolic and diastolic function must be physiologically sound and validated against pressure-volume relationships. The validity of measurements of function is sometimes evaluated by their effect on clinical stability or survival. This is clinically useful but not helpful when it comes to a better understanding of mechanisms of disease and mode of action of pharmacological interventions.

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