

## Chapter 2

# Physiology of the Right Ventricle

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*One must inquire how increasing pulmonary vascular resistance results in impaired right ventricular function*

(JT Reeves, 1988)

### Introduction with Evolutionary and Historical Perspectives

The right ventricle (RV) is functionally coupled to the pulmonary circulation. Evolution from ancestors of fishes to amphibians, reptiles, and finally birds and mammals has led to progressively greater oxygen consumption requiring a thinner pulmonary blood gas barrier built into a separated low-pressure/high-flow vascular system [1]. This has resulted in a progressive unloading and reshaping of the RV as a thin-walled flow generator. When pulmonary vascular resistance (PVR) is low and the peripheral requirements for flow minimal, RV pumping does not significantly contribute to the transit blood through the lungs and to the left heart. In 1943, Starr and his colleagues showed that ablation of the RV free wall in dogs is compatible with life without a substantial increase in systemic venous pressures [2]. Without a functional RV, the preloading of the left ventricle (LV) becomes exclusively dependent on systemic venous return, which is driven by a mean systemic filling pressure (Pms) of normally less than 10 mmHg [3]. However, Pms can be increased

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to 15–20 mmHg by an increase in effective blood volume and systemic nervous system activation without clinically identifiable edema. The limit of this adaptation is determined by the flow-resistive properties of the pulmonary circulation. Normal mean pulmonary artery pressure (Ppa)-flow (Q) relationships vary from 0.5 to 3 mmHg/L/min [4]. Thus in the absence of a RV but presence of steep Ppa-Q relationships, moderate levels of exercise with a cardiac output of 10 L/min would require a Pms of at least 35–40 mmHg, which would be unlikely to remain clinically silent.

With this already established knowledge at their time, Fontan and Baudet introduced in 1971 the first cavo-pulmonary anastomosis bypassing the RV as a palliative intervention for cardiac malformations [5] (see also Chap. 8). It has since been shown that patients with the so-called “Fontan circulation” may indeed enjoy a near-normal sedentary life for several decades, but rapidly deteriorate when Ppa increases due to pulmonary vascular remodeling (e.g., with altitude exposure) or increased LV filling pressures [6]. The RV becomes essential to the preservation of the quality of life, enabling exercise and survival as soon as the PVR reaches high-normal values, and definitely so in patients with all forms of pulmonary hypertension [7, 8].

## Do the Laws of the Heart Apply to the RV?

The RV differs from the LV not only in structure, but also because of its embryological development (see Chap. 1). The RV, including its outflow tract is derived from the anterior heart field, whereas the LV and the atria are derived from the primary heart field [7]. Accordingly, it is often assumed that the RV and the LV are functionally very different. As a matter of fact, a brisk increase in PVR produced by pulmonary arterial constriction to mimic massive pulmonary embolism, induces an acute dilatation and pump failure of the RV [9], and there is no clinical counterpart of this observation for the LV. However, a gradual increase in PVR allows for RV adaptation and remodeling, basically similar to the LV facing a progressive increase in systemic vascular resistance [10]. 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, often referred to as “Anrep’s law of the heart”.

In 1912, Gleb Vassilevitch von Anrep who had been trained by Ivan Petrovich Pavlov in St. Petersburg, reported on the rapid increase in LV contractility in response to an aortic constriction [11]. He explained this observation by a reflex adrenergic reaction because similar effects could be induced by the administration of adrenaline. Pavlov himself was actually more interested in gastrointestinal physiology and sent von Anrep to London to work under the supervision of Starling and Bayliss on the humoral control of digestion. Once in London, von Anrep confirmed his observation of an increased contractility induced by an increase loading in Starling’s heart–lung preparation. Further work in Starling’s laboratory definitely established that after an acute increase in either venous return or in systemic vascular

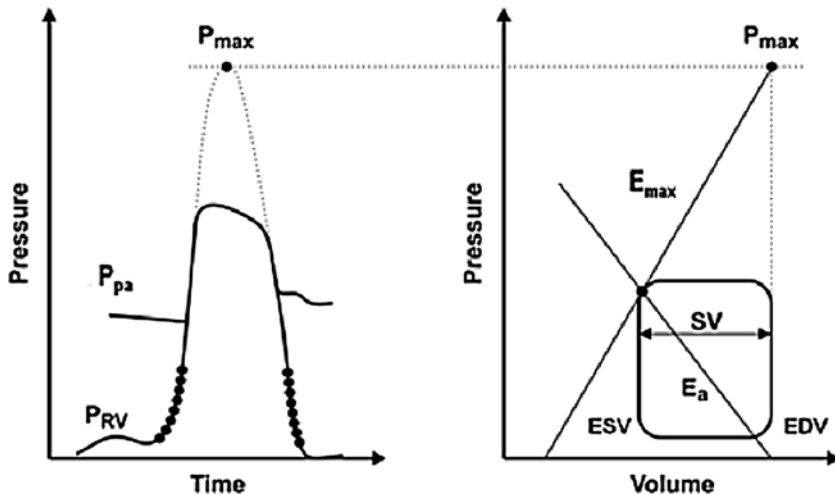
resistance, the heart initially dilates allowing for increased or maintained stroke volume (SV) respectively, but after a few minutes cardiac dimensions return to baseline in spite of persistently increased loading, indicating increased contractility. Starling thought that much of this “homeometric” adaptation exclusively observed in the LV was related to an increased metabolism which accompanies an increase in coronary blood flow when blood pressure was raised. Von Anrep rather hypothesized a release of myocardial stores of catecholamines by mechanical stretch, because the homeometric adaptation was observed in isolated hearts. Later studies have repeatedly confirmed the predominant role of homeometric, or systolic function adaptation to changes in loading conditions, leaving Starling’s heterometric adaptation for beat-to-beat adaptations in venous return, for example after changing body position, or for situations of failing systolic function adaptation, for example in advanced heart failure [12]. This homeometric adaptation to afterload has been demonstrated in the RV exposed to pulmonary arterial constriction and in conditions of constant coronary perfusion [13, 14].

It is therefore possible to define RV failure as a dyspnea-fatigue syndrome with eventual systemic congestion, caused by the inability of the RV to maintain flow output in response to metabolic demand without heterometric adaptation [9, 10]. This definition encompasses a spectrum of clinical situations, from preserved maximum cardiac output and aerobic exercise capacity at the price of increased RV end-diastolic volumes (EDVs) to low-output states with small RV volumes at rest.

This being said, many questions remain unanswered. Whether the time-course of chronic systolic function adaptation to afterload is the same for the RV and the LV remains unclear. Comparisons between studies are difficult because of differences in ventricular structure and relative changes in arterial pressure. Contractility responses to increased afterload may be affected by extrinsic factors such as volume status, ventricular interaction, coronary perfusion, and yet unknown circulating mediators related to the presence of systemic or pulmonary vascular diseases. Ventricular hypertrophy may contribute to contractile force and decrease wall tension, but the mechanisms of adaptation remain incompletely understood.

## Systolic Function

The gold standard measurement of contractility *in vivo* is the maximal elastance ( $E_{\max}$ ), or the maximum value of the ratio between ventricular pressure and volume measured continuously during the cardiac cycle (i.e., the “pressure–volume loop”) [10]. Left ventricular  $E_{\max}$  coincides with end-systole, and is thus equal to the ratio between end-systolic pressure (ESP) and end-systolic volume (ESV). End-systolic elastance ( $E_{\text{es}}$ ) is measured at the upper left corner of a square-shape pressure–volume loop [15]. 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 [16].



**Fig. 2.1** Single beat method to measure right ventriculo-arterial coupling. Left: a maximum pressure ( $P_{\max}$ ) is calculated from nonlinear extrapolation of early and late isovolumic portions of the right ventricular pressure ( $P_{RV}$ ) curve. A straight line is drawn from  $P_{\max}$  and the end-diastolic volume (EDV) tangent to the end-systolic pressure ( $P_{es}$ )-volume (ESV) point. In the case of this theoretical illustration, RV maximum elastance ( $E_{\max}$ ) coincides with end-systole, thus  $E_{\max} = (P_{\max} - P_{es})/SV$ , where SV is the stroke volume. The arterial elastance  $E_a$  is defined by the ratio  $P_{es}/SV$

With increasing impedance in pulmonary hypertension, the shape of the RV pressure-volume loop changes. RV pressure rises throughout ejection and peaks at or near end-systole.  $E_{\max}$  then typically occurs at ESP, similar to the LV loop.

Instantaneous measurements of RV volumes are difficult to obtain at the bedside, and so are manipulations of venous return. This is why single beat methods have been developed, initially for the LV [17], then transposed to the RV [18]. The single beat method relies on a maximum pressure  $P_{\max}$  calculation from a nonlinear extrapolation of the early and late portions of a RV pressure curve, an integration of pulmonary flow and synchronization of the signals.  $E_{\max}$  is estimated from the slope of a tangent from  $P_{\max}$  to the pressure-volume curve (Fig. 2.1).

The single beat method can be applied with relative changes in volume measured by integration of the ejected flow rather than with measurements of absolute volumes. This is due to the fact that  $E_{\max}$  is not dependent on preload, or EDV [10]. An excellent agreement between directly measured  $P_{\max}$  (by clamping the main pulmonary artery for one beat) and calculated  $P_{\max}$  has been demonstrated in a large animal experimental preparation without pulmonary hypertension [18]. In states of increased impedance, lower vascular compliance, and increased pulsatile loading, a late systolic rise in RV pressure occurs. Therefore, it remains unknown if fitting a sine wave to the isovolumetric portions of the RV pressure tracing will accurately determine  $P_{\max}$ . Thus the single beat method to estimate RV-arterial coupling will require further validation in patients with severe pulmonary hypertension (Table 2.3).

Measurements of RV  $E_{\max}$  by conductance catheter technology and inferior vena cava balloon obstruction have been reported in normal volunteers [19, 20]. More

recently, a limited number of  $E_{\max}$  determinations have been reported in patients with pulmonary arterial hypertension (PAH) either using the single beat approach, fluid-filled catheters, and magnetic resonance imaging (MRI) [21] or a multiple beat approach with venous return decreased by a Valsalva maneuver and conductance catheters [22]. The single beat approach with a high-fidelity Millar catheter and integration of a transonic measurement of pulmonary flow were reported in a patient with a systemic RV corrected and congenitally transposition of the great arteries [23]. These limited reports confirm the importance of systolic function adaptation to afterload previously demonstrated in various animal species [24], or experimental models of acute [24–26] or chronic [27–31] pulmonary hypertension.

## Coupling of Systolic Function to Afterload

Measurements of systolic function are ideally load-independent, which means constancy over a wide range of immediate changes in preload or afterload. The requirement is met with an acceptable approximation by  $E_{\max}$  in intact hearts. This is because  $E_{\max}$  is the only point of the pressure–volume curve that is common in systole to ejecting and non-ejecting beats, and thus the optimal translation to a pressure–volume relationship of an isolated muscle active tension length relationship. However, as already discussed,  $E_{\max}$  adapts to afterload after a few beats. It is therefore important to correct  $E_{\max}$  for afterload.

There are three possible measurements of afterload [32, 33]. The first is maximum ventricular wall stress, which is approximated by the maximum value of the product of volume and pressure, divided by the wall thickness. This is a transposition of Laplace’s law for spherical structures, and thus problematic for the RV because of considerable regional variations of the internal radius. The second is based on measurements of the forces that oppose flow ejection, or the hydraulic load. This calculation optimally requires a spectral analysis arterial pressure and flow waves, with derived impedance calculations [33]. A more straightforward approach is to derive arterial elastance ( $E_a$ ) as it is “seen” by the ventricle and thus graphically determined using a pressure volume loop and by dividing maximal elastance pressure by SV (Fig. 2.1) [10].

Thus contractility coupled to afterload is defined by a ratio of  $E_{\max}$  to  $E_a$ . The optimal mechanical coupling of  $E_{\max}$  to  $E_a$  is equal to 1. The optimal energy transfer from the ventricle to the arterial system occurs at  $E_{\max}/E_a$  ratios of 1.5–2 [10].

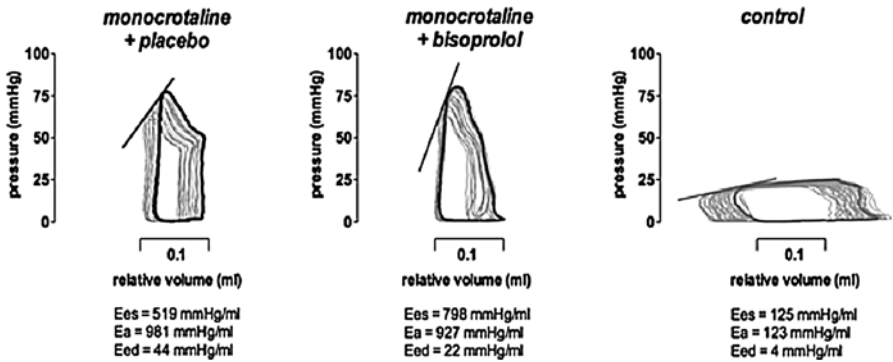
## RV-Arterial Coupling in Experimental Pulmonary Hypertension

RV-arterial coupling measured with the  $E_{\max}/E_a$  ratio has been investigated in various models of pulmonary hypertension. The results are summarized in Table 2.1. Acute hypoxia-induced increase in PVR was associated with a preserved RV-arterial coupling because of increased RV contractility [18, 24, 34–36]. Preserved RV-arterial coupling was also reported in pulmonary hypertension due to either microembolism

**Table 2.1** RV-arterial coupling in experimental models of pulmonary hypertension

Model	Animal	$E_{\max}$	$E_{\max}/E_a$	References
Acute hypoxia	Dog, goat, pig	↑	—	[18, 24, 34–36]
Monocrotaline	Rat	↑	↓	[31]
Sepsis, early	Pig	↑	—	[26]
Sepsis, late	Pig	—	↓	[26]
Acute embolism	Dog, goat, pig	↑	—	[24]
Acute PA banding	Dog, goat, pig	↑	—	[24]
AP shunting 3 mo	Pig	↑	—	[29]
AP shunting 6 mo	Pig	↓	↓	[29]
Acute RVF	Dog, pig	↓	↓	[38–41]
Chronic heart failure	Dog	—	↓	[42]

$E_{\max}$  maximum right ventricular elastance,  $E_a$  pulmonary arterial elastance, PA pulmonary artery, AP aorta-pulmonary, mo month, RVF right ventricular failure



**Fig. 2.2** Families of right ventricular pressure–volume loops at decreasing venous return in rats.  $E_{\max}$  is defined by a straight line tangent to the upper border of the pressure–volume loop families. Measurements are obtained in a control animal, after induction of pulmonary hypertension (PH) by the administration of monocrotaline and after induction of monocrotaline-PH under bisoprolol therapy. PH was associated with a marked adaptative increase in  $E_{\max}$ , which was further improved by bisoprolol therapy. From source data of Ref. [31]

or pulmonary arterial banding (PAB) [24]. Endotoxin shock was associated with a deterioration of RV-arterial coupling because of impaired contractility [26]. A chronic aorta-pulmonary shunt as a model of a persistent ductus arteriosus in growing piglets was associated with preserved RV-arterial coupling after 3 months [29, 37] but uncoupling occurred after 6 months because of decreased RV contractility resulting in a decreased cardiac output and increased right atrial pressure [30]. Persistent RV failure after tight transient PAB was characterized by a profound RV-arterial uncoupling because of a persistent decrease in contractility and reactive increase in PVR [38–41]. Monocrotaline-induced pulmonary hypertension was associated with RV-arterial uncoupling because of an insufficient increase in contractility to match increased afterload (Fig. 2.2) [31]. Mild pulmonary hypertension

in pacing-induced heart failure was associated with RV-uncoupling due to the absence of an adaptive increase in RV contractility [42].

Taken together, these studies support the notion of a predominant 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 sided heart failure.

## Pharmacology of RV-Arterial Coupling

In patients with severe pulmonary hypertension right ventricular function is a major determinant of quality of life, exercise capacity, and overall outcome [8]. Treatment strategies for these patients logically aim at the decrease in RV afterload often assessed by a measurement of PVR—or improvement in maximum cardiac output obtained by unloading the RV assessed by exercise capacity. However, it has been proposed that some of the vasodilators used for the treatment of PAH might also have intrinsic positive inotropic effects. There are data suggesting that this could be a mechanism of action of prostacyclins [43] or phosphodiesterase-5 inhibitors [44]. In addition to these perhaps “hidden” vasodilator drug actions, treatments specifically targeting the RV are now under consideration. The most obvious would be interventions aimed at the excessive neuro-humoral activation, which have been shown to improve survival in LV failure [45, 46]. Finally, patients with pulmonary hypertension may be exposed to the cardiovascular effects of general anesthesia or require treatments with inotropic drugs in case of severe RV failure [47, 48]. In all these circumstances, improved knowledge of the effects of the interventions on the components of RV-arterial coupling is desirable. Recent experimental animal studies reporting on the effects of pharmacological interventions on RV-arterial coupling are listed in Table 2.2.

**Table 2.2** Effects of pharmacological intervention in experimental pulmonary hypertension (see Table 2.1)

Model	Drug	$E_{\max}$	$E_a$	$E_{\max}/E_a$	References
Acute hypoxia	Dobutamine	↑	—	↑	[18]
Acute RHF	Dobutamine	↑	↓ or —	↑	[38, 39]
Acute RHF	Levosimendan	↑	↓	↑	[39, 41]
Acute RHF	Norepinephrine	↑	—	—	[38]
Chronic heart failure	Milrinone	↑	—	↑	[42]
Chronic heart failure	Nitroprusside	—	—	—	[42]
Chronic heart failure	Nitric oxide	—	—	—	[42]
Acute hypoxia	Propranolol	↓	↑	↓	[18]
Monocrotaline	Bisoprolol	↑	—	↑	[31]
AP shunting 3 mo	Epoprostenol	—	↓	↑	[37]
Acute RHF	Epoprostenol	—	↓	↑	[40]
Acute hypoxia	Sildenafil	—	↓	↑	[35]
Monocrotaline	Sildenafil	↑	↓	↑	[49]
Hypoxia	Isflurane	↓	↑	↓	[29]

**Table 2.3** RV-arterial coupling in patients with pulmonary arterial hypertension

Diagnosis	$E_{\max}$	$E_a$	$E_{\max}/E_a$	References
IPAH ( $n=11$ )	↑	↑	↓ or –	[21, 22]
CCTGA ( $n=1$ )	↑	↑	↓	[23]
SSc-PAH ( $n=7$ )	↑	↑	↓	[22]

*IPAH* idiopathic pulmonary arterial hypertension, *SSc-PAH* systemic sclerosis associated PAH, *CCTGA* congenitally corrected transposition of the great arteries (systemic right ventricle)

Catecholamines may cause pulmonary vasoconstriction and tachycardia [47]. Moreover, treatment with catecholamine has been associated with increased mortality in patients with acute or chronic RV failure [48] and these data cause concern. Low-dose dobutamine increased RV-arterial coupling by an inotropic effect without [18, 39] or with [38] a decreased afterload. Low-dose norepinephrine improved RV-arterial coupling through an exclusive positive inotropic effect, which was however less pronounced than that achieved with low-dose dobutamine [38]. Experimentally acute administration of propranolol caused deterioration of RV-arterial coupling through combined negative inotrope effect and pulmonary vasoconstriction during acute hypoxia [18]. In the context of chronic administration of bisoprolol improved RV-arterial coupling by an improved contractility in monocrotaline-induced pulmonary hypertension (Fig. 2.2) [31].

Acute administration of epoprostenol or inhaled nitric oxide improved RV-arterial coupling exclusively via pulmonary vasodilation effects in a model of high-flow-induced pulmonary hypertension [37]. Acute epoprostenol partially restored RV-arterial coupling through an exclusive pulmonary vascular effect in PAB-induced persistent RV failure [40] or was associated with maintained RV-arterial coupling because of decreased contractility in proportion to a decreased PVR during acute hypoxia [36]. Levosimendan improved RV-arterial coupling through combined positive inotropy and vasodilation in PAB-induced persistent RV failure [39, 41]. Sildenafil improved RV-arterial coupling in hypoxia because of exclusive pulmonary vasodilation [35], but improved coupling by a positive inotropic effect in monocrotaline-induced pulmonary hypertension [49]. Bosentan had no intrinsic effect on contractility in pulmonary hypertension after 3 months of aorta-pulmonary shunting [29]. Milrinone improved RV-arterial coupling by an improved contractility in pacing-induced congestive heart failure with mild pulmonary hypertension, while nitroprusside or inhaled nitric oxide had no effect [42]. Isoflurane and enflurane caused deterioration of RV-arterial coupling because of a combined decrease in contractility and increase in PVR [34].

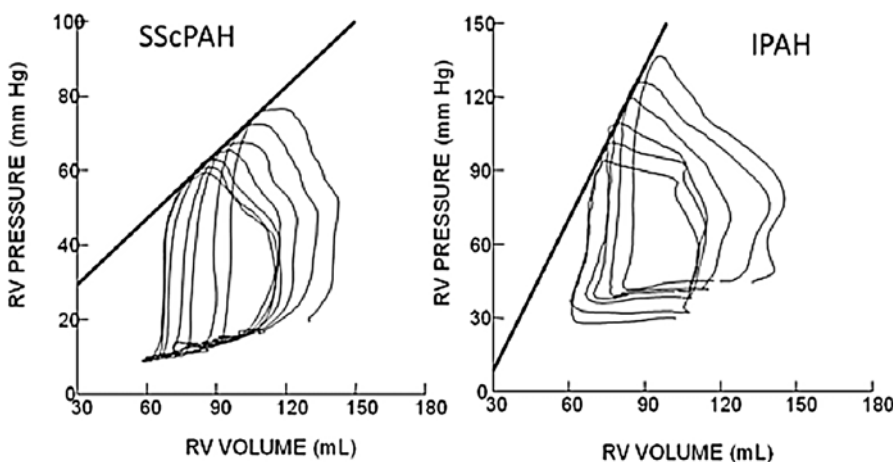
It is important to point out that acute and chronic effects of interventions on RV-arterial coupling in acute and chronic experimental pulmonary hypertension models may be quite different, as shown for  $\beta$ -blockers or sildenafil. This is a challenge to test of drugs in multiple experimental models and, makes the extrapolation to the clinical situation of patients with pulmonary hypertension difficult.



## RV-Arterial Coupling Measurements in Patients with Pulmonary Hypertension

Measurements of both  $E_{\max}$  and  $E_a$  have been reported in a small number of patients with pulmonary hypertension. In a first study of six patients with idiopathic PAH but no clinical RV failure, compared to six controls, Kuehne measured RV volumes by MRI and RV pressures using fluid-filled catheters, synchronized the signals and calculated  $E_{\max}$  and  $E_a$  using the single beat method [21].  $E_{\max}$  was increased threefold, from  $1.1 \pm 0.1$  to  $2.8 \pm 0.5$  mmHg/mL, but  $E_a$  was increased from  $0.6 \pm 0.5$  to  $2.7 \pm 0.2$ , so that the  $E_{\max}/E_a$  ratio decreased from  $1.9 \pm 0.2$  to  $1.1 \pm 0.1$ . Yet RV volumes were not increased, indicating “sufficient” coupling, at least under resting conditions.

Tedford reported on RV-arterial coupling in five patients with idiopathic PAH and seven with systemic sclerosis (SSc)-associated PAH [22]. In this study, RV volumes and pressures were measured with conductance catheters and  $E_{\max}$  defined by a family of pressure–volume loops as venous return decreased by a Valsalva maneuver (validated against inferior vena cava obstruction). Typical tracings are shown in Fig. 2.3. In IPAH patients,  $E_{\max}$  was  $2.3 \pm 1.1$ ,  $E_a$   $1.2 \pm 0.5$ , and  $E_{\max}/E_a$  preserved at  $2.1 \pm 1.0$ . In SSc-PAH patients,  $E_{\max}$  was decreased to  $0.8 \pm 0.3$  in the presence of an  $E_a$  at  $0.9 \pm 0.4$ , so that  $E_{\max}/E_a$  was decreased to  $1.0 \pm 0.5$ . The authors also showed that there was no disproportionate decrease in pulmonary arterial compliance in SSc-PAH patients, suggesting that the depressed  $E_{\max}$  in SSc-PAH was not caused by a relatively higher pulsatile hydraulic load. Additionally, seven



**Fig. 2.3** Right ventricular pressure–volume loops at decreasing venous return in a patient with systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH), left, and in a patient with idiopathic PAH (IPAH), right. The slope of linearized maximum elastance pressure–volume relationship is higher at similar mean pulmonary artery pressure in IPAH. Source data from Ref. [22]

patients with SSc but without pulmonary hypertension maintained preserved coupling ( $E_{\max}/E_a$   $2.3 \pm 1.2$ ).

Finally, there is a case report of RV-arterial uncoupling in an asymptomatic young man with a congenitally corrected transposition of the great arteries [23]. In this patient, the systemic RV  $E_{\max}/E_a$  ratio was of 1.2, in the range of the ratio reported in IPAH patients by Kuehne [21], while the pulmonary LV  $E_{\max}/E_a$  was perfectly preserved at a value of 1.7. A decreased systemic RV  $E_{\max}/E_a$  probably heralds failure, which is known to occur in these patients after several decades of life.

Together, these results confirm the dominant role of a homeometric adaptation of the RV to increased afterload, and document uncoupling when the hydraulic load remains too high for too long, or when systemic disease is present. From a methodological point of view,  $E_{\max}$  and  $E_a$  show variability with a trend towards higher control values when measurements are based on families of pressure–volume loops rather than on single beat analysis. Targeted therapies in PAH patients might also have affected the results.

Thus it appears that in general RV-arterial coupling is maintained by an adaptive increase of the  $E_{\max}$  in PAH models of chronic hypoxia or aorta-pulmonary shunting when associated with only a moderate increase in pulmonary artery pressures. However, prolonged mechanical stress such as induced by 6 months of overcirculation in piglets, or due to altered LV function following several weeks of pacing in dogs, may cause uncoupling of the RV from the pulmonary circulation, increased filling pressures, and congestion. Monocrotaline has extra-pulmonary toxic effects and causes an inflammatory pulmonary vascular disease [50]. This is associated with decreased RV systolic function adaptation and leads to increased RV volumes. A general trend of reported studies is that pulmonary arterial obstruction such as pulmonary stenosis or PAB allows for a better and more prolonged preservation of RV-arterial coupling than the increased PVR of various forms of pulmonary vascular diseases [46, 51]. A heterometric adaptation may contribute to RV systolic function adaptation in any model depending on the volume status and the impact of an increased preload to afterload-induced changes, with volume overload as a cause of enhanced RV hypertrophy [52].

The determinants of long-term preservation of RV-arterial coupling in patients with severe pulmonary hypertension or with a systemic RV are not known. The molecular events leading to RV-arterial uncoupling and increased RV volumes remain to be identified. Knowledge of the signaling pathways responsible for maintained RV function in the presence of severely increased afterload may guide the development of new therapies [46].

The current understanding of the pathophysiology of RV failure include neuro-humoral activation, expression of inflammatory mediators, apoptosis, capillary loss, oxidative stress, and metabolic shifts, with variable fibrosis and hypertrophy [45, 46] (see Chap. 13). The exact sequence of events and interactions are being explored and has to be referenced to measurements of RV function, as illustrated in recent studies which showed inflammation and apoptosis correlated with decreased  $E_{\max}/E_a$  in acute [53] as well as chronic [30, 54] models of RV failure.

## Simplified Methods for the Measurement of RV-Arterial Coupling

### *Volume Measurements*

A ratio of elastances can be simplified to a ratio of volumes, provided ESV is measured at the point of maximal elastance, not at the end of ejection. This is dependent on loading conditions. Pressure–volume relationships of the RV chronically exposed to increased pulmonary artery pressure tend to resemble LV pressure–volume loops, with a decreased difference between  $E_{\max}$  and  $E_{\text{es}}$ . LV pressure–volume loops after a Mustard procedure, which connects the LV to the pulmonary circulation are indistinguishable from the triangularly shaped normal RV, while the overall shape of the pressure–volume loop of the systemic RV resembles that of the normal LV [55].

Sanz measured ESV and SV by MRI and showed that the SV/ESV ratio is initially preserved in patients with mild pulmonary hypertension, but decreases with increasing disease severity [56]. One problem regarding the SV/ESV ratio is the inherent assumption that the ESP–ESV relationship is linear and that the line crosses the origin. This is incorrect, because ventricular volume at a zero filling pressure is positive. Therefore the ESP/ESV ratio under-estimates  $E_{\max}$ . There could be compensation by ESV being lower than the ventricular volume at the point of  $E_{\max}$ , but probably insufficiently so in pulmonary hypertension. Thus the SV/ESV as a simple volume measurement of RV-arterial coupling requires further evaluation and also of its functional and prognostic relevance. It can be reasoned that the SV/ESV ratio includes the information of RV ejection fraction (EF), or SV/EDV [32] in a less preload-dependent manner, but the validity of this remains to be established.

A recent study reported on the negative impact on outcome of a decreased RVEF in spite of a targeted therapy-associated decrease in the PVR in patients with PAH [57]. Systemic vasodilating effects of targeted therapies in PAH may increase systemic venous return and increase EDV, which decreases EF if the SV remains unchanged, while an increased cardiac output may decrease PVR without any change in pulmonary artery pressure [58].

Current progress in the field of echocardiography allows assessment of the pulmonary circulation and RV function [59, 60] even though the accuracy may be problematic for individual decision-making based on strict cut-off values [61]. Advances in three-dimensional echocardiography offer now the perspective of easier bedside measurements of RV volumes [62], and thus of EF or SV/ESV for the evaluation of RV-arterial coupling (see Chap. 10).

### *Pressure Measurements*

Another simplified approach for the measurement of RV-arterial coupling introduced by Trip relies on a  $P_{\max}$  calculated from a RV pressure curve, which is easily obtained during a right heart catheterization, mean Ppa (mPpa) taken as a surrogate

of ESP, and RV volume measurements by MRI [63]. The authors calculated  $E_{\max}$  as  $(P_{\max} - \text{mPpa})/(\text{EDV} - \text{ESV})$  and  $E_{\max}$  assuming  $V_0 = 0$  as  $\text{mPpa}/\text{ESV}$ .  $V_0$  is the extrapolated volume intercept of the linear best fit of a multipoint maximum elastance pressure–volume relationship. The results showed that  $\text{mPpa}/\text{ESV}$  was lower than  $(P_{\max} - \text{mPpa})/\text{SV}$ , on average about half the value, while  $V_0$  ranged from  $-8$  to  $171$  mL and was correlated to EDV and ESV. From this the authors concluded that  $V_0$  is dependent on RV dilatation, and thus the estimated  $E_{\max}$  more preload-dependent than previously assumed. This is possible, although an alternative explanation is in the uncertainties of extrapolations from linear fits of relationships that have been demonstrated to be curvilinear [64]. End-systolic elastance or  $E_{\max}$  is best determined by interpolation of pressure–volume coordinates [64], with tightening by a correction for EDV [10, 22]. Further uncertainty is related to the use of an  $\text{mPpa}/\text{SV}$  ratio or slope of  $(P_{\max} - \text{mPpa})/\text{SV}$  as a surrogate of  $E_{\max}$  determination from single or (better) multiple beat pressure–volume relationships.

## Alternative Methods to Evaluate RV-Arterial Coupling

### *The Pump Function Graph*

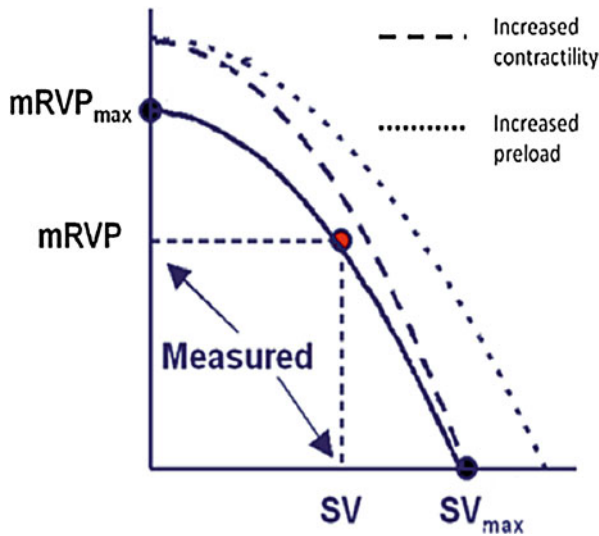
The coupling of RV function to the pulmonary circulation can also be described by pump function curves relating mean the RV pressure to SV [65]. A pump function graph is built from measurements of the mean RV pressure and SV, a calculated  $P_{\max}$  at zero SV and a parabolic extrapolation to a zero pressure SV (Fig. 2.4). 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.

The pump function graph helps to understand that at a high PVR, a fall in pressure markedly increases SV while at a low PVR, the pressure is more affected than SV [32].

The pump function graph has been used to demonstrate a greater degree of RV failure at any given level of  $\text{mPpa}$  in SSc-PAH as compared to idiopathic PAH [66], this has subsequently been confirmed by  $E_{\max}/E_a$  determinations [22]. The limitations of the pump function graph are its sensitivity to changes in preload and, as already mentioned, to the use of the mean RV or mean pulmonary artery pressure as surrogates for the maximum elastance RV pressure.

### *The Contractile Reserve*

Systolic function adaptation to afterload can also be tested dynamically to determine a contractile reserve, or the capacity to increase contractility at a given level of loading. Contractile or ventricular reserve is determined using exercise or



**Fig. 2.4** Pump function curve defined by mean right ventricular pressure (mRVP) as a function of stroke volume (SV). The maximum mRVP ( $mRVP_{max}$ ) at  $SV=0$  is calculated from a maximum RVP determination (see Fig. 2.1). 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

pharmacological stress tests (typically an infusion of dobutamine); the contractile reserve has been shown to be a strong predictor of outcome in heart failure [67]. The evaluation of the RV contractile reserve has not yet been reported in patients with pulmonary hypertension. In rats after PAB,  $E_{max}$  was increased to the same extent in response to 2.5  $\mu\text{g/kg/min}$  of dobutamine in controls, suggesting that systolic function is preserved in this pulmonary hypertension model [28].

A simple noninvasive approach was recently introduced by Grünig [68]. In that study, Doppler echocardiography was used to measure RV systolic pressure from the maximum velocity of tricuspid regurgitation at rest and at exercise in 124 patients with either PAH or chronic thrombo-embolic pulmonary hypertension (CTEPH). An exercise-induced increase of the RVSP by  $>30$  mmHg was a strong predictor of exercise capacity and survival. Further studies will explore improved indices with incorporation of volume measurements and ESP determinations, as this is now becoming possible using noninvasive bedside methodology.

## Surrogate Measurements of RV-Arterial Coupling

Right ventricular systolic function can be estimated by a series of invasive and noninvasive measurements, which are available in daily clinical practice.

Right heart catheterization allows for measurements of Ppa, right atrial pressure and cardiac output (Fick or thermodilution) and thus calculations of RV function curves such as cardiac output, SV or stroke work (SW,  $\text{mean Ppa} \times \text{SV}$ ) as a function of right atrial pressure. Stroke work calculated as  $\text{mPpa} \times \text{SV}$  ignores the pulsatile component of work. It has been recently estimated that the pulsatile component of SW amounts to 23 % of total work independently of type and severity of pulmonary hypertension, so that total  $\text{SW} = 1.3 \text{mPpa} \times \text{SV}$  [69]. This fixed relationship is explained by the fact that  $\text{PVR} \times \text{pulmonary arterial compliance (Ca)}$ , or RC-time of the pulmonary circulation, remains approximately at the same value in normal subjects and in patients with pulmonary hypertension [70]. The RC-time is actually decreased in left heart failure [71] and in patients with proximal operable CTEPH [72], but increased in purely distal pulmonary micro-vascular obstruction [73]. However, the deviations are relatively mild. The pulsatile component of RVSW varies on average from 20 to 26 %, with extremes of from 15 to 30 %. Therefore, total work is estimated to vary between 1.2 and 1.4 times steady-flow work. The near-constancy of the RC-time thus implies a relatively stable prediction of total RVSW. It remains that right atrial pressure is an imperfect surrogate of preload, which is measured in the intact heart by the EDV.

Right ventricular contractility can be measured by preload recruitable SW (PRSW) defined by SW–EDV relationships at variable venous return [74]. The slope of PRSW has been shown to be reproducible and sensitive to changes in contractile state. However, whether PRSW is useful to evaluate RV-arterial coupling has not been clearly shown. The measurement requires invasive volume and high-fidelity pressure measurements with a manipulation of venous return, and is thus difficult to implement at the bedside.

Measurements of RV volumes, ejection fraction, and SV/ESV ratios are possible by imaging techniques such as MRI or three-dimensional echocardiography. The limitation of imaging is the absence of direct pressure measurements. It has recently been proposed to use noninvasive Doppler echocardiographic measurements of a tricuspid annular plane excursion (TAPSE) as a measure of RV systolic function and of the maximum velocity of tricuspid regurgitation-derived systolic Ppa (SPpa) as a measure of afterload, and derive a TAPSE/SPpa ratio as an estimation of RV-arterial coupling [75]. This indirect index of RV-arterial coupling may be useful as it has been shown to predict survival in patients with left heart failure and decreased or preserved ejection fraction.

A series of imaging-derived indices of RV systolic function, such as MRI-determined EF or Doppler echocardiographic measurements of fractional area change measured in the four-chamber view (a surrogate of EF), TAPSE, tissue Doppler imaging (TDI) of the tricuspid annulus systolic velocity S wave and isovolumic acceleration (IVA) or maximum velocity (IVV), strain or strain rate have been shown to be related to functional state and prognosis in severe pulmonary hypertension [59, 60]. Isovolumic phase indices such as the IVA or IVV are probably less preload-dependent, and as such the closest estimates of  $E_{\text{max}}$  measurements [76, 77].

## Diastolic Function

So far we have focused on RV systolic function and RV-arterial coupling as the essential biomechanical mechanism of ventricular function adaptation to increased afterload. However, a Starling heterometric adaptation may occur at any stages the disease progresses to, depending on the rate of progression, degree of inflammatory component of the pulmonary hypertension, and systemic conditions which affect 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. It is curvilinear thus impossible to express as a single number. Several formulas have been proposed [32]. Most recently Rain reported on 21 patients with PAH in whom RV diastolic stiffness was estimated by fitting a nonlinear exponential curve through the diastolic pressure–volume relationships, with the formula  $P = \alpha(e^{\beta V} - 1)$ , where  $\alpha$  is a curve fitting constant and  $\beta$  a diastolic stiffness constant [78]. In that study, the diastolic stiffness constant  $\beta$  was closely associated with disease severity.

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 TDI E'/A' waves, increased right atrial or RV surface areas on apical four-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 isovolumetric time intervals to ventricular ejection time [59, 60].

## Ventricular Interaction

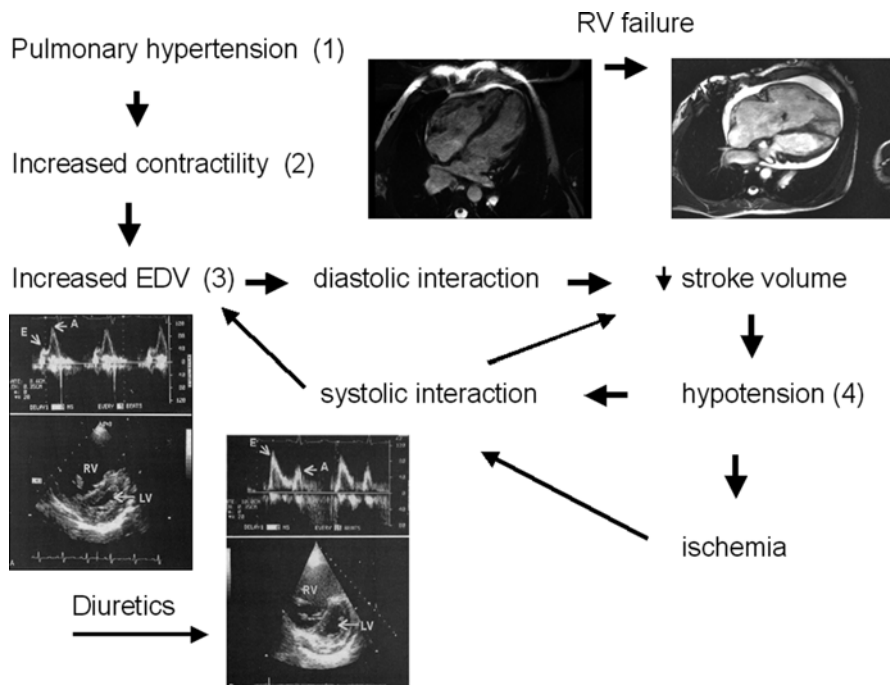
Right ventricular function must be put into the context of its direct and indirect interactions with LV function. Direct interaction, or ventricular interdependence, is defined by the forces that are transmitted from one ventricle to the other ventricle through the myocardium and pericardium, independent of neural, humoral, or circulatory effects [79]. Diastolic ventricular interaction refers to the competition for space within the indistensible pericardium when 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 increased in proportion to a decreased RV ejection fraction [80]. Systolic interaction refers to positive interaction between RV and LV contractions. It can be shown experimentally that aortic constriction, and enhanced LV contraction, markedly improves RV function in animals with PAB [81]. Similarly, in electrically isolated ventricular preparations in the otherwise intact dog heart, LV contraction contributes a significant amount (~30 %) to both RV contraction and pulmonary flow [82]. 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 a cause of RV ischemia and decreased contractility. An additional cause of negative ventricular interaction disclosed by imaging studies is asynchrony, which has been shown to develop in parallel to increased pulmonary artery pressures and contributes to altered RV systolic function and LV under-filling [83].

## A Global View on RV Failure

An integrated view of the pathophysiology of RV failure is depicted in Fig. 2.5.

Pulmonary hypertension increases RV afterload requiring a homeometric adaptation. When this adaptation fails, the RV enlarges, decreasing LV filling because of competition for space within the pericardium. This decreases stroke volume and



**Fig. 2.5** Pathophysiology of right ventricular (RV) failure. The magnetic resonance images show the evolution from homeometric to heterometric adaptation of RV function in advanced pulmonary hypertension. The echocardiographic images show an improved ventricular diastolic interaction with reversal of the transmittal flow E and A waves, indicating improved left ventricular diastolic function with diuretic therapy. Numbers indicate the targets of therapeutic interventions: (1) pulmonary vascular resistance, (2) contractility, (3) diastolic interaction, and (4) systolic interaction. *EDV* end-diastolic volume



blood pressure with a negative systolic interaction as a cause of further RV-arterial uncoupling. This may be aggravated by RV ischemia due to a decreased coronary perfusion pressure (gradient between diastolic blood pressure and right atrial pressure). Understanding these interactions may allow one to identify specific targets of therapeutic interventions.

## Perspective

In 1989 John (Jack) Reeves called a greater investment in research to explore the pathophysiology and pathobiology of RV failure in pulmonary hypertension. It was already known at his time that pulmonary hypertension is a common complication of cardiac and pulmonary diseases, and that symptoms, exercise capacity and outcome in the patients are considerably influenced by RV function. Yet, he deplored that the RV was getting insufficient attention in clinical and basic research pulmonary circulation programs [84]. Since then we have made progress, but not quite enough. There is much more work to do and more to be learned [46, 85].

## *What Are the Priorities?*

The first is to improve the translation to the intact heart of newly discovered molecular signaling pathways related to maintained or failing RV function in various models of pulmonary hypertension. This will require more measurements of systolic and diastolic function using pressure–volume relationships. As reviewed in the present chapter, the knowledge is available and should be more extensively applied.

The next priority is to improve RV function phenotyping in clinical research. Invasiveness of measurements is an obstacle to much needed faster progress. Experts in imaging and clinical physiologists are therefore urged to collaborate in the development of validated noninvasive methods of evaluation. This will be indispensable to improved definition of the biological determinants of RV adaptation to various pulmonary hypertensive states, and targeted therapeutic innovation.

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