

The left heart can only be as good as the right heart: determinants of function and dysfunction of the right ventricle

Sheldon Magder

Much more attention is paid in cardiovascular physiology to the left side of the heart than to the right. Intuitively, this seems to make sense. The left ventricle provides the force that creates arterial pressure and seems to be responsible for generating the flow of blood around the body. It is the final chamber before cardiac ejection into the systemic circulation. Also, acquired cardiac abnormalities are much more evident on the left side of the heart. Furthermore, the most common cardiovascular disease, coronary artery occlusive disease, is primarily associated with left ventricular dysfunction, as are many diagnostic tests. For example, the electrocardiogram, echocardiogram, and ventricular angiogram give excellent information about the left ventricle, but are not as useful for assessing right ventricular function. However, it is worth noting that cardiac output and stroke volume are assessed equally well in both ventricles as, in the steady state, they are essentially equal, except for contributions from the bronchial circulation and Thebesian veins. Aortic and mitral valvular diseases also account for the major burden of primary cardiac valvular disease, and these valves are again easier to assess than the right-sided valves.

Acute deterioration of left heart function without a decrease in right heart function rapidly results in pulmonary oedema and a dramatic clinical presentation that makes the left heart dysfunction obvious. On the other hand, acute right ventricular dysfunction presents with a more subtle low output state and, only when it is chronic, or in response to over-zealous fluid therapy, does it result in significant peripheral oedema. Although the actual prevalence of right heart dysfunction is not well studied, this is a common problem in intensive care units and seems to be more of a clinical problem than left heart failure. Five areas where right ventricular dysfunction seems to play a major role are: infarction of the right heart; cardiac surgery;¹ sepsis;² pulmonary embolic disease and pulmonary hypertension;³ and in patients with increased alveolar pressures.⁴

Is the right heart necessary?

In a classic and often quoted experiment, Starr et al cauterised the free wall of the right ventricle of dogs and found this did not affect cardiac function. However, this conclusion was based solely on a lack of change in central

ABSTRACT

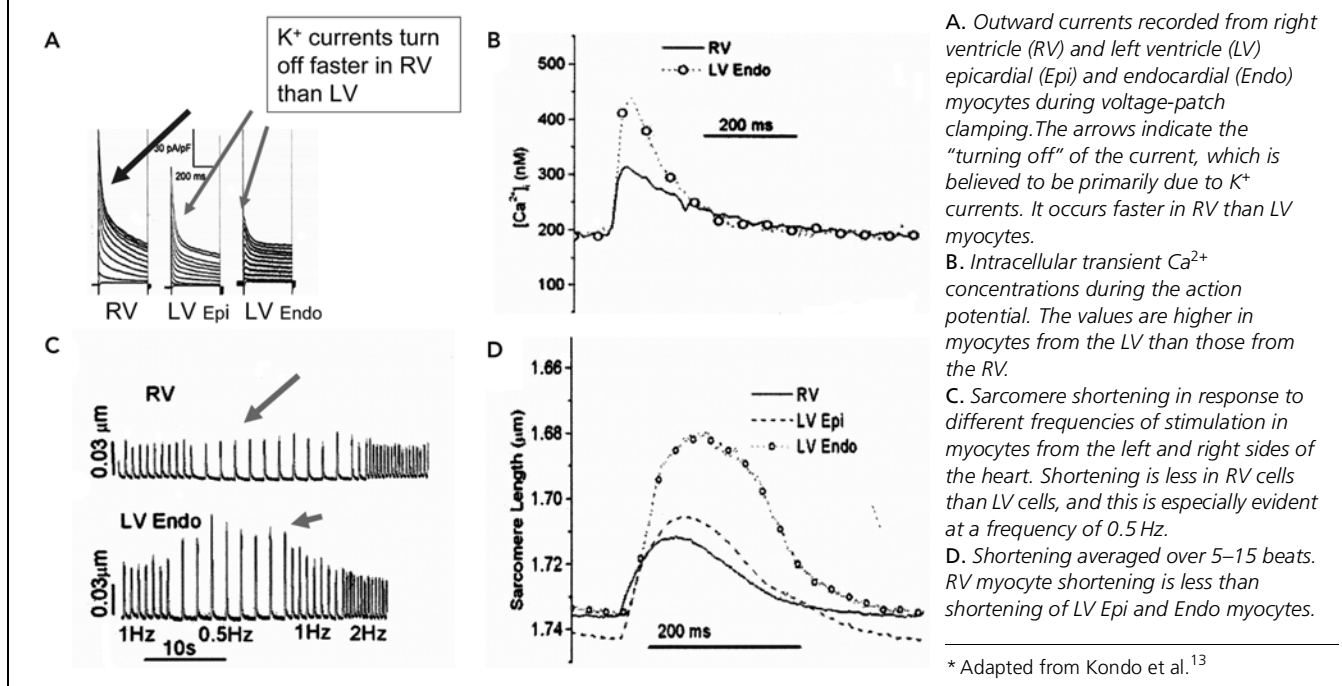
Discussions of cardiac physiology and pathophysiology most often emphasise the function of the left heart. However, right heart dysfunction plays an important role in critically ill patients and is often not recognised. This is probably because the role of the right ventricle is for generating flow more than pressure, and flow is not easy to evaluate. Of importance, when right ventricular function limits cardiac output, assessing left ventricular function gives little indication of overall cardiac performance. It has recently become evident that the right ventricle also has different genetic origins and characteristics from the left ventricle. The right and left ventricles interact through series effects, diastolic interactions and systolic interactions. The mechanisms of these, and their physiological and pathological significance are discussed.

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venous pressure,⁵ and cardiac output was not measured. What is often not mentioned is that when the researchers attempted to create a chronic preparation, "several died", another dog lasted 36 hours, and only one was a long-term survivor. Most importantly, their observations failed to address what happens when the right ventricle is damaged, and cardiac demands are increased. Furthermore, in their study, the pulmonary artery pressure was likely not elevated. When other investigators added increased pulmonary pressure to right ventricular free-wall damage, the role of the right ventricular free wall became more evident.⁶

Another argument for the lack of importance of the right ventricle is based on experience with children with a hypoplastic right ventricle or tricuspid valve atresia. These conditions have been treated surgically by the Fontan repair, in which the vena cavae are directly connected to the pulmonary artery, and there is no right ventricle. These children have normal resting cardiac output even though they do not have a functioning right ventricle, which would seem to indicate that the right ventricle is superfluous. In one series of patients with a Fontan repair, 45% reported class I symptoms, and another 47%, class II symptoms.⁷ However,

Figure 1. Electrophysiological differences between trabeculae from the right and left ventricles of mice*



when they underwent exercise testing, their aerobic capacity was only one third that of normal individuals. These observations give insight into the different roles of the right ventricle and left heart, which will be discussed next.

In my opinion, the importance of right heart function is underestimated because its primary role, in contrast to that of the left heart, is to generate flow, whereas the primary role of the left ventricle is to generate a high pressure as well as flow. Importantly, pressure loads are much easier to study than flow. The ability of the right heart to function as a flow generator is evident when one considers what happens during exercise. In a man with good aerobic capacity, cardiac output can increase more than fivefold above resting levels, to more than 25 L/min, while, except for a small increase in filling pressures at the start of exercise,⁸ right atrial pressure remains constant.⁹ This means that right heart function has to increase in proportion to the increase in flow because, if it had not kept up with the return of blood, right atrial pressure would have increased. Thus, the right heart actually has amazing pumping capacity. It is worth considering the quantitative implications of a mismatch between right ventricular function and the return of blood to the heart. At peak exercise, cardiac output of 25 L/min, and heart rate of 180 beats/min (thus 3 beats/s), over 800 mL/s return to the heart. As about half the cardiac cycle is systole, blood flow returns to the heart at a transient flow rate of about 1.5 L/s, which is more than five times the

normal end-diastolic volume. Interestingly, the pressures generated by both ventricles change very little during exercise. The pulmonary artery pressure does not increase much because pulmonary resistance is so low to begin with, and is likely reduced further by recruitment and distension of pulmonary vessels. Although the left ventricle pumps this same flow against a pressure that is at least five times greater than pulmonary pressure, the systemic arterial pressure increases by only a small amount in healthy individuals. This is because peripheral resistance decreases with the redistribution of flow to the working muscles. This means that the pressure load of the left ventricle also remains relatively stable during exercise.

A key clinical significance of these points is that the right ventricle is not designed for increases in pressure load, and an increase in right ventricular pressure causes major changes in right ventricular performance. This may not be evident when the demand for cardiac output is low, as was the case in Starr et al’s experiment,⁵ but can become very important when cardiac output needs to increase, as occurs normally during exercise, but also in the hyperdynamic state that accompanies the systemic inflammatory states.

Differences between the right and left ventricles

Consistent with their different functions, the right and left ventricles are structurally very different. The left ventricle

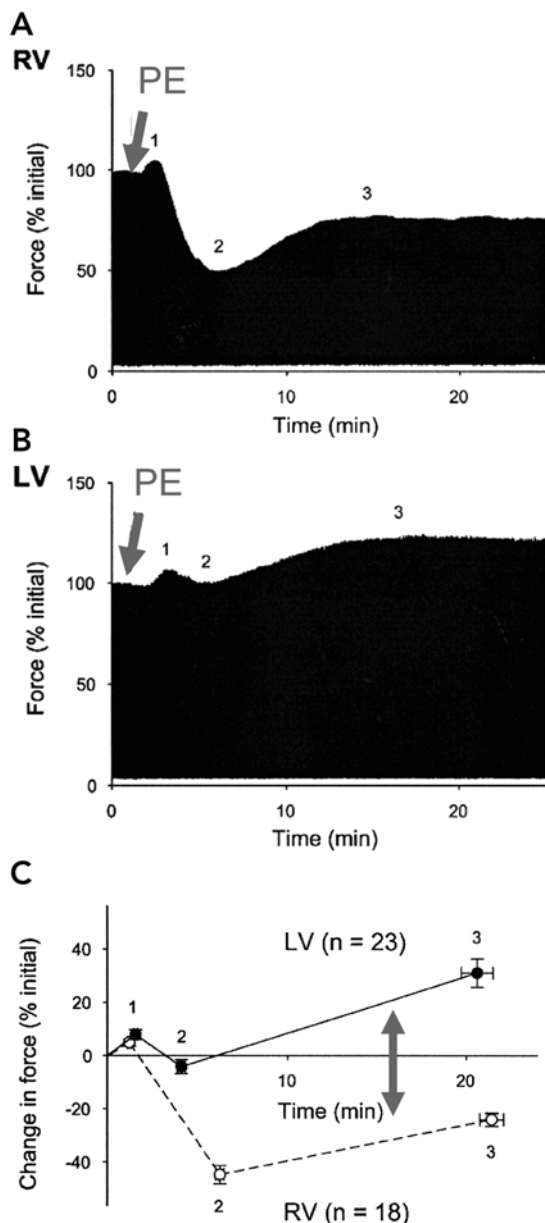
has a much larger muscle mass than the right heart, and a relatively circular structure, which evenly distributes the stress.³ In contrast, the right ventricle has a shape more like a bellows, which makes it an efficient flow generator as long as ejection pressure is not high.¹⁰

It has recently become evident that the right and left ventricles have different embryological origins. The left ventricle arises from the “anterior heart field”, and the right ventricle from another field.^{11,12} It has also been shown that right ventricular development is regulated by the gene *Hand2*, whereas left ventricular development is controlled by *Hand1*, with *Hand2* not found in that ventricle. It seems that *Hand2* is actually the more primitive gene, found in reptiles that have only a single ventricle. Mice that lack *Hand2* do not develop a right ventricle, and this cannot be rescued by overexpressing *Hand1*.

These genetic differences are associated with electrophysiological, contractile and pharmacological differences in isolated myocytes. Right ventricular myocytes have a more rapid early phase of repolarisation that is thought to be related to differences in the density of potassium channels¹³ (Figure 1). This is associated with less influx of calcium and less shortening of sarcomeres for a given stimulus than in myocytes isolated from the left heart. In contrast to left ventricular myocytes, right ventricular myocytes do not show a change in shortening with changes in frequency (Figure 1).

A marked difference in the response to α_1 -adrenergic stimuli has also been noted. Phenylephrine produces a moderate increase in the force generated by trabeculae isolated from the left ventricle, whereas it produces a marked fall in force in trabeculae from the right ventricle¹⁴ (Figure 2).

Figure 2. Force generation by trabeculae from right and left ventricles of mice treated with phenylephrine



Phenylephrine (PE) decreased the force of trabeculae from the right ventricle (RV) (A), but increased the force of trabeculae from the left ventricle (LV) (B). C shows summary data. (Adapted from Wang et al.¹⁴)

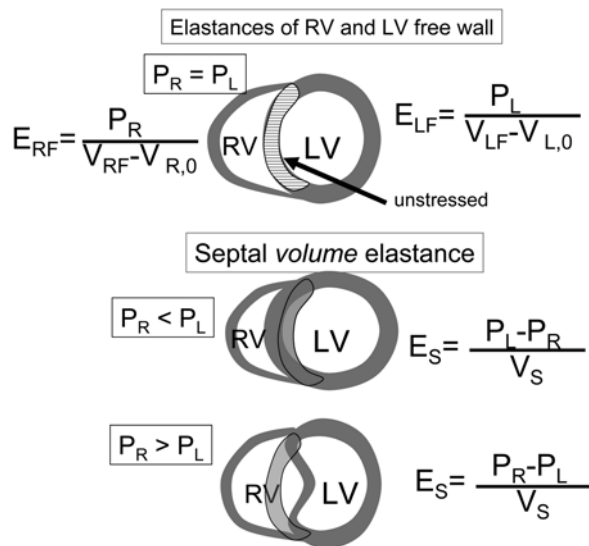
Series effect

A seemingly obvious, but frequently ignored, point is that the right and left hearts are in series. Thus, except for a few beats, the left heart can only pump out what the right heart gives it. This means that, once the right heart is functioning on the plateau of the cardiac function curve, left ventricular output is also limited, and assessment of left heart cardiac function curves or stroke-work curves gives little insight into the regulation of cardiac output, as the flow is determined by upstream factors. Right heart dysfunction is often described as decreasing left ventricular preload, but conceptually I prefer to think of this as the right heart not providing the flow, as this emphasises that it is not a preload problem, but an actual absence of delivered volume.^{15,16} I will come back to this issue when discussing ventricular interactions.

Determinants of cardiac output

As reviewed elsewhere, cardiac output is determined by the interaction of cardiac function and venous-return function,¹⁷ and these functions interact at the right atrial pressure. In this model, the primary energy for the flow of blood around the body is the mean circulatory filling pressure (MCFP), which is

Figure 3. Three-compartment analysis of the elastance of the heart



The top panel shows the condition in which pressures in the right ventricle (RV) and left ventricle (LV) (P_R and P_L , respectively) are equal. This allows measurement of RV and LV free wall elastance (E_{RF} and E_{LF} , respectively) with knowledge of the stressed volume of the RV and LV (V_{RF} and V_{LF} , respectively) and the unstressed volume of each chamber ($V_{R,0}$ and $V_{L,0}$, respectively).

The middle and bottom panels show the calculation of septal elastance (E_S) based on the "volume" of the septal curvature (V_S) and the pressure in the RV and LV (P_R and P_L , respectively). The unstressed volume of the septum (shaded area) was obtained from the septal curvature with $P_R = P_L$ (top panel).

the elastic recoil produced by the volume filling the vasculature.^{18,19} The role of the heart in generating blood flow is to lower right atrial pressure relative to MCFP, and thus to allow volume to return to the heart. The heart then provides a restorative force, by returning the blood volume to the compliant region of the circulation and thus maintaining the elastic recoil pressure that determines flow.¹⁸ The normal pressure gradient for venous return is of the order of 4 mmHg, and, if there were no right heart, an increase in blood flow could only come from a proportional increase in MCFP and/or a decrease in venous resistance.

Heart rate has an interesting role in this process. If heart rate were not to increase, then the heart would have to be very large, or diastolic pressure markedly elevated, to produce the marked increase in stroke volume needed to achieve the maximum cardiac outputs that occur in a normal adult.

The heart is surrounded by pleural pressure, so that the pressures in the heart change relative to the systemic circulation during the ventilatory cycle. Because the normal gradient for venous return is only about 4 mmHg, swings in pleural pressure during the ventilatory cycle can produce

large changes in the gradient for venous return.²⁰ A fall in pleural pressure increases flow, as long as the pressure in the right heart is greater than pleural and atmospheric pressures. As well, the heart must be functioning on the ascending part of the Starling curve as, when it is functioning on the plateau part of the curve, a fall in pleural pressure does not increase flow.²¹ A rise in pleural pressure above atmospheric pressure decreases the gradient.²²

Ventricular interdependence

Three types of ventricular interdependence can be considered: the series effect; diastolic interactions; and systolic interactions.²³ The most dominant is the series effect because, as already discussed, right and left heart outputs have to be essentially equal. Furthermore, most often the right ventricle is the dominant partner in this relationship, as changes in left heart function can only alter right heart output through the series effect by altering pulmonary artery pressure, which then alters right ventricular loading conditions, an effect "buffered" by the intervening pulmonary vascular compliance. However, as discussed below, raising pulmonary artery pressure can become a factor when right ventricular output is limited.

The large changes in ventricular filling associated with the series effect confound efforts to identify and quantify the other aspects of ventricular interdependence and limit the interpretation of studies in intact animals.^{24,25} This also limits the evidence obtainable from angiographic and echocardiographic studies of humans with various abnormalities,²³ because it makes the initial conditions so variable. To control for this problem, investigators have used preparations with fluid-filled balloons in isolated animal ventricles to try to quantify diastolic and ventricular interactions.²⁶ However, these studies require removal of the pericardium, which plays an important role in ventricular interaction in the intact organism through the series effect.²⁷ Ventilatory cycle effects are also removed. Thus, experimental examination of ventricular interaction is limited, somewhat as the Heisenberg Uncertainty Principle limits atomic particle analysis — attempts to measure interactions change aspects of the interactions, so that the contributions of individual parts cannot be quantified. However, some basic principles need to be appreciated, as discussed next.

The basic mechanism by which the heart ejects blood and creates pressure is through a change in elastance of cardiac muscle during the cardiac cycle. This concept has been called time-varying elastance by Sagawa and Suga and colleagues.²⁸⁻³⁰ Elastance is the inverse of compliance and determines the pressure for any given volume in an elastic container. The slope of the maximum pressure-volume relationship is a good measure of the contractile function of the heart. Maughan and coworkers working with Sagawa

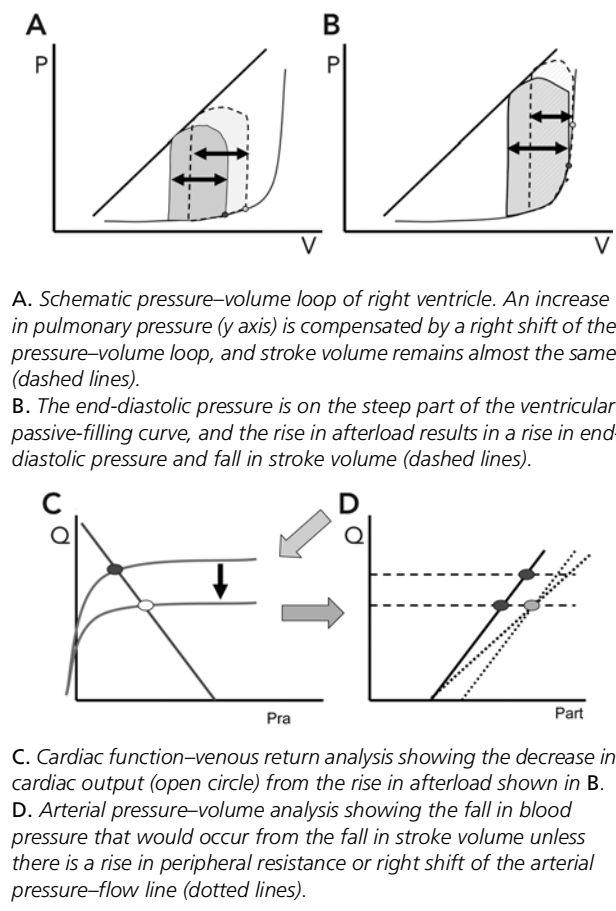
applied these concepts to the functioning of the right heart, and its interaction with the left heart in systole and diastole.^{26,31} They developed a three-compartment model for understanding ventricular interactions (Figure 3). The model incorporates the elastance of the right and left ventricular free walls and of the septum, which can then be used to express the change in pressure in one ventricle chamber based on the volume or pressure in the other chamber.²⁶ Of note, the effective volume septal elastance used in their analysis is not to be equated with a muscle property, and cannot be simply related to the shape of the septum on echocardiography.

The model and experimental results indicate that the pressure in one ventricle augments the pressure in diastole and systole of the other ventricle. This effect is actually greater per unit increase in pressure on the right side. However, because the generated pressures are so much larger in the left heart, the overall effect of the force generated by the left ventricle is greater than that of the right. The model also predicts that when septal elastance is decreased, as would occur if the septum is infarcted, there is a greater transmission of pressure from one ventricle to the other. The effects of volume changes are more complex than the effects of pressure changes, as they are also affected by the elastance of the ventricular free walls. Thus, if the elastance of the ventricular walls increases, as could occur when cardiac filling is maximal, or there is increased compression of the heart by the lungs, the transmission of pressure from one side of the heart to the other as a consequence of volume change is increased. This is true for systole as well as diastole.

An interesting example of the potential importance of ventricular interaction was demonstrated by Atherton et al.³² They showed that applying lower-body negative pressure to normal individuals resulted in a decrease in left ventricular volume but, when they did the same to patients with heart failure, there was an increase in left ventricular volume. The explanation was that decompression of the right ventricle by pooling of blood in the lower extremities allowed better left ventricular filling.

As already noted, the right ventricle is largely a volume generator and is much less tolerant of increases in afterload than the left ventricle. This should be expected given its smaller muscle mass and thinner walls, which result in less tension for any force. There is also an important consequence of the series effect on the load tolerance of the right ventricle. When the load on the right heart is too great, its output decreases,³³ probably because of inadequate blood flow for tissue needs and myocardial ischaemia.³⁴ This induces a vicious cycle. The decrease in cardiac output results in a decrease in arterial pressure when there is insufficient compensation in the arterial systemic resistance. The decrease in arterial pressure results in a decrease in perfusion of the right heart, which results in a further loss

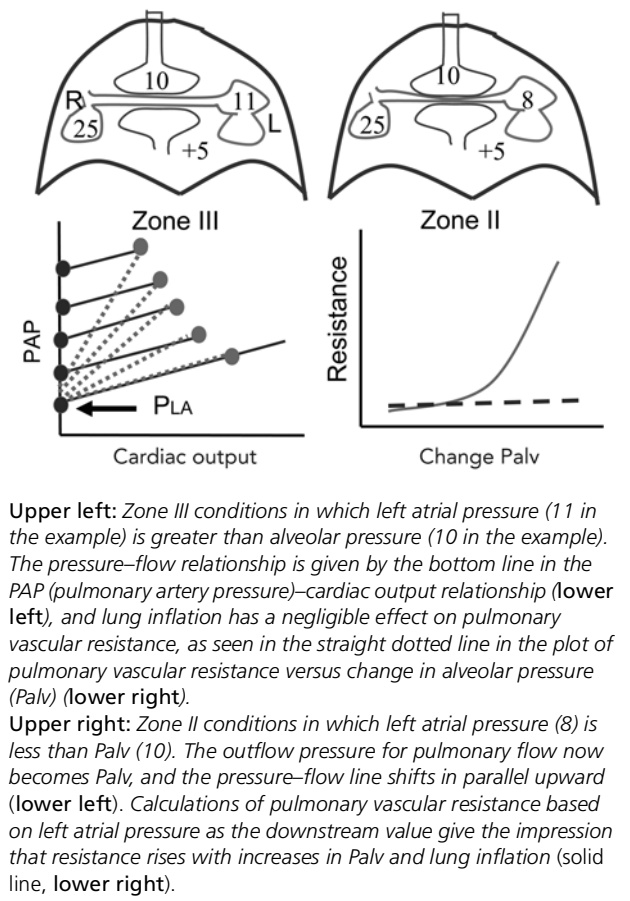
Figure 4. Schema of effects of afterload on right ventricle output



of right ventricular function, further decreases in cardiac output and, finally, death. As would be expected, increasing arterial pressure increases the load tolerance of the right ventricle.³³⁻³⁵ However, this is not simply due to preservation of coronary flow. It is likely that the increased left ventricular force generation required for the increase in arterial pressure results in increased force of septal contraction, which increases force production and emptying of the right ventricle through ventricular interdependence.^{25,36,37}

When ventricular afterload is increased, there is a consequent increase in ventricular end-diastolic volume due to the decrease in ejected volume (Figure 4). The increase in end-diastolic volume partially compensates for the increase in afterload on the next beat. However, when the increase in right ventricular end-diastolic volume is large enough, the volume limit of ventricular filling is reached. This is normally due to pericardial constraint but can also be produced by the cardiac cytoskeleton. When filling is limited, a further increase in afterload results in a marked rise in end-diastolic pressure. The marked rise in end-diastolic pressure for a small change in volume indicates the heart is constrained, and the

Figure 5. Analysis of pulmonary flow in Zone III and Zone II conditions (waterfall effect)



elastance of the free wall is high. From the discussion above, this will result in an increase in transmission of right ventricular end-diastolic pressure to the left heart. The rise in left-sided pressures will tend to decrease pulmonary emptying and thus increase pulmonary pressures, which will consequently further increase the load on the right ventricle. Through this process, right-sided preload (right ventricular end-diastolic pressure) becomes right-sided afterload (rise in pulmonary artery pressure), and can further contribute to the downward spiral of right ventricular function.

Lung inflation can result in some distortion of pulmonary vessels and increase pulmonary vascular resistance but the effect is small. However, the much more important effect of lung inflation on the right heart with positive pressure ventilation is the production of vascular waterfalls or West Zone II in regions of the lung where alveolar pressure rises above pulmonary venous pressure; in that situation, alveolar pressure becomes the outflow pressure for the pulmonary vasculature^{4,38-40} (Figure 5). For blood flow to remain constant, the increase in alveolar pressure in areas under Zone II conditions requires a direct increase in pulmonary artery

pressure. Without a change in the ejection force of the right heart, there will be a marked fall in pulmonary flow.^{4,41} The key variable is transpulmonary pressure, which can easily be roughly estimated in the normal lung by comparing tracheal pressure to pleural pressure.⁴¹ However, it is much more complicated in diseased lungs. Consider the extreme case of a major tracheal obstruction distal to the tracheal measurement: the inspiratory pressure gradient would be high, but alveolar pressure would not be elevated, and therefore transpulmonary pressure would be unchanged. Furthermore, an atelectatic alveolus may have a high internal pressure, but, if it cannot be distended, it will not transmit the pressure to the adjacent pulmonary vessels. Some vessels are probably even splinted open, as must be the case to produce shunts. For that reason, I would not use airway plateau pressure to indicate the load on the right heart, as some have suggested.⁴²

Clinical implications

It is one thing to understand the pathological processes behind right ventricular dysfunction, but it is another to come up with therapeutic solutions. An even greater problem is how to define right ventricular dysfunction. Most often we consider right ventricular failure as the inability to generate a pressure, but, as already discussed, the primary role of the right ventricle is to generate flow, and this may not be evident until there is a demand for increased flow, as in sepsis. As a starting point, right ventricular dysfunction can be diagnosed when there is:

- a high right-sided filling pressure, which I would define as >12 mmHg (based on a reference level 5 cm below the sternal angle);⁴³ and
- a low cardiac index, which I would define as <2.2 L/min/m².

The right-sided filling pressures should refer to transmural pressure, so that it is important to note whether there is a high positive end-expiratory pressure (PEEP) or high abdominal pressure, which would mean that the observed pressure is not the transmural pressure. I base this recommendation on the argument that a cardiac index less than 2.2 L/min/m² is associated with poor outcome. Central venous pressure (CVP) values above this level are much more likely to produce peripheral oedema and are outside the normal range. In my experience, patients with compensated pulmonary hypertension usually have CVP in the normal range, and normal or low-normal cardiac outputs. The status of the right heart can be operationally tested by giving a fluid challenge and observing whether there is a rise in cardiac output. However, limits to right heart filling can be found in everyone, so that CVP by itself should not be used to define right ventricular dysfunction, but rather a suboptimal value of cardiac index should be included, such as the suggested 2.2 L/min/m². Generally, the ratio of right atrial pressure to CVP (Pra/CVP) should be higher than pulmonary artery occlusion pressure, but not always, as at higher

pressures they tend to equalise, and there could also be concomitant left ventricular dysfunction. The actual transmission of pressure between the ventricles, as discussed above, depends on the status of the ventricular free walls and septum. The interaction can be complicated. For example, cardiac output decreases in left ventricular failure because the failure of left ventricular output results in a rise in pulmonary artery pressures, which increases the load on the right ventricle, eventually causing right ventricular failure.

Some have used echocardiographic measurements to define right ventricular dysfunction, and require the area of the right ventricle on oesophageal echocardiography to be greater than the area of the left ventricle.^{42,44} This identifies right-sided response to load, but does not mean the right heart is failing; to answer that question requires measurements of pressure and flow. For example, an enlarged right heart with a right atrial pressure of 4 mmHg and normal cardiac output is very different from one with a right atrial pressure of 20 mmHg and a low cardiac output. Right ventricular volumes can also be difficult to assess.⁴⁵ A particularly difficult issue can arise in sepsis, when a patient may have a normal to above-normal cardiac index (eg, 3.5 L/min/m²), but also be receiving high doses of vasopressors and have an elevated right-sided filling pressure of 15 mmHg. Clearly, this right heart is functioning, but it is not generating sufficient flow to match the decrease in resistance and peripheral needs.

Once right ventricular dysfunction develops from excessive loading of the ventricle, the evidence suggests that recovery is slow.⁴⁶ Thus, it is important to try to avoid this dysfunction developing. An important principle for managing right ventricular dysfunction should be to avoid overloading the right ventricle in diastole by pushing fluids when the heart is no longer responsive to these.⁴⁷ I argue that the optimal volume for cardiac preload should always be based on the Pra/CVP value rather than pulmonary occlusion pressure, as the right atrial pressure indicates how the heart is interacting with the return of blood.⁴⁸ Furthermore, Pra/CVP should be used in conjunction with a measure of cardiac output, so that the response of the heart to changes in Pra/CVP can be assessed.⁴⁹

A second factor to avoid is excessive systolic loading of the right ventricle. This includes avoiding ventilatory strategies that load the right heart,⁴ as well as treating elevated pulmonary pressures. Treatment of pulmonary hypertension should include correcting increased left atrial pressure caused by left ventricular dysfunction, as well as decreasing pulmonary vascular resistance pharmacologically.

As well established more than 50 years ago by Guyton et al³³ and Salisbury,⁵⁰ a fundamental principle for the management of right ventricular dysfunction is the maintenance of systemic arterial pressures. This is crucial for the maintenance of coronary perfusion and, as also

discussed above, for right heart force generation through the increased septal contraction associated with the more forceful left ventricular contraction. This means that drugs that reduce systemic pressures, such as dobutamine and milrinone, must be used very cautiously in these patients, and, when they are used, a vasoconstrictor, such as norepinephrine (noradrenaline), should be ready for rapid use if necessary. It also raises questions about the appropriateness of use of intra-aortic balloon pumps in these patients; although augmenting diastolic pressure aids coronary perfusion of the right heart, the decrease in left ventricular afterload might decrease the right ventricular force of contraction. A key factor is probably the degree of left ventricular dysfunction as, if present, the afterload reduction by the balloon will result in decreased pulmonary congestion and thus decrease the load on the right ventricle, which means that the right ventricle will require less force generation.

The move to smaller tidal volumes following the ARDs Network trial⁵¹ has likely helped reduce the load on the right ventricle. It has been argued that high PEEP may be harmful,⁴ but this is not borne out by the trials.⁵¹ This is likely because high levels of PEEP are generally used when the abnormality is severe, so that simple rules of transmission of airway pressure to the alveolae do not apply.

Manipulation of right ventricular afterload is an important part of managing right ventricular failure. For this purpose, the phosphodiesterase inhibitor, milrinone, can be very useful, albeit potentially dangerous, because of its potential to decrease systemic arterial pressure. Milrinone provides a potent increase in cardiac contractility and also decreases pulmonary vascular resistance. Especially after cardiac surgery, inhaled nitric oxide (NO) can be a very useful agent to allow time for the right ventricle to recover and adapt. Orally acting agents that increase NO, such as sildenafil, have been shown to be of some help for chronic pulmonary hypertension,⁵² but they do not have as favourable an effect on gas exchange and can lower systemic pressures. Right ventricular assist devices can also be used as temporising tools.

Summary

Right heart function is essential for the wide range of demands on cardiac output during normal life and in disease states, as the left heart can only pump out what the right heart gives it. However, in the resting state, and when pulmonary pressures are normal, there may be minimal evidence of right heart dysfunction, which may only be evident when there is an increased load on right ventricular ejection and, importantly, when there is a demand for increased flow.

Author details

Sheldon Magder, Professor of Medicine

Division of Critical Care Medicine, McGill University Health Centre, Montreal, Quebec, Canada.

Correspondence: sheldon.magder@muhc.mcgill.ca

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