The Right Heart and Pulmonary Circulation (I)

The Right Ventricle and Pulmonary Circulation: Basic Concepts

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The primary purpose of the right ventricle and pulmonary circulation is gas exchange. Because gas exchange occurs in thin, highly permeable alveolar membranes, pulmonary pressure must remain low to avoid pulmonary edema; because the right ventricle and the lungs are in series with the left ventricle and the systemic circulation, the entire cardiac output must pass through the lungs. This low pressure, high volume system, makes dramatically different demands on the right ventricle compared with the demands made on the left ventricle by the systemic circulation. Moreover, the right ventricle and pulmonary circulation must buffer dynamic changes in blood volume and flow resulting from respiration, positional changes, and changes in left ventricular cardiac output.

The optimizations needed to meet these conflicting demands result in reduced capacity to compensate for increased afterload or pressure. Unfortunately, a large number of pathologic processes can result in acute and or chronic increases in afterload stress. As afterload stress rises, right heart failure may develop, and hemodynamic instability and death can occur abruptly. Several biochemical pathways have been identified that may participate in adaptation or maladaptation to excessive pressure loads.

Key words: *Right ventricle. Hypertension. Pulmonary arterial. Heart failure. Physiology.*

Ventrículo derecho y circulación pulmonar: conceptos básicos

La función principal del ventrículo derecho y de la circulación pulmonar es el intercambio de gases. Dado que el intercambio de gases se produce en membranas alveolares finas y altamente permeables, la presión pulmonar debe mantenerse baja para evitar el edema pulmonar, debido a que el ventrículo derecho y los pulmones están en serie con el ventrículo izquierdo y la circulación sistémica, y todo el gasto cardiaco debe pasar a través de los pulmones. Este sistema de baja presión y volumen alto somete al ventrículo derecho a exigencias completamente distintas de las que la circulación sistémica implica para el ventrículo izquierdo. Además, el ventrículo derecho y la circulación pulmonar deben amortiguar los cambios dinámicos en el volumen y el flujo sanguíneo resultantes de la respiración, los cambios posicionales y los cambios en el gasto cardiaco del ventrículo izquierdo. Las adaptaciones necesarias para satisfacer estas exigencias contrapuestas tienen como consecuencia una capacidad de compensación reducida frente a un aumento de poscarga o presión. Desgraciadamente, un elevado número de procesos patológicos pueden tener como consecuencia aumentos agudos o crónicos en la poscarga. A medida que aumenta tal exceso de poscarga, puede aparecer insuficiencia cardiaca derecha y pueden sobrevenir repentinamente inestabilidad hemodinámica y muerte. Se han identificado varias vías bioquímicas que pueden participar en la adaptación apropiada o inadecuada a las sobrecargas de presión.

Palabras clave: *Ventrículo derecho. Hipertensión pulmonar arterial. Insuficiencia cardiaca. Fisiología.*

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INTRODUCTION

For over a thousand years, the world's view of the pulmonary circulation hewed to the teachings of Galen, who believed that blood was produced in the liver, then delivered by the right ventricle (RV) to the tissues and organs where it was consumed. In Galen's view, blood "seeped" into the left ventricle (LV) directly from the RV via invisible pores in the interventricular septum. While it may now seem self evident that this is impossible, Galen viewed blood movement as a low volume ebb and flow.[1]

In the 13th century, Ibn al-Nafis of Syria rejected Galen's description and speculated that blood from the RV reached the LV via the lungs. While he deserves credit for the first accurate description of the pulmonary circulation, his works were lost and largely forgotten until quite recently, and it does not seem likely that they influenced the understanding of circulatory physiology in the western world.[2]

The first detailed description of the RV and pulmonary circulation to receive significant attention in the western world appeared near the beginning of the 16th century in the midst of a religious discourse by Michael Servetus of Spain. In this work (for which Servetus was later burned at the stake, although presumably for the heretical nature of its religious content, rather than primarily because of his views on circulatory physiology), Servetus wrote:

[The vital spirit] is generated in the lungs from a mixture of inspired air with elaborated, subtle blood which the right ventricle of the heart communicated to the left. However, this communication is made not through the middle wall of the heart, as is commonly believed, but by a very ingenious arrangement the subtle blood is urged forward by a long course through the lungs; it is elaborated by the lungs, becomes reddish-yellow and is poured from the pulmonary artery into the pulmonary vein.[3]

This model, based strictly on structural observations rather than on any experimental measurements, was a dramatic departure from Galen, but like Galen before him, Servetus assumed blood was continuously produced and consumed rather than re-circulated.[3]

Fifty years later, William Harvey would develop the first experimentally based model of the circulation. Despite not being the first to describe the pulmonary circulation, Harvey is considered the father of modern physiology because he was the first to perform detailed measurements and calculations[1] that allowed him to deduce the existence of blood recirculation, and he demonstrated the pulmonary blood flow experimentally.[4]

Over the next 400 years, the importance of the RV would be debated, with some investigators opining well into the 20th century that the RV served no purpose other than to provide capacitance to the pulmonary circulation.[5,6] In large part because of these early investigations, right heart failure was believed to be a problem mainly confined to idiopathic pulmonary hypertension and congenital heart disease, where it is a common cause of death. However, it is now known that pulmonary hypertension (PH) and right heart failure, far from being rare, complicate numerous other disease processes: RV failure is one of the most powerful predictors of mortality in left heart failure,[7] right heart failure is the proximate cause of death in most of the 50 000 fatal cases of pulmonary embolism in the United States each year,[8] and by some estimates, two to six in 1000 people with chronic lung disease will develop right heart failure, for several tens of thousands of new cases a year.[9]

This review will explore how the interaction of the pulmonary circulation and RV contribute to their impact on health and disease.

FETAL AND NEONATAL PULMONARY CIRCULATION AND RIGHT VENTRICLE DEVELOPMENT

By the 3rd week of human gestation, passive diffusion of oxygen into the developing embryo becomes insufficient to support metabolism, blood has formed, and the primitive heart tube has begun beating; by the end of the 4th week, active circulation begins. Distinct components of the pulmonary and systemic circulation emerge from folding and twisting of the heart tube between the 3rd and 5th weeks of gestation, under control of a complex signaling network that includes the retinoic acid and neuregulin pathways. Soon after, the RV and pulmonary circulation begin to separate from the LV and systemic circulation by formation of the interventricular septum from the endocardial cushion, and the valves develop. At birth, full septation of the interatrial septum is normally complete, with only the foramen ovale remaining as a potential shunt between the right and left atria.[10-12]

In the embryo and fetus, the RV is the dominant chamber, accounting for about 60% of total cardiac output. Because the embryo receives oxygen and nutrients from the placenta, only 15%-25% of total cardiac output enters the lungs. The remainder of right sided cardiac output is diverted to the systemic circulation via the foramen ovale to the left atrium and via the ductus arteriosis from the pulmonary artery to the aorta. Between 40%-60%

of descending aortic flow enters the placenta via the umbilical artery, then returns via the umbilical vein to the liver or through the ductus venosus to the inferior vena cava.[13,14]

At birth, pulmonary vascular resistance falls rapidly after expansion and oxygenation of the lungs, and right ventricular cardiac output begins to flow predominantly through the pulmonary artery into the lungs. At that point, rising left atrial pressure seals off the one way "flap valve" of the foramen ovale.[15] At birth, RV pressures still exceed systemic pressures, but these begin to fall over the next few hours to days.[16] Shortly thereafter, the ductus arteriosus, under control of prostaglandin, begins to close,[14] the LV hypertrophies as it takes over the systemic circulation, and the RV atrophies. By 3 weeks of age, pulmonary pressure has normally fallen below systemic pressure, and by adulthood the normal RV is incapable of generating more than 40-60 mmHg acutely.[17]

ADULT PULMONARY ANATOMY AND CIRCULATION

The pulmonary artery consists of a thin, elastic vessel that ramifies to supply the various lobar pulmonary arteries, pulmonary arterioles and alveolar capillaries. Blood exits the alveolar capillaries via the pulmonary venules, and returns through a system of pulmonary venules and branches similar in structure to the pulmonary arterial tree to the left atrium.[18-20] Because gas exchange occurs in thin, highly permeable alveolar membranes, pulmonary pressure must be low to avoid pulmonary edema from elevated Starling forces.[21]

Unlike the systemic circulation, where a circumferential layer of smooth muscle cells in the media of the arterioles clearly regulates resistance, pulmonary arterioles less than 70 microns in diameter appear to have at most incomplete layers of smooth muscle in the media, leading to an assumption in the past that blood flow regulation was limited to vessels greater than 100 microns in diameter. Nevertheless, studies show that regulation also occurs at the level of pulmonary micro vessels between 30 and 200 microns.[22] Regulation is under the control of a poorly understood oxygen sensing mechanism that may depend on calcium or voltage gated potassium channels, reactive oxygen species, or other mechanisms,[23] as well as on nitric oxide, prostaglandins, endothelin, and catecholamines.[24-26]

A number of concepts are commonly applied to describe the resistance to flow in the pulmonary circulation, and the consequent "afterload" experienced by the RV. The most complete description is provided by *pulmonary input impedance*. However, full characterization of input impedance is technically demanding, requiring frequency domain analysis of simultaneously measured pressure and flow.[27,28] The derived frequency domain factors are not easily related to common clinical concepts, so simplified models are generally preferred. The so-called *windkessel model*[29] encompasses three major components of input impedance: pulmonary vascular resistance, pulmonary arterial compliance, and a dynamic component called inductance.

Pulmonary vascular resistance (PVR) is defined as the mean pressure drop from the main pulmonary artery to the left atrium divided by average cardiac output, expressed in dynes-second-cm^{-5}. For convenience of calculation, Wood units are more commonly used, defined as mean pulmonary artery pressure minus mean pulmonary capillary occlusive pressure in mmHg, divided by cardiac output in L/min. One Wood unit is equivalent to 80 dyne-second-cm^{-5}. PVR is primarily determined by small vessel resistance, although extrinsic compression or mechanical obstruction of larger arteries (eg, by emboli) may also alter PVR. *Pulmonary artery compliance* refers to the elastic properties of the system, and is defined as the ratio of a change in volume to a change in pressure; pulmonary artery compliance buffers flow during RV ejection, reducing pulmonary artery pulse pressure. *Inductance* describes the dynamic response to changes in flow due to mass and inertia of the blood.

In so-called lumped parameter models (including the windkessel framework), resistance is modeled by one or more electrical resistors, compliance is modeled by a capacitor, and inductance is modeled as either an inductor or as a resistor in more simplified models. Various combinations of these elements are possible, but three or four element models are most commonly used in physiologic investigations. Windkessel models provide considerably better estimates of system behavior than pulmonary vascular resistance alone.

Several other terms are commonly used in physiologic studies, although inconsistencies in their definition in the literature may lead to confusion. Effective arterial elastance is defined as the ratio of end systolic pressure to stroke volume, although classically the term "elastance" is simply the reciprocal of compliance. This simple measure lumps together static and dynamic components of impedance and performs reasonably well in experimental studies.[30,31] While best characterized for use in modeling the systemic circulation, it has been successfully applied to the pulmonary circulation as well.[32]

PULMONARY HYPERTENSION

Table 1[33,34] shows typical pressures and resistances of the pulmonary and systemic circulations. Under

TABLE 1. Typical Measurements of Pressure and Resistance Compared in the Right and Left Circulations in Adults

	Pulmonary/RV/RA	Systemic/LV/LA
Pressure, average (range), mm Hg		
Atrial mean	3 (2)	7 (5)
Ventricular systolic	25	130
Ventricular diastolic	4 (3)	8 (4)
Vascular mean	15 (5)	85 (20)
Resistance, average (SD), dynes-sec-cm^{-5} × m^2	123 (54)	2130 (450)

LA indicates left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.
Adapted from Davidson et al[33], and Grossman et al[34].

normal conditions, PVR is 1/20 of systemic vascular resistance, and mean pulmonary artery pressure may not be much higher than central venous pressure. Because a 5 mm Hg pressure gradient across the pulmonary circulation is sufficient to maintain a normal cardiac output under conditions of normal PVR and normal LV filling pressures, minimal RV contractile function is normally necessary to maintain cardiac output, permitting congenital heart disease repair procedures such as the Fontan, where the RV is excluded from the pulmonary circulation entirely.[35]

In contrast to the focus on pulmonary vascular impedance taken by experimental physiologists, clinicians largely focus on pulmonary arterial pressure as the important operative concept, defining *pulmonary hypertension* (PH) as a mean pulmonary artery pressure greater than 25 mm Hg, or a peak pressure greater than 35 mm Hg. However, pulmonary artery pressure rises with age, the range of normal is wide,[36] and pulmonary artery pressure is a function of pulmonary vascular resistance, cardiac output, and pulmonary vein outflow pressure. Thus, a focus on pulmonary artery pressure alone obscures the etiology and potential therapeutic options for PH.

In the past, PH was conceptually divided into acute and chronic, and primary and secondary. Because these terms did not provide insight into etiology or potential therapy, the World Health Organization developed a new classification system summarized in Table 2.[37,38]

Group I PH (commonly referred to as pulmonary *arterial* hypertension) is defined as PH arising from primary abnormalities of pulmonary vasculature anatomy or function. It includes idiopathic pulmonary arterial hypertension (previously known as "primary pulmonary hypertension," a term now abandoned by PH specialists but still in common use). Group I PH is most commonly due to abnormalities in the vascular wall of the pulmonary arterioles, although it also includes pulmonary veno-occlusive disease. The exact underlying pathologic changes (reviewed in detail elsewhere)[24,39] vary somewhat depending on the etiology, but in most cases there appears to be a mechanical obstruction to flow and a reduced responsiveness to vasodilators, accounting for the common term *fixed* PH (although this is something of a misnomer since the disease process can be modified by various therapies). Despite the comparative rarity of idiopathic PH (a few thousand new cases per year worldwide), it receives a disproportionate share of attention from PH specialists.

Group II PH (commonly referred to as pulmonary *venous* hypertension) is defined as PH due to retrograde transmission of abnormally elevated pulmonary vein pressures from a variety of causes. Group II PH is largely secondary to abnormalities of left sided heart anatomy or function, eg, LV systolic or diastolic dysfunction, mitral and aortic valve disease, and is essentially a passive process with respect to the pulmonary vasculature. Group II PH may theoretically be "reversed" by correction of the underlying pathologic process that led to elevated pulmonary vein pressure. However, in many conditions (eg, mitral stenosis) increases in pulmonary arteriole resistance may develop over time and become irreversible, presumably due to similar mechanisms as in some forms of Group I PH. Although Group II PH is very common (and indeed, some authors claim that the most common cause of right heart failure is left heart failure), it is uncertain how much right heart failure in Group II actually contributes to mortality versus simply being a marker for more advanced left heart disease.

Group III and Group IV PH are due to alterations in pre-capillary pulmonary arterioles, but in Group III these alterations are secondary to lung disease or hypoxemia and can to some extent be considered a normal, physiologic response to external stimuli. Hypoxic pulmonary vasoconstriction, which normally matches

TABLE 2. **Summary of Venice 2003 Revised Classification for PH**[38]

WHO group I: Pulmonary arterial hypertension (PAH)
    Idiopathic (IPAH)
    Familial (FPAH)
    Associated with other diseases (APAH): collagen vascular disease (eg, scleroderma), congenital shunts between the systemic and pulmonary
       circulation, portal hypertension, HIV infection, drugs, toxins, or other diseases or disorders
    Associated with venous or capillary disease
WHO group II: Pulmonary hypertension associated with left heart disease
    Atrial or ventricular disease
    Valvular disease (eg, mitral stenosis)
WHO group III: pulmonary hypertension associated with lung diseases and/or hypoxemia
    Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD)
    Sleep-disordered breathing, alveolar hypoventilation
    Chronic exposure to high altitude
    Developmental lung abnormalities
WHO group IV: pulmonary hypertension due to chronic thrombotic and/or embolic disease
    Pulmonary embolism in the proximal or distal pulmonary arteries
    Embolization of other matter, such as tumor cells or parasites
WHO group V: miscellaneous

WHO indicates World Health Organization.

pulmonary ventilation to pulmonary perfusion, may become pathologic when too many segments of lung become hypoxic and PVR rises too far. PH due to Group III processes may be "reversed" by vasodilators such as calcium channel blockers, direct pulmonary vasodilators such as nitroprusside, and inhaled agents such as nitric oxide, but over time abnormalities of the pulmonary vascular system may develop and become essentially permanent as in Group I PH. Moreover, reversal of hypoxic pulmonary vasoconstriction through extrinsic means carries the potential to worsen hypoxemia through increased ventilation perfusion mismatch. Group III PH likely accounts for many more PH cases than all other groups combined, although severity of Group III PH tends to be somewhat lower than in Group I or Group IV.[9]

Group IV PH is due to mechanical obstruction or pulmonary arteries or arterioles secondary to pulmonary emboli (whether chronic or acute) and tumor emboli. Global statistics are not readily available for this group, but in the United States there are likely more than 600 000 pulmonary embolism cases causing more than 60 000 deaths per year.[8] Group V PH is a catchall for processes that are either entirely unknown or that do not fit into one of the other categories.

ADULT RIGHT VENTRICLE ANATOMY

The anatomy of the RV has been reviewed in detail by Ho et al.[40] Conceptually, the RV may be divided into an inflow tract (beginning with the tricuspid annulus), an apical region, and an RV outflow tract (terminating in the pulmonic valve). The RV free wall constitutes the anterior border of the RV and consists of a relatively thin crescent of muscle, lying anterior to the LV and interventricular septum. The RV is normally less than 1-3 mm in thickness, in comparison with the 10 mm thick left ventricular free wall, and comprises roughly 1/6th of the total mass of the heart.[17] Functionally, the interventricular septum constitutes the other half of the RV. Spiral muscle bundles form a contiguous band-like structure functionally linking the RV and the LV, likely resulting in transmission of contractile force directly from the LV to the RV.[17,41] Short axis cross sections through the heart from apex to base vary from a roughly triangular contour at the apex to a crescentic appearance at the base. This complex shape accounts for the difficulty in assessing RV size and function based on two dimensional imaging techniques,[40] and also accounts for the dramatic changes in RV size and shape that occur with varying loading conditions.

RIGHT VENTRICLE CORONARY CIRCULATION

In humans, the RV is largely perfused from the right coronary artery. In the LV, myocardial perfusion occurs predominantly in diastole when intramyocardial tissue pressure falls below aortic root pressure. Under normal loading conditions, RV intramyocardial tissue pressure remains below aortic root pressure throughout the cardiac cycle, permitting continuous coronary flow, but in severe RV pressure overload the RV coronary perfusion pattern begins to approximate that of the LV.[42]
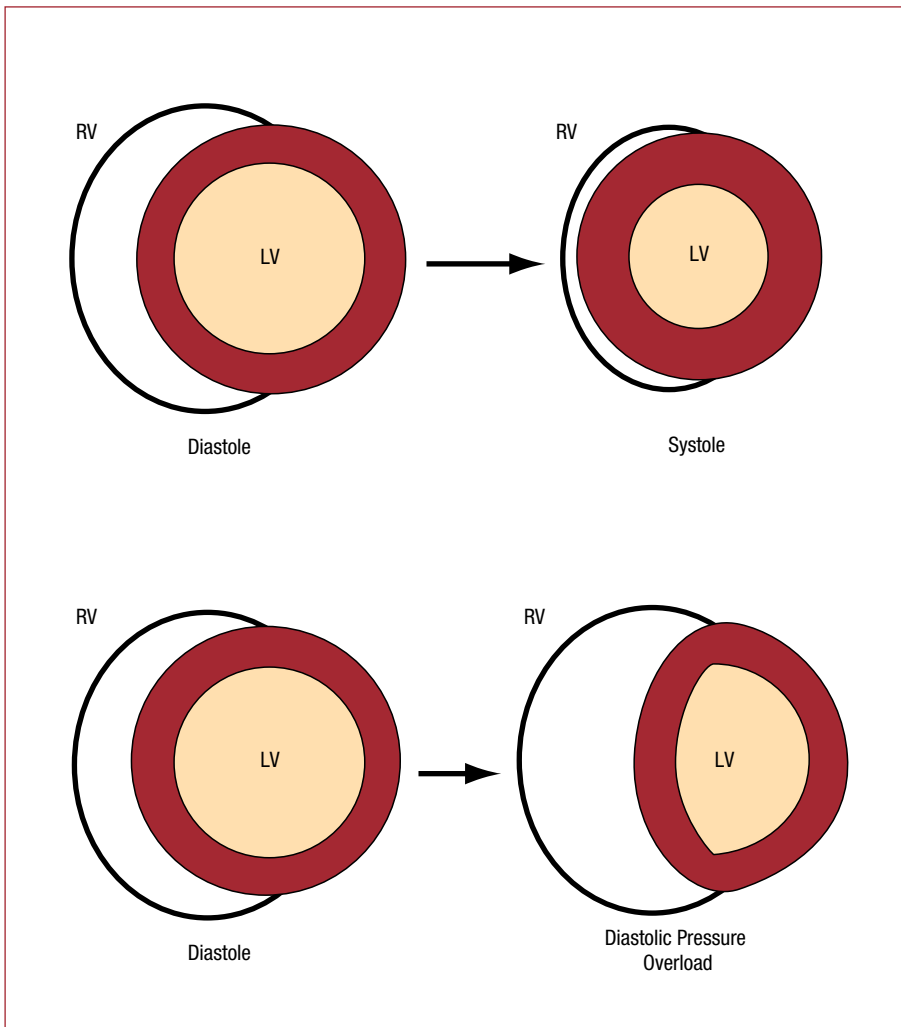
Figure 1. Illustration of shape changes in the heart during contraction. The circular cross section LV contracts by a uniform reduction in endocardial surface area, maintaining a nearly constant relationship between volume and surface area. The crescentic RV flattens in systole, leading to a large volume change with minimal change in RV free wall area. During severe pressure overload, the interventricular septum shifts, increasing RV diastolic volume with little increase in RV free wall surface area. Without an increase in surface area, the RV cannot recruit additional function via the Frank-Starling mechanism. At the same time, there is a reduction in LV end-diastolic volume and surface area, resulting in impaired LV pump function. (Reproduced from Greyson CR. Crit Care Med. 2008;36:S57-65. Copyright 2008, with permission from Lippincott, Williams & Wilkins.[46]). LV indicates left ventricle; RV, right ventricle.

NORMAL RIGHT VENTRICLE CONTRACTION

In the LV, development of ventricular pressure and ejection of blood is due to a concentric contraction of the LV free wall and septum, along with a twisting or "wringing" motion of the heart. In contrast, ejection of blood by the RV proceeds with a sequential contraction beginning in the inflow tract, and moving in a wave toward the outflow tract.[17,43] Normal ejection from the RV is a function of both a reduction in RV free wall surface area and a reduction in RV free wall septal distance.[44,45]

Figure 1[46] schematizes how the RV and the LV eject blood (neglecting any twisting motion of ventricular motion). Since surface area of a cylinder is proportional to its radius, and volume is proportional to the square of the radius, ejection fraction in the LV is roughly proportional to the square of the change in endocardial surface area. In contrast, because of the greater surface area to volume ratio of the RV, a greater ejection fraction is produced by a smaller change in surface area than would be required in the LV. The bellows-like arrangement of the RV not only allows large changes in RV volume with small changes in RV free wall surface area, but also helps buffer respiratory changes in RV output[47] without necessitating altered contractile function on a breath-to-breath basis.

While the series configuration of the pulmonary and systemic circulation require average RV and LV stroke volume to be the same (in the absence of intracardiac shunts), RV end-diastolic volume is normally somewhat greater than LV end-diastolic volume, while ejection fraction is smaller. As afterload increases, RV end diastolic volume rises while ejection fraction falls.[48]

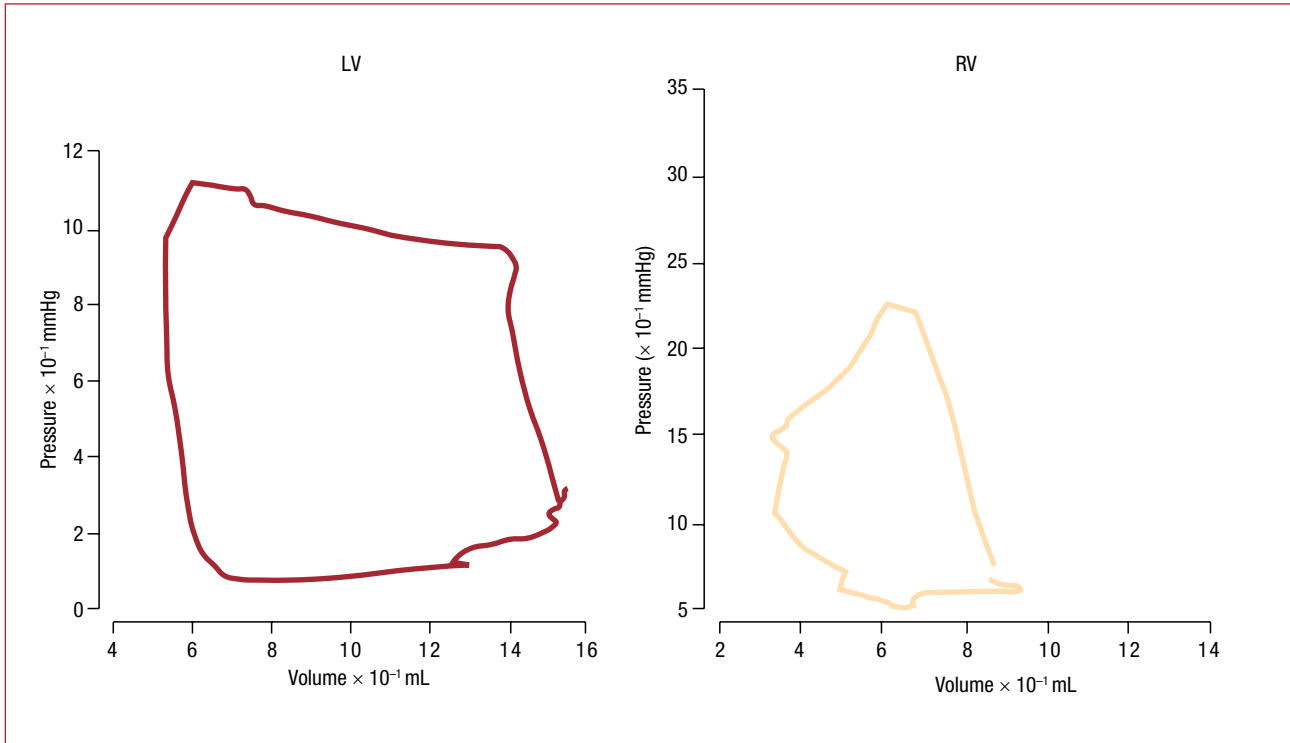The dynamics of the contracting heart are commonly analyzed in the context of pressure-

Figure. 2. Comparison of pressure volume loops obtained in humans with micromanometer catheters and ventriculography in the LV (left) and RV (right). LV pressure volume loops are nearly square, simplifying identification of isovolumic contraction and relaxation phases. In contrast, the RV loop is more triangular, with poorly defined end-systole. (Reproduced from Redington AN. Br Heart J. 1988;59:23-30. Copyright 1988, with permission from BMJ Publishing Group Ltd.[49]). LV indicates left ventricle; RV, right ventricle.

dimension plots such as in figure 2.[49] The square shape of the LV pressure-volume loop suggests defining isovolumic (constant volume) contraction and relaxation phases, and simplifies identification of end-systole and aortic valve closure, which occur close to the inflection point of the ejection phase. Suga and Sagawa developed the methodology for describing left ventricular function in terms of a "time varying elastance", where elastance is equal to the slope of the pressure volume relation at specific ("isochronal") times in the cardiac cycle.[50] Experimentally, it has been found that the maximum slope of the pressure-volume relation of the LV, called E_{max}, usually occurs at end-systole and is directly related to the contractile state of the LV.[49] In most cases it is essentially equivalent to the end-systolic elastance, E_{es}. In contrast, ejection of blood through the pulmonary valve may continue even when RV pressure is falling due to momentum of the blood into the low input impedance pulmonary circuit. This late ejection, or "hangout period",[51] makes identification of "end-systole" problematic in the RV, and contributes to the more triangular shape of the RV pressure-volume loop. The result is that pressure-volume loops are more difficult to

interpret in the RV than in the LV,[49,52] and the end-systolic pressure volume relation is not necessarily the preferred method for assessing RV contractile function.[53]

VENTRICULAR-VASCULAR COUPLING

In any mechanical or electrical system, transmission of power from one part of the system to another is maximized when the output impedance of the power producing part and the input impedance of the power receiving parts of the system are equal. As described previously, elastance is related to impedance, so maximal power transfer from the ventricle to the vascular system is achieved if ventricular (E_{max}) and vascular (E_a) elastance are equal.[54] However, in the beating heart, where the mechanical properties are changing over time, theoretical and experimental studies have shown that maximum efficiency of work production (ie, stroke work to oxygen consumption ratio) is achieved when the ratio of E_{max} to E_a is closer to 2.[55] Under normal conditions, systemic circulation ventricular-vascular coupling is found experimentally to achieve near maximum efficiency. The RV has a less clearly defined end-systole, and E_{max}

is consequently more difficult to define. Nevertheless, several investigators have found that RV-pulmonary vascular coupling can be analyzed in a similar way, and that, if end-systole is suitably defined, coupling is also nearly optimal under normal conditions (ie, the ratio of RV E_{max} to pulmonary artery elastance E_a is close to 2).[56,57]

CONTRIBUTION OF RIGHT VENTRICLE TO CARDIAC OUTPUT

In 1943, Starr et al ablated the RV in open chest dogs with "a red hot soldering iron," and found little alteration in systemic circulation or venous pressure. They speculated that the RV free wall served no other purpose than to provide capacitance to the pulmonary circulation.[5] Other investigators subsequently came to similar conclusions,[6] and interest in the RV began to wane.

However, RV pressure development is a combination of interactions among the RV free wall, the interventricular septum, and the LV free wall,[58,59] and the importance of RV free wall contractile function depends in large part on pulmonary vascular resistance and RV pressure. For example, while right coronary artery (RCA) occlusion and RV free wall contractile dysfunction may have little effect on RV pressure development or systemic hemodynamics under normal conditions, RV ischemia results in systemic hypotension when pulmonary vascular resistance increases.[60] Experimental evidence of the importance of RV contractile function was given increased credit following Cohn's case series of hemodynamically unstable isolated RV infarcts, and subsequent reports that RV contractile dysfunction in the setting of myocardial infarction (MI) resulted in substantially increased morbidity and mortality.[61,62]

RESPONSE OF RIGHT VENTRICLE TO ACUTELY INCREASED PRESSURE

How the heart responds to pressure overload has been studied for more than a hundred years, beginning with Otto Frank's efforts to systematize the study of ventricular function.[63] Suga and Sagawa extended and developed these concepts during the 1960s and 70s to the point where pressure volume relations are now routinely discussed in a clinical context.[64] Figure 3 shows pressure volume loops in an isolated RV as end-systolic pressure is altered. Each loop represents a single cardiac cycle.[52] In broad terms, over a physiologic range, end systolic volume is roughly inversely proportional to end systolic pressure, while stroke volume (and hence stroke work) increases with increasing end-diastolic volume.
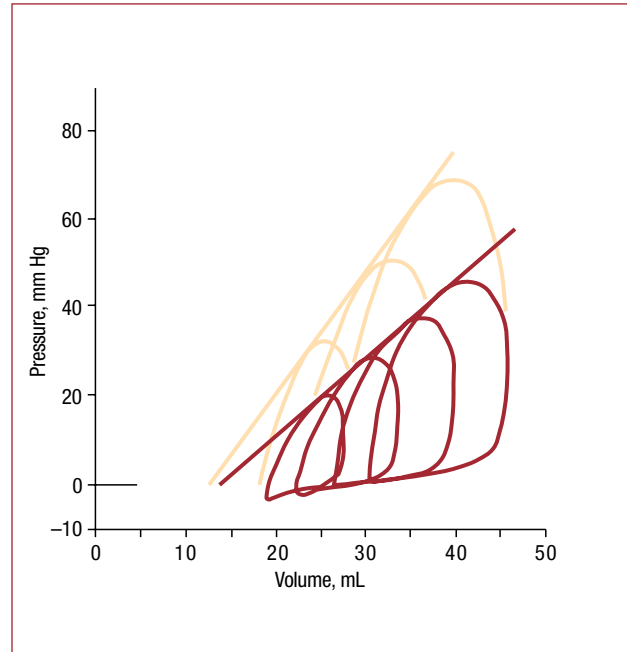

Figure 3. Example of RV pressure-volume loops obtained in an isolated working dog heart under baseline conditions (red lines) and following inotropic stimulation with epinephrine (salmon lines). The series of loops in each case is obtained by varying the outflow resistance. Note that a nearly straight line can be drawn that is tangent to each loop under a particular condition; although end-systole is difficult to identify, this line is essentially equivalent to the end-systolic pressure volume relation as obtained in isolated left ventricles, where the slope is a reflection of underlying contractile state. (Reproduced from Maughan WL. Circ Res. 1979;44:309-15. Copyright 1979, with permission from Wolters Kluwer Health.[52]). RV indicates right ventricle.

However, in comparison with the LV, the adult RV has very limited capacity to produce elevated pressure. Those limits are illustrated in Figure 4, which shows that stroke volume as a fraction of control declines much more quickly in the RV than in the LV as mean ejection pressure increases.[65] The Laplace relation helps explain the RV's more limited ability to contract against a load. First, the thinner RV free wall experiences a greater rise in wall tension with increments in RV pressure. Second, the radius of curvature of the RV increases during contraction rather than decreasing as happens in the LV, which means that shape dependent reduction of stress during contraction due to declining radius of curvature does not occur in the RV as it does in the LV.[66] There also appear to be biochemical differences, with RV myocardium being more optimized for rapid contraction,[67] although whether differences in myosin heavy chain isoform composition explain this is uncertain, since RV-LV differences in myosin isoform expression appear to be present in rodents[68] but not in dogs.[69]
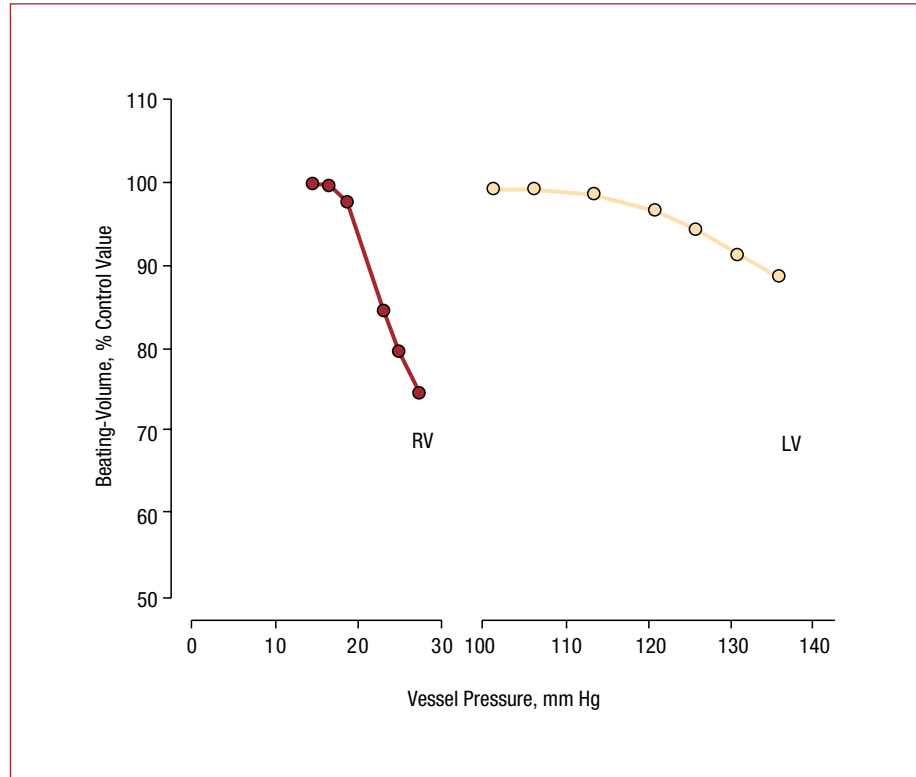
Figure 4. Comparison of the effect of ejection pressure on ejection fraction in the RV and the LV. Note that for any increment in ejection pressure, the decrement in ejection fraction is much greater in the RV than in the LV. (Reproduced from Heart Disease, Braunwald E., ed., by Wiedemann HP, Saunders Company, 1997, p. 1606. Copyright 1997, with permission from Elsevier.[65]). LV indicates left ventricle; RV, right ventricle.

Several mechanisms potentially contribute to increased contractile function in the setting of increased demand. These include the Anrep effect (homeometric auto regulation), the Frank-Starling mechanism (sometimes referred to as heterometric auto regulation), and catecholamine induced inotropy.

The Anrep effect is an intrinsic increase in contractile function that occurs in response to increased afterload in the absence of external regulatory changes such as catecholamine stimulation. Anrep effect can be demonstrated in isolated muscle strips,[69] but its presence in vivo has been controversial. Some evidence suggests that Anrep effect is the primary mechanism for initial adaptation to pressure overload in the RV,[70,71] although this may be more important in neonatal than in adult RVs.

The Frank-Starling mechanism is often viewed as the primary means by which the heart adapts to an increase in demand, but shape differences between the RV and the LV alter how the Frank-Starling mechanism operates. In both RV and LV, an increase in end-systolic pressure is normally accompanied by an increase in both end-systolic and end-diastolic volume. However, in the RV under normal loading conditions, much of the increase in volume is due to an increase in RV free wall septal dimension, with much less increment in RV free wall surface area.

Because the increment in RV free wall area for a given increment in central venous pressure is small, recruitment via the Frank-Starling mechanism is reduced. Thus, Frank-Starling mechanism plays a smaller role in RV adaptation to increased afterload at low RV pressures than it does in the LV. At increased afterload, as the RV becomes more cylindrical and other compensatory mechanisms are exhausted, the Frank-Starling mechanism becomes more important.[70,71] Sympathetic stimulation also increases contractile performance in the RV just as in the LV.[52]

RESPONSE OF RIGHT VENTRICLE TO CHRONICALLY INCREASED PRESSURE

As mentioned previously, RV pressures are normally higher than systemic pressures in the fetus and neonate, but fall to adult levels in the first few days or weeks after birth. However, neonatal RVs can tolerate ongoing PH, and congenital heart disease patients tolerate supersystemic pulmonary pressures for years with little disability (eg, Eisenmenger syndrome).[72] In contrast, once the RV atrophies and pressures fall, future pressure increases (even those that develop over prolonged periods) are poorly tolerated. The reason for this difference is unknown.

RV hypertrophy may develop in chronic pressure overload,[73] although whether this helps to normalize stress or results in contractile dysfunction is uncertain.[74] At the same time, RV dilation may lead to greater recruitment of function through the Frank-Starling relation.

Numerous biochemical alterations have been reported in various models of chronic RV pressure overload:[75] rodent models of RV pressure overload exhibit fetal gene program re-expression[76,77] and alterations in metabolic, stress-related and structural proteins,[78,79] although large animal models are scarce and not necessarily concordant with findings in rodents.[80] Human data obtained from transvenous endocardial biopsies should be interpreted cautiously because alterations in the RV septum, from which biopsies are normally obtained, may differ from alterations in the RV free wall, where much of the structural alteration is occurring.

RESPONSE OF RIGHT VENTRICLE TO CHRONICALLY INCREASED VOLUME

RV volume overload due to intracardiac shunts or tricuspid or pulmonic regurgitation is normally well tolerated, likely because the RV is optimized to accommodate large changes in volume. Experimentally, chronic RV volume overload does not appear to impair RV contractile function,[81] and clinically, patients with volume overload due to congenital heart disease appear to do well for many years.[82]

However, severe RV dilation ultimately impairs further volume increase (either due to pericardial constraint or because of the shared architecture of the RV and LV), such that additional increments in RV volume recruit minimal increments in RV free wall surface area; instead, as RV pressure rises further, increased RV volume occurs at the expense of the LV. This is seen most clearly in pulmonary embolism, where volume loading may adversely affect LV function.[83]

DEVELOPMENT OF RIGHT HEART FAILURE

Right heart failure, defined as the inability of the RV to generate adequate forward flow with normal central venous pressure,[46] can develop acutely in response to increases in pulmonary vascular resistance for many reasons, such as mechanical obstruction of the pulmonary vasculature by pulmonary emboli, or from reactive vasoconstriction in response to hypoxemia. Experimental data obtained more than 50 years ago showed that the RV has a very limited capacity to compensate for such loads. Figure 5 shows the result of progressively occluding the pulmonary artery in open chest dogs.[84] Initially, the rise in pulmonary artery pressure is well tolerated, with essentially unchanged systemic pressure (likely due to Anrep effect, as discussed previously). At point A, central venous pressure begins to rise, recruiting function via the Frank-Starling relation; when RV pressure reaches a threshold level at point B, systemic pressure drops abruptly and catastrophically.

The mechanism of RV failure and hemodynamic collapse at this point is due to the interaction of several factors. Just prior to hemodynamic collapse, reduced cardiac output may occur consequent to interventricular interaction. As the RV dilates in response to pressure overload, restraint from the pericardium and from shared muscle fiber bundles of the RV and LV constrain further RV dilation and shift the RV diastolic pressure-volume relation to a steeper portion of the curve, so that further increases in RV pressure result in less RV free wall stretch and hence less recruitment of function via the Frank-Starling relation. At the same time, interventricular septal shift impairs LV ejection. This combination results in a net decrease in cardiac output. Figure 6 shows short axis views of dog hearts subjected to experimental pulmonary embolism: much of the increase in RV volume comes at the expense of LV volume.[85]

Once cardiac output begins to fall, hemodynamic collapse progresses rapidly. Figure 7[46] schematizes the likely mechanism of hemodynamic collapse: increased RV pressure overload due to elevated afterload results in reduced cardiac output and systemic hypotension; this reduces RV tissue perfusion pressure; once this drops below a critical value, RV free wall ischemia develops.[86,87] RV ischemia causes reduced contractile function, compromising the RV's capacity to handle the elevated RV afterload, further reducing cardiac output, and causing a rapidly progressive downward spiral to hemodynamic collapse.

Because hemodynamic collapse in this scenario is abrupt (and frequently irreversible), and right heart failure does not become manifest by elevated central venous pressure until RV compensation is nearly exhausted, many (if not most) patients who present with signs and symptoms of right heart failure are likely found within a very narrow hemodynamic range, where central venous pressure has begun to rise but systemic pressure has not yet begun to fall (between points A and B in fig. 5). Recent experimental evidence suggests that progressive RV contractile dysfunction unrelated to ischemia develops in acute RV pressure overload[25,88-90] within this range, and potentially contributes to sudden hemodynamic deterioration in patients who otherwise appear hemodynamically stable.

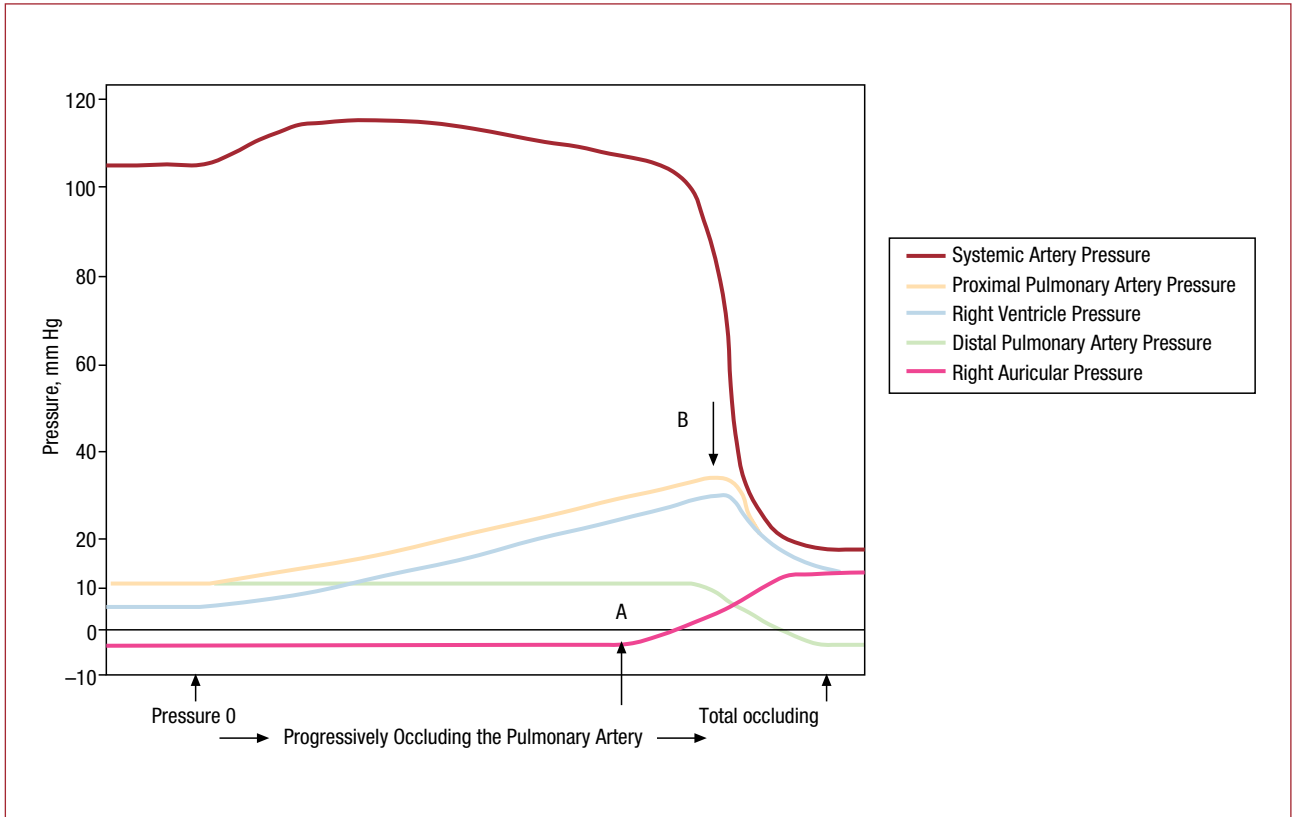Several mechanisms may contribute to progressive RV dysfunction in this setting. Abnormalities

Figure 5. Result of progressively occluding the pulmonary artery in an open chest dog. Initially, a progressive rise in pulmonary artery pressure is well tolerated, with essentially unchanged systemic pressure. At point A, central venous pressure begins to rise, permitting recruitment of function via the Frank-Starling relation, until RV pressure reaches a threshold level at point B, at which point systemic pressure drops abruptly and catastrophically. (Reproduced from Guyton AC. Circ Res. 1954;2:326-32. Copyright 1954, with permission from Wolters Kluwer Health.84). RV indicates right ventricle.

of ventricular-vascular coupling can reduce the efficiency of power transmission from the RV to the pulmonary circulation.[25] While some investigators believe that chronic ischemia plays a role in right heart failure, interventions to increase RV coronary perfusion in models of pressure-overload induced failure have not consistently improved RV contractile function,[91] and it is clear that progressive contractile dysfunction can occur in the absence of any evidence of ischemia at all.[25,88-90] Activation of intracellular proteases such as calpain,[92] or activation of apoptotic (programmed cell death) pathways[93,94] may contribute to dysfunction in this setting. Calpain inhibition appear to attenuate dysfunction[92] and reduce RV apoptosis[94] from pressure overload. Calpain may cause contractile
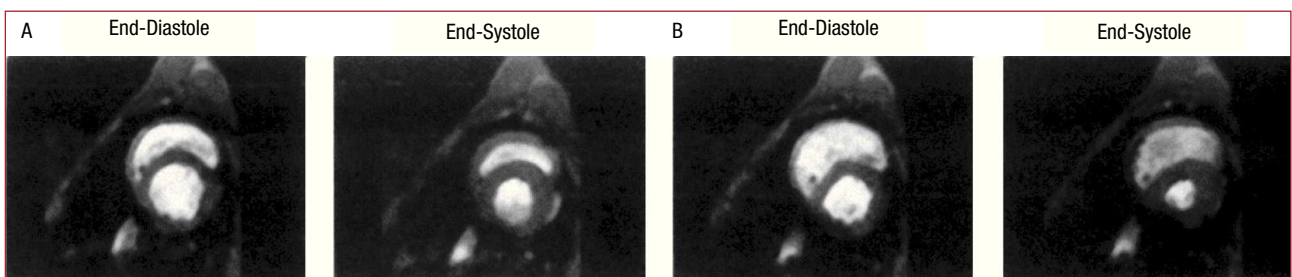

Figure 6. Short axis images from the ventricle of a dog obtained using magnetic resonance imaging in diastole and systole under baseline conditions (A) and following experimental pulmonary embolization (B). Increased RV pressure overload results in RV diastolic dilation and septal shift from the RV to the LV, compromising LV filling and reducing LV output. (Reproduced from Dell'Italia LJ. J Appl Physiol. 1995;78:2320-7. Copyright 1995, with permission from The American Physiological Society[85]). LV indicates left ventricle; RV, right ventricle.
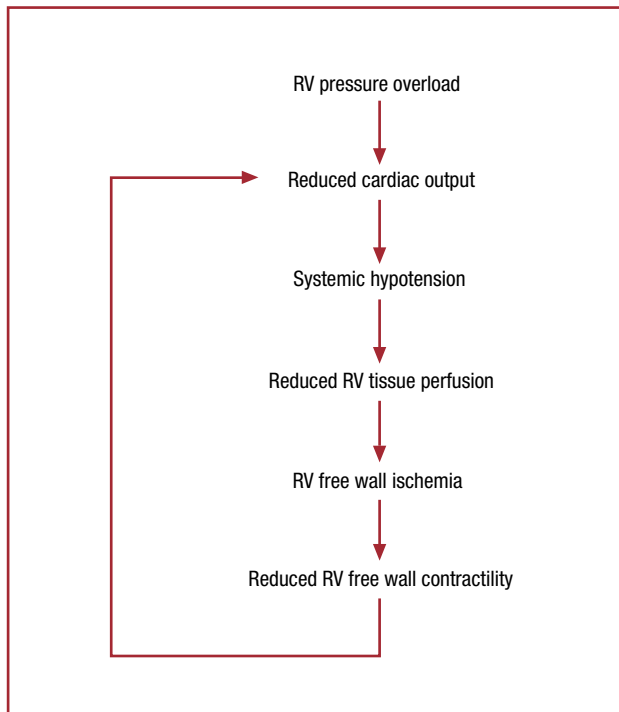
Figure 7. Proposed schema for the mechanism of abrupt hemodynamic decompensation in the setting of a severe increase in pulmonary inflow impedance. Once pulmonary resistance reaches level B in figure 5, RV output falls below a critical level, resulting in systemic hypotension, precipitation of RV ischemia, a decline in intrinsic RV contractile function, further decrease in RV output, and a progressive downward spiral to hemodynamic collapse and death. In the absence of some intervention to reduce pulmonary impedance or increase cardiac output, this process is irreversible. Reproduced from Greyson CR. Crit Care Med. 2008;36:S57-65. Copyright 2008, with permission from Lippincott, Williams & Wilkins[46]). RV indicates right ventricle.

dysfunction via degradation of intercellular adhesion proteins such as talin that coordinate cardiac contraction.[95,96] A recent report identifies tenascin, an extracellular matrix linking protein, as a possible culprit in chronic heart failure.[97] Whether the changes in gene expression discussed previously are adaptive or maladaptive is unknown.

IMPLICATIONS FOR FUTURE RESEARCH

In theory, progressive contractile dysfunction could alter the threshold at which the downward spiral of hemodynamic collapse begins. Perhaps this could explain why patients with apparently stable pulmonary hemodynamics can abruptly decompensate. Alternatively, RV contractile dysfunction might render a patient more susceptible to hemodynamic collapse following a subsequent event that further compromises RV contractile function. Improved understanding of the mechanism of RV failure in the setting of PH is likely to increase interest in this neglected disorder, and may facilitate development of new therapeutic approaches that go beyond merely reducing pulmonary vascular impedance and begin to address the underlying mechanisms of RV failure.

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