Pathophysiology of right ventricular failure

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Right ventricular failure may be defined as the inability of the right ventricle of the heart to provide adequate blood flow through the pulmonary circulation at a normal central venous pressure. Critical care specialists encounter right ventricular failure routinely in their practice, but until recently right ventricular failure as a primary clinical entity received scant consideration. Indeed, there is still not a single published practice guideline focused on right ventricular failure. Right ventricular failure is usually due to a combination of right ventricular pressure overload and contractile abnormalities of the right ventricular free wall. Decompensa-tion may occur abruptly and catastrophically because of unique aspects of right ventricular physiology. This review will focus on the pathophysiology of acute right ventricular failure in the critical care setting and summarize the limited management options available. (Crit Care Med 2008; 36[Suppl.]:S57–S65)

KEY WORDS: right ventricle; pulmonary hypertension; Frank-Starling relation; contractile dysfunction; hypoxic pulmonary va-soconstriction; coronary ischemia; ventricular wall stress; central venous pressure; heart failure; cor pulmonale

In contrast to the left ventricle (LV) of the heart, the right ventricle (RV) receives little attention. Pulmonary disease specialists concentrate on disorders of the pulmonary circulation that affect right heart function directly but tend not to study disorders of right heart function *per se*. At the same time, cardiovascular disease specialists interested in heart failure have largely ignored the right heart as a distinct area of investigation. Indeed, American Heart Association/American College of Cardiology practice guidelines for management of heart failure barely mention the RV and provide no guidance for management of either acute or chronic RV failure (1). Not a single professional society has published a practice guideline concentrating on RV failure.

Nevertheless, right heart failure remains a major public health problem. Respiratory failure causing hypoxic pulmonary vasoconstriction, pulmonary hypertension, and consequent right ventricular dysfunction is seen routinely in critically ill patients (2). Sepsis may cause right heart failure directly by inducing RV dysfunction (3). Pulmonary embolism is far more common than generally appreciated, with an estimated 600,000 cases in the United States each year, and causes >50,000 deaths annually, largely due to acute RV failure (4). RV failure occurs in the setting of idiopathic dilated cardiomyopathy, probably as a consequence of the same mechanism causing LV dysfunction and also as a consequence of pulmonary hypertension secondary to elevated left-sided filling pressures in ischemic LV cardiomyopathy (5). RV failure may be an independent risk factor for morbidity and mortality in patients with left heart failure (6). RV failure is still a leading cause of death and morbidity early after cardiac transplant (7) and following several other cardiothoracic procedures (8). Primary pulmonary hypertension, while relatively rare with only 300 new cases annually in the United States, is difficult to manage and results in RV failure (9). By some estimates, 1 in 2000 of the 10–15 million people with chronic obstructive pulmonary disease will develop RV failure, accounting for several thousand new cases per year (10). Coronary ischemia may cause RV failure, both directly (as in RV myocardial infarction) (11) and indirectly (as in acute ventricular septal defect or from acutely decompensated left heart failure). Ultimately, many of these patients end up in critical care units, where RV failure may be the primary manifestation of their disease or a major complicating factor in the management of their underlying conditions. Altogether, RV failure is estimated to account for 3% of all acute heart failure admissions and confers worse mortality rates than acutely decompensated left heart failure (12).

While the function of the RV has long been recognized, awareness of its importance has waxed and waned over the years. The importance of the RV was first recognized by William Harvey in 1616 (13), but in 1943 Starr et al. (14) concluded that the RV functioned only as a passive conduit, since there were "no increments of venous pressure" following electrocautery ablation of the RV free wall in dogs. A resurgence of interest in the RV followed reports by Cohn and colleagues (15) in 1974 that RV infarction was common and difficult to manage, that RV involvement in inferior myocardial infarction conferred an eight-fold increase in mortality (16), that RV dysfunction in acute pulmonary embolism is a predictor of mortality independent of systemic hemodynamics (17), and that RV dysfunction is an independent predictor of poor outcome in left heart failure (6).

Why have investigators only recently rediscovered the clinical importance of the RV of the heart? Limited understanding of the physiology of the RV by clinicians who view the RV merely as a weak

LV has likely contributed to the problem. Fortunately, along with the growing body of clinical data indicating a critical role for RV function in health and disease has come a stream of experimental data that help to explain the disparate conclusions from the past. In recognition of a National Institutes of Health working group's conclusion that increased emphasis on the pathophysiology of the right heart is warranted (18), there is now a National Institutes of Health special emphasis area concentrating on RV function.

Normal Physiology of the RV

The RV is not simply a weak LV. Macroscopically, ultrastructurally, and biochemically, the RV differs dramatically from the LV. The normal RV seldom exceeds 2–3 mm wall thickness at end-diastole, compared with 8–11 mm for the LV. A distinct pattern of conduction results in a bellows-like or peristaltic-like contraction beginning near the apex of the heart and moving in a wave toward the outflow tract (19). The biochemical composition of the RV and LV differs, with the RV having a higher proportion of the α-myosin heavy chain isoform that results in more rapid but less energy-efficient contraction (20). Recent data suggest there may be dramatic differences in the response of the RV to adrenergic agents (21).

The coronary perfusion pattern of the RV differs significantly from that of the LV. Because tissue pressure in the LV rises during systole to systemic levels, coronary perfusion of the LV is largely confined to the diastolic interval. Tissue pressure in the RV does not normally exceed aortic root systolic pressure, permitting continued coronary flow throughout the cardiac cycle; thus, under typical hemodynamic conditions, coronary flow to the RV is roughly balanced between systolic and diastolic time periods (22).

Ejection of blood into the highly compliant, low-resistance pulmonary circulation results in dramatically different hemodynamics. Table 1 shows differences in normal hemodynamic measurements for the LV and the RV (23, 24). The normal RV generates less than one sixth the work of the LV while moving the same volume of blood. Compared with the LV, a much lower proportion of RV stroke work goes to pressure generation, with a correspondingly higher proportion going

Table 1. Typical values for systemic and pulmonary pressure and resistance

	Pulmonary/RV/RA	Systemic/LV/LA
Pressure, mm Hg, average ± range		
Atrial mean	2–7	2–12
Ventricular systolic	15–28	90–140
Ventricular diastolic	0–8	4–12
Vascular mean	10–16	65–105
Resistance, dyne·sec·cm^{-5}·M^2, average ± SD		
Vascular	123 ± 54	2130 ± 450

RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium.
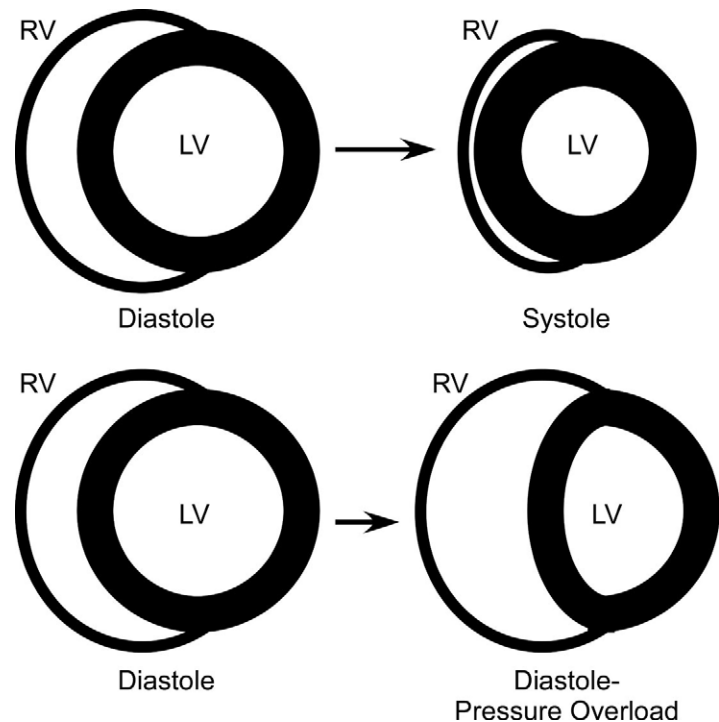Data from Grossman and Baim (23), Davidson and Bonow (24), and others.

Figure 1. Illustration of how the geometry of the right ventricle (*RV*) changes with contraction and is affected by pressure overload. *Top*, the crescentic RV flattening in systole, leading to a large-volume change with minimal change in RV free wall area. *Bottom*, how a shift of the interventricular septum during acute pressure overload permits RV end-diastolic volume to increase with no change in end-diastolic RV free wall area, a decrease in interventricular septal surface area, and a corresponding decrease in left ventricle (*LV*) end-diastolic volume. Because the RV free wall does not stretch, there is no recruitment of RV function via the Frank-Starling mechanism, while at the same time there is a loss of function via the Frank-Starling mechanism in the LV.

to blood momentum; the relatively high momentum of blood movement ejecting into the low-pressure pulmonary circulation results in RV ejection continuing after ejection from the LV has ended, and even during RV relaxation (25).

The RV accommodates dramatic variations in venous return resulting from changes in volume status, position, and respiration while maintaining more or less constant cardiac output (26). In part this is because the thin RV is easily distensible, but to a larger extent it is a direct result of RV geometry. While the more or less circular cross-sectional pro-

file of the LV results in a geometrically predictable relationship between LV surface area and LV volume, the bellows-like contraction of the RV free wall (Fig. 1, *top*) results in a much higher ratio of RV volume change to RV free wall surface area change and allows the RV to eject a large volume of blood with little alteration in RV wall stretch. This pattern of contraction is optimized for moving large and varying volumes of blood but is poorly adapted to generating high pressure. For example, at end-systole, LV free wall radius of curvature decreases, which facilitates further development of pres-

sure by decreasing wall stress, but RV free wall radius of curvature increases at end-systole (Fig. 1), resulting in higher stress at peak pressure than would be developed were the geometry more like the LV, and consequently hinders further pressure development.

Like the LV, the RV can use the Frank-Starling mechanism to increase stroke work as a consequence of an increase in RV stretch (27). However, the relatively flat relationship between RV surface area and RV volume described previously means that large changes in RV volume are necessary before the Frank-Starling mechanism is recruited. Since relatively large increments in RV volume result in relatively small increments in RV stretch, minimal recruitment of function via the Frank-Starling mechanism occurs at baseline (28). Once the RV begins to dilate and becomes more circular in contour, a steeper relationship between volume and stretch develops, and the Frank-Starling relation becomes more important (29).

Global function of the RV depends on independent but coordinated contributions from both the RV free wall and the interventricular septum. In an experimental system, Damiano et al. (30) electrically isolated the RV from the left atrium and LV to allow changing the interval between RV and LV activation. Using this approach, they were able to show that the RV and the LV both make independent contributions to RV output.

Despite the contribution of the interventricular septum to RV output, under normal circumstances RV function is relatively independent of LV loading conditions. Chow and Farrar (31) supported dogs with an LV assist device to permit independently altering RV and LV loading conditions; even after reducing LV intracavitary pressure to zero, normal RV pressure was maintained, indicating that the RV free wall is able to generate substantial external work without assistance from interaction with the LV. However, functions of the RV and LV become more directly intertwined (so-called "interventricular interdependence") under a number of pathologic conditions that either increase total cardiac volume (such as LV or RV heart failure) or decrease effective intrapericardial volume (such as pericardial effusion). In such cases, an increase in RV volume results in a corresponding decrement in LV volume (32), and because of interventricular septal shift, the increase in RV volume can occur with no change in RV free wall surface area or stretch (Fig. 1, *bottom*). Since an increase in volume is less effective at recruiting the Frank-Starling effect in the RV than in the LV, an increase in RV volume at the expense of LV volume may have a net negative effect on overall cardiac output.

The pericardium plays a major role in modulating the interaction between the RV and the LV and in limiting RV dilation during volume or pressure overload. By limiting total cardiac volume, the effects of interventricular interaction may be magnified, as described previously, and recruitment of RV function by the Frank-Starling mechanism may be impaired. Conversely, by preventing RV dilation and reducing end-systolic RV free wall stress, contractile function may actually be preserved in some cases (33).

Response of the RV to Increased Pressure

In both the LV and the RV, an increase in end-systolic pressure results in a corresponding increase in end-systolic volume and a decrease in ejection fraction, through the well-known end-systolic pressure-volume relation (34, 35). If nothing else changed, an increase in pulmonary artery pressure would result in a decrease in RV ejection fraction and stroke volume and a corresponding decrease in cardiac output. Thus, for the RV to maintain cardiac output when confronted with an increase in afterload or pressure, RV performance must increase to generate the required increase in stroke work. The RV could potentially compensate through either an increase in contractile state or the Frank-Starling mechanism. In a model of acute RV pressure overload through pulmonary artery banding in lambs (28, 36) and sheep (36), increased stroke work during acute RV pressure overload was shown to be mediated primarily through an increase in contractility, with at most a small contribution from the Frank-Starling mechanism using increased RV end-diastolic volume. The rapid increase in contractile function in response to an increase in demand, called *homeometric autoregulation* or *the Anrep effect*, appears to be mediated through rapid alterations in calcium dynamics (37) and may occur without a change of adrenergic state. As pulmonary impedance rises, endogenous or exogenous catecholamines may permit a further increase in RV pressure via an increase in inotropy (38). With further increments in afterload, the RV ultimately begins to dilate and recruit function via the Frank-Starling mechanism. Once all mechanisms of contractile reserve are exhausted, systemic pressure begins to fall, with a dramatic, sudden, and irreversible decrease in RV contractile function. This sudden catastrophic hemodynamic collapse was first demonstrated in 1954 by Guyton et al (39). Figure 2, taken from Guyton's report, shows a steady rise in RV-generated pressure during progressive constriction of the main pulmonary artery, until the RV can no longer compensate, at which point a sudden decline in systemic pressure and cardiac output ensues.

This catastrophic hemodynamic collapse occurs at the onset of, and is exacerbated by, RV ischemia (40, 41). As RV systolic pressure increases, the dynamics of RV coronary perfusion change, with a decline in coronary perfusion during the systolic interval (42). At very high RV pressure, RV coronary vasodilator reserve is lost entirely, and RV ischemia may ensue. Several investigators have found that improving RV coronary perfusion through aortic constriction during acute RV pressure overload has a modest beneficial effect on RV pressure, suggesting that RV failure during acute pressure overload is at least in part due to ischemia (40, 41, 43). However, enhancing coronary flow using coronary vasodilators does not improve RV contractile function (40, 44), and the effect is substantially attenuated when the RV and the LV are mechanically uncoupled and coronary perfusion is independently controlled (45), suggesting that aortic constriction may improve RV function indirectly through interventricular interaction. Thus, it is controversial to what extent RV ischemia is responsible for the onset of RV contractile failure. Nevertheless, once RV coronary perfusion pressure begins to fall due to systemic hypotension, RV contractile failure progresses rapidly and catastrophically.

Figure 3 illustrates the catastrophic downward spiral once RV compensatory mechanisms are exhausted. This catastrophic change is irreversible in the absence of relief of RV outflow obstruction because the fall in systemic pressure results in a loss of RV tissue perfusion, a further decline in RV contractility, and a further decline in systemic pressure, in a feed-forward downward spiral.

Right coronary ischemia, which is the primary cause of this rapid decompensa-
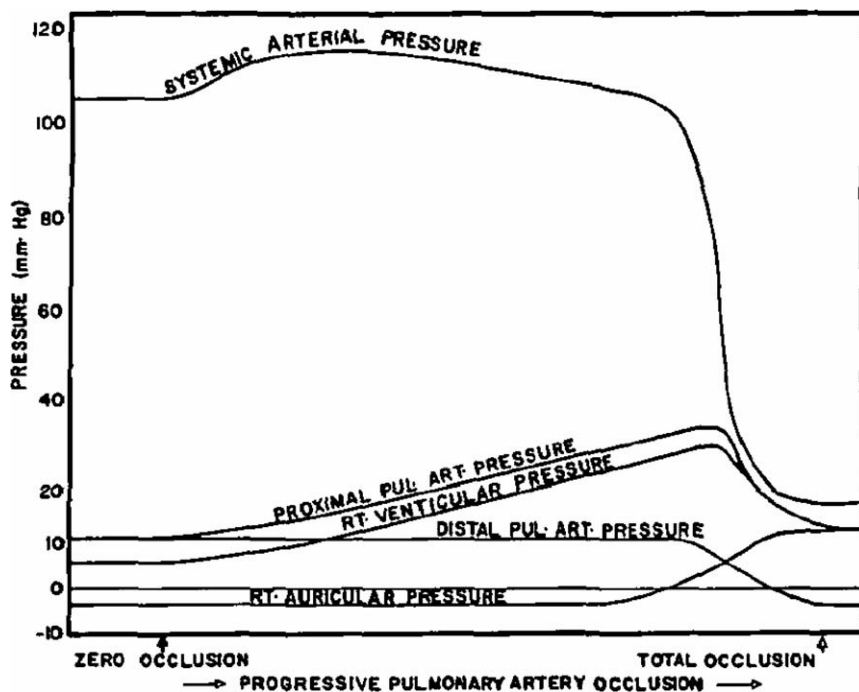
Figure 2. Main figure from the seminal investigation by Arthur Guyton and colleagues (39) showing the limits of right (*RT.*) ventricle (RV) contractile function in the setting of increasing pulmonary artery (*PUL. ART.*) outflow obstruction, with the resulting abrupt and catastrophic collapse in systemic hemodynamics once RV compensatory mechanisms are exhausted. The original figure legend reads "Effect of increasing pulmonary arterial constriction on the mean pressures at different points in the circulatory system."

Figure 3. Illustration of the downward spiral of right ventricle (*RV*) function that ensues once RV compensatory mechanisms are exhausted in the face of rising RV systolic pressure stress. With the RV teetering on the edge of compensation, even a small additional increment in pulmonary outflow resistance, or a small decrement in RV contractile function, can precipitate an abrupt decline in function through a feed-forward mechanism involving decreased systemic pressure, decreased RV coronary perfusion, RV ischemia, RV contractile dysfunction, and further reduction in cardiac output. The decline is irreversible if pulmonary vascular impedance is not reduced or RV contractility is not increased.

tion, is probably not the only contributor to altered RV contractile function during acute pressure overload and may not play a significant role in right heart failure from pulmonary hypertension in a majority of stable patients (46). While homeometric autoregulation and increased adrenergic tone both up-regulate RV contractility during acute pressure overload, there is evidence that pressure overload down-regulates RV contractility during (47) and following (48, 49) acute RV pressure overload even in the absence of ischemia. The mechanism of the downward regulation is not known; however, the severity of this element of contractile dysfunction is directly related to end-systolic wall stress and is exacerbated by end-systolic RV dilation, presumably because end-systolic RV dilation results in RV wall thinning, increased RV radius of curvature, and increased wall stress at the same RV systolic pressure (49).

Shortly after acute RV pressure overload ensues, ultrastructural changes consisting of focal myocyte necrosis can be identified in the RV free wall (50). While some of these are potentially due to direct mechanical disruption of myofibrils or focal adrenergic overstimulation, the possible contribution of activation of pro-
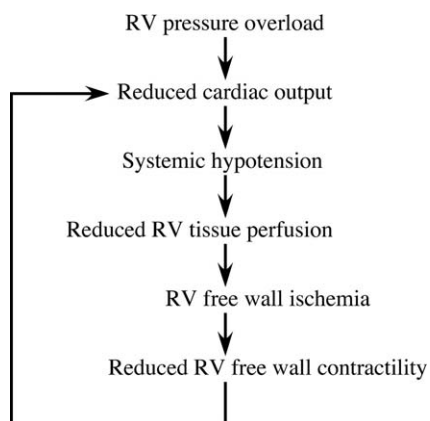
teases, such as calpain to dysfunction, as occurs in skeletal muscle subjected to high loads (51), is suggested by recent reports that calpain inhibitors may partially attenuate the development of RV contractile failure in acute pressure overload (52).

Acute pressure or volume overload induces expression of B-type natriuretic protein, various cytokines, growth factors, and calcium handling genes (53). When RV pressure persists, changes in cytoskeletal structure occur (54), with longer term pressure overload resulting in a shift in glucose and fat metabolism akin to that seen in LV pressure overload (55). Whether these changes are adaptive or maladaptive is unknown.

RV Response to a Primary Reduction in Contractility

Pulmonary vascular resistance is normally ≤10% of systemic vascular resistance, and mean pulmonary artery pressure is normally not much higher than 15 mm Hg. If LV filling pressure is low and pulmonary vascular resistance is normal, active contraction of the RV, or even the interventricular septum, is not necessary to maintain cardiac output. For example, to maintain a cardiac output of 6 L/min with a normal left atrial pressure of 8 mm Hg requires a mean pulmonary artery pressure of only 14 mm Hg; with no contribution from the RV at all, this can be developed entirely by a modest increase in central venous pressure.

Thus, a reduction in RV contractility may not by itself result in RV failure, and even very severe isolated RV ischemia may be well tolerated because elevated central venous pressure provides sufficient driving force to maintain flow across the pulmonary circulation. This was demonstrated in a report by Brooks and colleagues (43), in which complete right coronary occlusion had essentially no impact on RV developed pressure, cardiac output, or left ventricular developed pressure, when pulmonary artery pressure was normal. Congenital heart disease corrective procedures, such as the Fontan procedure, exploit this low-resistance state of the normal pulmonary circulation, bypassing the RV entirely (56).

However, in the setting of increased pulmonary vascular resistance or elevated left atrial filling pressure, central venous pressure may not be sufficient to maintain pulmonary arterial flow and RV

failure ensues. When Brooks and colleagues (43) repeated right coronary artery occlusion in the setting of a modest increase in pulmonary artery pressure, there was a profound reduction in cardiac output and systemic pressure. In other words, under normal circumstances, the RV free wall's contribution to circulation is not terribly important; impairments in RV contractile function may become clinically significant only when demand on the RV increases.

The consequence of these two facts, that global RV performance is not solely a result of RV free wall contraction and that normal pulmonary vascular resistance is very low, is that RV failure does not occur in the absence of elevated pulmonary artery input impedance. This largely explains why Starr et al. (14) found "no increment in venous pressure" and the hemodynamic consequences of RV infarction went unrecognized in many early experimental preparations.

In summary, RV pressure overload, if sufficiently severe, will inevitably result in RV failure; for all practical purposes, RV failure never occurs in the absence of RV pressure overload; and successful relief of pressure overload will usually ameliorate RV failure, even if manipulation of energy supply (e.g., coronary perfusion) is unsuccessful at changing the threshold at which RV failure occurs.

Clinical Syndrome of RV Failure

Cardiovascular disease specialists have struggled with the definition of heart failure for years. Current American College of Cardiology/American Heart Association guidelines define *heart failure* as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood" (1). This very broad and nonspecific definition was developed to accommodate the fact that LV dysfunction alone may not result in clinical manifestations of heart failure and that, conversely, clinical manifestations of heart failure may occur in the absence of demonstrable LV systolic dysfunction. Similarly, RV dysfunction alone does not usually result in clinical right heart failure, while clinical right heart failure may occur in the absence of preexisting RV contractile dysfunction.

An essentially universal feature of clinical LV failure is an elevation of left atrial pressure. By analogy, and taking into account the fact that central venous pressure may be elevated for reasons completely unrelated to the function of the RV, *RV failure* may be defined as "the clinical syndrome resulting from the right heart's inability to provide adequate blood flow to the pulmonary circulation at a normal central venous filling pressure."

This definition of RV failure provides a practical means of identifying RV failure clinically: RV failure is not present if there is adequate cardiac output and central venous pressure is normal. However, if cardiac output is inadequate, central venous pressure is high, RV contractile dysfunction is apparent on imaging studies, and abnormalities of LV function are not sufficient to explain the clinical syndrome, RV failure must be present.

Clinical RV failure may be due primarily to excessive contractile demand or to impaired contractile function. However, in general both increased contractile demand (pulmonary hypertension) and impaired contractile function will be present to some extent. In either case, once the normal compensatory mechanisms of the RV (such as Anrep effect or circulating catecholamines) have been exhausted, central venous pressure will begin to rise. Thus, some evidence of central venous pressure overload in conjunction with RV contractile dysfunction is universally present in the setting of manifest RV failure.

Elevated central venous pressure ultimately leads to RV dilation, which, if modest, may be adaptive through the Frank-Starling mechanism. However, as central venous pressure continues to rise, further RV dilation becomes maladaptive, both through an increase of RV end-systolic wall stress and consequent impairment of contraction and through impingement on the LV via the interventricular septum. Finally, output from the RV will fall due to ischemia, with progressive systemic hypotension, or output from the LV will begin to fall through a direct impediment to LV filling, and the downward spiral previously described rapidly ensues.

No single sign, symptom, or laboratory test can perfectly identify all episodes of RV failure. Nevertheless, it is probably fair to say that decompensated RV failure is not present if jugular venous pressure is normal, regardless of any measured index of RV contractile function (although in some cases RV dysfunction may be occult during intravascular volume depletion, and RV failure only becomes evident with repletion of volume).

Elevated central venous pressure is commonly, although not invariably, associated with other evidence of elevated body water and salt in the form of peripheral and visceral edema. The failing right heart may dilate, leading to a parasternal heave, or decreased RV compliance may lead to a right-sided third heart sound. Virtually all other signs and symptoms of right heart failure are a direct consequence of the underlying etiology of RV failure rather than RV failure *per se* and therefore may or may not be present depending on the etiology. For example, in RV failure due to primary pulmonary hypertension, there may be a loud pulmonary component to the second heart sound, although this may be lost as RV failure worsens and pulmonary artery pressure falls. A tricuspid regurgitation murmur secondary to RV dilation or tricuspid valve incompetence may or may not be present. A large number of signs and symptoms of RV failure have been listed in other reviews (57), but none of them is particularly sensitive or specific.

Many patients endure a prolonged period of moderate RV failure before catastrophic hemodynamic collapse. The investigation by Guyton et al. (39) provides insight into this unpredictable event. With the RV teetering on the edge of its reserve, any slight impairment in contractile function or slight increment in demand (e.g., through an increase in pulmonary vascular resistance or through an increase in pulmonary vein pressure) results in further reduction in RV output, further impairment of LV filling, impairment of RV coronary perfusion, further reduction in RV contractile function, and rapid decompensation progressing to death.

Absence of pulmonary congestion with elevated central venous pressure is often considered to be the most specific finding of isolated RV failure; however, severe RV failure may result in elevated left ventricular end diastolic pressure due to interventricular septal shift, so at least in theory pulmonary venous pressure may be able to rise to the point of causing pulmonary congestion (58).

Clinical Conditions Resulting in Increased RV Pressure

Numerous clinical conditions can result in excessive RV pressure and/or increased pulmonary vascular resistance.

Most common in the critical care unit are acute increases in small-vessel pulmonary vascular resistance due to hypoxia and pulmonary vascular constriction (59), direct lung injury in acute respiratory distress syndrome (2), and positive pressure ventilation (60). Obstruction of the pulmonary artery circulation, such as with pulmonary embolism or direct pulmonary artery constriction or injury, may result in sudden sustained increases in pulmonary artery pressure. Adult congenital heart disease is another potential cause of RV failure due to pressure overload, although such patients appear to have a better prognosis than those with primary pulmonary hypertension (61). A sudden increase in RV afterload may occur in cardiac grafts transplanted into a patient with long-standing heart failure and pulmonary hypertension (7), and cardiopulmonary bypass may precipitate acute pulmonary hypertension and RV failure through poorly understood mechanisms (62).

Acute pressure overload can occur suddenly or in the context of long-standing RV pressure overload. Long-standing RV pressure overload may result in RV hypertrophy, and patients with long-standing pulmonary hypertension and Eisenmenger syndrome may tolerate astonishingly high, even suprasystemic, RV pressures with minimal evidence of RV failure (63). Conversely, relatively modest increases in RV pressure may precipitate sudden RV failure in patients with no preceding pulmonary hypertension or when RV contractile reserve is already depressed. Because the transition from compensated to decompensated RV failure may be abrupt, it is often not possible to identify the specific event that ultimately led to clinical deterioration in any given case.

Treatment of pulmonary hypertension *per se* in the critical care setting will not be discussed in detail here. Few therapeutic interventions have proven to be of significant value. Thrombolysis and thrombectomy for selected patients with pulmonary embolism may or may not be helpful (64–66). RV failure due to elevated left-sided filling pressures may respond to left heart failure treatments, such as diuresis, afterload reduction, positive inotropes, revascularization, and intra-aortic balloon counterpulsation. Pulmonary hypertension from hypoxic pulmonary vasoconstriction may respond acutely to vasodilators, such as prostacyclin or nitric oxide, but caution is necessary since hypoxemia may worsen as a result of increased perfusion of poorly ventilated lung, and trials of these agents have been disappointing (67). Scattered reports of beneficial acute effects of agents more commonly used in chronic pulmonary hypertension, such as bosentan and sildenafil (68), while encouraging, have not yet been verified in well-controlled trials. An experimental report that levosimendan might improve pulmonary hemodynamics (69) showed promise in a small clinical study (70), but this agent does not yet have an established indication for treatment of acute RV failure.

Conditions Resulting in Decreased RV Contractile Function

Decreased RV contractile function may develop due to decreased energy supply (coronary ischemia) or other primary abnormalities of the contractile apparatus. RV ischemia may develop as a consequence of severe pulmonary hypertension and/or decreased systemic pressure but more commonly occurs as a consequence of an acute coronary syndrome. The RV usually receives its blood supply via the right coronary artery. Since the right coronary artery is dominant (i.e., supplies the inferior wall of the heart) in approximately 90% of individuals, the overwhelming majority of clinically evident RV infarcts occur in the setting of inferior myocardial infarction. RV ischemia may occur in up to half of all inferior wall myocardial infarctions, although hemodynamic compromise due to RV dysfunction is apparent in a relatively small proportion of these (11). RV myocardial infarction is often unrecognized; the syndrome was not well appreciated until Cohn and colleagues' (15) report in 1974. While isolated RV infarcts may occur, due either to thrombosis of a nondominant RCA or to an isolated RV septal branch, as discussed previously, isolated decreases in RV contractile function may be clinically silent if elevations in RV outflow pressure are not present. Conversely, since inferior myocardial infarction may cause LV dysfunction and elevated LV filling pressure, the combination of a simultaneous decrease in RV contractile function and an increase in pulmonary artery input impedance (via an increase in LV and left atrial filling pressure) provides the perfect substrate for development of acute RV failure, since an increase in LV filling pressure automatically requires a corresponding increase in mean pulmonary artery pressure to maintain the same cardiac output at the same pulmonary vascular resistance.

During hemodynamically significant RV infarction, right atrial function becomes much more important to maintain cardiac output. Loss of atrioventricular synchrony in the setting of RV infarct and inferior myocardial infarction may contribute to cardiogenic shock; in such cases, synchronous atrioventricular pacing may be helpful (11).

RV failure due to RV infarct may improve spontaneously over time (71). The reason for this is not entirely clear; however, some investigators have argued that the RV is more tolerant of ischemia than the LV because of lower oxygen demand, collateral coronary flow, or other reasons. Alternatively, it may be that increased RV afterload in the setting of acute LV infarct improves with resolution of LV abnormalities, permitting the underlying contractile abnormality of the RV to be better tolerated. Regardless, hemodynamically significant RV infarct confers a high mortality, and reperfusion therapy directed at RV myocardial infarction has been shown to be effective at reducing morbidity and mortality (72).

Primary abnormalities of right heart function may occur due to the long-term consequences of pressure overload, as described here. In addition, toxic circulating factors may impair RV function despite normal nutrient supply during septic shock (3).

Miscellaneous Causes of RV Failure

RV failure usually requires either a large increase in RV afterload or a modest increase in RV afterload coupled with a reduction in RV contractility. Although volume overload, either from atrial septal defect, tricuspid regurgitation, or pulmonic regurgitation, is commonly considered a cause of RV failure, in general this will not cause RV failure acutely in the absence of increased pulmonary artery pressure. For example, resection of the tricuspid or pulmonic valves for isolated endocarditis frequently does not result in decompensated RV failure (73, 74). Many patients tolerate high flows from atrial septal defect without difficulty (75). However, conditions such as acute ventricular septal defect, which simulta-

neously increases pulmonary flow and pressure, may rapidly result in RV failure.

Pulmonary hypertension and RV failure may be attributed to LV diastolic dysfunction, but identifying the inciting cause can be difficult. As the RV dilates, there may be a shift of the interventricular septum toward the LV, resulting in impaired LV filling and a shift to a higher point on the LV pressure-volume relation. Doppler echocardiography of the LV may then become consistent with impaired relaxation, but this is a manifestation of interventricular interaction rather than a direct abnormality of LV myocardial function or material properties (76). Thus, it may be difficult to determine whether abnormalities of LV diastolic function are primarily a cause or an effect of RV failure without some means for temporarily altering RV loading conditions.

Other causes of RV failure, such as RV dysplasia and infiltrative cardiomyopathies, are relatively rare but should be considered when no other etiology for RV failure can be identified.

Conditions Masquerading as RV Failure

Several other settings may mimic RV failure but would not reasonably be construed as an abnormality of right heart function. First, elevated central venous pressure, along with clinical signs of RV failure, may be present in the setting of pure volume overload (e.g., excessive postoperative volume repletion, acute renal failure); in these cases, RV contractile function is normal, and intravascular volume reduction eliminates the secondary findings without impairing overall cardiac output and should not be considered to be a result of RV failure. Second, direct compression of the RV, from pericardial effusion, pericardial fibrosis, tumor, or massive pleural effusion, may impair RV filling, resulting in decreased RV output simultaneously with increased central venous pressure. Imaging studies are most helpful in eliminating these as causes of elevated central venous pressure. Lower extremity edema, while commonly attributed to right heart failure, is often due to extrinsic compression of venous or lymphatic return, renal failure, alterations in the renin-angiotensin system, or drug therapy. If central venous pressure is normal, edema is generally not attributable to RV failure even if RV contractile function appears abnormal on imaging studies.

Treatment of Refractory RV Failure

In acute RV failure, the underlying cause of RV failure should be addressed to the extent possible. If treatment of the underlying etiology is impossible or unsuccessful, attempts should be made to optimize RV loading conditions. Even in the setting of intrinsic RV contractile dysfunction, the RV may have some compensatory reserve through the Frank-Starling relation. Thus, volume loading may improve RV output. However, since RV contractile failure is directly related to RV wall stress, excessive volume loading may paradoxically worsen RV contractile function through RV dilation; the subsequent impediment to LV filling through the interventricular septum or through pericardial restriction can result in worsened total cardiac output, ultimately leading once again to the vicious cycle of RV hypoperfusion and further impairment of RV contractility. Once central venous pressure has exceeded 10–14 mm Hg, further volume loading is usually detrimental (77, 78). However, optimal loading conditions can be difficult to determine. Invasive hemodynamic monitoring (e.g., central venous or pulmonary artery catheters) may be useful in testing various interventions. For example, if cardiac output falls in response to an increment in central venous pressure, volume reduction with a diuretic agent or renal replacement therapy may be indicated despite systemic hypotension. Echocardiography may be helpful in revealing whether further RV volume loading is having an adverse effect on LV geometry.

Once any underlying cause of RV contractile failure has been addressed and loading conditions optimized, attempts at improving RV contractile function may be attempted. Dobutamine has been shown to have beneficial effects on RV contractile function in pulmonary hypertension without affecting pulmonary vascular resistance (79). During RV infarction, dobutamine has been shown to exert overall favorable hemodynamic effects and is considered an agent of choice (78, 80); however, while dobutamine may improve overall hemodynamics without worsening RV ischemia, it likely does not enhance function of ischemic segments of the RV (81) and instead improves function of nonischemic regions of the RV or interventricular septum. Digoxin has been suggested as an effective inotropic agent in the setting of RV failure from pulmonary hypertension, although the beneficial effects are modest, and it is unknown whether they are sustained (82). Other inotropic agents, such as norepinephrine and levosimendan, may be effective in part through their positive inotropic effects and in part through favorably modulating the interaction between the RV and the pulmonary vascular system (so-called ventricular-vascular coupling) (47, 69, 70).

In a few cases, RV assist devices (83) and even intra-aortic balloon counterpulsation devices placed in the pulmonary artery (84) have been used with variable success.

As described previously, limited data suggest that proteases may contribute to ongoing, or even acute, RV contractile failure in some settings; however, evidence supporting this hypothesis has been developed only in animal models (52, 85).

CONCLUSIONS

RV failure occurs when the RV is unable to provide adequate blood flow through the pulmonary circulation at a normal central venous pressure. The underlying physiology of the RV explains why its response to stress is fundamentally different from the LV response to stress and provides a framework for understanding the clinical manifestations of and the potential therapeutic approaches to RV failure. RV failure is inherently an unstable condition, with a tendency toward abrupt and irreversible decompensation. Empirical therapy, such as volume loading, may be counterproductive and precipitate sudden decompensation. The complex interaction of the RV and the LV makes clinical assessment of RV failure and its response to therapy difficult; noninvasive imaging or invasive hemodynamic monitoring may be necessary to identify the etiology of RV failure and determine optimal therapy. Further research into the mechanism of RV contractile dysfunction in the critical care setting is necessary, since current therapeutic options are extremely limited.

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