Pulmonary Hypertension, Right Ventricular Failure, and Kidney: Different from Left Ventricular Failure?

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In this article, the pathophysiology of left ventricular failure is reviewed. By contrast, the paucity of information about pulmonary arterial hypertension and right ventricular failure is acknowledged. The potential mechanisms whereby renal sodium and water retention in right ventricular failure secondary to pulmonary arterial hypertension can occur, despite normal left ventricular function, are discussed. With right ventricular failure as the primary cause of death in patients with pulmonary hypertension, more information about the mechanisms of renal sodium and water retention in these patients is direly needed. Specifically, studies to examine the activation of the neurohumoral axis at various stages of pulmonary arterial hypertension and right ventricular failure, including inhibition of mineralocorticoid and V2 vasopressin receptors, are indicated.

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The renal sodium and water retention that occurs with advanced left ventricular failure is associated with substantial morbidity and mortality. This sodium and water retention, which can lead to pulmonary edema, pleural effusion, and peripheral edema, occurs despite an increase in total blood volume. In normal individuals, a rise in total blood volume increases renal sodium and water excretion. The kidney is intrinsically intact with left ventricular failure, because the renal sodium and water retention does not persist after a successful heart transplant.

This seeming paradox of increased blood volume yet renal sodium and water retention in cardiac failure has been explained by the body fluid volume regulation hypothesis (1–3). This hypothesis proposes that the kidney does not respond to changes in total blood volume but rather responds to what has been termed effective arterial blood volume. In general terms, approximately 85% of circulating blood volume is in the low-pressure venous side of the circulation, whereas only 15% is in the high-pressure arterial circulation. The integrity of the arterial circulation depends on cardiac output and systemic vascular resistance and is modulated by arterial stretch baroreceptors in the carotid sinus, aortic arch, and afferent arteriole of the glomerulus (4). Thus, despite an increase in total blood volume, arterial underfilling can occur secondary to a decrease in cardiac output in low-output heart failure or decreased systemic vascular resistance in high-output heart failure. With arterial underfilling secondary to either condition, arterial baroreceptor–mediated activation of the neurohumoral axis occurs. The resultant increase in renin-angiotensin-aldosterone system (RAAS) leads to sodium retention, and the increase in the nonosmotic release of arginine vasopressin (AVP) is associated with water retention and hyponatremia in advanced left ventricular failure, a known risk factor for increased mortality (5). This water retention is due to AVP activation of the V2 vasopressin receptors on the basolateral surface of the principal cells of the collecting duct, which increases aquaporin 2 water channel expression and trafficking to the apical membrane of the collecting duct (6–8).

There is also evidence that increased plasma AVP concentration with left ventricular failure stimulates V1 vasopressin receptors on blood vessels, which contributes, along with angiotensin II and the sympathetic nervous system, to increasing systemic vascular resistance in low-cardiac output failure (9). This arterial baroreceptor–mediated neurohumoral activation maintains arterial pressure but at the expense of renal vasoconstriction and sodium and water retention. The pathophysiology of left ventricular cardiac failure is shown in Figure 1.

These arterial baroreceptor pathways seem to override any of the low-pressure reflexes in the atria during left ventricular failure. An increase in transmural atrial pressure normally suppresses AVP and stimulates atrial natriuretic peptide (ANP), which leads to increased sodium and water excretion (10). With advanced left ventricular failure, however, left atrial pressure rises, yet sodium and water retention occurs. This suggests that activation of the arterial stretch receptors in cardiac failure predominates over any atrial pressure receptor reflex. There is also evidence that these normal atrial reflexes are blunted in patients with left ventricular failure (11).

An increase in the ventricular synthesis of brain natriuretic peptide (BNP) and, thus, circulatory BNP concentration also occurs in left ventricular failure and may attenuate the degree of renal sodium and water retention. BNP may decrease the edema formation by both suppressing the RAAS and inhibiting tubular sodium reabsorption (12).

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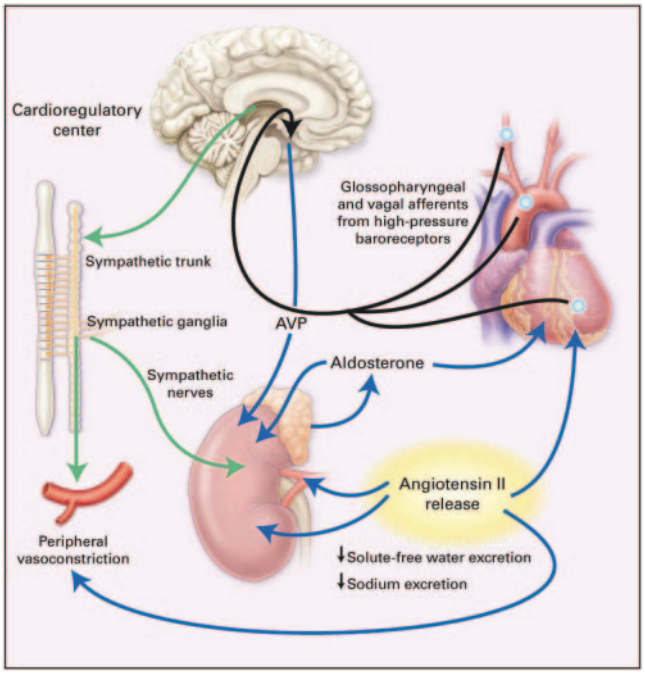

Figure 1. Unloading of high-pressure baroceptors (blue circles) in the left ventricle, carotid sinus, and aortic arch generates afferent signals (black) that stimulate cardioregulatory centers in the brain, resulting in the activation of efferent pathways in the sympathetic nervous system (green). The sympathetic nervous system seems to be the primary integrator of the neurohumoral vasoconstrictor response to arterial underfilling. Activation of renal sympathetic nerves stimulates the release of renin and angiotensin II, thereby activating the renin-angiotensin-aldosterone system (RAAS). Concomitantly, sympathetic stimulation of the supraoptic and paraventricular nuclei in the hypothalamus results in the nonosmotic release of arginine vasopressin (AVP). Sympathetic activation also causes peripheral and renal vasoconstriction, as does angiotensin II. Angiotensin II constricts blood vessels and stimulates the release of aldosterone from the adrenal gland, and it also increases tubular sodium reabsorption and causes remodeling of cardiac myocytes. Aldosterone may also have direct cardiac effects on fibrosis, in addition to increasing the reabsorption of sodium and the secretion of potassium and hydrogen ions in the collecting duct. The blue lines designate circulating hormones. Reprinted from reference 2 (Schrier RW, Abraham WT: Hormones and hemodynamics in heart failure. *N Engl J Med* 341: 577–585, 1999), with permission. Copyright © 1999 Massachusetts Medical Society. All rights reserved.

Right Ventricular Failure

What then occurs with pulmonary hypertension (PH) and isolated right ventricular failure? In this setting, left ventricular function is normal as may occur with primary pulmonary hypertension, chronic obstructive pulmonary disease (COPD), and connective tissue diseases.

PH was previously categorized into primary PH or secondary PH depending on the absence or presence of identifiable causes or risk factors. Subsequently World Health Organization classified PH into five groups on the basis of mechanisms, rather than associated conditions. Pulmonary arterial hypertension is group 1 and is defined as a sustained elevation of pulmonary arterial pressure to >25 mmHg at rest or to >30 mmHg with exercise, with a mean pulmonary-capillary wedge pressure and left ventricular end-diastolic pressure of <15 mmHg (13). Pulmonary arterial hypertension comprises idiopathic pulmonary arterial hypertension (formerly primary pulmonary hypertension); pulmonary arterial hypertension in the setting of collagen vascular disease (*e.g.*, in localized cutaneous systemic sclerosis, also known as the CREST syndrome [calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia]), portal hypertension, congenital left-to-right intracardiac shunts, and infection with the HIV; and persistent PH of the newborn. The histologic appearance of lung tissue in each of these conditions is similar: intimal fibrosis, increased medial thickness, pulmonary arteriolar occlusion, and plexiform lesions predominate (14). PH associated with left ventricular dysfunction comprises of group 2, and PH associated with hypoxemia such as COPD, interstitial lung diseases, and sleep-ventilation disorders constitutes group 3. Group 4 includes PH associated with chronic thromboembolic diseases, and group 5 encompasses miscellaneous disorders such as sarcoidosis, pulmonary Langerhans cell histiocytosis, and lymphangiomatosis. Among these PH groups, groups 1 and 3 are conditions in which right ventricular failure is associated with intrinsically normal left ventricular function.

There is evidence that in patients with COPD with right ventricular failure (group 3 PH), the RAAS axis is stimulated (15,16). This effect may relate to arterial underfilling associated with a decrease in systemic vascular resistance. One theory is that carbon dioxide, commonly elevated in patients with COPD, is a potent vasodilator and lowers the systemic vascular resistance and increases the arterial capacitance. Consequently, arterial underfilling occurs, leading to stimulation of the neurohormonal axis (norepinephrine, RAAS, and AVP) and, hence, sodium and water retention (15). Elevated $Paco_2$ also may lead to sodium retention through increased Na-H exchange in the renal tubules (17). Moreover, hypoxemia associated with hypercapnia may influence urinary sodium excretion. In one study, Reihman *et al.* (18) demonstrated a significant fall in urinary sodium output on withdrawal of supplemental oxygen. In another study by Mannix *et al.* (19), oxygen supplementation resulted in enhanced natriuresis, independent of hypercapnia.

Elevated plasma volume has been demonstrated in patients with pulmonary arterial hypertension and found to be associated with poor outcome (20); however, the mechanisms that cause sodium and water retention have not been explained in these patients, because hypercapnia was not present. The neurohumoral axis has been rarely studied in pulmonary arterial hypertension with right ventricular failure in humans. Induction of early experimental models of right ventricular failure by graded valvular damage showed a decrease in renal blood flow, preserved GFR, and intense salt and water retention (21). The underlying neurohormonal state in this model was not examined. Despite the presence of pulmonary artery baroreceptors (22,23), other investigators concluded that when cardiac output is kept constant, pulmonary arterial distention has no

direct effect on renal hemodynamics (24,25). The renal hemodynamic changes and the retention of sodium and water observed in patients with pulmonary arterial hypertension therefore may be mediated by systemic, rather than pulmonary, arterial baroreceptors, as has been shown in other edematous states (1,4). One study of patients with pulmonary arterial hypertension showed increases in plasma endothelin, ANP, and norepinephrine concentrations but not in the plasma renin levels. Plasma aldosterone and AVP concentrations were not assessed (26).

In contrast to left ventricular failure (27,28), the role of aldosterone and vasopressin in renal sodium and water retention in patients with pulmonary arterial hypertension has not been examined, even though mineralocorticoid and V2 vasopressin receptor antagonists are clinically available. Mineralocorticoid antagonists have been shown to afford cardiovascular protection in patients who had left-sided heart failure receiving angiotensin-converting enzyme inhibitors. In the Randomized Aldactone Evaluation Study (RALES), improved survival in patients with left ventricular failure was demonstrated using dosages of spironolactone (25 to 50 mg/d), which did not alter urinary sodium excretion (29). Whether the results of this trial are applicable to patients with pulmonary arterial hypertension and intact left ventricular function but right ventricular failure is not known.

There are many other unanswered questions relating to pulmonary arterial hypertension and isolated right ventricular failure. Echocardiogram studies have shown normal left ventricular function and ejection fraction in these patients. Cardiac-renal neural reflexes initiated from the pulmonary arterial circulation and/or right atrial and ventricle have not been well delineated. Plasma ANP and BNP concentrations have been found to be elevated in pulmonary arterial hypertension in proportion to the degree of right ventricular dysfunction (30,31); however, these peptides increase urinary sodium excretion and thus cannot account for the renal sodium and water retention in right ventricular failure. Increased concentrations of these peptides do, however, correlate with mortality in patients with PH (32).

Without sufficient treatment, the natural course of pulmonary arterial hypertension is characterized by a high mortality rate and limited survival. The National Institutes of Health registry (1981 through 1987) included patients with idiopathic/familial PH and reported a median survival of 2.8 yr with 1-yr survival rate of 68% and a 5-yr survival rate of 34% before the availability of sufficient treatment options (33). In a recent single-center cohort, the 1- and 5-yr survival rates were 84 and 58%, respectively, and the median survival time was 3.6 yr with currently available treatments (34). Although newer treatments for pulmonary arterial hypertension have emerged, including prostacyclins, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, only modest functional improvement with minimal change in hemodynamic measurements at cardiac catheterization have been achieved (35).

Survival in pulmonary arterial hypertension correlates inversely with hemodynamic parameters such as mean pulmonary arterial pressure, right atrial pressure, cardiac index, and right ventricular failure (36). A recent study demonstrated that, similar to left heart failure, hyponatremia was associated with advanced right heart failure and dramatically reduced survival in patients with pulmonary arterial hypertension as compared with individuals with normal serum sodium. Hyponatremia predicted death even after adjustment for hemodynamic, echocardiographic, and clinical variables of known prognostic importance in PAH (37). Peripheral edema and ascites are common in advanced pulmonary arterial hypertension, and resistance to diuretics often occurs as the disease progresses. Patients eventually die from right ventricular failure. Conversely, except for chronic obstructive pulmonary disease, there is scant knowledge about the pathophysiology of hyponatremia, volume overload, neurohumoral axis, particularly the RAAS, in patients with pulmonary arterial hypertension with right ventricular failure. If increased activation of the RAAS does not occur, then it could be due to several factors. First, arterial underfilling, as a result of either a decrease in cardiac output or systemic arterial vasodilation, may not be present with pulmonary arterial hypertension. This is compatible with the observed normal left ventricular function, normal ejection fraction (1), and normal plasma renin activity (26). The question, then, is which factors mediate renal sodium and water retention with pulmonary arterial hypertension and right ventricular failure? ANP and BNP are known to exert an inhibitory effect on the RAAS and catecholamines, but this observation would not explain the renal sodium and water retention in patients with pulmonary arterial hypertension.

Studies of conscious dogs with pulmonary stenosis, which might bear on the renal sodium and water retention with primary PH, were undertaken more than three decades ago (38). In those studies, there was an initial decrease in cardiac output, a lower mean arterial pressure, and activation of the RAAS. Over a period of time, however, sodium and water retention occurred, and cardiac output and mean arterial pressure returned to baseline, as did the RAAS. These compensatory responses, however, occurred at the expense of substantial edema formation. Because patients with PH are frequently seen for only a snapshot in time, this sequence of compensatory events cannot be excluded. This potential sequence of compensatory events that could lead to sodium and water retention and return of cardiac output and RAAS to the normal range are shown in Figure 2. Follow-up studies from the early to late stages of pulmonary arterial hypertension will be necessary to explore whether this sequence of events occurs. These patients could have normal left ventricular function and ejection fraction when seen but earlier in their disease may have activated the neurohumoral axis secondary to a decrease in cardiac output. In this latter setting, an apparent normal RAAS in patients with pulmonary arterial hypertension could be relatively increased given the positive sodium and water balance. An increase in renal venous pressure with right ventricular failure also could decrease GFR and contribute to sodium and water retention.

Other potential mechanisms for decreased left ventricular output in the setting of normal ejection fraction in pulmonary arterial hypertension with isolated right heart failure could be

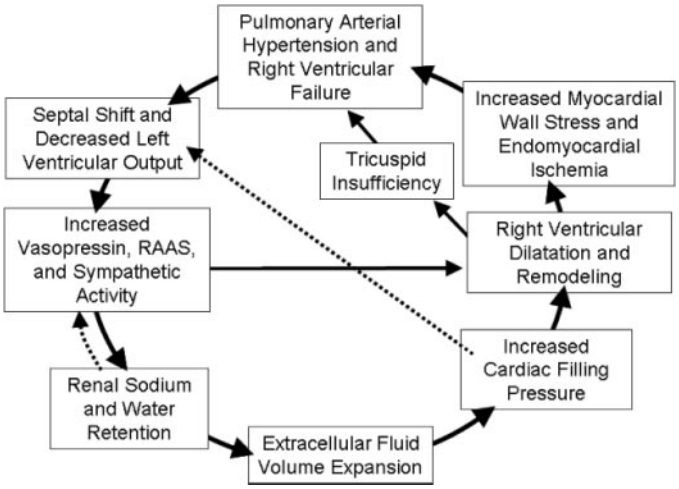

Figure 2. Feedback mechanisms for normalizing neurohormones and cardiac index with myocardial injury. The dashed lines indicate the compensatory responses that could return cardiac index and the RAAS to within normal range.

explained by interventricular asynchrony and/or pericardium-mediated right ventricle–left ventricle interaction. Synchronous right and left ventricular pressure measurements in patients with pulmonary arterial hypertension demonstrated a significant right-to-left transseptal pressure gradient at the time of maximal leftward septal displacement measured by magnetic resonance imaging (39). The mechanism behind this asynchrony is that right ventricular pressure overload leads to prolonged contraction of the right ventricular free wall (40). At the time that the left ventricle has entered its early diastolic phase, right ventricular pressure exceeds left ventricular pressure. As a result, a transseptal pressure gradient leads to paradoxic septum movement (41). The consequence of this leftward septal bowing is not only ineffective right ventricular end-systolic contraction but also impaired left ventricular early diastolic filling (41). A decreased left ventricular end-diastolic volume directly impairs left ventricular output according to the Frank-Starling mechanism (42,43).

Next, because both ventricles share the same pericardial space, dilation of the right ventricle will be accompanied by increased pericardial stretch. This inward directed force may impair left ventricular filling. An effect of such pericardial constraint on left ventricular filling has been demonstrated in an acute model of right ventricular pressure overload in dogs (44). Opening of the canine pericardium facilitated left ventricular filling and consequently improved cardiac output (44,45). The consequences of pericardial constraint in chronic pressure overload are less clear (46). Pericardial constraint and impaired left ventricular filling may influence the perfusion of the right coronary artery and thus oxygen supply to the left ventricle.

Conclusions

In summary, patients with pulmonary arterial hypertension and right ventricular dysfunction may have decreased cardiac output, activation of the neurohormonal axis, and renal retention of sodium and water. The analysis of systemic and renal hemodynamics and activation of the neurohormonal axis (norepinephrine, RAAS, and AVP) in patients with right ventricular failure secondary to pulmonary arterial hypertension has not been undertaken. Moreover, the response to mineralocorticoid antagonist and vasopressin receptor antagonist has not been studied in patients with right ventricular failure. Studies at various stages of pulmonary arterial hypertension need to be undertaken to examine sodium and water balance, neurohumoral axis, particularly the RAAS, and the response to V2 vasopressin receptor and mineralocorticoid antagonists.

Disclosures

None.

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