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Review

Pathophysiology of cardiorenal syndrome in decompensated heart failure: Role of lung–right heart–kidney interaction

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ABSTRACT

Cardiorenal syndrome (CRS) is defined as an interaction of cardiac disease with renal dysfunction that leads to diuretic resistance and renal function worsening, mainly with heart failure (HF) exacerbation.
Hemodynamic variables linking heart and kidney are renal blood flow (cardiac output) and perfusion pressure, i.e., the aortic – renal venous pressure gradient. CRS has traditionally been interpreted as related to defective renal perfusion and arterial underfilling and, more recently, to elevation in central venous pressure transmitted back to renal veins.
Our suggestion is that in a setting where aortic pressure is generally low, due to heart dysfunction and to vasodrepressive therapy, the elevated central venous pressure (CVP) contributes to lower the renal perfusion pressure below the threshold of kidney autoregulation (≤80 mm Hg) and causes renal perfusion to become directly pressure dependent. This condition is associated with high neurohumoral activation and preglomerular vasoconstriction that may preserve pressure, but may decrease filtration fraction and glomerular filtration rate and enhance proximal tubular sodium absorption. Thus, congestion worsens and drives the vicious cycle of further sodium retention and HF exacerbation. Lowering CVP by targeting the lung–right heart interaction that sustains elevated CVP seems to be a more rational approach rather than reducing intravascular volume. This interaction is crucial and consists of a cascade with stepwise development of pulmonary post-capillary hypertension, precapillary arteriolar hypertone, right ventricular overload and enlargement with tricuspid incompetence and interference with left ventricular filling (interdependence). The resultant CVP rise is transmitted to the renal veins, eventually drives CRS and leads to a positive feedback loop evolving towards HF refractoriness.
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1. Introduction

Cardiorenal syndrome (CRS) describes a coexistence and an interaction of cardiac disease, mainly chronic heart failure (HF), with renal dysfunction, that may lead to diuretic resistance and worsening of renal function [1,2]. The former condition is currently named CRS Type 2 and refers to a chronic state of kidney and heart disease in which a reciprocal negative interaction is apparent, although the complexity of the mechanisms makes the pathogenesis difficult to define [3].

On the other hand, therapy aimed at relieving congestive signs and symptoms of acute HF exacerbation and diuretic resistance, defined as persistent pulmonary congestion despite attempts at diuresis [3], may be associated with further renal function deterioration [3–5]. Although this condition which is currently named Type 1, more appropriately represents the acute subcategory, cardiologists currently identify it with the CRS. The present review will focus the lung–right heart–kidney interaction as a key multiorgan system dysfunction possibly triggering and sustaining the pathophysiology of the disease.

2. Hemodynamic background

In chronic HF and in acute exacerbation, renal impairment [3,6], mainly if associated with venous congestion [7,8], is one of the most significant determinants of prognosis. The generally accepted hemodynamic variables linking heart function to the kidney are renal blood flow and renal perfusion pressure (RPP). RPP is the gradient between aortic and renal venous (right atrial) pressures and is a determinant of the flow along with the cardiac output. CRS has traditionally been interpreted as a consequence of an insufficient renal perfusion, which decreases disproportionally fast with declining cardiac output [9], and of hypovolemia generally due to overzealous prescription of diuretics. Nevertheless, it has long been recognized that a backward transitory transmission of central venous pressure (CVP) elevation leads to direct renal dysfunction [10–12].

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Recent human data provide convincing evidence that high CVP opposing venous return from kidney, and lowering the RPP, is associated with impaired renal function [6]and independently related to all-cause mortality in a broad spectrum of patients with cardiovascular disease [12]. In the presence of pulmonary hypertension with right ventricular dysfunction and relatively preserved cardiac output, CVP elevation is associated with reduced glomerular filtration rate [6]. In a prospective study of 145 patients with advanced decompensated HF, Mullens and co-workers [13] have shown that venous congestion (both with increased CVP on admission and inadequate decrease of venous pressure with treatment) is the strongest hemodynamic determinant of CRS, whereas progressive or persistent reduction of cardiac output may not have a primary role in the development of the disorder. Thus, according to the current literature, hypervolemia with increased central venous and renal vein pressures is suggested as the primary cause for congestion of the kidney and CRS. The most accredited interpretation of the pathophysiological substrate is that raised central venous pressure causes extravasation with congestion of the kidney, increase of the renal interstitial pressure leading to hypoxic state of the renal parenchyma, tubular dysfunction and activation of the renin–angiotensin system (RAS) [14,15].

A complementary or alternative way of interpreting the mechanistic role of the renal venous pressure in CRS is considering the venous pressure as a component of the perfusion pressure and not simply as a consequence of congestion. When venous pressure is exceedingly raised, mainly if in combination with a reduced mean aortic pressure, the RPP may be lowered to ≤80 mm Hg, that is the threshold of kidney autoregulation. Related to this, three points are firmly established: (i) below the threshold of autoregulation, renal perfusion becomes directly pressure dependent [9]; (ii) in acute decompensated HF, mean aortic pressure, because of pump inadequacy and/or therapy with diuretics, beta-receptor blockers, RAS inhibitors, tends to become reduced and mean right atrial pressure tends to become raised because of right ventricular dysfunction and tricuspid regurgitation; (iii) in this setting, a high degree of neural and humoral activation produces preglomerular vasoconscriction that sustains blood pressure, but decreases filtration fraction and glomerular filtration rate [15] and enhances proximal tubular sodium and water reabsorption [16,17].

According to the renal function curve [18] depicted in Fig. 1, when arterial pressure (that in normal individuals closely corresponds to renal perfusion pressure) rises above a critical level, loss of extracellular fluid from the body becomes greater than fluid intake, and this decreases both blood volume and cardiac output, returning the pressure back to normal. On the contrary, when aortic pressure falls below this same critical level, the kidney reduces fluid excretion, blood volume and cardiac output increase and pressure returns toward the equilibrium point between salt intake, fluid and salt excretion and renal perfusion pressure.

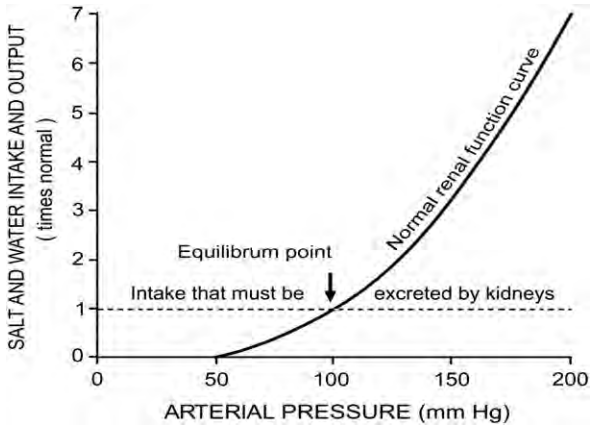

Fig. 1. Equilibration of the normal renal function curve with salt and water intake. The equilibrium point gives pressure level at which kidney-fluid mechanism will control arterial pressure. From reference 18, by permission.

The picture is different in decompensated HF patients in whom pump failure can prevent recovery of aortic pressure despite an increase in blood volume, and the elevated right atrial pressure assumes a critical role in reducing the driving pressure through the kidney. In this setting, the possible benefits of a decrease back towards normal of right atrial and renal venous pressure can be easily perspected. Otherwise, the potential results may be oliguria, fluid retention, worsening of congestion, drive of the vicious cycle of further sodium retention, volume expansion, HF exacerbation.

That in decompensated HF excessive CVP, defective RPP and neurohumoral activation are linked with renal function, oliguria and fluid retention, is convincingly supported by results with fluid withdrawal and congestion relief with ultrafiltration (UF) [19,20]. In these, studies patients having oliguria, congestion, higher CVP and lower RPP had also higher levels of circulating norepinephrine (NE), renin and aldosterone. In these patients, and not in those without overhydration and venous congestion, UF caused an extreme potentiation of sodium and water excretion associated with neurohumoral modulation, CVP reduction and RPP recovery.

3. Diuretics and UF as remedies to venous congestion

Diuretic therapy tailored to overcome diuretic resistance, and extrarenal methods, such as UF, aimed at fluid withdrawal and relief of congestion, are the main currently available strategies for reducing venous congestion in decompensated HF. Which of the two is safer and more effective, is a matter of debate and still unsettled [21–24]. There are, however, three peculiar features of the extrarenal method that deserve mention. One is that in continuous hemofiltration, fluid and medium-sized solutes are removed, allowing for clearance of various agents, some of which may be contributing to CRS. Subtraction of proinflammatory cytokines [3,5,25,26] or sodium-retaining vasoconstrictive agents, is potentially involved in improvement in urinary output or restoration of diuretic responsiveness [19,20,27]. A typical example is that of circulating NE, whose inactivation process by the lung endothelium [28] may become exhausted with cathecholamine overflow. NE withdrawal by the mechanical method of UF has been proven to reactivate the metabolism process, to trigger a positive feedback loop between fall of circulating NE and recovery of the lung metabolic activity [29] and to result in sustained modulation of the catecholaminemia [29,30].

A second peculiarity is that the ultrafiltration-mediated neurohumoral regulation, as reflected by a drop in plasma BNP [31], norepinephrine, renin and aldosterone [19,20], is sustained (Fig. 2). This is probably a reason why improvement in clinical signs and symptoms of volume overload were found to be persistent at 90-day follow-up after isolated UF [31], functional capacity was enhanced in another same duration trial of patients undergoing UF [32] and the procedure was associated with fewer rehospitalizations compared in to diuretic therapy [33]. Interestingly, when a similar amount of fluid was removed by furosemide, both neurohumoral and exercise performance did not improve (Fig. 2).

A third topic which deserves mention is the mechanisms whereby UF reduces the right atrial pressure. Patients with acute decompensated HF and ≥2 of the following: peripheral or sacral edema, enlarged liver or ascites, orthopnea, pulmonary rales or pleural effusion, jugular venous distention, diuretic resistance, were subjected to UF with contemporary monitoring of right atrial pressure, hematocrit and serum sodium concentration taken as indices of the relative water content of the blood [34]. As shown in Fig. 3, hematocrit and serum sodium concentration were steady until an average of 2000 ml of fluid was withdrawn, indicating that water removed from the intravascular space was replaced by a similar amount of reabsorbed fluid from the extravascular phase. In parallel with and in spite of this, a stepwise drop in mean right atrial pressure was observed. With further fluid withdrawal, some hemoconcentration

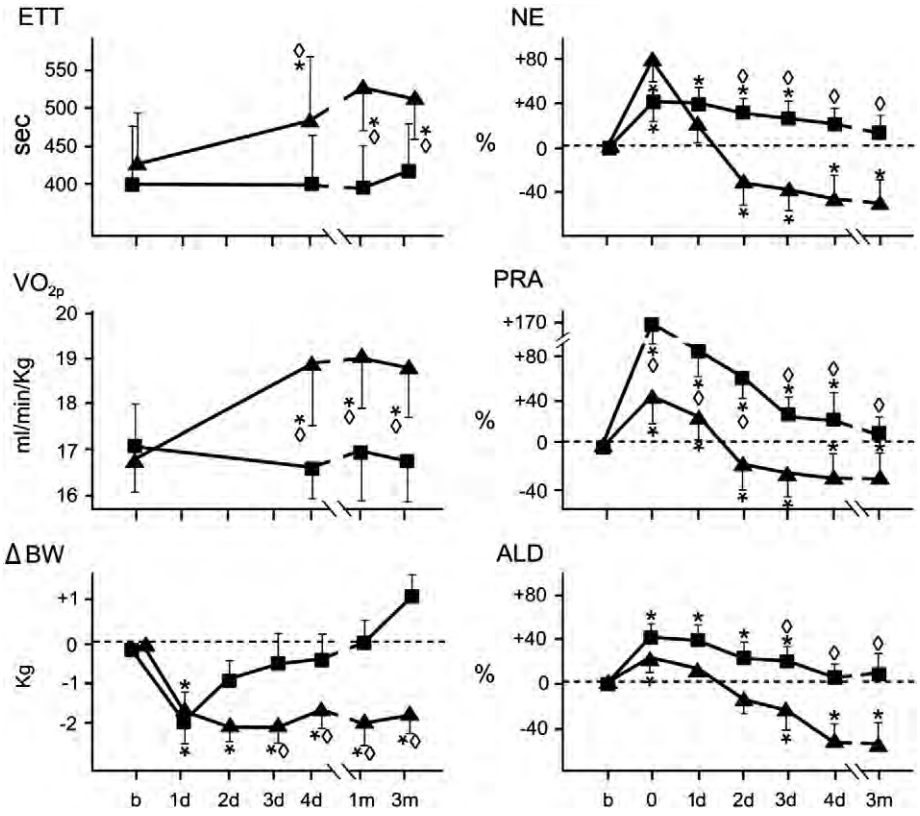

Fig. 2. Exercise tolerance time (ETT), peak exercise oxygen consumption (VO_{2p}) in acute decompensated heart failure patients at baseline (b) and at 4 days (d), 1 month and 3 months (m) after isolated ultrafiltration (▲) or i.v. furosemide (■) and corresponding changes in body weight (ΔBW), circulating norepinephrine (NE), aldosterone (ALD) and plasma renin activity (PRA). * $p < 0.01$ vs baseline; ◊ $p < 0.01$ vs furosemide. Adapted with permission from reference 32.

would appear, reflecting reduction in intravascular volume. Thus, postulation of a decrease in circulating blood volume may not be necessary to justify the decrease in right atrial pressure in the earlier stages of UF. A reasonable interpretation may be that interstitial fluid accumulation makes the lungs stiffer requiring higher intrapleural pressure for distention. This would raise pressure on the outside of the heart and cause increase in transmural pressure. Interstitial fluid reabsorption would lead to extramural pressure modulation. Alternatively, the excess of fluid in the loose interstitial space of the lung increases the interstitial pressure, thus compressing and affecting the caliber of extra-alveolar arterioles, increasing the right heart hemodynamic load. Fluid removal would unload the ventricle and decrease the right atrial pressure. Whatever the mechanism at work, it seems possible that removal of excessive extravascular fluid from lung, pleural and abdominal [35] cavities, can lower right atrial pressure and contributes to modulate venous congestion, the hemodynamic alteration driving the CRS.

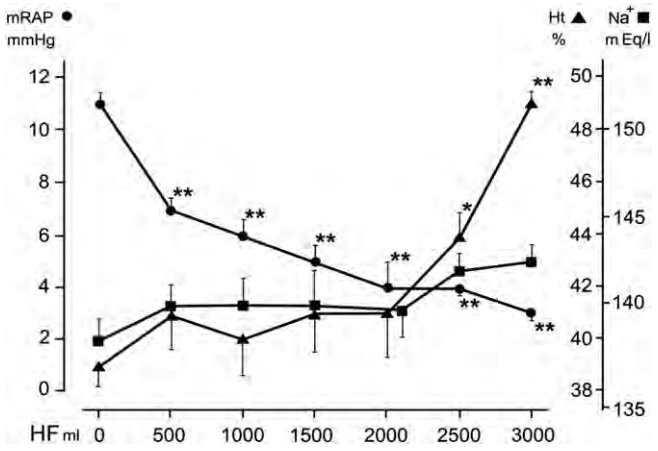

Fig. 3. Mean right atrial pressure (m RAP ●), hematocrit (Ht ▲) and serum sodium concentration (Na^+ ■) at different stages of fluid withdrawal with hemoflitration (HF) * $p < 0.05$ and ** $p < 0.01$ vs baseline. From reference 34, by permission.

4. Lung–right heart coupling and systemic venous pressure elevation

More than two thirds of patients with severe left ventricular function deterioration (mainly diastolic, regardless of ejection fraction) develop impaired right ventricular performance and failure. The evidence that right heart dysfunction [36] and CRS [3,4] both are predictors of poor prognosis in HF patients, reinforces, on a clinical basis, the concept that there is a link between the two disorders. Whether the connection is a complementary or synergic one, is not known. A brief review of the upstream factors that generate central venous pressure elevation may be informative.

The right ventricle empties its volume into a very low impedance circulation and maintains stroke output according to venous return. The ventricle is quite sensitive to variations in afterload and responds with significant fall in stroke volume to increases in pulmonary vascular tone. Adaptive mechanisms to overload are development of hypertrophy and, subsequently, dilatation, leading to tricuspid incompetence. The progressive transformation of the normal crescent shape of the right ventricle into a more spherical structure, subtracts pericardial space to the left ventricle, causes leftward shift of the septum, impairs diastolic filling of the ventricle, leading to decreased stroke volume and cardiac output and arterial underfilling [37].

In the lung, a single capillary network accomplishes both organ nutrition and gas exchange. Nutrition requires fluid to filter to the extra vascular phase, while gas exchange preservation needs filtered interstitial fluid to be finely adjusted by venous and, mainly,

lymphatic reabsorption [38]. Under this respect, it is remarkable that leaked protein does not re-enter the blood vessels unless by the lymphatic system; this system is the primary safety factor protecting the lung against edema [39]; the lymph drained from the lungs converges to the superior vena cava and the right heart. It is intuitive that any reason increasing central venous pressure and, thus, impeding the lymphatic drainage, has the potential to expand the lung interstitial fluid. Right ventricular failure, mainly if associated with tricuspid regurgitation, is one of these reasons. The consequences of excess of fluid in the pulmonary interstitium on the cardiac extramural pressure and lung arteriolar lumen, have been described in a section above.

When the left ventricle is failing and preload is excessive, the raised pulmonary vein and capillary pressure require the pulmonary perfusion pressure to increase correspondingly; this leads to hypertrophy and fibrous changes of arteries and veins [37]. Another retrograde effect of left-sided disease is endothelial dysfunction with impaired vascular smooth muscle relaxation [37]. This "restrictive" pattern and the disturbed lung diffusion capacity can produce hypoxia and contribute to further pulmonary arterial pressure rise. Thus, the primary causes of right ventricular involvement in HF seem to be post-capillary pressure rise, pre-capillary arteriolar reactive hypertone and compression or intrinsic remodeling, increased transpulmonary pressure gradient superimposed on venous pressure, excessive afterload. In this setting, three events are most likely: (i) the right ventricle enlarges and causes tricuspid incompetence and mechanical left ventricular filling impairment; (ii) CVP rises and impedes the lung lymphatic drainage; (iii) the elevated CVP is transmitted to the renal veins and kidney. This triggers the so-called CRS and ultimately leads to a positive feedback loop whose final result is HF refractoriness. Therefore, the clinical and prognostic significance of right ventricular failure is not simply a further deterioration of cardiac output, but it is a multi-factorial process based on multi-organ interaction, in which renal dysfunction may have an important complementary role. Fig. 4 depicts the multiple pathophysiological adaptations and their interactions, occurring in the heart and the lungs when the failing heart leads to renal venous pressure rise.

Thus, the assumption is that the right heart has the potential to trigger a cascade of life-threatening events that involve the kidney and that the pulmonary circulation, by raising right ventricular afterload, is the upstream elicitor. The demonstration would be crucial that modulation of right ventricular afterload benefits venous congestion and renal function and the vicious cycles that feed the cascade are interrupted. Agents targeted pulmonary vascular tone reduction may deserve consideration under this respect.

5. Right ventricular unloading agents and changes in central venous pressure

Pulmonary hypertension (PH) due to left heart disease is classified as group 2 according to the Dana Point 2008 classification. The key hemodynamic differentiation of Group 2 PH from others is pulmonary capillary wedge pressure ≥15 mm Hg. When pulmonary artery pressure is elevated without or with only minimal increase in transpulmonary gradient (TPG), PH is referred as "passive" or "post-capillary" and is a reflection of downstream (left heart) pressure rise. Group 2 PH may progress to a "reactive" stage with increase in TPG and pulmonary arterial resistance. This form is often called "precapillary" or "mixed" [37]. It follows that for unloading the right ventricle in Group 2 PH the rational is reducing left ventricular preload in the "post-capillary" form and improving left ventricular diastolic properties and pulmonary arterial lumen biology in the "precapillary" one.

In Group 2 PH, intravenous prostacyclin, a powerful pulmonary vasodilator, reduces pulmonary vascular resistance and increases cardiac

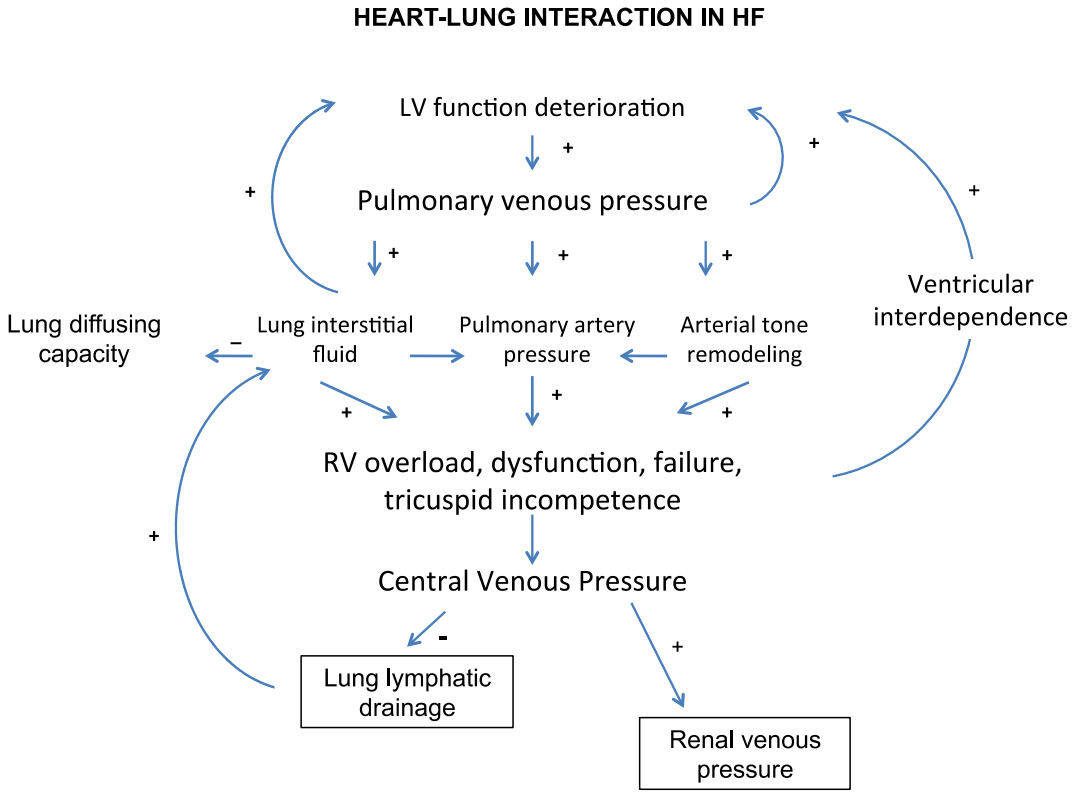

Fig. 4. The cascade of changes, and their interactions, involving heart and lungs in cardiac failure and resulting in renal venous pressure rise.

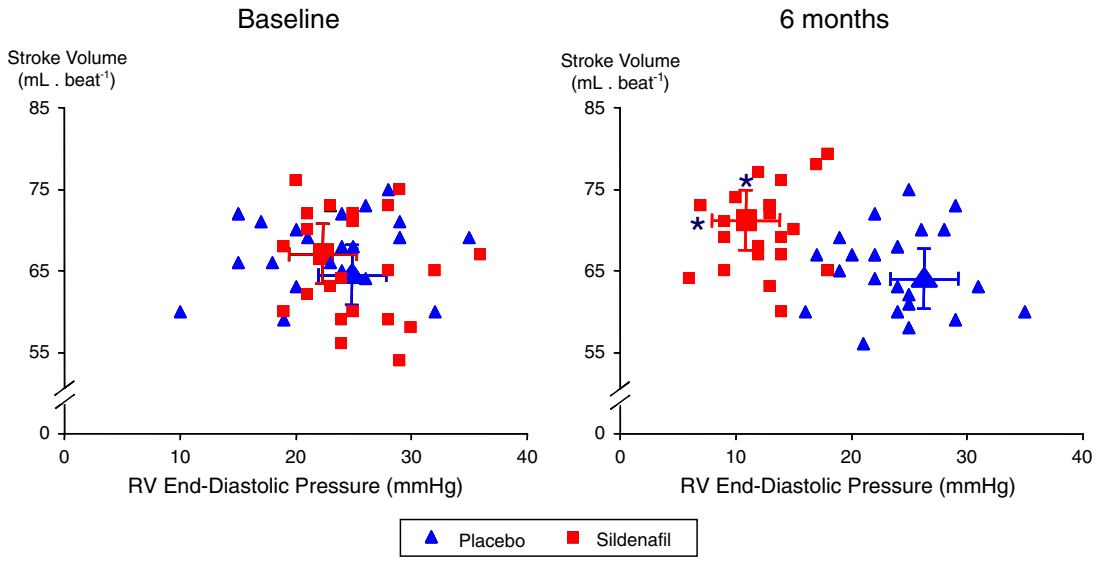

Fig. 5. Individual and mean values of the right ventricular (RV) end-diastolic pressure–stroke volume relationship at baseline and after 6 months of placebo (▲) or sildenafil (■) in patients with decompensated HFpEF. * $p < 0.01$ vs placebo. From reference 56, by permission.

output, but is also associated with marked decrease in systemic resistance and with secondary neurohormonal activation [40]. Despite positive early hemodynamic reports, in the Flolan International Randomized Survival Trial (FIRST) intravenous epoprostenol therapy was associated with a trend toward increased mortality leading to premature trial termination [41].

In a small HF trial, intravenous nonselective endothelin receptor blockade with bosentan reduced pulmonary artery and right atrial pressures and pulmonary vascular resistance and increased stroke volume and cardiac output [42]. However, a series of large scale trials performed in chronic HF patients did not produce corresponding favorable results on harder endpoints [43,44].

Inhaled nitric oxide in post-transplant PH induced a selective decrease in pulmonary vascular resistance without systemic resistance changes [45]. A concern regarding inhaled nitric oxide therapy in left-sided pulmonary hypertension stems from the effects of unbalanced pulmonary vasodilatation which may lead to dramatic increases in wedge pulmonary pressure from an excess of preload in the setting of a poorly compliant left ventricle. The consequence may be precipitating of pulmonary edema [46]. Acute infusion of L-arginine, the substrate for nitric oxide production, reduces pulmonary artery pressure and resistance in PH, but has not been tested in patients with HF [47].

In HF, nitric oxide dependent pulmonary vasodilatation is impaired and primarily contributes to pulmonary endothelial dysfunction [48]. Accordingly, therapeutic strategies with agents that increase the nitric oxide pathway, such as phosphodiesterase 5 inhibitors (PDE5I) have been tested [49]. Administration of the PDE5I sildenafil reduces pulmonary arterial pressure and resistance without substantial changes in the systemic circulation [50–52], and attenuates the increase in TPG during exercise [53].

Pulmonary pressure rise in HF patients with preserved ejection fraction (HFpEF) is of frequent occurrence and often severe [54], CRS is equally or even more prevalent in these patients than in those with reduced ejection fraction [55]. In a recent controlled study [56] of patients with HFpEF and increased TPG, sildenafil given for 1 year, improved pulmonary arterial pressure and vasomotility, right ventricular function and dimension, left ventricular filling pressure, relaxation and distensibility, lung interstitial water metabolism and central venous pressure. Fig. 5 shows the right ventricular end-diastolic pressure–stroke volume relationship (Frank–Starling relationship) in these patients at baseline and after 6 months of sildenafil or placebo. Importantly, the relationship was shifted leftward and the right ventricular preload in the active treatment arm was half reduced. These findings may suggest that PDE5I have the potential to favorably affect both the postcapillary and precapillary determinants of the excessive right ventricular afterload and CVP rise in HF failure patients and to counteract their influence on the driving pressure through the kidney.

A controlled randomized study of PDE5I in heart failure patients with CRS is ongoing to identify whether pulmonary and right heart hemodynamic improvement can affect renal function and diuretic resistance and support a participation of lung–right heart–renal interaction in the pathogenesis of the syndrome.

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