Neurohormonal modulation in right ventricular failure

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Sympathetic system stimulation, followed by activation of the renin, angiotensin, and aldosterone system, is an important contributor to the vicious circle of chronic heart failure (CHF). Accounting for this excessive neurohormonal response resulted in major and highly effective changes in therapeutic approach to CHF, primarily due to left ventricular (LV) dysfunction. Indeed, this disturbed neurohormonal balance can be at least partly restored by adrenergic beta-receptor blockers, angiotensin-conversion inhibitors and receptor blockers, and aldosterone antagonists, with beneficial functional and prognostic effects. Right ventricular (RV) dysfunction due to severe pulmonary hypertension (PH) ultimately results in similar changes in systemic haemodynamics, which trigger neurohormonal response in LV failure, including low cardiac index and hypotension. However, the evidence related to the presence and clinical significance of neurohormonal activation in primarily RV failure is very limited. Are similar neurohormonal mechanisms contributing to vicious circle of RV failure induced by PH? Could experience gained from left heart failure treatment be useful to protect RV? This somewhat provocative article will review the existing evidence, current recommendations, and future directions related to these problems.

KEYWORDS
Pulmonary hypertension; Chronic heart failure; Right ventricular function; Prognosis

Pathophysiology and clinical significance of neurohormonal modulation in chronic heart failure

Chronic heart failure (CHF) resulting in decreased systemic cardiac output generates two main and different lines of neurohormonal response. The first one aims to restore systemic blood pressure by vasoconstriction and through increase in circulating blood volume. The other controls a potential overshoot of the first response, especially related to excessive fluid retention, and its effects on the filling pressures of the heart.

Analysing the first line of neurohormonal response using teleological approach, it appears that it was ‘designed’ to save life of a wounded and bleeding creature, be it an animal or a man. Acute hypovolaemia due to bleeding required pumping up haemodynamics in order to escape from a predator. Run for your life–hide–heal-and-survive chance could be offered to resolve reversible problems. The natural law of the jungle did not consider survival of a creature with a chronically failing heart. Although potentially lifesaving in the case of a haemorrhage, chronic neurohormonal activation was found to be detrimental in CHF.

Mechanisms, pathways, and consequences of neurohormonal modulation in CHF were extensively described in a special supplement to Eur Heart J and elsewhere. Briefly, they are initiated by excessive sympathetic activity, followed by activation of the renin, angiotensin, and aldosterone system (RAAS) with contribution from arginin vasopressin.1,3 Sympathetic over-activity results mostly from deranged autonomic balance which is dominated by sympathetic system because of decreased baroreceptor discharge. The latter is due to both reduced systemic pressure and decreased baroreceptor sensitivity. Urine and plasma norepinephrine (NE) as well as directly measured sympathetic nerve traffic are all augmented in CHF. Interestingly, the failing myocardium shows downregulation of adrenergic receptors, and especially beta-1 receptors, making it less responsible to inotropic stimuli. This is mostly due to their decreased density, attributed to prolonged sympathetic system activation. Downregulation of the adrenergic receptors is...
mostly limited to the heart and do not prevent from systemic vasoconstriction induced by sympathetic over-activity. It contributes to the decreased renal perfusion pressure and to the activation of RAAS system. This results in further systemic and renal vasoconstriction, decreased NE clearance but most of all in excessive fluid and salt retention, putting additional load on the failing heart.

Clearly, the detrimental effects of this line of neurohormonal response to CHF extend beyond purely haemodynamic overload. It enhances pathological myocardial hyper trophy, oxygen demand, and apoptosis/necrosis of the myocytes. Non-uniform downregulation of beta-adrenergic receptors further increases arrhythmogenic risk induced by increased sympathetic activity. Moreover, RAAS and especially aldosterone promote pathological ventricular hypertrophy with increased collagen synthesis, resulting in progressive fibrosis of the myocardial wall. Although natriuretic peptides are excreted in response to excessive diastolic atrial and ventricular wall stress and counterbalance excessive vasoconstriction and fluid retention, their protective effects at cellular level are not clinically relevant. In fact, higher levels of ANP and especially B-type natriuretic peptide (BNP) indicate worse prognosis in advanced CHF, placing natriuretic peptides more as markers of severity than modulators of the disease.

Most of the neurohormonal pathways, leading ultimately to vicious circle of progressive heart failure as well as increased risk of sudden cardiac death can be approached by specific pharmaceutical interventions. Of note, their effects on exercise tolerance and survival are documented when applied on top of traditional treatment of CHF such as diuretics and/or vasodilators. This is particularly evident in the case of beta-blockers. Despite negative inotropic effects, which kept them for decades on the list of prohibited drugs in heart failure, prolonged administration of beta-blockers improve left ventricular (LV) function and survival in CHF. The evidence supporting low-dose spironolactone as an add-on therapy to ACE-inhibitors to reduce mortality in CHF indicates how important it is to consider all clinically relevant neurohormonal modulations induced by heart failure.

Current standards of protection from neurohumoral factors in CHF due to LV dysfunction, as presented above, seem to be close to optimal. Further improvements in outcome using this approach seem unlikely. On the other hand, potential neurohormonal modulations are not accounted for current management strategies used in right ventricular (RV) failure.

**Similarities and differences in signals triggering neurohormonal response in left and right ventricular failure**

Although initial triggers of neurohormonal modulation in CHF are still a matter of controversy and research, main variables and sensors responsible for clinically relevant sustained neurohormonal modulations in LV failure seem to be identified: systemic arterial baroreceptors respond to systemic hypotension whereas peripheral and carotid chemoreceptors to hypoxaemia, both contributing to sympathetic activation. Most of those sensors should be activated by LV and RV failure, alike. Systemic hypotension at rest and especially during exercise is an important feature of RV failure due to PH, carrying adverse prognostic implications. It is caused by reduced LV diastolic filling and resulting decreased systemic cardiac output. Hypoxaemia is also common in PH-induced RV failure. It is attributed to combined effects of significant desaturation of blood in hypo-perfused peripheral tissues and perfusion/ventilation mismatch caused by non-homogeneous distribution of pulmonary vascular disease at the level of microcirculation. As a result of systemic hypotension and sympathetic stimulation, RAAS activation should also be expected in isolated RV failure. Therefore, the only apparent difference is related to stretch sensors in left heart and pulmonary veins (if any) which should remain unloaded in isolated RV failure.

**Evidence for neurohormonal modulation in right ventricular failure**

Few reports focus on ‘sympathetic’ neurohormonal activation in isolated RV failure, such as induced by idiopathic pulmonary arterial hypertension (IPAH). Nootens et al. assessed plasma levels of NE and renin activity (RA) in samples from right atrium, pulmonary, and femoral artery in 21 patients with IPAH (formerly called primary PH). Median NE levels were 501, 441, and 443 pg/mL, respectively—almost twice as high as those found in peripheral vein in control healthy subjects. In contrast, RA was similar in patients and controls. Among patients with IPAH plasma NE levels correlated with pulmonary haemodynamic variables, most closely with PVR ($r = 0.69$, $P < 0.001$). Nootens et al. used the formula derived from large PPH registry to predict 5-year survival in three groups created according to increasing plasma NE levels. Patients with plasma NE < 370, 370–500 pg/mL and more than 500 pg/mL had expected 5-years survival of 44, 31, and 17%, respectively. However, formal long-term follow-up was not done.

Nagaya reported on plasma NE correlation with NYHA functional class in 60 patients with PAH. Plasma NE levels were higher among patients in class IV than in class III and in class II (Figure 1). However, in contrast to Nootens et al. no correlations with plasma NE levels and haemodynamic indices were found. Nevertheless, plasma NE levels were significantly higher both at baseline and after 3 months of (mostly oral beraprost) treatment in patients who died during a mean 24 ± 2 months of follow-up (Figure 2). In contrast to NE, plasma epinephrine was not elevated in patients with PAH and did not correlate with their NYHA functional class or survival.
Other \textsuperscript{23} but not all authors \textsuperscript{24,25} confirmed plasma NE elevation in IPAH. However, circulating catecholamines are not considered as ideal markers of sympathetic activation. A recent attempt to assess sympathetic system activity by direct recording of sympathetic nerve traffic [measured sympathetic nerve activity (MSNA)] to muscle circulation found it increased in IPAH.\textsuperscript{25} Seventeen patients had higher burst frequency (67 ± 4 vs. 40 ± 3 bursts/min, \( P < 0.0001 \)) than 12 age, gender, and body-mass matched controls. Mean systemic blood pressure was lower (81 ± 3 vs. 89 ± 2 mmHg, \( P = 0.046 \)) and heart rate (HR) was higher (82 ± 4 vs. 68 ± 3 b.p.m.; \( P < 0.02 \)) in patients than in controls (Figure 3). In eight out of 17 patients, plasma NE was assessed and was found normal, but MSNA was not reported for this subgroup. In the whole group, HR strongly correlated with MSNA, as assessed by the number of bursts/min. Because of lower oxygen saturation in IPAH patients and a potential contribution of hypoxaemia to sympathetic over-activity, oxygen was used to restore normal SaO\textsubscript{2}. Fifteen minutes of hyperoxic breathing significantly improved but not normalized MSNA tracings among 14 patients submitted to this intervention. This confirms earlier report in patients with PAH, in which plasma NE levels could be decreased following the 10 min of oxygen breathing and correction of hypoxaemia.\textsuperscript{23} A current study, however, indicated that only about one-fourth of sympathetic over-activity in PAH can be attributed to chemoreceptors, whereas most of it is probably due to haemodynamic or other still unrecognized factors related to pulmonary vascular disease.\textsuperscript{25}

Heart rate variability (HRV) is an accepted reliable non-invasive method for the assessment of the autonomic balance. HRV of 15 min long ECG recordings was evaluated in 75 patients with CHF referred for heart transplantation screening.\textsuperscript{26} Analysis of standard frequency domain parameters revealed significant correlation between NE plasma levels and low to high frequency ratio (LF/HF, \( r = -0.34; P = .03 \)), which was an independent predictor of cardiac events at follow-up. Interestingly, a reduced HRV was predominantly related to indexes of RV and not LV dysfunction, with the best correlations between LF and RVEF (\( r = 0.47, P < 0.001 \)). This may suggest significant contribution of the RV dysfunction to abnormal autonomic balance even in primarily LV-dependent CHF.

Significance of increased sympathetic neurohormonal activity in RV failure

As previously mentioned, NE levels seem to be related to prognosis both in LV and RV failure. Whether sympathetic activity should be considered a marker or a factor contributing to organ and particularly RV damage and failure remains unclear. Data suggesting the latter are scarce but conceptually interesting. Some of them indicate that both ventricles suffer from sympathetic neurohumoural over-activity, regardless whether it was induced by CHF primarily caused by LV or RV dysfunction. In a recent report, rats with monocrotaline-induced PAH were used to examine whether upregulated neurohumoural factors may induce LV remodelling and
affect prognosis. Measured plasma levels of angiotensin II, noradrenaline, and BNP were all significantly elevated in the PAH rats. In contrast to a previous report, morphological analysis revealed a significant increase in the weight of the free walls of both ventricles, despite normal systemic blood pressure. The activation of a foetal gene programme, similar to that induced by continuous infusion of angiotensin II, was also evidenced in both ventricles.

Interestingly, survival rate was significantly improved when rats with monocrotaline-induced pulmonary hypertension (PH) were treated with an angiotensin II type 1 receptor blocker, valsartan, or an adrenergic \( \alpha_1 \) and \( \beta_1 \) blocker, carvedilol. The authors concluded that upregulated neurohumoural factors play a role in LV remodeling, despite lack of its haemodynamic overload and that protection from neurohormonal factors seemed to improve outcome in rats with monocrotaline-induced PAH. Similar findings indicating LV myocardial involvement were recently reported by a Portugal group using the same model of monocrotaline-induced PAH and RV failure. However, in this case, the authors found endotelin overexpression as a more probable cause of abnormal LV indexes of contractility and relaxation as well as force–frequency relationships of the muscle strips, when compared with sham rats.

A recent trial assessing the mechanism of protective effect of the LV assist device on reverse remodelling of both ventricles suggested that it could depend upon normalization of neurohormonal milieu. Explanted hearts from medically treated patients were compared with those explanted from patients who benefited from LV mechanical support, resulting in higher cardiac output. When compared with the hearts from medically treated patients, the hearts which benefited from LV mechanical support showed improved force generation in response to beta-adrenergic stimulation not only in isolated LV muscle trabeculae but also in those taken from the RV. The hearts of patients benefiting of mechanical LV support had also higher myocardial beta-adrenergic receptor density both in LV and in RV than those explanted from the remaining patients. The authors interpreted their findings as indicating that improved systemic haemodynamics contribute to remodelling of the beta-adrenergic pathway in both ventricles, most probably due to normalization of neurohormonal environment. Limitation of this trial includes lack of direct assessment of neurohormonal activation. Also, indirect beneficial influence of LV mechanical support on the RV afterload, as indicated by lower mean pulmonary arterial pressure in mechanically assisted patients, could account for some of the observed RV reverse remodelling.

Is there evidence that RV myocardium suffer from increased sympathetic activity in PAH?

In a trial assessing prognostic markers in patients with precapillary PH, we found detectable troponin T levels in eight out of 56 patients. Survival estimated by Kaplan–Meier curves was significantly worse at 24 months in patients with detectable troponin leakage (29% vs. 81%, respectively, log-rank test \( P < 0.001 \)). Those differences in prognosis between patients with and without detectable plasma troponin levels were found, despite their similar haemodynamic characteristics, including PAP, right atrial pressure, and cardiac index. The two exceptions were lower mixed venous oxygen saturation (50 ± 10% vs. 57 ± 9%, \( P < 0.04 \)) and markedly higher heart rate (92 ± 15 vs. 76 ± 14 b.p.m., \( P < 0.004 \)). HR is an accepted marker of sympathetic activity. In patients with IPAH, HR was reported to correlate with directly measured MSNA. Taken together, those data may suggest a potential impact of increased sympathetic activity on the integrity of contractile proteins and/or myocardial cells in patients with RV pressure overload. Interestingly, all three patients who survived the period of follow-up, despite initially detectable plasma troponin levels became troponin-negative as a result of introduced treatment.

MSNA activity in patients with PAH has been also found to decrease after atrial septostomy—an intervention increasing systemic cardiac output and unloading the RV (A. Ciarka and R. Naeije, personal communication). Although the quoted study did not look at long-term prognosis, earlier reports suggested that atrial septostomy,
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despite being a ‘palliative’ intervention, improved survival.\textsuperscript{32} Whether this is partly due to the reported improvement in neurohormonal balance remains to be assessed.

Current clinical and potential future research implication

Spironolactone remains the only classical neurohormonal modulator which found place in the treatment of isolated RV failure. It is used in PAH as an adjunct to loop diuretics, but also with the hope of limiting the aldosterone-induced myocardial fibrosis.\textsuperscript{12} Digoxin, another drug often used also for the treatment of isolated RV failure, was reported to decrease plasma NE in patients with PAH, at least in acute experiment.\textsuperscript{33}

Other neurohormonal modulators used in LV failure are so far prohibited in PH. ACE-inhibitors, angiotensin receptor blockers, and beta-adrenergic blockers all may induce systemic hypotension. Beta-blockers add to the risk their negative inotropic and chronotropic properties. Of note, these very properties kept beta-blockers away from patients with LV failure for two decades.

However, it should be remembered that systemic vaso-dilatation is per se beneficial in LV failure, reducing its afterload and increasing cardiac output. In contrast, any degree of hypotension can be expected to worsen RV coronary perfusion\textsuperscript{34} and interventricular support\textsuperscript{34} of the failing RV, resulting in net decrease in cardiac output.\textsuperscript{35,36} Indeed, the holy grail in PAH so far was to improve improvement in cardiac output and systemic pressure applied with the hope that even mild to moderate improvement in cardiac output and systemic pressure offered by available pharmacotherapy will improve neurohormonal balance, hopefully preventing vicious circle of RV failure from spinning round.

Conflict of interest: none declared.

References


