Adrenomedullin in Heart Failure

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Patients with heart failure have frequently been reported to show elevated levels of plasma adrenomedullin. These levels generally correlate with severity of hemodynamic dysfunction and also with neurohormonal indices which are activated according to the severity of heart failure. Furthermore, adrenomedullin gene expression in the heart and kidney is increased in experimental and clinical heart failure. A small number of studies have examined the responses to infusion of adrenomedullin in experimental and clinical heart failure. These studies have generally shown that infusion of adrenomedullin has beneficial hemodynamic effects and promotes maintenance or improvement in renal function, although most of these trials were of short duration. The available data suggest that adrenomedullin in the heart, kidney and plasma is increased in heart failure, possibly to counter the activation or actions of vasoconstricting and sodium-retaining hormone systems. An improved understanding of the role of adrenomedullin in heart failure might lead to the development of therapeutic agents acting through adrenomedullin receptors.

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Introduction

Heart failure is an increasing problem in most societies (1). For the afflicted individual, the quality of life is affected considerably (2) and longevity is markedly attenuated. The cost of managing established heart failure represents between 1% and 2% of the total health care budget in Western societies (3) and is increasing.

Whatever the initial insult to the heart, whether it be hypertension, acute myocardial infarction, or any one of the less common etiologies, a range of neurohormonal systems are activated in proportion to the severity of cardiac dysfunction. Beginning in the 1960s, it became clear that aldosterone levels and activity of the renin-angiotensin system were increased; later, circulating levels of the cardiac natriuretic peptides were found to be augmented. The sympathetic system likewise was found to be activated as indicated initially by measurements of urinary and plasma catecholamines or metabolites, and later by more sophisticated techniques. The development of agents which selectively blocked some or all actions of these neurohormonal systems confirmed the pathophysiologic importance of hormone activation and, perhaps more importantly, led to the development of therapeutic agents which have revolutionized the treatment of cardiac failure. The most obvious examples are the angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists, aldosterone receptor antagonists and beta blockers—all of which are already, or are becoming, standard therapeutic agents.

In more recent decades it has become evident that hormones produced within blood vessels (but also elsewhere, including in the heart and kidney) might play a pathophysiologically important role in heart failure. Examples include endothelin, nitric oxide, C-type natriuretic peptide (CNP), and prostaglandins. In 1993, Kitamura and colleagues reported the discovery of adrenomedullin from human pheochromocytoma tissue (4). Since that time considerable attention
has been focused on the potential role of this hormone in experimental heart failure in animals, as well as in human heart failure. This review focuses on our current understanding of adrenomedullin in heart failure—its plasma levels, its concentrations in the heart and kidney, its biologic effects when administered to animals or humans with heart failure and its potential importance in therapeutics. It complements a more detailed exposition on the same topic (5).

**Plasma Adrenomedullin Levels in Heart Failure**

Adrenomedullin normally circulates in plasma at low picomolar concentrations in healthy humans. In cardiac failure, the levels are increased, although there is considerable overlap with normal values (6–9). Research in this area has been dominated by workers from Miyazaki and Osaka in Japan. These investigators have noted that immunoreactive adrenomedullin levels increase with the clinical severity of heart failure, and show a positive statistical association with pulmonary artery pressure and pulmonary wedge pressure, an inverse relationship to left ventricular ejection fraction, and positive correlations with neurohormonal indices such as plasma atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and renin (7–9). These same workers demonstrated an increase in both intermediate form (inactive) glycine-extended adrenomedullin and the amidated mature form of adrenomedullin, and whereas both increase according to the severity of heart failure (New York Heart Association (NYHA) functional class), the ratio of mature to total (mature plus intermediate form) adrenomedullin remains similar to that in controls (10). They have further shown that effective treatment of heart failure gradually results in a reduction in circulating levels of adrenomedullin (10, 11). In addition, they have reported that pericardial fluid adrenomedullin immunoreactivity is increased slightly compared with plasma, but mature adrenomedullin, and the mature/total adrenomedullin ratios are much higher than in plasma (12). The authors considered it possible that this pericardial adrenomedullin might reflect increased cardiac synthesis of the peptide, and that it might play a compensatory role through its positive inotropic action, through coronary vasodilatation, and via an anti-remodelling action.

The same researchers documented increased plasma levels of adrenomedullin in patients with hypertrophic cardiomyopathy. These patients showed a positive correlation between circulating adrenomedullin and endothelin-1 levels and also with voltage on the electrocardiograph (ECG) (13). In a cohort of patients with mitral stenosis, they demonstrated increased plasma levels of adrenomedullin and a minor but statistically significant drop in concentrations between the pulmonary artery and left atrium (14). Again, positive associations were seen between circulating adrenomedullin levels and pulmonary artery pressure as well as total pulmonary vascular resistance. Treatment of mitral stenosis by mitral commissurotomy induced a gradual decline in circulating adrenomedullin levels (14).

Researchers at the Mayo Clinic noted that patients with heart failure had not only increased circulating levels of immunoreactive adrenomedullin but also increased immunoreactivity within the failing human ventricle (6). Piquard and colleagues reported that plasma adrenomedullin levels were increased in patients after heart transplantation with a strong positive statistical association between adrenomedullin levels and left ventricular mass index (15). Furthermore, they noticed an increase in the peptide levels with exercise and an inverse relation between peak blood pressure achieved during exercise and the plasma adrenomedullin level. Accordingly they surmised that adrenomedullin might participate in blood pressure regulation during exercise after heart transplantation (15).

Researchers at Christchurch Hospital in New Zealand have also reported increased levels of plasma adrenomedullin in patients with heart failure. However, they found that average plasma adrenomedullin levels were even higher in a cohort of 121 patients in whom measurements were recorded 2–4 days after acute myocardial infarction (5). While the level of plasma adrenomedullin soon after myocardial infarction provided some discrimination for those at high risk of death or heart failure over the subsequent 24 months, this was a much weaker indicator than the natriuretic peptides, particularly N-terminal BNP (16). In another cohort of 297 patients with chronic ischemic left ventricular dysfunction, above-median plasma adrenomedullin levels conferred an increased risk of mortality and hospitalization for heart failure over an 18 month period (17). In this same cohort it was noted that the introduction of carvedilol therapy reduced mortality and heart failure in patients with higher pre-treatment levels of either adrenomedullin or N-terminal BNP (17). Along similar lines, Pousset and colleagues found in 117 patients that elevated plasma levels of adrenomedullin were an independent predictor of prognosis in mild-to-moderate heart failure treated by conventional therapy (18).

As noted above, a variety of treatment modalities have been reported to reduce circulating adrenomedullin levels in patients with heart failure (10, 11, 14). By contrast, treatment with the combined ACE/neutral endopeptidase inhibitor omapatrilat has been shown to induce an increase in circulating adrenomedullin levels both in experimental heart failure models and humans (19, 20).

**Cardiac, Renal and Vascular Adrenomedullin in Heart Failure**

Cardiac adrenomedullin gene expression is increased in experimental animal models by acute arterial pressure overload (21) or by myocardial ischemia or infarction (22, 23). Nagaya and colleagues noted an increase in gene expression in both infarcted and non-infarcted areas after acute myocardial infarction in rats (22). Further, they noted a positive association between the adrenomedullin peptide level in the non-in-
farcted region and left ventricular end diastolic pressure. Interestingly, an ACE inhibitor suppressed the over-production of adrenomedullin at one week post-infarction (22). Workers from Norway (23) and Japan (24) both documented an increase in the gene expression of adrenomedullin and receptor-activity modifying protein (RAMP 2) during or after myocardial ischemia in rats. Öe and colleagues reported increased adrenomedullin mRNA expression both in ischemic and non-ischemic regions of the left ventricle (23).

They also noted a substantial increase in immunoreactive adrenomedullin in the microvascular endothelium and perivascular interstitial cells within the heart (23). Whereas the Norwegian and Japanese groups noted increased expression of RAMP 2 (23, 24), a French group, studying rats with chronic pressure overload due to aortic banding, reported increased myocardial expression of RAMP 1 and RAMP 3, but expression of RAMP 2 was not augmented (25). Perhaps differences in the experimental models and the time frames utilized might explain these discrepancies. In regard to temporal profiles, Willenbrock and colleagues reported, contrary to some earlier findings, that ventricular adrenomedullin-RNA expression and adrenomedullin concentrations were up-regulated only in advanced stages of heart failure in rats with aorticaval shunts (26).

In regard to the kidney in heart failure, Yoshihara and colleagues reported that renal adrenomedullin levels were augmented in decompensated heart failure due to aorticaval shunts in rats, although RAMP 2 and RAMP 3 mRNA levels were not different between controls and heart failure animals (27). Interestingly, there was a significant positive association between urine sodium excretion and renomedullary adrenomedullin levels (27). Jougasaki and colleagues, in their study on dogs with rapid ventricular pacing-induced heart failure, observed that adrenomedullin immunoreactivity appeared to be increased at various sites within the kidney (28). They also noted that ventricular adrenomedullin in this same model appeared to be a powerful marker of left ventricular mass, and circulating adrenomedullin levels were increased and correlated with hemodynamic indices (28). And in a subsequent study employing a pacing-induced, canine model of heart failure, they found that ACE inhibitors reversed both the activation of ventricular adrenomedullin and the increase in circulating levels of this hormone (29).

In regard to vascular hormones in heart failure, Hillier and colleagues from Glasgow studied small resistance arteries obtained from gluteal biopsies in patients with chronic heart failure. They noted that a high concentration of adrenomedullin (200 pmol/l) reduced the vasoconstrictor effect of endothelin-1, suggesting a functional interaction between these two hormones in resistance arteries in cardiac failure (30).

The functional importance of enhanced adrenomedullin production in the heart, kidneys and blood vessels in heart failure requires further study. It is possible that enhanced adrenomedullin production within the heart counters some of the proliferative and growth-promoting actions of hormones such as angiotensin II and endothelin-1 (31). Similar actions may, of course, exist within blood vessels and in the kidneys. In the case of the kidneys, it is also possible that enhanced adrenomedullin expression and activity contribute to the preservation of urine sodium excretion (27).

Hemodynamic Effects of Adrenomedullin in Heart Failure

Rademaker and colleagues from Christchurch infused adrenomedullin at 10 and 100 ng/kg/min for 90 min each in sheep with pacing-induced heart failure (32). The hormone clearly reduced ventricular preload and afterload and improved cardiac output while augmenting both creatinine clearance and sodium excretion. Plasma aldosterone levels were suppressed but plasma concentrations of ANP, BNP, catecholamines, renin and cortisol were not altered, although the cardiac natriuretic peptides rose upon completion of adrenomedullin infusion (32). Rademaker and colleagues extended these studies in sheep with pacing-induced heart failure using adrenomedullin alone or in combination with an endopeptidase inhibitor (33). Co-administration produced greater hemodynamic effects than use of either drug alone, and renal function (urine volume, sodium excretion and creatinine clearance) was well maintained despite a vigorous decline in systemic arterial pressure. The Mayo Clinic group infused adrenomedullin at 1 and 25 ng/kg/min directly into a renal artery in dogs with pacing-induced heart failure (34). Compared with a control group of normal animals, the glomerular and tubular actions of adrenomedullin, and in particular the urine sodium excretory response, were attenuated in the animals with heart failure. Perhaps unexpectedly, these workers noted an increase in systemic arterial pressure with intra-renal adrenomedullin infusion, and this response was greater in the animals with acute heart failure than in controls (34). The mechanisms for this hemodynamic response remain to be defined.

The above studies were carried out over a matter of hours. There is a dearth of information regarding the effects of chronic administration of adrenomedullin in heart failure. Rademaker and colleagues recently infused adrenomedullin at 10 ng/kg/min for 4 days in sheep with pacing-induced heart failure (unpublished data). Compared to time-matched control data, adrenomedullin induced a prompt and sustained increase in cardiac output, and sustained reductions in peripheral resistance, mean arterial pressure, and left atrial pressure. Furthermore, the hormone enhanced urine sodium excretion, creatinine excretion and creatinine clearance over the entire four-day study period. Plasma renin activity was increased but aldosterone levels in plasma fell. These hemodynamic, renal and hormonal changes were accompanied by an increase in plasma adrenomedullin of only 9.5 pmol/l on average. The findings lend support to the premise that adrenomedullin may act as a “protective” hormone during
the hemodynamic compromise of heart failure.

There have been few studies documenting the effects of infused adrenomedullin in patients with heart failure, and those studies that have been performed have all been short-term. The Christchurch group infused adrenomedullin at 2.7 pmol/kg/min or 5.4 pmol/kg/min for 2 h either alone or in combination with BNP (35). Adrenomedullin induced a substantial fall in arterial pressure and an increase in heart rate, but cardiac output was unchanged (Fig. 1). While adrenomedullin did not augment sodium excretion, it maintained the increase in urine sodium excretion induced by BNP when the two peptides were infused together. Adrenomedullin stimulated plasma renin levels but suppressed plasma aldosterone. Furthermore, adrenomedullin augmented plasma norepinephrine levels and inhibited the plasma cGMP response to BNP (35).

Nagaya and colleagues infused a much higher dose (9 pmol/kg/min) of adrenomedullin for 30 min in patients with congestive heart failure (36). The hormone increased the cardiac index and reduced pulmonary capillary wedge pressure while augmenting urine volume and sodium excretion and inhibiting plasma aldosterone levels. Plasma renin levels were unaltered (36). The same group infused equimolar doses of adrenomedullin and ANP over a 30-min period in patients with heart failure (37). Compared with ANP, adrenomedullin at 16 pmol/kg/min induced greater reductions in arterial pressure and increments in heart rate and cardiac output, though a lesser decline in pulmonary capillary wedge pressure and a more sustained fall in systemic vascular resistance. By contrast, ANP had a greater effect on urine volume and sodium output than did adrenomedullin (37).

Overview

It is apparent that adrenomedullin levels in the plasma, heart and kidneys are increased in heart failure roughly in proportion to the severity of the cardiac dysfunction. Infusion of exogenous adrenomedullin into animal models of heart failure and into patients with established cardiac failure has been shown to result in beneficial hemodynamic and renal effects.

However, the studies have been of short duration and it is unclear whether these benefits would be sustained beyond the longest study period of 4 days. Although available evidence supports the contention that increased production of adrenomedullin in the heart and kidneys and into plasma might be beneficial through antagonism of, for example, endothelin, aldosterone and the actions of the renin-angiotensin system, the full pathophysiologic significance remains to be determined.

Development of selective antagonists of the actions of adrenomedullin would provide a useful tool for dissecting the role of adrenomedullin in heart failure. Further studies should clarify whether addition of adrenomedullin to the currently available treatments would constitute an effective new strategy for patients with heart failure. Of course, at the moment adrenomedullin can only be given intravenously. It remains to be seen whether orally effective agents that act on adrenomedullin receptors will be developed in the future.

References

34. Jougasaki M, Heublein DM, Sandberg SM, Burnett JC Jr:

