Adrenomedullin in heart failure: pathophysiology and therapeutic application

Adriaan A. Voors1*, Daan Kremer1, Christopher Geven2, Jozine M. ter Maaten1, Joachim Struck3,4, Andreas Bergmann3,4, Peter Pickkers2, Marco Metra5, Alexandre Mebazaa6, Hans-Dirk Düngen7, and Javed Butler8

1 Department of Cardiology, University of Groningen, Groningen, The Netherlands; 2 Department of Intensive Care Medicine, Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands; 3 Sphingotec GmbH, Hennigsdorf, Germany; 4 Adrenomed AG, Hennigsdorf, Germany; 5 Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, Institute of Cardiology, University of Brescia, Brescia, Italy; 6 APHP, Hôpitaux Universitaires Saint-Louis Lariboisière, INIL-CRCT, University Paris Diderot, Paris, France; 7 Department of Cardiology, Charité Universitätsmedizin, Campus Virchow-Klinikum, Berlin, Germany; and 8 Division of Cardiology, Stony Brook University, Stony Brook, NY, USA

Received 4 September 2018; revised 18 October 2018; accepted 22 October 2018; online publish-ahead-of-print 28 December 2018

Adrenomedullin (ADM) is a peptide hormone first discovered in 1993 in pheochromocytoma. It is synthesized by endothelial and vascular smooth muscle cells and diffuses freely between blood and interstitium. Excretion of ADM is stimulated by volume overload to maintain endothelial barrier function. Disruption of the ADM system therefore results in vascular leakage and systemic and pulmonary oedema. In addition, ADM inhibits the renin–angiotensin–aldosterone system. ADM is strongly elevated in patients with sepsis and in patients with acute heart failure. Since hallmarks of both conditions are vascular leakage and tissue oedema, we hypothesize that ADM plays a compensatory role and may exert protective properties against fluid overload and tissue congestion. Recently, a new immunoassay that specifically measures the biologically active ADM (bio-ADM) has been developed, and might become a biomarker for tissue congestion. As a consequence, measurement of bio-ADM might potentially be used to guide diuretic therapy in patients with heart failure. In addition, ADM might be used to guide treatment of (pulmonary) oedema or even become a target for therapy. Adrecizumab is a humanized, monoclonal, non-neutralizing ADM-binding antibody with a half-life of 15 days. Adrecizumab binds at the N-terminal epitope of ADM, leaving the C-terminal side intact to bind to its receptor. Due to its high molecular weight, the antibody adrecizumab cannot cross the endothelial barrier and consequently remains in the circulation. The observation that adrecizumab increases plasma concentrations of ADM indicates that ADM-binding by adrecizumab is able to drain ADM from the interstitium into the circulation. We therefore hypothesize that administration of adrecizumab improves vascular integrity, leading to improvement of tissue congestion and thereby may improve clinical outcomes in patients with acute decompensated heart failure. A phase II study with adrecizumab in patients with sepsis is ongoing and a phase II study on the effects of adrecizumab in patients with acute decompensated heart failure with elevated ADM is currently in preparation.

Keywords Heart failure • Adrenomedullin • Congestion • Vascular permeability • Decompensation

Introduction

Hospitalizations for heart failure are a major burden for patients, relatives, health care providers and society. Despite improvements in therapy for patients with heart failure with a reduced ejection fraction, we have not been able to reduce the risk of heart failure readmissions after a hospitalization for worsening heart failure. Approximately 35–50% of heart failure patients are rehospitalized within 6 months of discharge, making heart failure the most frequent diagnosis for 30-day readmissions and incurring billions in costs.1–3 Therefore, preventing hospital (re-)admissions is recognized as a major unmet need in the treatment of heart failure.

Risk prediction models have become reasonably accurate for predicting (cardiovascular) mortality, but models to predict hospital (re-)admissions perform much worse.4 Given its poor predictive
value, identifying patients for clinical trials who are at high risk of hospital (re-)admission is difficult. Therefore, there is a need for markers to better identify patients who are at high risk for heart failure (re-)hospitalization. Preferably, these markers should reflect a process that can be pathophysiological linked to worsening heart failure.

Several studies have consistently shown that the main reason for (re-)hospitalization for worsening heart failure is related to dyspnoea or breathlessness, mainly caused by pulmonary congestion. The great majority of patients are treated with loop diuretics to relieve congestion, but a large number of patients are discharged without losing body weight and with persistent signs of congestion. This is particularly true when patients are discharged early and in patients without weight loss despite loop diuretic therapy. Consequently, studies have shown higher risks of hospital readmission in patients with a shorter duration of hospitalization, with a poor diuretic response, and with residual signs of congestion at discharge. Therefore, markers that reflect residual congestion might be useful to identify patients that are both epidemiologically and pathophysiological at higher risk of hospital (re-)admission. Currently, clinical signs at physical examination such as oedema, rales and jugular venous pressure are the mainstay for assessment of congestion. However, this examination is often not performed in clinical practice, is very dependent on the clinician’s skills, has a low interrater reliability and specificity and is subjective due to the lack of standardized metrics or (de)congestion scores. In view of the high incidence of rehospitalization, clinical assessment of congestion is clearly insufficient. What clinicians therefore need is an easy-to-use surrogate for the assessment of a patient’s (de)congestion status that may facilitate clinical decision making. The use of biomarkers for this purpose is attractive, since they are objective, easily available and have a known sensitivity and specificity. While heart failure patients natriuretic peptides are regarded as the main biomarker for congestion, recent studies show that there are several limitations in the use of natriuretic peptides as markers of congestion. Since natriuretic peptides reflect stretch and pressure of the heart, they mainly reflect intravascular volume overload, but do not reflect tissue and interstitial fluid. Therefore, better and more specific markers for tissue congestions are needed.

Adrenomedullin: an introduction

Adrenomedullin (ADM) is a peptide hormone discovered in 1993 by Kitamura et al. ADM is a 52 amino acid peptide, containing a ring structure and a C-terminal amide, both of which are essential for binding to ADM receptors. The ADM gene is located on chromosome 11 and consists of four exons. One of the key determinants for biological activity of ADM is the group of receptor activity-modifying proteins (RAMP). The combination of RAMP 2 or 3 with the calcitonin receptor-like receptor (CRLR) confers specificity of the receptor for ADM, and thus both RAMPs and CRLR are key in ADM expression. While ADM was first discovered in pheochromocytoma originating from the adrenal medulla (hence the name ‘adrenomedullin’), further investigation showed that it was synthesized by many other tissues/cells, especially endothelial and vascular smooth muscle cells, and due to its small size (6 kDa) diffuses freely between blood and interstitium. By proteolytic fragmentation of the pro-hormone (pro-ADM), a glycine-extended, inactive ADM is formed, which subsequently is enzymatically converted from ADM-glycine to the biologically active ADM-amide. ADM receptors and binding sites are widespread in the body, but cardiovascular and lung tissues have highest density of these binding sites. The in vivo half-life of ADM is approximately 22 min. ADM is assumed to mainly be metabolized by neutral endopeptidase, also known as neprilysin – a molecule that clinicians might recognize from the recent beneficial findings with sacubitril/valsartan as a novel treatment for patients with heart failure.

Vascular effects of adrenomedullin

The most recognized function of ADM is vasodilatation in both vascular resistance and capacitance vessels. ADM lowers blood pressure, yet increases blood flow. Even low doses induce vasodilatation, indicating that the plasma levels of ADM under conditions such as heart failure are in the range that directly affect vascular tone. Beside vasodilatation, ADM seems to play an important role in preservation of endothelial integrity. ADM expression can be induced by various stimuli, one of them being volume overload, and increased plasma ADM reflects excessive fluid volume. This is most likely the consequence of a counteracting response, as the ADM-induced stabilization of endothelial barrier function is thought to limit tissue fluid overload. Indeed, disruption of the ADM system results in vascular leakage and systemic and pulmonary oedema. Also the role of the ADM–RAMP 2 system has been investigated. Mice lacking the gene encoding for RAMP 2 showed enhanced vascular permeability and systemic oedema. Similarly, mice with a conditional knock-out of ADM in endothelial cells revealed increased vascular permeability in comparison with wild-type littermates.

Further support for the effects of ADM in maintaining vascular integrity comes from experimental studies showing that experimental overexpression of ADM inhibits systemic and pulmonary vascular leakage in animals. For example, in a rat model of Staphylococcus aureus-toxin induced systemic inflammation, accompanied by extensive vascular leakage, ADM infusion protected endothelial barrier function via cyclic adenosine monophosphate (cAMP) elevation. Also, ADM dose-dependently reduced experimentally induced endothelial hyperpermeability of cultured human umbilical vein endothelial cell and porcine pulmonary artery endothelial cell monolayers. Suppression of ADM contributes to vascular leakage and altered epithelial repair during asthma. In two animal models, intranasal ADM completely attenuated the acute-induced airway hyper-responsiveness and mucosal © 2018 The Authors. European Journal of Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.
Adrenomedullin in heart failure and related to congestion and clinical outcome in heart failure

In healthy humans, ADM circulates in the plasma in low concentrations. In 1995, it was first reported that ADM levels were elevated in heart failure. Plasma ADM concentration was 13 pg/mL in healthy subjects and 3–4 times higher in patients with chronic heart failure. The observation that ADM levels decreased after treatment with diuretics and digitalis led to the assumption that ‘volume expansion and an activated sympathetic nervous system may be associated with this increase and that plasma ADM levels change in response to the pathophysiologic changes of heart failure. After this, many studies have shown elevated levels of ADM in patients with heart failure. In addition, several studies found a strong association between higher levels of ADM and adverse clinical outcome. The majority of these studies used a stable part of the ADM precursor peptide, mid-regional pro-ADM (MR-proADM). The drawback to this assay, however, is that it measures a stable fragment of a non-functional ADM peptid, and therefore does not distinguish between the biologically active amidated ADM and the non-functional ADM variant containing a glycine-extended C-terminal residue. Recently, a new immunoassay that specifically measures biologically active ADM (bio-ADM) has been developed. Plasma bio-ADM was measured in 246 patients admitted at the emergency department with suspicion of acute heart failure. Plasma bio-ADM concentrations were higher among patients who experienced a cardiovascular event [median 80.5 pg/mL; interquartile range (IQR) 53.7–151.5 pg/mL] compared with those who did not (median 54.4 pg/mL; IQR 43.4–78.4 pg/mL) (P < 0.01). After adjusting for the other biomarkers, plasma bio-ADM remained a strong predictor of a cardiovascular event. Another study showed that bio-ADM was a marker of impaired haemodynamics, organ dysfunction, and poor prognosis in patients with cardiogenic shock. We recently studied the clinical correlation and prognostic value of serial measurements of plasma bio-ADM levels in 1562 patients admitted for acute decompensated heart failure. We showed that plasma bio-ADM had the strongest association with clinically assessed congestion during hospital admission for acute decompensated heart failure. Moreover, bio-ADM was a better predictor of residual congestion than any other individual baseline variable. In patients with clinical signs of residual congestion 7 days after hospital admission, bio-ADM levels were high at baseline and remained high throughout the first week of hospitalization. This in contrast to brain natriuretic peptide (BNP) levels, which decreased in all patients irrespective of the presence and degree of residual congestion. Finally, plasma bio-ADM concentrations, both at baseline and at day 7, provided significant added predictive value for 60-day heart failure rehospitalization, even after adjustment for a pre-defined 11-item rehospitalization risk model, residual congestion by day 7 and BNP at day 7.
Rationale for bio-adrenomedullin as a biomarker for tissue congestion

Adrenomedullin is a vasoactive peptide that is increased in patients that are volume overloaded. Main functions of ADM are vasodilatation and to maintain vascular integrity and decrease vascular leakage. Elevated levels are found in heart failure, but ADM is particularly elevated in patients with septic shock. A common factor between both diseases is vascular leakage and organ hypoperfusion. In heart failure, higher levels of ADM are associated with more severe heart failure, and are the strongest predictor of (residual) congestion in patients with acute decompensated heart failure. Increased ADM concentrations have been associated with impaired clinical outcome in several studies of patients with heart failure. In a recent study, higher levels of bio-ADM were independently associated with a higher risk of hospital readmissions. We therefore propose the following concept, as depicted in Figure 2. We propose that higher bio-ADM levels reflect residual tissue congestion, and residual tissue congestion is related to worse outcome after discharge, and a higher likelihood for frequent hospital readmissions in particular. Therefore, such a measurement might guide physicians to treat certain patients more intensively, and this might also facilitate discharge decisions.

Adrenomedullin as a target for therapy

Several pre-clinical (Table 1) and small clinical (Table 2) studies have established the effects of exogenous administration of ADM in heart failure. Briefly, these effects included a reduction in myocardial infarct size, cardiac myocyte apoptosis, left ventricular remodelling (in animals) and aldosterone levels (animals and humans), while haemodynamics (in both humans and animals) and survival (in animals) were improved. In a rat coronary ligation model, ADM administration during the early period of a myocardial infarction improved survival and ameliorated progression of left ventricular remodelling and heart failure. Similar results were found in another study where chronic administration of ADM attenuated transition from left ventricular hypertrophy to heart failure in rats. In a case series of seven acute heart failure patients with dyspnoea and pulmonary congestion, the effects of long-term intravenous administration of ADM in acute decompensated heart failure were studied. ADM infusion significantly reduced mean arterial pressure, pulmonary arterial pressure and systemic and pulmonary vascular resistance without changing heart rate, and increased cardiac output over most time-points compared with those at baseline. In another small study of seven chronic heart failure patients and seven healthy subjects, ADM significantly decreased mean arterial pressure and increased heart rate in the healthy volunteers. In patients with heart failure, ADM also decreased mean arterial pressure and increased heart rate, but to a much lesser degree. ADM markedly increased cardiac index while decreasing pulmonary capillary wedge pressure.

Taken together, these data consistently show that ADM induces beneficial haemodynamic, hormonal and myocardial changes in both experimental models and patients with heart failure. These effects are likely related to the vasodilatory properties of intravascular ADM, although other pathways may also be involved. Many vasodilators have been studied in acute and chronic heart failure with mixed results. Therefore, it would be more interesting to be...
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<tr>
<th>Author (year)</th>
<th>Intervention</th>
<th>Animal model</th>
<th>Effects</th>
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</thead>
<tbody>
<tr>
<td>Nakamura(^57) (2002)</td>
<td>ADM infusion for 4 weeks via osmotic pump versus saline</td>
<td>Left coronary ligation-induced myocardial infarction in rats</td>
<td>↓ Heart weight/body weight, ↓ Myocyte size, ↓ Collagen volume fraction of non-infarct LV area, without affecting infarct size, ↓ LV end-diastolic pressure</td>
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<tr>
<td>Okumura(^58) (2003)</td>
<td>ADM infusion for 60 min after coronary ligation</td>
<td>Ischaemia–reperfusion (30 min of left coronary artery ischaemia) in rats</td>
<td>↓ LV end-diastolic pressure and ↓ cardiac myocyte apoptosis After 24 h: ↓ LV end-diastolic pressure and ↓ cardiac myocyte apoptosis After 4 weeks: ↓ Myocardial fibrosis, ↓ Myocardial infarct size</td>
</tr>
<tr>
<td>Niu(^59) (2003)</td>
<td>Heterozygous ADM(+/−) knock-out mice compared to wild-type</td>
<td>Stress-induced cardiac hypertrophy by angiotensin II infusion</td>
<td>Knock-out resulted in: ↑ Cardiac hypertrophy (heart weight/body weight and LV thickness), ↑ Renal dysfunction</td>
</tr>
<tr>
<td>Nishikimi(^60) (2003)</td>
<td>ADM infusion over 7 weeks using a micro-osmotic pump, compared with placebo and diuretic treatment groups</td>
<td>Heart failure model of Dahl salt-sensitive rats</td>
<td>ADM infusion: ↓ LV end-diastolic pressure, ↓ RV systolic pressure, ↓ RA pressure, ↓ LV weight/body weight, ↓ Renin–aldosterone and ANP, ↑ Cardiac output and systemic vascular resistance, ↑ LV end-systolic elastance</td>
</tr>
<tr>
<td>Okumura(^61) (2004)</td>
<td>ADM infusion, or ADM + wortmannin, or placebo, for 60 min after coronary ligation</td>
<td>Ischaemia–reperfusion (30 min of left coronary artery ischaemia) in rats</td>
<td>↓ Infarct size, ↓ LV end-diastolic pressure, ↓ Myocardial apoptotic death</td>
</tr>
<tr>
<td>Nakamura(^62) (2004)</td>
<td>I.p. ADM or placebo over 7 days, immediately after induction of myocardial infarction</td>
<td>Left coronary ligation-induced myocardial infarction in rats. Observed over 9 weeks</td>
<td>At 9 weeks: ↑ Survival, ↓ heart/lung weight, ↓ Oxidative stress and ACE transcription, ↓ LV end-diastolic pressure, ↓ Collagen volume fraction of the non-infarcted LV. No effect on infarct size During 7 days of infusion: No effects on urinary output or haemodynamic parameters</td>
</tr>
<tr>
<td>Niu(^63) (2004)</td>
<td>Heterozygous ADM(+/−) knock-out mice compared to wild-type</td>
<td>Stress-induced cardiac hypertrophy by aortic constriction or angiotensin II infusion</td>
<td>More pronounced in ADM knock-out mice: ↑ Heart weight/body weight ratio, ↑ LV wall thickness, ↑ Perivascular fibrosis, ↑ Expression of ACE, angiotensinogen, collagen type 1, BNP and c-fos, ↑ Renal damage with glomerular sclerosis, Involvement of a PKA/PKC pathway</td>
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Adrecizumab for the treatment of heart failure and sepsis

Adrecizumab is a humanized, monoclonal, non-neutralizing antibody against the N-terminus of ADM. It has a half-life of 15 days when administered by a single intravenous infusion. The mode of action of adrecizumab is presented in Figure 3. Administration of adrecizumab leads to a dose-dependent increase in plasma ADM bound to the administered antibody. The increase occurs within a few minutes and is not caused by induction of de-novo synthesis, because concentrations of MR-proADM are not increased (an inactive peptide fragment originating from the same precursor as ADM, which is synthesized in a 1:1 ratio). It is hypothesized that translocation of pre-existing ADM accounts for the observed increase in circulating ADM. Briefly, circulating adrecizumab cannot leave the blood compartment due to its high molecular weight (160 kDa), whereas ADM (with a much lower molecular weight of 6 kDa) can freely cross the endothelial barrier between the interstitium and the circulation. Binding of ADM by adrecizumab (present in the circulation in a large excess over ADM) prevents ADM from leaving the blood vessel, effectively ‘trapping’ ADM in the circulation. In addition, adrecizumab may translocate ADM from the interstitium into the circulation. Because adrecizumab is a non-neutralizing antibody, the net effect is a significant increase of functional plasma ADM which leads to – as we hypothesize – the restoration of vascular integrity (endothelial effect) and less vasodilatation (vascular smooth muscle cell effect due to decreased concentrations of ADM in the interstitium). Further, it is thought that adrecizumab prevents ADM from being degraded by proteases and prolongs half-life of ADM.

In animal models of systemic inflammation and septic shock, adrecizumab improved haemodynamics, renal function, systemic inflammation and reduced inducible nitric oxide synthase expression. Currently, adrecizumab is being evaluated in a phase II trial in human septic shock (http://clinicaltrials.gov identifier: NCT03085758). There were no safety concerns observed in pre-clinical studies, as well as in two phase I studies in which 0.5, 2 and 8 mg/kg were administered to healthy volunteers. Importantly, even though adrecizumab induced great increases in circulating levels of ADM, this did not cause hypotension. In a phase Ib study, where healthy subjects received an infusion of bacterial lipopolysaccharide to induce a systemic inflammatory response, administration of adrecizumab significantly reduced the perception of illness/sickness, as assessed by clinical scores.

A phase II proof of concept study in patients with worsening heart failure and elevated bio-ADM levels after initial stabilization is currently being considered. Patients with elevated bio-ADM have (residual) congestion and are at high risk for clinical events, and a heart failure readmission in particular. Adrecizumab is expected to increase intravascular ADM and decrease interstitial ADM, since adrecizumab may translocate ADM from the interstitium into the

Table 1 continued

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<tr>
<th>Author (year)</th>
<th>Intervention</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Looi64 (2006)</td>
<td>ADM bolus</td>
<td>↓ Ventricular arrhythmias</td>
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<td></td>
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<td>↑ 14-day survival</td>
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<td>↓ LDH levels</td>
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<td></td>
<td>↓ DOX-induced cardiac tissue damage, mitochondrial abnormalities</td>
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<tr>
<td>Yoshizawa65 (2016)</td>
<td>Subcutaneous infusion of ADM using an osmotic min pump for 3 or 7 days</td>
<td>↑ 14-day survival</td>
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<tr>
<td></td>
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<td>↓ LDH levels</td>
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<tr>
<td></td>
<td></td>
<td>↓ DOX-induced cardiac tissue damage, mitochondrial abnormalities</td>
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<tr>
<td>Li66 (2018)</td>
<td>Myocardial transplantation of MSCs overexpressing ADM compared to GFP MSCs</td>
<td>↑ Cardiac function</td>
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<td>↓ Cardiac fibrosis</td>
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Table 2 Overview of studies investigating adrenomedullin in human patients with forms of heart failure

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<tr>
<th>Author (year)</th>
<th>Intervention</th>
<th>Condition</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Nakamura67 (1997)</td>
<td>FBF and SBF test with intra-arterial ADM</td>
<td>Healthy subjects (n = 10) Patients with CHF (n = 18)</td>
<td>↑ FBF &amp; ↑ SBF Effects partially NO-mediated Impaired FBF and SBF responses in CHF group</td>
</tr>
<tr>
<td>Nagaya68 (2000)</td>
<td>I.v. infusion of ADM (n = 7) or placebo (n = 6), 90 min total</td>
<td>Patients with precapillary pulmonary hypertension (n = 13 total)</td>
<td>↑ Cardiac index (44%) ↓ Pulmonary arterial pressure (32%) ↓ MAP (9 mmHg), ↑ HR ↓ Plasma aldosterone (but not renin) No effect ANP/BNP</td>
</tr>
<tr>
<td>Nishikimi69 (2009)</td>
<td>I.v. infusion of ADM + hANP for 12 h, followed by 12 h of hANP</td>
<td>Acute heart failure patients with dyspnoea and pulmonary congestion (n = 7)</td>
<td>↓ MAP, PAP, systemic and pulmonary vascular resistance ↑ Cardiac output, urine volume and urinary sodium excretion ↓ Aldosterone, BNP, free-radical metabolites</td>
</tr>
<tr>
<td>Kataoka70 (2010)</td>
<td>I.v. infusion of ADM for 12 h No placebo arm</td>
<td>Patients with acute myocardial infarction before undergoing PCI (n = 10)</td>
<td>During infusion, two patients showed unstable haemodynamics MRI 3 vs. 1 month after PCI: ↑ Wall motion index, ↓ infarct size</td>
</tr>
</tbody>
</table>

ADM, adrenomedullin; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CHF, chronic heart failure; FBF, forearm blood flow; hANP, human atrial natriuretic peptide; HR, heart rate; MAP, mean arterial pressure; MRI, magnetic resonance imaging; NO, nitric oxide; PAP, pulmonary artery pressure; PCI, percutaneous coronary intervention; SBF, skin blood flow.

Adrenomedullin is an endogenous hormone that is released as a counteracting response to volume overload. Levels of ADM are clearly increased in patients with heart failure, and higher levels are related to more advanced heart failure and worse outcomes. Since elevation of ADM is a feedback response to volume overload to maintain vascular integrity and decrease vascular leakage of fluid from the vasculature to the tissues, measurement of ADM might reflect tissue and pulmonary oedema. Such a measurement might guide physicians to more intensively treat patients with heart failure hospitalization and facilitate discharge decisions. In addition, ADM might become a target of therapy in heart failure. The mode of action of adrecizumab, a humanized monoclonal antibody that binds but does not significantly inhibit ADM, might be of particular interest, since it is assumed to translocate ADM from the interstitium into the vasculature to improve vascular integrity and prevent tissue congestion. The hypothesis of this study is that by improving vascular integrity, it is expected that adrecizumab will decrease tissue congestion and thereby improve dyspnoea, potentially reducing heart failure readmissions. However, it should be noted that long-term effects of ADM on development and/or progression of heart failure have never been clinically investigated. In addition, adrecizumab itself has not been investigated in pre-clinical models of heart failure, but only in septic shock and systemic inflammation. Tissue congestion was never an outcome parameter in pre-clinical studies with ADM.

Figure 3 Mode of action of adrecizumab. Administration of adrecizumab leads to a dose-dependent increase of plasma adrenomedullin (ADM) bound to the administered antibody. Circulating adrecizumab cannot leave the blood compartment due to its high molecular weight (160 kDa), whereas ADM (with a much lower molecular weight of 6 kDa) can freely cross the endothelial barrier between the interstitium and the circulation. Binding of ADM by adrecizumab (present in the circulation in a large excess over ADM) prevents ADM from leaving the blood vessel, effectively ‘trapping’ ADM in the circulation.
vascular leakage. A clinical study with adrenergum is currently being conducted in patients with sepsis and a study in hospitalized heart failure patients is currently being prepared.

Conflict of interest: A.A.V. has received research support from Sphingotec GmbH. C.G. has received travel reimbursements from Adrenomed AG. J.S. is employed by Adrenomed AG and Sphingotec GmbH and holds shares in both. P.P. received travel reimbursements and consultancy fees from Sphingotec GmbH. The other authors report no conflicts of interest.

References

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