Review

Science review: Natriuretic peptides in critical illness

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Abstract

The present review will cover the mechanisms of release and the potential pathophysiological role of different natriuretic peptides in critically ill patients. By focusing on the cardiovascular system, possible implications of natriuretic peptides for diagnosis and treatment will be presented. In critical illness such as sepsis, trauma or major surgery, systemic hypotension and an intrinsic myocardial dysfunction occur. Impairment of the cardiovascular system contributes to poor prognosis in severe human sepsis. Natriuretic peptides have emerged as valuable marker substances to detect left ventricular dysfunction in congestive heart failure of different origins. Increased plasma levels of circulating natriuretic peptides, atrial natriuretic peptide, N-terminal pro-atrial natriuretic peptide, brain natriuretic peptide and its N-terminal moiety N-terminal pro-brain natriuretic peptide have also been found in critically ill patients. All of these peptides have been reported to reflect left ventricular dysfunction in these patients. The increased wall stress of the cardiac atria and ventricles is followed by the release of these natriuretic peptides. Furthermore, the release of atrial natriuretic peptide and brain natriuretic peptide might be triggered by members of the IL-6-related family and endotoxin in the critically ill. Apart from the vasoactive actions of circulating natriuretic peptides and their broad effects on the renal system, anti-ischemic properties and immunological functions have been reported for atrial natriuretic peptide. The early onset and rapid reversibility of left ventricular impairment in patients with good prognosis associated with a remarkably augmented plasma concentration of circulating natriuretic peptides suggest a possible role of these hormones in the monitoring of therapy success and the estimation of prognosis in the critically ill.

Keywords critical illness, cytokines, heart failure, natriuretic peptides

Introduction

Critical illness, such as sepsis, trauma and major surgery, is accompanied by an activation of the immune system and mediator cells; that is, macrophages elaborating soluble inflammatory products such as cytokines and vasoactive compounds. Acting in a complex network of mediator and cell to cell interactions, inflammatory response in the most severe clinical scenario evolves in multiple organ failure and death [1]. Sepsis is defined by the presence of an infective agent in combination with typical clinical and laboratory findings of infection [2], although an infective organism is found in fewer than 50% of cases [3]. It has been increasingly recognized that sepsis represents only one example of a systemic inflammatory response syndrome (SIRS) that can be triggered not only by infection, but also by noninfective disorders such as trauma or major surgery [4,5].

Additive therapy strategies could not substantially lower the mortality of sepsis and SIRS during the past 15 years [6]; mortality remained as high as 30–50%, accounting for at least 225,000 deaths annually alone in the United States [7,8]. In a recent large clinical trial, however, recombinant human activated protein C, a compound with anticoagulant and anti-inflammatory properties, has been found to reduce mortality in patients with severe sepsis [9].

ANP = atrial natriuretic peptide; ARDS = acute respiratory distress syndrome; BNP = brain natriuretic peptide; CNP = C-type natriuretic peptide; IL = interleukin; NP = natriuretic peptides; NPR = natriuretic peptide receptor; NT-proBNP = N-terminal proBNP; SIRS = systemic inflammatory response syndrome.

The cardiovascular system in sepsis and SIRS

The cardiovascular system is a major target in patients with sepsis or SIRS, and depressed functions of this system might directly influence outcome [10]. Thus, in the 40% of patients with sepsis who develop cardiovascular impairment, mortality rises to 70–90%, a percentage with only marginal changes in recent years [11]. Peripheral vasodilatation typically manifests as a systemic hypotension, hyporesponsive to pressor agents, and an intrinsic myocardial dysfunction commonly masked by a concomitant elevation in cardiac index can be observed in these patients [10]. Most severe alterations of the cardiovascular system were frequently seen in patients with septic shock. The mechanisms of myocardial depression in human septic shock involve a complex network of vasoactive, Ca^{2+}-regulative and inflammatory mediators [12–15].

Myocardial depression and outcome in septic shock

Survivors of septic shock were found to have a decreased systolic function to an ejection fraction of about 33% and an increase in left ventricular end-diastolic diameter. These changes are of rapid onset and are reversible in survivors within several days. In contrast, in nonsurvivors a progressive myocardial depression early in the disease course has been observed [16]. It has further been shown using transoesophageal echocardiography that, apart from left ventricular systolic dysfunction, left ventricular diastolic dysfunction may also occur in patients with septic shock [17]. The significance of diastolic dysfunction in sepsis and septic shock has not yet been elucidated.

The natriuretic peptide system

The family of natriuretic peptides (NP) comprises at least eight structurally related amino acid peptides stored as three different prohormones: 126 amino acid atrial natriuretic peptide (ANP) prohormone, 108 amino acid brain natriuretic peptide (BNP) prohormone, and 126 amino acid C-type natriuretic peptide (CNP) prohormone [18].

The ANP prohormone is synthesized mainly within the atrial myocytes and in a variety of other tissues [19]. The prohormone consisting of 126 amino acids contains several peptides with blood pressure lowering properties, natriuretic properties, diuretic properties and/or kaliuretic properties [20]. These peptide hormones, numbered by their amino acid sequences beginning at the N-terminal end of the ANP prohormone, consist of the first 30 amino acids of the prohormone (i.e. proANP 1–30; long-acting natriuretic peptide), amino acids 31–67 (i.e. proANP 31–67; vessel dilator), amino acids 79–98 (proANP 79–98; kaliuretic peptide) and amino acids 99–126 (ANP) [20]. The ANP prohormone processing is different within the kidney, resulting in an additional four amino acids added to the N-terminus of ANP (i.e. proANP 95–126; urodilatin) [21].

BNP, so named because of its initial isolation from the porcine brain [22], has subsequently shown to be 10-fold more abundant in the heart than in the brain [23]. BNP is processed within the human heart to form 32 amino acid BNP, consisting of amino acids 77–108 of its 108 amino acid prohormone, and an N-terminal proBNP peptide (amino acids 1–76; NT-proBNP), both of which circulate in humans [24].

CNP was originally found in the brain [25] and has been subsequently suggested to be present also within the heart [26]. In fact, CNP has been detected in human coronary arteries [27] and in the peripheral circulation in endothelial cells of human veins and arteries at various sites [28]. Two CNP molecules, 22 and 53 amino acids in length, have been identified within the circulation [25,26]. The 22 amino acid form predominates in plasma and is more potent than the 53 amino acid form [26]. CNP lacks a significant natriuretic function [29], and serves as a regulator of vascular tone [30,31] and growth [32,33] in a paracrine or autocrine fashion.

Actions of circulating NP

Apart from blood pressure lowering properties, natriuretic, diuretic and/or kaliuretic properties of the NP originating from the ANP prohormone [20] and from BNP, inhibition of the renin–angiotensin system, sympathetic outflow, and vascular smooth muscle and endothelial cell proliferation have been attributed to NP [34]. Furthermore, a link of ANP to the immune system has been suggested [35], and a receptor-mediated modulation of macrophage function [36–38] and priming of polymophonuclear neutrophils [39] have been observed. Priming of neutrophils in endotoxemia is one of the earliest alterations of these cells in the course of activation, preceding expression of adhesion molecules and respiratory burst triggered by inflammatory mediators (i.e. tumor necrosis factor alpha and complement cascade) [40]. Whether NT-proBNP has biological effects on its own is currently unknown. The function of dendroaspis natriuretic peptide, the most recent addition to the family of NP first isolated from the venom of the green mamba, in humans still remains unclear [41]. Atrial and ventricular volume expansion and pressure overload are an adequate stimulus for secretion of circulating natriuretic peptides deriving from ANP and BNP prohormones, respectively [42,43].

Receptors of NP

Most biological effects of ANP and BNP are mediated by a guanylate cyclase coupled cell surface receptor, the A-receptor (NPR-A) [44]. Long-acting natriuretic peptide and vessel dilator have distinct receptors separate from the ANP receptors [45]. The natriuretic effects of the long-acting natriuretic peptide and the vessel dilator have a different mechanism of action from ANP, in that they inhibit renal Na^+-K^+-ATPase secondary to their ability to enhance the synthesis of prostaglandin E_2 [46,47], which ANP does not do [46,47].

CNP is a specific ligand for the B-receptor (NPR-B), another guanylate cyclase coupled NP receptor [48]. The third NP receptor, the so-called NP clearance receptor (NPR-C), binds ANP, BNP and CNP. Apart from a major role in the clearance of NP in the whole body [48], an increasing number of reports describe that several effects of ANP are mediated via the NPR-C receptor [49]. Stimulation of the NPR-C seems to be related to a G-protein coupled inhibition of adenylate cyclase [50]. Apart from binding to the NPRs, NP are cleared also through proteolysis by peptidases, the most closely studied being neutral endopeptidase 24.11. Renal excretion is currently regarded as the main clearance mechanism for NT-proBNP, but this topic awaits further study. All three subtypes of natriuretic peptide receptors (i.e. NPR-A, NPR-B and NPR-C) have been demonstrated to be expressed in diverse tissues including the renal system and the animal and human hearts [51].

NP in ischemia-reperfusion

In recent years it has been increasingly recognized that the functions of the NP are not restricted to the regulation of volume homeostasis. For instance, protective actions of ANP against ischemia-reperfusion injury on whole organs have been described first in the kidney [52] and in the liver [53]. This effect of ANP has been attributed to an antagonism of catecholamine-mediated renal vasoconstriction [52], a cGMP-mediated direct cytoprotective action on hepatocytes [54] and a regulation of Kupffer cell function [55], respectively. Protective actions against hypoxia and ischemia have also been described for ANP and urodilatin at the heart [56]. Since tissue hypoxia due to a deterioration of oxygen utilization has been suspected in patients with sepsis [57], antihypoxic and/or anti-ischemic effects of ANP at the cellular level might be important also in primarily nonischemic diseases such as sepsis. Apart from potential direct anti-ischemic actions, the cardiac NP have received close attention as cardiovascular markers. Following acute myocardial infarction, plasma levels of ANP, N-terminal proANP, vessel dilator, long-acting natriuretic peptide, BNP and NT-proBNP have been found to be increased in patients suffering from myocardial infarction [58–62]. BNP measured between 1 and 4 days after an ST-segment elevation myocardial infarction provides long-term prognostic information [58,63] independent of left ventricular ejection fraction [64]. Predictive information for use of risk stratification has been provided for BNP in the whole spectrum of acute coronary syndromes including patients with nonpersistent ST-segment elevation [65]. N-terminal proANP has also been reported to be an independent predictor of long-term prognosis in humans when measured 3–16 days after infarction [66]. A prognostic value for long-term prognosis after acute myocardial infarction [67,68] and short-term prognosis after treatment with primary percutaneous coronary intervention have also been described for NT-proBNP [69].

NP and left ventricular dysfunction

Increased plasma levels of circulating NP have been described in patients with congestive heart failure, and a direct proportion assigned to the severity of congestive heart failure as classified by the symptomatic New York Heart Association has been reported for vessel dilator, for long-acting natriuretic peptide, for BNP and for NT-proBNP [70–73]. N-terminal proANP and BNP have been reported to be more sensitive indicators of systolic left ventricular dysfunction [74–76].

N-terminal proANP has been reported to identify patients with asymptomatic left ventricular dysfunction with a sensitivity and specificity of more than 90% [75]. For vessel dilator as the only peptide (including ANP, BNP, NT-proBNP, etc.), 100% sensitivity and 100% specificity have been reported in differentiating persons with mild congestive heart failure from healthy individuals [71]. N-terminal proANP has also been reported to be an independent predictor of the development of congestive heart failure and of cardiovascular mortality [66].

BNP and NT-proBNP have been shown to be useful markers for prognosis in patients with asymptomatic left ventricular dysfunction and different degrees of congestive heart failure [76–78]. The major site of synthesis and release of BNP, the cardiac ventricles, and BNP's rapid upregulation by gene expression followed by a remarkably augmented plasma concentration exceeding that of ANP in severe cases [79], make this peptide not only especially suitable to estimate the severity of disease in patients with left ventricular dysfunction [70], but may also help guide the treatment of systolic left ventricular impairment in the future [80].

NP and pulmonary disease

In the urgent care setting it is often difficult to distinguish between cardiac and pulmonary causes of dyspnea. Physical signs, routine laboratory tests, electrocardiograms and chest films are not diagnostically consistent in differentiating heart failure from other disease, such as pulmonary disease [81]. Rapid testing of BNP and NT-proBNP has been reported to differentiate pulmonary etiologies from cardiac etiologies of dyspnea [82–84]. Some types of pulmonary disease, such as cor pulmonale, pulmonary embolism and lung cancer, however, are also associated with elevated natriuretic peptide levels, but not generally to the same extent as those in patients with acute left ventricular dysfunction. BNP levels in the intermediate range from 100 to 500 pg/ml have been reported to be attributable to causes other than congestive heart failure [85].

Increased plasma levels of NP (i.e. ANP [86], N-terminal proANP [87] and BNP [88]) have also been found in patients with acute respiratory distress syndrome (ARDS). Acute cor pulmonale as a consequence of increased pulmonary vascular resistance occurs in up to 60% of patients with

ARDS submitted to conventional mechanical ventilation [89]. An increase of pulmonary vascular resistance observed in ARDS may lead to right ventricular overload and decreased right ventricular output in presence of impaired right ventricular contractility [90,91]. BNP levels secreted by the right ventricular myocardium are said not to exceed 300–600 pg/ml [82]. However, there might be a considerable overlap of patients with increased BNP due to ARDS and patients with primary symptomatic congestive heart failure, where BNP levels have to reach more than 500 pg/ml to ensure the diagnosis with a probability greater than 95% [92].

In support of this concept, elevated values reported for ANP [86], N-terminal proANP [87], BNP [88] and NT-proBNP [93] in patients with acute lung injury and/or sepsis are well in the range found in patients with severe heart failure. These data suggest at least for BNP a limited value of intermediate BNP values for the discrimination of primary pulmonary disease (i.e. ARDS) or cardiac disease. Sufficient data for other NP are still lacking. In contrast, a BNP cutoff value of 100 pg/ml measured at admission of patients presenting in the emergency department has been reported to have a strong negative predictive value for congestive heart failure in acute dyspneic patients [73]. Nevertheless, a BNP cutoff value of 80 pg/ml was not able to exclude patients with 'flash' pulmonary edema [94]. Pulmonary edema and heart failure are often found in patients (who are frequently old) with diastolic dysfunction and a preserved systolic left ventricular ejection fraction [95]. BNP might be useful in establishing the diagnosis of (concomitant) diastolic dysfunction [96], which is common in the elderly population with pulmonary disease. However, although it could be confirmed by other investigators that patients in the presence of diastolic dysfunction had higher BNP levels compared with healthy controls, in terms of absolute values symptomatic patients with mild diastolic heart failure might have BNP levels in the normal range [97].

Because of the overlap of BNP levels in the lower and intermediate concentration, to date, the diagnostic value of BNP in this concentration range seems to be poor. The major role of BNP is thus still the separation of symptomatic patients without congestive heart failure. Taking into consideration the poor prognosis and higher readmission rate in heart failure patients with increased levels of BNP (values >500 pg/ml) [92], BNP and possibly further NP might have a place in monitoring therapy success in the future. In this regard, BNP might be of value also in patients with ARDS, where a lack of BNP decrease has been related to prognosis [88].

NP in the critically ill

Relation to endotoxin and proinflammatory cytokines

Hemodynamic changes typically seen in sepsis and septic shock (i.e. reduced ejection fraction in presence of an increased diastolic volume and pressure of both ventricles, and an increase in pulmonary arterial pressure [10,98]) might explain increased plasma levels of circulating NP derived from both ventricles of the heart in those patients. ANP has consistently been shown to increase in plasma during hyperdynamic ovine endotoxemia associated with right ventricular distension due to pulmonary hypertension, and in acute respiratory failure associated with sepsis related to pulmonary arterial and occlusion pressures [86,99–101]. Furthermore, a diminished pulmonary uptake in the case of a reduced organ perfusion might contribute to the elevation in plasma levels of ANP in sepsis. The lung is a major clearance organ of ANP besides the liver, the kidney and the peripheral and splanchnic circulation [102,103].

Plasma BNP has also been described as increased in animal models dealing with endotoxemia [104]. However, it has been questioned whether BNP expression and secretion in endotoxemia is solely explained upon cardiac overloading due to alterations of the cardiovascular system. A direct upregulation of the BNP gene by lipopolysaccharide, not mediated by other cytokines and independent from mechanical loading in endotoxemia, has recently been described in rats [104]. In fact, increased plasma levels of endotoxin have also been found in other conditions accompanied with increased BNP plasma levels (i.e. congestive heart failure) [105], and endotoxin exerts deleterious effects on cardiac performance itself [106,107]. Based on these findings, one might speculate that endotoxin itself contributes to left ventricular dysfunction and modulates BNP expression and secretion in addition to elevated ventricular wall stress in endotoxemia in man.

Apart from endotoxin, proinflammatory cytokines stimulated in different forms of heart failure and dramatically increased in sepsis and septic shock might also contribute to ANP and BNP secretion from the heart. *In vitro* studies have shown an enhanced gene expression of BNP and prepro-ANP, the precursor form of circulating ANPs, following stimulation of cultured cardiomyocytes with IL-1β [108,109]. Increased secretion of both ANP and BNP following stimulation with members of the IL-6-related family (i.e. cardiotrophin-1) has recently been reported in cultured cardiomyocytes [110]. In heart failure, cardiotrophin-1 and IL-6 levels increase [111,112], and cosecretion of IL-6 and ANP as well as of cardiotrophin-1 and pro-BNP has been reported [111,113].

In human septic shock, ANP is related to IL-6 rather than to the altered hemodynamics of these patients [114]. In septic shock, IL-6 levels exceed those in ischemic or severe congestive heart failure more than 100-fold [114,115], and the relation between ANP and IL-6 seems to be rather specific since no association between ANP and other inflammatory mediators of septic shock (i.e. soluble tumor necrosis factor receptors) could be observed [114]. These findings argue for a possible role for members of the IL-6-

related family in the modulation of both NP (ANP and BNP) in patients suffering from ventricular impairment in septic shock.

Estimation of disease severity and prognosis

A negative relationship between heart function indices and elevated plasma levels of ANP [116], N-terminal pro-ANP [87] and, recently, for BNP [117] and NT-proBNP [93] has been reported in human septic shock. These findings suggest that these peptides might reflect myocardial dysfunction as described in congestive heart failure in septic shock as well. The relative value of ANP compared with BNP in recognition of myocardial depression, severity of disease and outcome prediction has been prospectively evaluated in human septic shock [114]. In this study, cardiac impairment was reflected by plasma BNP rather than by ANP [114]. Interestingly, neither ANP nor BNP was related to the severity of disease judged by the Acute Pathophysiology and Acute Chronic Health Evaluation (APACHE) II score [114], and neither ANP nor BNP was able to differentiate survivors from nonsurvivors [114]. Although these results should be interpreted cautiously because of the relatively small number of patients included, the finding of a lack of value for prediction of the severity of disease judged by the APACHE II score and estimation of mortality is in good agreement with former results in critically ill patients with a medium degree of severity of illness [118]. Thus, in patients with trauma or different kinds of surgery, neither ANP nor BNP were useful for either estimation of disease severity or outcome prediction [118].

In summary, BNP and to a minor degree ANP are associated with the degree of cardiac impairment in septic shock. BNP might therefore be the more suitable and valuable marker to monitor therapy success. Actually, however, there is no convincing evidence to establish a role of NP in estimation of disease severity. Further studies are needed to clarify a feasible role of NP in outcome prediction in human septic shock.

CNP in sepsis and inflammatory response

Although CNP is known to be a local regulator of vascular tone and growth, CNP can be detected in human circulation [119]. In contrast to other members of the natriuretic peptide family, however, the plasma concentration of CNP is not altered in heart disease such as congestive heart failure [119]. So far, sepsis and further septic shock is the only condition where sharply increased plasma levels of CNP have been observed [119]. Tumor necrosis factor alpha, inducible nitric oxide synthase and endotoxin, mediators all shown to be increased in sepsis, are potent stimulators of CNP from endothelial cells and might contribute to elevated plasma levels of this peptide in sepsis [119]. Furthermore, macrophages represent a source for and a target of CNP [120]. In these mediator cells of inflammation, endotoxin has been shown to induce CNP [121], and a B-receptor-mediated inhibition of inducible nitric oxide synthase has been described [122].

At the level of the vascular wall, CNP seems to act predominantly at the vein [123]. It has been suspected that increased concentrations of CNP might contribute to venous pooling by vasodilative action on the vein in septic shock [123].

Conclusion

Circulating NP such as ANP, peptides derived from the N-terminal prohormone, BNP and its N-terminal moiety NT-proBNP reflect a decreased left ventricular function in patients with congestive heart failure, and play a role in risk stratification in the whole spectrum of acute coronary syndromes. Tissue hypoxia and impairment of left ventricular function are often found in critically ill patients. NP such as ANP, N-terminal proANP, BNP and NT-proBNP seem useful to detect myocardial dysfunction early in the clinical course of the critically ill. Myocardial dysfunction has been shown to be associated with poor outcome in the critically ill, and reversibility of cardiac impairment in patients with good prognosis has been described. First results suggest a possible role of circulating NP in monitoring of therapy success in septic shock and perhaps in acute lung injury associated with sepsis. Future studies are needed to confirm a prognostic value of these natriuretic peptides in the critically ill.

Competing interests

The author declares that he has no competing interests.

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