RAPID COMMUNICATION

Pro-atrial natriuretic peptide hormone from right atria is correlated with cardiac depression in septic patients

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ABSTRACT. N-terminal pro-atrial natriuretic peptide [proANP(1-98)] has been extensively investigated in patients with chronic heart failure and ishemic heart disease. It is found to be a better marker of cardiac dysfunction than atrial natriuretic peptide (ANP). The possible involvement of proANP(1-98) in cardiac depression caused by sepsis has not been studied yet. Therefore, we analyzed atrial plasma concentration of proANP(1-98) in 17 septic patients with hemodynamic variables measured or calculated using pulmonary artery catheter. The results of altogether 96 measurements show a significant negative correlation of proANP(1-98) and cardiac index ($p<0.024$), oxygen delivery ($p<0.03$) and oxygen consumption ($p<0.03$). There is also a positive correlation with pulmonary vascular resistance ($p<0.03$). ProANP(1-98) is significantly higher in patients who developed acute respiratory distress syndrome (ARDS) ($p<0.001$). This study implies that proANP(1-98) is a possible novel hormone marker of cardiac depression caused by sepsis that could be used for prediction of ARDS.

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INTRODUCTION

Atrial natriuretic peptide (ANP) is a peptide hormone synthesized in atrial myocites as a prohormone and stored in secretory granules as a 120 amino acid prohormone (1). The most important stimulus for the release of hormones into circulation is stretch of the myocyte fibers (2). On release the prohormone is slit into equimolar amounts of the highly biologically active proANP (99-126), also known as α-ANP and the N-terminal part proANP(1-98) (3). Alpha-ANP binds to specific receptors and therefore is rapidly cleared from circulation with a half-life of 3-4 min. No receptors for proANP(1-98) are known today, therefore this peptide circulates longer, which leads to significant higher concentrations in blood compared to α-ANP (4). Thus, circulating levels of proANP(1-98) are less sensitive to pulsatile secretion of ANP and may better reflect chronic levels of ANP secretion than the rapidly fluctuating levels of α-ANP.

ANP has vasorelaxing, natriuretic and diuretic effects and in this way is involved in fluid, electrolyte and blood pressure homeostasis (5). Effects of ANP have been well investigated in chronic heart failure (6), myocardial infarction (7) and acute renal failure (8); it is a reliable marker of cardiac dysfunction in congestive heart failure. proANP(1-98) is found to be even a better prognostic marker in patients with ishemic heart disease and myocardial infarction than ANP (9).

The role of proANP(1-98) in hemodynamic changes caused by severe sepsis is less extensively investigated, although cardiac depression and disturbances in fluid hemostasis are major problems in these patients. Therefore, we analyzed the correlation between atrial plasma level of proANP(1-98) and hemodynamic variables.

MATERIALS AND METHODS

Patients

Seventeen critically ill septic patients were included in the study. Sepsis was defined as a positive systemic inflammatory response (SIRS) and a positive microbiological finding or an ultrasound or X-ray examination consistent with inflammatory focus. An attending physician according to clinical indication inserted pulmonary artery catheter. We used Opti-Q or Oximetrix catheter (Abbot – Critical Care System, Abbot Laboratories, North Chicago, IL, USA). Blood samples for determining proANP(1-98) were taken from the proximal part of pulmonary artery catheter that

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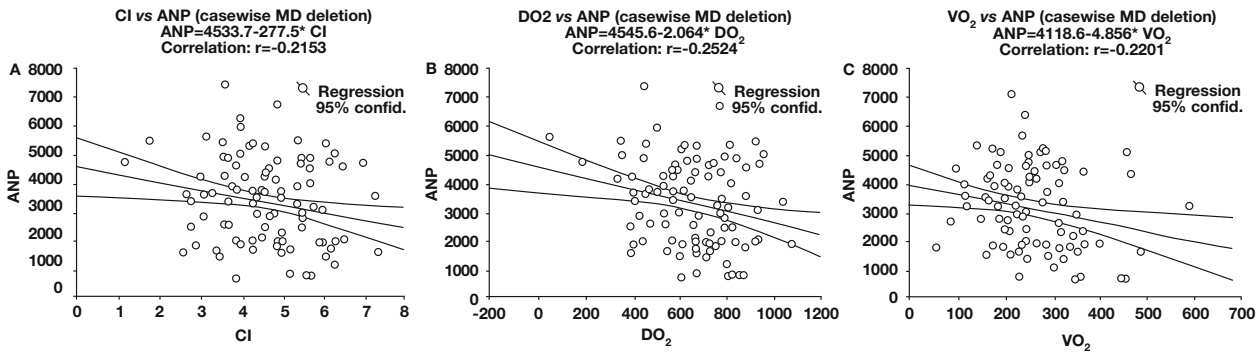

Fig. 1 - *Correlation between pro-atrial natriuretic peptide (proANP; fmol/ml) and: A) cardiac index (CI; l/m²); B) oxygen delivery (DO_2 ml/min/m²); C) oxygen consumption (VO_2; ml/min/m²).*

is situated in right atria where ANP is predominantly released. At the same time, a blood sample for analysis of oxygen parameters was taken. Hemodynamic measurements were made immediately after drawing blood samples. Pressure variables were directly measured from pulmonary artery catheter. Cardiac output was determined by termodilution technique. All calculated variables are expressed as index values adapted to body surface area. The Hospital Ethics Committee approved the study.

Blood samples

Blood samples (3 ml) were taken from the proximal part of the pulmonary artery catheter. It was collected into prechilled glass tubes containing EDTA (1 ml/ml blood) and aprotinin 75 KIU per tube). Blood was spun down and serum stored deep-frozen.

Assays

proANP(1-98) Immunoassay Novel genuine proANP(1-98) ELISA (Biomedica, Austria) was used. The proANP(1-98) test kit is a sandwich enzyme immunoassay designed to determine proANP(1-98) directly in biological fluids – human serum or plasma.

Statistics

Linear regression analysis was used to determine correlation of proANP(1-98) and hemodynamic variables. Nonparametric statistics – Kruskall – Wallis test was used to analyze if patients with and without acute respiratory distress syndrome (ARDS) belong to the same distribution concerning proANP(1-98).

RESULTS

There is a significant negative correlation between cardiac index and proANP(1-98) ($p<0.024$) (Fig. 1A). Oxygen delivery is also negatively correlated with proANP(1-98) atrial concentration ($p<0.03$) (Fig. 1B). Oxygen consumption is inversely correlated with proANP(1-98) (Fig. 1C).
Among resistance variables, there was statistically signifi-

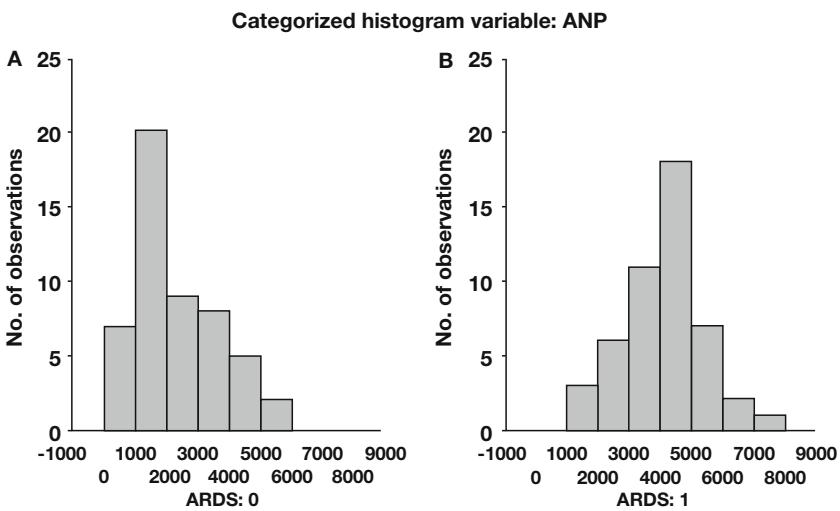

Fig. 2 - *Different distribution of pro-atrial natriuretic peptide (proANP) (1-98) values (fmol/ml) in two groups of patients: patients without (A, ARDS 0) and with (B, ARDS 1) acute respiratory distress syndrome (ARDS).*

cant correlation only with pulmonary vascular resistance. We did not find a correlation between any pressure variable and proANP(1-98).

ProANP(1-98) is significantly higher in patients with ARDS. Mean value in ARDS patients was 4165±1236 fmol/ml, while in patients who did not have ARDS mean proANP(1-98) value was 2388±1285 fmol/ml. Difference is significant at $p<0.001$ (Fig. 2).

DISCUSSION

Pathophysiological role and gene expression of natriuretic peptide have been extensively investigated in subgroups of patients with congestive heart failure and ishemic heart disease. High plasma concentrations of α-ANP correlate with the degree of hemodynamic dysfunction and predict poor long-time survival. ProANP(1-98) has been investigated in patients with acute myocardial infarction and its plasma level correlated better with left ventricular dysfunction and survival than α-ANP (9). The current concept is that natriuretic peptides exert beneficial effects in congestive heart failure by promoting diuresis, reducing systemic vascular resistance, production of cateholmines and inhibiting grow of cardiac fibroblasts (5).

In contrast to numerous studies among chronic cardiac patients (10), there are no investigations analyzing the correlation of proANP(1-98) and cardiac function in critically ill patients who have cardiac dysfunction caused by severe sepsis. The results of our study show a negative correlation of atrial plasma proANP(1-98) concentrations and cardiac index. There is also a negative correlation with oxygen transport variables, which include cardiac index: oxygen delivery and oxygen consumption. These results imply that proANP(1-98) could be a marker of cardiac depression in septic patients.

Highly significant correlation of proANP(1-98) and the diagnosis of ARDS are similar to results of studies that investigated α-ANP in critically ill patients (11), hence it also confirms applicability of the novel proANP(1-98) immunoassay used in the study. The interpretation of the finding is still speculative: the possible mechanism is that ANP stimulates capillary leak from intravascular to interstitial space and contributes to accumulation intrapulmonary water. A recent study determing α-ANP, which is less stable than proANP, suggests ANP as a mediator of cardiac depression in septic patients, although a-ANP was determined in peripheral blood of 14 patients not in samples of atrial plasma (12). Our study implies that proANP(1-98) is not only indicative for pathobiology of ARDS in septic patients, but is also a possible marker of cardiac depression caused by sepsis.

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