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ORIGINAL RESEARCH

The Correlations of Human Atrial Natriuretic Peptide on Cardiac Function and Hemodynamics in Pediatric Septic Shock

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Purpose: We aimed to determine the correlations of human Atrial Natriuretic Peptide (ANP) on cardiac function and hemodynamics in pediatric septic shock.

Patients and Methods: We conducted an observational and prospective study on 30 children with septic shock. Measurement of the level of human atrial natriuretic peptide was determined in the serum of patients. Cardiac power (CP) is a cardiac function parameter measured with cardiac output (cardiovascular flow) and mean arterial (intravascular) pressure. Cardiac output and mean arterial pressure were monitored using pressure recording analytical methods (PRAM). Hemodynamic status was represented by a vasoactive inotropic score.

Results: Thirty pediatric septic shock patients fulfilled the eligibility criteria. The human ANP level was not significantly different in pediatric septic shock on three days of examination. Cardiac power was significantly different in pediatric septic shock on three days of examination. There was a correlation between human ANP and cardiac power on day 3 and human ANP and VIS on day 2.

Conclusion: There was a significant correlation between human ANP level and cardiac power on day 3 and ANP level and VIS on day 2. The cardiac power on day 3 and VIS on 48 hours can be alternatives to evaluate the hemodynamic status and cardiac function concerning human ANP in pediatric septic shock.

Keywords: Human Atrial Natriuretic Peptide, cardiac power, vasoactive inotropic score, pediatric septic shock

Introduction

Human Atrial Natriuretic Peptide (ANP) is a natriuretic hormone responsible for maintaining homeostasis circulation. This hormone modulates cardiac preload and afterload through diuresis, natriuresis, and vasodilatation, therefore affecting myocardial function.[1] The atrium secretes Human Atrial Natriuretic Peptide in response to increased plasma volume. Human ANP acts on natriuretic peptide receptors on ventricular myocytes and directly affects myocardial contraction and relaxation. Conditions where ANP levels are increased, include valvular heart disease, coronary artery disease, pulmonary hypertension, constrictive pericarditis, and sepsis.[2] Patients with congestive heart failure and predicted poor prognosis had been reported to have increased plasma levels of ANP. To date, there has been no evaluation of plasma levels of ANP in patients with septic shock concerning the cardiovascular function.[3]

In critically ill children, sepsis is one of the major global causes of morbidity and mortality. Refractory sepsis or septic shock and/or multiple organ dysfunction syndromes are the primary causes of mortality in children with sepsis.[4] The diagnosis of septic shock is established based on evidence of inadequate tissue perfusion, persistent hypotension after initial fluid resuscitation, and the need for a vasoactive agent to maintain normotension.[5]

The most common complication of sepsis is cardiovascular dysfunction. It is induced by the mediators of sepsis affecting the normal heart physiology and disrupting the normal homeostatic and reflex responses.[6] Cardiovascular

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dysfunction is characterized based on the following clinical symptoms: hypotension, vasoactive requirement to maintain blood pressure despite rapid administration of intravenous fluid in 1 hour, or two or more symptoms of abnormal perfusion (metabolic acidosis, increased lactate level, decreased urine output, and capillary refill of more than 5 seconds).[7] The highest septic shock mortality rates occurred 48–72 hours after initial treatment.[8]

Important components in the clinical course of septic shock (from systemic inflammation to mortality) include circulatory instability and myocardial dysfunction. The many consequences of severe sepsis and septic shock include myocardial depression. A previous study showed that children with septic shock commonly respond to both inotropic and vasodilating agents. On the other hand, adults are more likely to suffer from vasomotor dysfunction and require vasopressor therapy. This finding raises the possibility that myocardial dysfunction may be more of a factor in children than adults.[9]

The pathophysiology and therapeutic response in septic shock is age-specific. For example, cardiac failure is a leading cause of death in neonates and children, as opposed to a vascular failure in adults. Pediatric populations may benefit more from inotropes, vasodilators (children), inhaled nitric oxide (neonates), and extracorporeal membrane oxygenation, whereas vasopressors are more important in adult survival.[10]

In the cardiovascular system, the heart's ability to pump is determined by cardiac power. Cardiac power (CP) is measured according to cardiac output (cardiovascular flow) and mean arterial (intravascular) pressure. Previous studies showed that cardiac power was significant for diagnosing cardiogenic shock and an essential determinant of prognosis. Lower CP served as a reliable mortality predictor in cardiogenic shock. It should be noted that myocardial dysfunction may also be presented in septic shock. A recent study by Roper et al indicated that CP is a potent predictor of death and can be utilized to further risk-stratify patients with sepsis and septic shock.[11]

In pediatric patients, septic shock is associated with severe hypovolemia. Children often showed good responses following aggressive fluid resuscitation. However, this pediatric population also has a different hemodynamic response to fluid resuscitation than adults. Children tend to have lower cardiac output without low systemic vascular resistance, resulting in higher mortality rates.[12] Early diagnosis and treatment of sepsis can prevent septic shock and decrease mortality. Hemodynamic status can be described in a simpler, more accessible method using a vasoactive inotropic score (VIS).[13] Vasoactive Inotropic Score is a scoring system used to calculate the vasopressor and inotropic dose needed to maintain stable hemodynamics. The VIS was initially designed for pediatric cardiogenic shock and post-surgical patients to quantify the cumulative effect of numerous vasoactive or inotropic drugs on a single patient. It has recently been validated in a pediatric septic shock patient population.[14] Studies showed a correlation between high VIS and poor outcomes.[15] Hemodynamic monitoring is needed to assess the hemodynamic status and guide the treatments for cardiovascular dysfunction.[16]

Studies on the effect of ANP on cardiac and hemodynamic functions in children with septic shock who had received fluid resuscitation remain limited. A study by Nakajima et al on adults suggested that ANP infusion may improve left ventricle diastolic function, even in patients with moderate heart failure and high plasma brain natriuretic peptide levels.[1] The role of ANP in pediatric septic shock patients is yet to be explored. Therefore, we conducted a study that evaluates the correlations of ANP on cardiac function and hemodynamics in children with septic shock who had received fluid resuscitation.

Patient and Methods

Study Design

This prospective cohort study conducted from 15 August 2020 to 31 December 2021 in the Pediatric Intensive Critical Care Unit (PICU) of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The included subjects were critically ill children with septic shock, aged 6 months – 18 years old, weighed > 7.5 kg, admitted in less than 24 hours to PICU, and the parent(s) consented to participate in the study. The exclusion criteria were subjects with congenital heart disease.

Cardiac power is used to represent the cardiac function. It is measured by multiplying mean arterial pressure and cardiac output, divided by a constant of 451.[9] According to a study by Baysal et al, the hemodynamic status was represented by a vasoactive inotropic score calculated with the formula as dopamine dose ($\mu g\ kg^{-1}\ min^{-1}$) + dobutamine

dose (μg kg^{-1} min^{-1}) + 100 × epinephrine dose (μg kg^{-1} min^{-1}) + 100 × norepinephrine dose (μg kg^{-1} min^{-1}) + 10,000 × vasopressin dose (U kg^{-1} min^{-1}) + 10 × milrinone dose (μg kg^{-1} min^{-1}).[17]

Blood Collection and Analysis

The blood sample was collected after the patient's parents gave consent. Two mL of blood was drawn from the cubital vein and injected into a VENOJECT® tube containing EDTA anticoagulant. The tube was centrifuged at 1000 revolutions per minute (RPM) for 15 minutes to separate plasma and pellet. Centrifugation was performed within 30 minutes after drawing blood. If a quick analysis is not possible, the serum is kept at −20 °C. An ELISA test was performed to measure ANP level using the Human ANP ELISA Kit (catalog no. E-EL-H0532). The quantification was completed using ELISA Reader (iMark Microplate Absorbance Reader).

Data Collection

Data collection included patients' names, ages, sex, vital sign, and primary diagnosis. The blood sample was taken after fluid resuscitation on days 1, 2, and 3. All subjects received timely initial treatments, which comprised appropriate antibiotics, hemodynamic resuscitation, and organ support therapy with mechanical ventilation according to the 2016 Surviving Sepsis Campaign (SSC) guideline. All patients were hemodynamically monitored using pressure recording analytical methods (PRAM).

Data Analysis

Human ANP, cardiac power, and VIS data were analyzed using SPSS software for Windows 20.0 (IBM, Armonk, NY, USA). We performed the Shapiro–Wilk test to determine the normality of numerical data distribution. A comparison of numerical data was performed with the *t*-test and Mann–Whitney or Friedman test for normal and non-normal data distribution, respectively. Bivariate analysis was used to measure the correlation between variables. We performed Pearson and Spearman correlation tests were used to test the correlation between variables with normal and non-normal distribution, respectively.

Results

Subjects Characteristics

Thirty children with septic shock fulfilled the eligibility criteria. Children aged between 9 months and 17 years diagnosed with septic shock were included. During observation, 27 children with complete data were divided into two groups, survived (n = 8; 5 boys and 3 girls) and did not survive (n = 19; 7 boys and 12 girls) (Table 1). Human ANP level was found to be a not significant difference in pediatric septic shock on three days of examination with a mean of 104.66 ±

Table 1 Baseline Patient Characteristics

Variables	N = 27
Median age, months (range)	84 (9–204)
Gender, n (%) Male Female	 12 (44.4) 15 (55.6)
Median weight, kg (range) Median height, cm (range)	19 (7–49) 110 (60–160)
Mechanical ventilation Yes (%)	 24 (88.9)

(*Continued*)

Table 1 (Continued).

Variables	N = 27
Primary sites of infection	
Lung, n (%)	7 (25.9)
Renal, n (%)	3 (11.1)
Abdominal, n (%)	4 (14.8)
Blood, n (%)	5 (18.5)
Soft tissue, n (%)	1 (3.7)
Central nervous system, n (%)	7 (25.9)
Median Levels of ANP day-1 (pg/mL)	
Survivors (range)	78.4 (55.3–237.8)
Non-Survivors (range)	85.6 (7.9–337.6)
Median Levels of ANP day-2 (pg/mL)	
Survivors (range)	90.1 (39.2–441.6)
Non-Survivors (range)	84.9 (3.7–236.4)
Median Levels of ANP day-3 (pg/mL)	
Survivors (range)	86.7 (17.3–299.9)
Non-Survivors (range)	73.2 (1.2–261.6)
Mortality, n (%)	19 (70.3)

Abbreviation: ANP, Atrial Natriuretic Peptide.

86.71 pg/mL on day 1, a mean of 109.27 ± 92.66 pg/mL on day 2, and a mean of 91.07 ± 76.71 pg/mL on day 3 (Figure 1, Table 2).

Cardiac power was found to be a significant difference in pediatric septic shock on three days of examination, with a mean of cardiac power of 0.38± 0.35 on day 1, a mean of cardiac power of 0.54 ± 0.37 on day 2, and a mean of 0.51 ± 0.36 on day 3 (Figure 2, Table 2).

The pediatric septic shock group had a significantly different vasoactive inotropic score on observation days 1, 2, and 3, with a mean of VIS 8.11± 7.8 on day 1, a mean of VIS 13.89 ± 10.23 on day 2, and a mean of 25.37 ± 21.13 on day 3 (Figure 3).

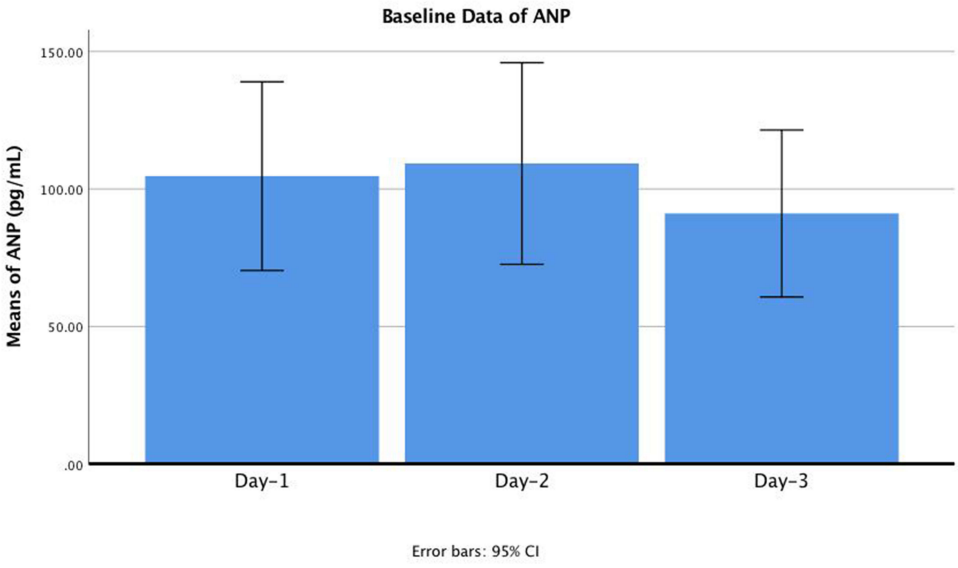

Figure 1 Human ANP levels on days 1, 2, and 3.

Table 2 Serial Measurement of ANP, Cardiac Power, and VIS

Variables	Serial Measurement	Result	P
		Median (Min-Max)	
ANP (pg/mL)	Day 1 Day 2 Day 3	80 (7.85–337.56) 84.9 (3.71–441.63) 74.93 (1.17–299.94)	0.717
Cardiac Power	Day 1 Day 2 Day 3	0.296 (0.03–1.63) 0.468 (0.03–1.28) 0.446 (0.01–1.32)	0.012*
VIS (µg/kg/minutes)	Day 1 Day 2 Day 3	5 (3–36) 10 (3–45) 21.5 (5–78)	0.000*

Note: *Significant p-value.
Abbreviations: ANP, Atrial Natriuretic Peptide; VIS, Vasoactive Inotropic Score. .

Correlation analysis was performed to analyze the association of ANP levels and cardiac power over three days of examination. It was found that the ANP level was positively correlated with cardiac power for three days. However, it was not significantly different on day 1 (r 0.299, p>0.05; Figure 4) and day 2 (r 0.240, p>0.05; Figure 5). A significant positive correlation between ANP level and cardiac power was observed on day-3 (r 0.578; p<0.05; Figure 6).

We analyzed the association between ANP levels and vasoactive inotropic score for three days. On day 1, a non-significant negative correlation between ANP and the vasoactive inotropic score was observed (r −0.253; p>0.05; Figure 7). On day 2, a significant negative correlation was observed (r −0.475, p<0.05; Figure 8). We found no significant correlation on day 3 (r −0.145, p>0.05; Figure 9).

Discussion

The objective of this study was to evaluate the correlations between ANP, cardiac function, and hemodynamics in pediatric septic shock patients. In the three days of measurement, we observed no significant difference in ANP levels; however, there were significant differences in CP and VIS. On day 3, there was a decrease in ANP levels and an increase

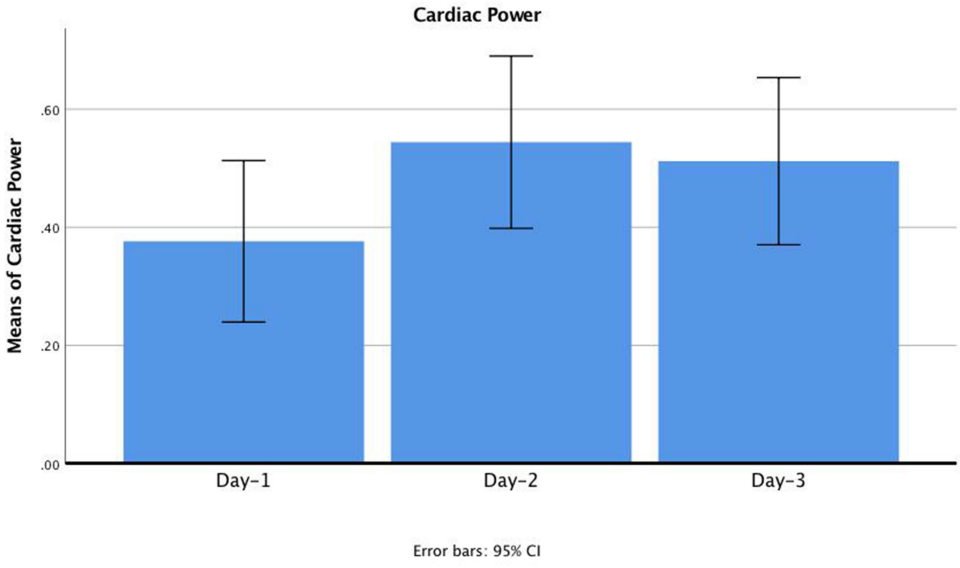

Figure 2 Cardiac Power on days 1, 2, and 3.

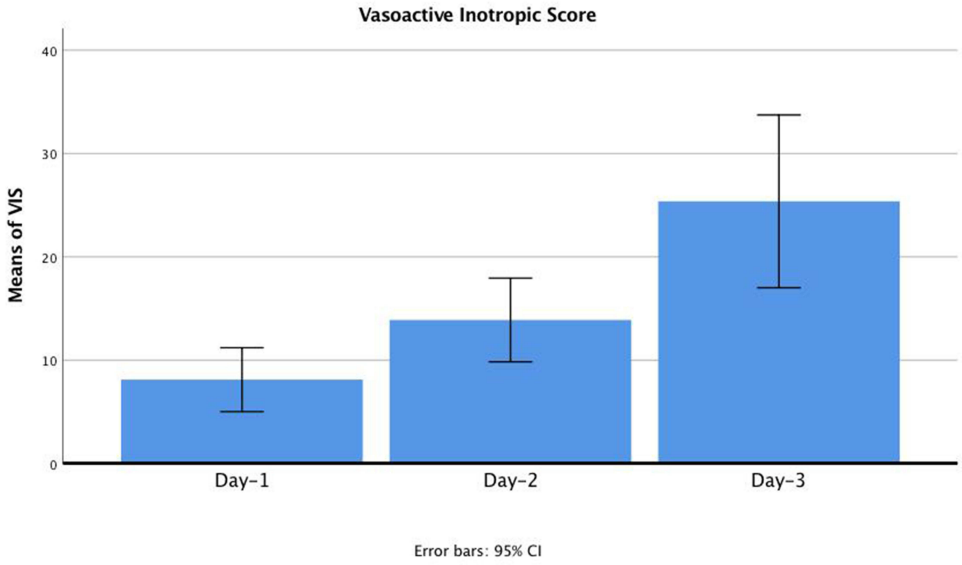

Figure 3 Vasoactive Inotropic Score on days 1, 2, and 3.

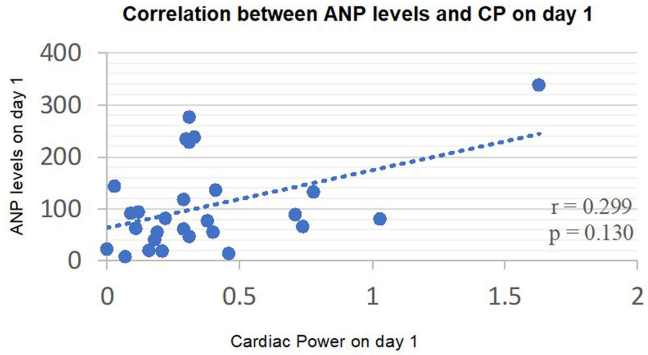

Figure 4 Linear correlation between ANP levels and Cardiac Power on day 1.

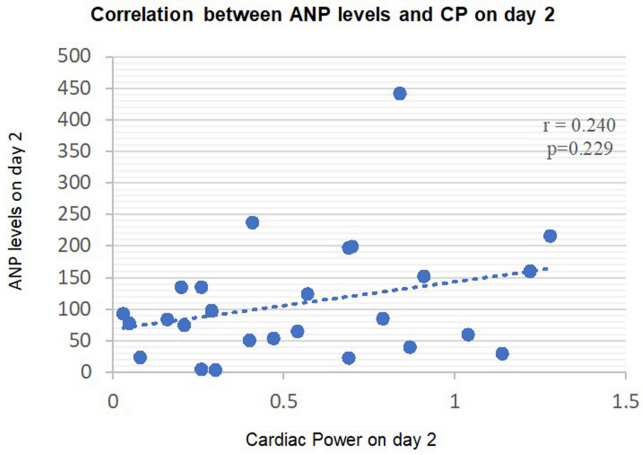

Figure 5 Linear correlation between ANP levels and Cardiac Power on day 2.

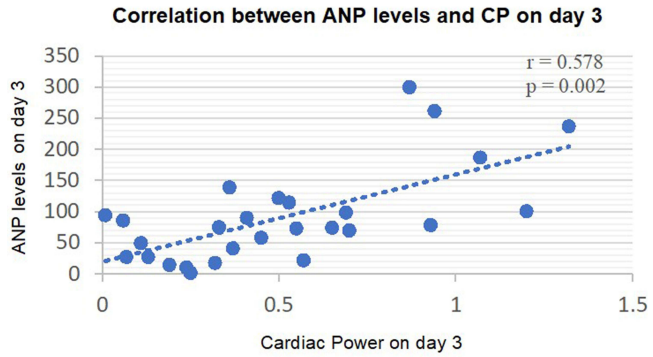

Figure 6 Linear correlation between ANP levels and Cardiac Power on day 3.

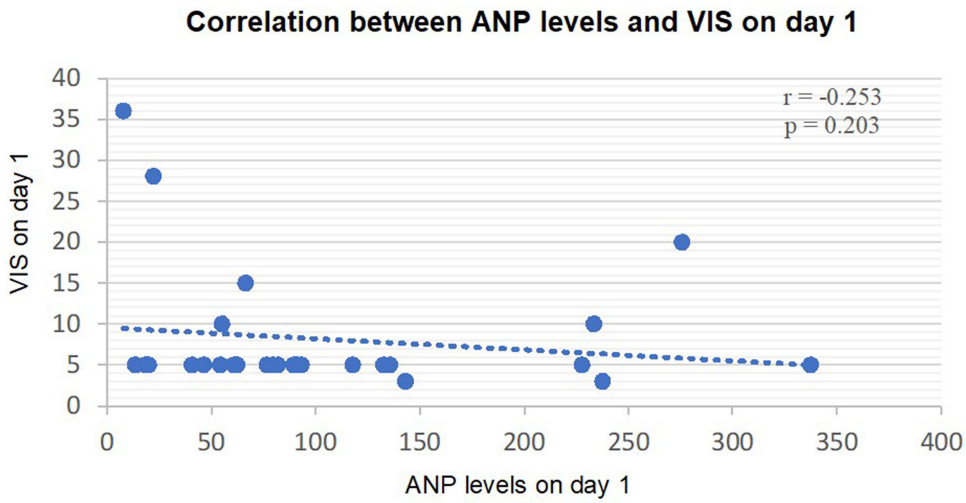

Figure 7 Linear correlation between ANP levels and VIS on day 1.

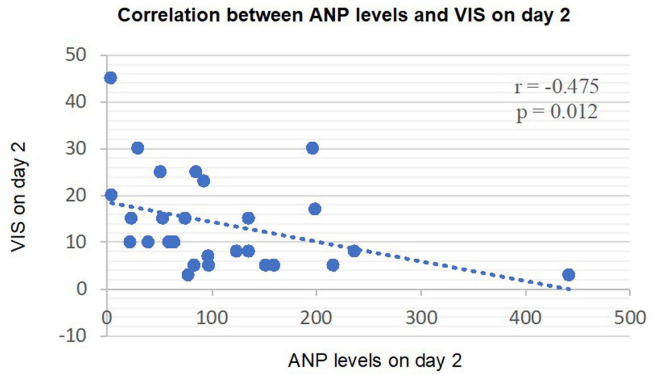

Figure 8 Linear correlation between ANP levels and VIS on day 2.

of VIS. The effect of ANP on left ventricle contractility was challenging to assess due to the vasodilating properties of ANP that changed loading conditions and increased cardiac output.[8,18] The correlation between ANP level and cardiac power was evaluated to avoid this. There were significant correlations between ANP level and cardiac power on day 3 and ANP level and VIS on day 2. ANP is a marker for congestive heart failure. Nevertheless, its pathophysiological and prognostic significance in pediatric patients with severe sepsis and septic shock is not yet fully understood.[19] In the present study, we found a decrease in ANP in the plasma of non-survivor pediatric septic shock patients.

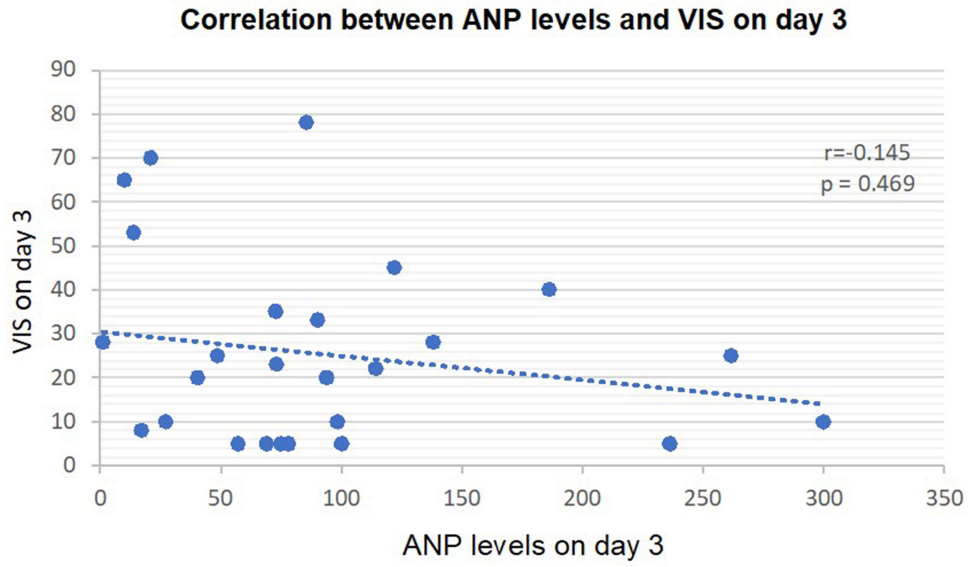

Figure 9 Linear correlation between ANP levels and VIS on day 3.

The use of VIS in the pediatric population with septic shock has been validated in several studies.[20–22] The largest study by McIntosh et al[23] evaluated primary outcomes of length of stay in ICU and ventilator days on 138 children (aged 60 days to 18 years old) admitted to ICU due to sepsis requiring vasoactive support. Upon admission, VIS was evaluated at 6 hours, 12 hours, 24 hours, and 48 hours. At 48 hours after admission, VIS was the highest and a strong predictor for primary outcomes. VIS evaluated 12 hours after admission was independently associated with composite cardiac arrest outcomes, the need for extracorporeal membrane oxygenation (ECMO), and in-hospital mortality. This study found a significant correlation between VIS and ANP levels on day 2. This explained the role of VIS as the strongest predictor at 48 hours of examination. In a study by Pudjiadi et al, VIS > 11 was a good predictor of mortality in children with septic shock.[24] In a study by Fatimah et al reported that the cut-off value of the ROC curve of VIS concerning mortality was 6 with a sensitivity and specificity of 82.1% and 64.5%, respectively.[25] Previous studies on VIS in children have only associated VIS with cardiac surgery in pediatrics. To date, no study has investigated the correlation between ANP, cardiac power, and VIS as a marker for hemodynamic status and cardiac function in pediatric septic shock. It should also be noted that the need for vasoactive and inotropic drugs can also predict mortality in children.

The present study extends the concept of decreased levels of ANP. Our findings may warn the pediatric ICU professionals about sepsis-induced cardiac dysfunctions, which was associated with an increased mortality rate. Several limitations to our study are as follows. First, the small sample size limited statistical power. Second, the present study was conducted in a referral tertiary care hospital where most of the patient population had multiple preexisting co-morbidities.

Conclusion

There was a significant correlation between Human ANP level and cardiac power on day 3, and ANP level and VIS on day 2. The cardiac power on day 3 and VIS on 48 hours can be alternatives to evaluate the hemodynamic status and cardiac function concerning human ANP in pediatric septic shock.

Abbreviations

ANP, atrial natriuretic peptide; CP, cardiac power; PRAM, pressure recording analytical methods; VIS, vasoactive inotropic score; PICU, Pediatric Intensive Critical Care Unit; RPM, revolutions per minute; SSC, Surviving Sepsis Campaign .

Ethical Consideration

This study was conducted in compliance with the Declaration of Helsinki. We obtained ethical approval from the Ethical Committee of the Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Academic Hospital (ethical clearance number 0166/105/3/VIII/2020).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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