Correlation between heart failure score and estimation glomerulus filtration rate based on cystatin C in children

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ABSTRACT

**Background:** Heart failure is a clinical syndrome due to decreased cardiac output affecting body perfusion, including the kidneys. An acute or chronic relationship between the heart and the kidney is called cardiorenal syndrome. Cardiorenal syndrome worsens the clinical state and prognosis of patients with heart failure. This study aimed to analyse correlation heart failure score and estimate GFR based on cystatin C.

**Methods:** This cross-sectional study subject of children aged 0-12 years with a diagnosis of heart failure caused by congenital and acquired heart disease. The data were recruited consecutively in the children emergency room with the period January 2016 to July 2017. The decrease in cardiac output was enforced based on cardiac failure score according to modification of Ross when arrived at the hospital and followed by determining the estimated GFR based on cysC base on formula 75.94/CysC. Correlation between heart failure score and estimated GFR was tested using Spearman correlation.

**Results:** Forty-one subjects were analysed, had median heart failure score 10 (minimum/min 7, maximum/max 12). Median estimate GFR based on cysC 81.65 (min 12.31, max 133.23) ml/minute/1.73m². There was a moderate negative association between heart failure score and estimated GFR based on cystatin C (r=-0.53; p<0.001).

**Conclusion:** A moderate negative correlation between heart failure score and estimated glomerular filtration rate based on cystatin C levels in children.

**Keywords:** children, heart failure score, GFR, cystatin C

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INTRODUCTION

Heart failure is a progressive clinical syndrome due to decreased cardiac output acute or chronic that affecting body perfusion, including the kidneys. The compensatory response to decreased cardiac output with activation of renin-angiotensin, sympathoadrenal, and arginine vasopressin systems leads to intrarenal and peripheral vasoconstriction resulting in decreased renal blood flow. Heart failure therapy using high-dose nephrotoxic drugs, diuretics and vasodilators also contributes to decreased renal perfusion.

An acute or chronic relationship between the heart and the kidney is called cardiorenal syndrome. The cardiorenal syndrome can worsen the clinical state and prognosis of patients with heart failure. A decrease in glomerulus filtration rate (GFR) every 10 ml/min/1.73 m² increased mortality 1.56 times in patients with heart failure.

Acute decreased of GFR is required using endogenous markers, such as cystatin C (cys-C). Cystatin C is infiltrated free by the glomerulus, not secreted tubules, reabsorbed and metabolised entirely by the tubule epithelial cells so that no one returns to the bloodstream. Cystatin C levels will increase if there is a decrease in GFR between 88-95 ml/min/1.73m², then it can detect kidney disorders 24-48 hours earlier than creatinine.

The formula for measuring estimates GFR based on cys-C has been widely developed. The formula has 90% sensitivity and 100% specificity in measuring GFR <30 ml/min/1.73 m², whereas for GFR <90 ml/min/1.73 m², the sensitivity is 94% and specificity is 67%.

The diagnosis of GFR reduction in childhood with heart failure is often delayed due to lack of early renal function monitoring. To prevent worsening of the clinical state and prognosis of patients with heart failure, and limited research looking for a correlation between heart failure score and GFR estimate based on cystatin C in children. Therefore this research needs to be done. This study was a cross sectional study to analyse correlation heart failure score and estimate GFR based on cystatin C.

METHODS

A cross-sectional study with the subject of children aged 0-12 years with a diagnosis of heart failure caused by congenital and acquired heart disease. The data were recruited consecutively in...
the children emergency room of Sanglah General Hospital with the period January 2016 to July 2017. The inclusion criteria in this study were childhood heart failure who established based on clinical diagnosis of heart failure by using Ross modification classification criteria and agree to participate in research. The subject who has a history of kidney disease, sepsis, diarrhoea with severe dehydration, consume prednisone more than two weeks, has the symptom of dysfunction thyroid were excluded.

All eligible subjects had determined the degree of heart failure by Ross modification score. The child's parents are given a full explanation of the procedures and purposes of this study and are asked to be willing to cooperate by signing informed consent, then samples will be checked for cystatin C. Calculated estimation GFR based on cystatin C and analysis between cardiac failure score and estimated glomerular filtration rate based on cystatin C.

The number of samples was calculated using the formula for the single group sample based on the correlation values from the previous study. According to formula, the minimum number of samples required were 30 subjects. Correlation between heart failure score and estimated GFR was tested using Spearman correlation.

RESULTS

The average of age of 41 subjects of this study was 3.83 years old. The causes of heart failure were cyanotic heart disease, 13 subjects with large VSD, six subjects with large PDA and four subjects with CAVSD; cyanotic heart disease, three subjects with TGA with large VSD and two subjects with large PDA; cardiomyopathy, five subjects with dilatated cardiomyopathy and one subject with rheumatic heart disease. Median heart failure score in this study was 10 (minimum value/min 7, maximum value/max 12). The median cystatin C level was 0.93 (min 0.57, max 6.17) mg/L. The median eGFR based on cystatin C was 81.65 (min 12.31, max 133.23) ml/min/1.73m2. The subject characteristic of the research is shown in Table 1.

Normality test is done before doing data analysis, by using Shapiro-Wilk test obtained p<0.05, which mean data have abnormal distribution, despite having done a transformation of the logarithm of data.

Analysis of the association of heart function reduction based on heart failure score with estimated glomerular filtration rate based on cystatin C, negative correlation (r = -0.53) with p-value <0.001 was obtained.

The equation of correlation formula, y = 2.97E2 + 2.23E2X, with r² = 29.1%, (y = eGFRcys; 2.97E = value unexplained in the model or mathematically which is the difference of the predicted value and the sample value ; -2x = log of heart failure score, r² = large percentage effect of eGFRcys on cardiac failure score). This equation means that each drop of eGFRcys 1 ml/minute/1.73 m² affects the increase of log of heart failure score two times. The variation of eGFRcys can be explained by log variations in heart failure score of 29.1% (Figure 1).

DISCUSSION

Subjects of this study were 41 with 22 male subjects. The most age group was >5 years. The subjects who came to the emergency of children with heart failure had the most causes of acyanotic CHD (13 subjects with large VSDs, followed by 6 subjects with large PDAs and 4 subjects with CAVSD), followed by rheumatic heart disease (7 subjects with rheumatic heart disease, 5 subjects with cardiomyopathy due to dilatation and 1 subject with infections) and cyanotic CHD (3 subjects with TGA with large VSD and 2 subjects with large PDA). Another study reported different results, the most age group in children's heart failure was >5 years, with the most causes are acquired heart diseases (72%) such as rheumatic heart disease and cardiomyopathy. In developing countries, congenital heart disease is a cause of heart failure in infants and children with an incidence of 0.8%. The cause of the difference may be due to differences in the range of catheterisation

| Characteristics                           | N = 41 |
|-------------------------------------------|--------|
| Gender, Male, n (%)                       | 22 (53.7) |
| Age, n (%)                                |        |
| < 1 years                                  | 19 (46.3) |
| 1-5 years                                  | 9 (22.0) |
| > 5 years                                  | 13 (31.8) |
| Place of origin, n (%)                     |        |
| Badung                                     | 20 (48.8) |
| Gianyar                                    | 10 (24.4) |
| Karangasem                                 | 6 (14.6) |
| Others                                     | 6 (14) |
| Heart disease, n (%)                       |        |
| Cyanotic CHD                               | 5 (12.2) |
| Acyanotic CHD                              | 23 (56.1) |
| Cardiomyopathy                             | 6 (14.6) |
| Acquired heart disease                     | 7 (17.1) |
| Nutritional status, Well Nourished, n (%)  |        |
| Cardiomegaly, n (%)                        | 31 (75.6) |
| Diuretic usage history, n (%)              | 34 (82.9) |
measures or surgery to close the defect within the first year of life.

Median GFR estimation based on cystatin C in this study was 81.65 (min 12.31, max 133.23) mL/min/1.73m2. Estimates of GFR based on cystatin C have a sensitivity of 90% and a specificity of 100% in measuring GFR <30 ml/min/1.73 m2, while for GFR <90 ml / min / 1.73 m2 the sensitivity is 94%, and specificity is 67%. Research on the correlation of heart failure score with an estimated decrease in GFR based on cystatin C levels in this study was the first study conducted on children. The correlation between cardiac failure score and eGFRcys in this study was found to have a negative correlation with moderate correlation strength (r=-0.53) with p-value <0.001. Research Cody et al. (1988), found there was a strong correlation between decreased cardiac output and decreased GFR (r=0.8; p<0.01), whereas in Guglin et al. (2015), there was no correlation relationship between decreased cardiac output and estimated glomerular filtration rate. The differences due to in this study using a sample of children aged ≤12 years, while in research Cody et al. (1988), using adult subjects who also have degenerative diseases such as hypertension and diabetes mellitus. Hypertension causes macrovascular and renal microvascular changes. Increased chronic blood pressure results in damage to the renal endothelium, resulting in stenosis and ischemia of the kidneys. Hypertension also causes hyperfiltration and increased intraglomerular capillary pressure leading to sclerosis resulting in decreased renal function. Diabetes mellitus has long-term complications, one of which is nephropathy. Increased chronic blood sugar causes damage to endothelial renal blood vessels, leading to sclerosis and decreased renal function. The differences of this study with Guglin et al. (2015), due to the use of the subject. Guglin et al. use mild heart failure, whereas this study used moderate and severe heart failure. The degree of severity of heart failure is significantly associated with decreased glomerular filtration rate. In 300 European studies, one-third of patients with acute heart failure had decreased renal function. Decreased kidney function in children with acute heart failure, although in small amounts may increase the risk of a more severe decrease in heart function. Decreased cardiac output causes hypotension and decreases the kidneys perfusion, thus triggering the occurrence of ischemic pre-renal. Also, the heart compensation mechanism is in the form of activation of the renin-angiotensin-aldosterone system (RAAS), producing angiotensin II, which stimulates endothelin 1 in the kidneys. Endothelin I is a strong vasoconstrictor and pro-inflammatory factor, which further reduces the GFR.

Adenosine is also said to be a factor that plays a role in the pathophysiology of reduced GFR in heart failure. Adenosine is released by the kidneys during decreased of perfusion, bound to afferent arteriolar receptors, causing vasoconstriction and decreasing kidney blood flow. This stimulation of receptors causes an increase in sodium reabsorption in the tubule which has an impact on fluid and sodium retention.

In this study, each decrease of eGFRcys 1 ml/min/1.73 m2 affected two times the score of log score of heart failure. The variation of eGFRcys can be explained by log variations in heart failure score of 29.1%. Heart failure score is associated with a decreased ejection fraction. Decreased ejection fraction/cardiac output, causing hypotension, so that blood flow and perfusion to the kidney decreases, activation of heart compensation mechanism in the form of activation of RAAS system, produce angiotensin II which stimulates endothelin 1 in kidney functioning as a strong vasoconstrictor and pro-inflammation factor, thus further reducing GFR.

Limitation of this study is this research correlation can not show a casual relationship, and this study only excludes factors affecting GFR (sepsis, thyroid disorder and history of kidney disease) based on history taking and physical examination.

ETHICAL CLEARANCE
This study has been approved by a research ethics committee from the Medical Faculty of Universitas Udayana (No. 1747/UN.14.2/Litbang/2015).

CONFLICT OF INTEREST
There was no conflict of interest regarding this study.
FUNDING
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AUTHOR CONTRIBUTIONS
All authors have contributed to this study.

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