Usefulness of Cystatin C in the Postoperative Management of Pediatric Patients With Congenital Heart Disease

Akiko Yana, MD; Satoshi Masutani, MD; Takuro Kojima, MD; Hirofumi Saiki, MD; Mio Taketazu, MD; Masanori Tamura, MD; Hideaki Senzaki, MD

**Background:** The characteristics of the renal marker cystatin C (Cys-C) in association with the postoperative management of children with congenital heart disease (CHD) remain unclear.

**Methods and Results:** Serum Cys-C and creatinine (Cr) levels were measured preoperatively and on the third postoperative day in 53 consecutive CHD patients (age, 1 day–11 years). On the third postoperative day, the patients were divided into 2 groups: the clinically severe group, requiring continuous infusion of diuretic drugs or peritoneal dialysis; and the non-severe group, composed of those without such needs. Preoperative Cys-C level decreased with age (by month) during the first year of life and remained almost constant thereafter, while Cr level increased with age. The Cys-C ratio (Cys-C level on the third postoperative day/preoperative level) was positively correlated with Cr ratio ($R=0.57$, $P<0.001$). Both Cys-C and Cr levels increased in correlation with the clinical severity of renal impairment. Receiver operating characteristic curve analysis failed to demonstrate an advantage of Cys-C over Cr in detecting severity.

**Conclusions:** Cys-C may be a useful marker of renal function in terms of hemodynamic status in the postoperative management of CHD, although its superiority over Cr could not be confirmed. Future studies should clarify the role of Cys-C in clinical decision-making and evaluate the relationship of Cys-C with factors that may affect its levels.

**Key Words:** Creatinine; Intensive care; Postoperative state; Renal function

In the postoperative management of pediatric patients with heart disease, cardiac loading conditions and functions change dramatically, sometimes requiring large amounts of diuretics or dialysis. Moreover, drugs that require adjustment according to renal function, such as antibiotics, are often used. Thus, simple and accurate methods of determining renal function are extremely useful in this setting. Renal function is often assessed by measuring glomerular filtration rate (GFR) and is regarded as the international standard. Because this method is cumbersome, however, and requires fluid load, inulin clearance is inappropriate for routine medical practice, especially when repetitive use is required as in the postoperative management of pediatric patients with heart disease. Other assessment methods using exogenous substances are also impractical. Similarly, special diagnostic imaging, such as renal scintigraphy, is also inappropriate.

Creatinine (Cr) clearance based on 24-h urine collection and endogenous Cr level have been used as a surrogate of GFR. Cr clearance, however, is higher than the actual GFR because of tubular excretion of Cr. As GFR decreases, the differences between Cr clearance and GFR become larger. Moreover, because urine collection through voluntary voiding can be difficult for children, placement of an invasive bladder catheter is necessary even in pediatric patients being weaned from intensive care. Although a method of estimating GFR based on Cr level, sex, and body size is frequently used in adults, there is, as yet, no clinically established method for children.

Serum Cr level itself can be measured with a single blood test and is now a routine test at many institutions. Because it can be measured rapidly with a small sample at low cost, Cr is a useful and very frequently used marker of renal function. Cr, however, is systemically produced from creatine, and the creatine pool in the body is affected by muscle mass and exercise. In addition, unless GFR decreases to a certain extent, Cr level will not change. Therefore, considered limitations for the application of Cr level as an accurate marker of renal function.

Serum cystatin C (Cys-C), a cysteine protease inhibitor that

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Department of Pediatric Cardiology (A.Y., S.M., H. Saiki, M. Taketazu, H. Senzaki), Department of Pediatrics (M. Tamura), Saitama Medical Center, Saitama; Department of Pediatric Cardiology, International Medical Center, Saitama Medical University, Kawagoe (A.Y., T.K.); Hara Child Clinic, Tokorozawa (A.Y.); and Momotaro Clinic, Kawagoe (M. Taketazu), Japan

Mailing address: Satoshi Masutani, MD, PhD, FAHA, Department of Pediatric Cardiology, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama 350-8550, Japan. E-mail: masutani@saitama-med.ac.jp


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is produced and secreted by nucleated cells in the body, is a GFR marker that does not depend on muscle mass. Cys-C is a low-molecular-weight protein that passes freely through renal glomeruli, and at least 99% of it is reabsorbed and catabolized by proximal renal tubules. Thus, Cys-C may serve as a better glomeruli, and at least 99% of it is reabsorbed and catabolized by proximal renal tubules. Thus, Cys-C may serve as a better Glomeruli, and at least 99% of it is reabsorbed and catabolized by proximal renal tubules. Thus, Cys-C may serve as a better marker of renal function, mainly in adults, has been reported

As previously reported by Dittrich et al. and Cys-C has also gradually come into use in children. Although Cys-C would be expected to be useful in the postoperative management of pediatric patients with heart disease, detailed studies are limited. Here, we examined whether Cys-C is potentially a more useful marker of renal function than conventional serum Cr in the postoperative management of pediatric patients with heart disease.

**Methods**

**Patients**

This study involved 53 consecutive pediatric patients (29 boys and 24 girls) with congenital heart disease (CHD) who underwent surgery at Saitama Medical University. Their age ranged from 1 day to 11 years (mean ± SD, 1.6±2.3 years; median, 0.7 years). Table lists heart disease type.

**Age Dependency of Cys-C and Cr**

Because previous studies suggested that Cys-C and Cr may vary with age in children, we first examined the age dependency of these markers by using preoperative samples. As shown in Figure 1, preoperative Cys-C level decreased with age (by month) during the first year of life and remained almost constant thereafter, regardless of age. Preoperative Cys-C ranged from 0.71 mg/L (2 and 5 years old) at the lowest to 2.45 mg/L (25 days old) at the highest. The 5 patients with Cys-C ≥2.0 mg/L were all younger than 3 months. In patients aged ≥1 year, the range was narrow, from 0.71 to 1.30 mg/L (mean, 0.97 mg/L).

Meanwhile, as was the case with Cys-C, preoperative Cr level was high before the age of 3 months and then decreased with age (in months). Unlike Cys-C, Cr level tended to show an age-dependent increase after the first year of life (Figure 1). Preoperative Cr level ranged from 0.21 mg/dl (1 year old) to 1.1 mg/dl (12 days old). The Cr level of all patients before surgery was below the 90th centile of the reference range. The increase after the first year of life was age dependent. Based on these results showing the age-dependent distribution of preoperative serum Cys-C and Cr, all analyses were performed separately in the 3 different age groups (<3 months of age, n=17; age 3 months–<1 year, n=12; and ≥1 year, n=24).

**Clinical Severity and Cys-C or Cr**

Serum Cys-C and Cr levels were measured again on the third postoperative day, when the large perioperative shifts in hemodynamic and fluid status were resolved in most patients. Based on the clinical findings on the third postoperative day, the patients were divided into 2 groups for analysis of renal function and circulatory status: the clinically severe group, composed of patients who required peritoneal dialysis or continuous i.v. furosemide; and the non-severe group, which included patients without such needs. The requirement for furosemide or peritoneal dialysis was determined by intensive care physicians who were unaware of the study design and were blinded to serum Cys-C level. Peritoneal dialysis was initiated within 2 h after surgery based on a detailed assessment of the complexity of the operation and the hemodynamic status after cardiopulmonary bypass, and independent of the serum Cr level, as previously reported by Dittrich et al. Continuous infusion of furosemide was performed when sufficient diuresis was not obtained with a single dose (0.3–1 mg/kg) or when the poten-
Figure 1. Age-dependent changes in preoperative cystatin C (Cys-C) and creatinine (Cr) level in pediatric patients with heart disease. Preoperative Cys-C level decreased with age (in months) during the first year of life and remained almost constant thereafter. Preoperative Cr level was high before the age of 3 months and then decreased with age (in months). Unlike Cys-C, there was a tendency for an age-dependent increase in Cr after the first year of life.

Figure 2. Changes in (Top row) cystatin C (Cys-C) and (Middle row) creatinine (Cr) before and after surgery and (Bottom row) receiver operating characteristic (ROC) curve analyses for detection, by age, of clinically severe postoperative pediatric patients with heart disease. Comparison between the groups classified on the third postoperative day as (●) clinically severe and (△) non-severe indicated statistically significant differences in both Cys-C and Cr in the age group <3 months of age. The (Bottom row) ROC curve analyses were performed using the levels on the third postoperative day for detection of clinically severe status. The areas under the ROC curve were larger for Cys-C in all age groups.
Cr increased thereafter (0.45–1.78 mg/dl) to a level meeting the criteria of acute kidney injury, defined as a >50% increase compared to the previous value. With regard to changes in Cys-C and Cr before and after surgery, statistically significant increases were observed in patients <3 months of age in the clinically severe group (Figure 2). The clinically severe and non-severe groups were statistically significantly different in both Cys-C and Cr only in patients <3 months of age. To assess whether Cys-C or Cr better reflects clinical severity, the accuracy of each for identifying the clinically severe patients was analyzed based on ROC curves generated using the levels measured on the third postoperative day (Figure 2). Although the areas under the ROC curve tended to be larger for Cys-C in all age groups (Cys-C vs. Cr: <3 months of age, 0.93 vs. 0.86; 3 months–<1 year old, 0.77 vs. 0.69; ≥1 year, 0.74 vs. 0.69), the differences were not statistically significant.

To exclude the potential therapeutic bias caused by peritoneal dialysis on Cys-C and Cr level, we further performed subgroup analysis including only patients who did not undergo peritoneal dialysis. Whereas Cr level did not differ significantly between the severe and non-severe groups, Cys-C level was significantly higher in the clinically severe group than in the non-severe group in patients <3 months of age (Figure 3).

Postoperative Percent Changes in Cys-C and Cr
Figure 4 shows the relationship between the percent changes in Cys-C and Cr levels after surgery. Changes in Cys-C level generally had a good correlation with those of Cr (R=0.57, P<0.0001), but there was 1 patient who had a divergent change: the increase in Cys-C level was remarkable, as compared to that in Cr level (Figure 4; arrow). This patient had subvalvular aortic stenosis complicated by Ebstein’s anomaly and surgery was performed at the age of 4 days. The patient remained critically ill postoperatively and eventually died.
Cystatin C in CHD

Discussion

Preoperative Cr level decreased age-dependently (in months) during the first year of life and increased age-dependently thereafter, whereas preoperative Cys-C level decreased age-dependently during the first year of life and remained almost constant thereafter regardless of age (Figure 1). The age-dependent changes in Cys-C and Cr were largely consistent with the results of studies on pediatric patients with disorders other than CHD. Thus, it is suggested that GFR can be assessed using Cys-C without considering age and body size, as is necessary for Cr, even in pediatric patients with CHD, as long as the patients are >1 year of age. Because many pediatric patients with severe CHD who require evaluation are younger than 1 year of age, however, Cys-C level must be interpreted with regard to age in months.

Previous studies have suggested the potential superiority of Cys-C over Cr as a marker of renal function in several respects. Cys-C may be more sensitive to changes in GFR than Cr. Stickle et al compared Cr and Cys-C with inulin clearance, the gold standard for GFR measurement, in children aged 4–19 years. The reciprocals of Cr and Cys-C positively correlated with inulin clearance. Stickle et al found that Cr does not change until inulin clearance is less than approximately 80 ml/min−1·1.73 m−2. In contrast, no such threshold is observed for Cys-C, and a milder decrease in inulin clearance leads to an increase in Cys-C. The difference in elevation thresholds in these indices indicates that Cys-C might detect decreased GFR earlier than Cr. This is further supported by Krawczeski et al, who examined the predictability of the onset of acute kidney injury defined as a ≥50% increase in Cr after cardiopulmonary bypass for CHD. Even when Cr was taken into consideration, Cys-C level at 12h after surgery remained an extremely powerful predictive factor. In addition, unlike Cr, serum Cys-C level is not affected by muscle mass. Cys-C can freely pass through renal glomeruli, and at least 99% of it is reabsorbed and catabolized by proximal renal tubules. Thus, Cys-C may be regarded as a better marker of GFR than Cr.

Despite the evidence suggesting the potential superiority of Cys-C over Cr as a marker of renal dysfunction, the present results failed to demonstrate that Cys-C was more sensitive for detecting clinically defined renal impairment in postoperative pediatric patients with CHD. There are several possible reasons for this observation. First, serum Cys-C was measured on the third postoperative day, when continuous diuretics or peritoneal dialysis had already been introduced. The intensive care physicians who decided whether to use diuretic drugs and to introduce peritoneal dialysis were unaware of the study design and were blinded to Cys-C level. Patient management was aimed at maintaining adequate preload and cardiac output; therefore, we cannot exclude the possibility that the results were biased by the therapeutic effects of diuretics or dialysis. Second, the definition of renal impairment in this study was based on the clinical status rather than a more robust index, such as GFR, which could have affected the results. Last, several factors have been shown to affect Cys-C level including inflammation, thyroid function, and steroid use. Although none of the present patients had positive newborn screening for thyroid dysfunction, occult thyroid dysfunction, which may have accompanied cardiopulmonary bypass surgery, could have altered the results. Moreover, surgery in pediatric patients with CHD is associated with various degrees of inflammation, and steroids were given, as required, before neonatal open heart surgery or for postoperative management. Future studies with a larger number of patients should consider different factors potentially affecting Cys-C level, such as medication use including steroids. It is also of note that the present study did not provide information that is useful in...
clinical decision-making, such as cut-offs for Cys-C to detect abnormal renal conditions. Because these biomarkers are expected to have a key role in clinical decision-making, future studies should define how to specifically use blood Cys-C level to evaluate children with renal impairment.

Although the limitations noted here made it difficult to draw a definitive conclusion regarding the superiority of Cys-C or Cr as a marker of renal dysfunction in the present pediatric patients, the result showing the divergent change between the 2 markers (Figure 4) may be worth noting. Moreover, subgroup analysis in patients without peritoneal dialysis (Figure 3) indicated a statistically significant difference between the severe and non-severe groups only in Cys-C. These findings may suggest a more sensitive behavior of Cys-C in the presence of severe hemodynamic disarrangement. This is another issue that merits further study.

Conclusion
Cys-C may be useful as a marker of renal dysfunction associated with hemodynamic instability, although the superiority of Cys-C over the conventional marker Cr was not confirmed in this regard. To further elucidate the clinical usefulness of Cys-C in the management of pediatric patients with heart disease, future studies with a larger number of patients are necessary and should be aimed at defining the role of Cys-C in clinical decision-making and evaluating the relationship of Cys-C with factors that may affect its levels.

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References