Serum Cystatin C, Renal Filtration Function, and Left Ventricular Remodeling

Mark D. McMurray, MD; Justin E. Trivax, MD; Peter A. McCullough, MD, MPH

It is estimated that heart failure (HF) affects 5.7 million Americans and will have an estimated cost of $34.8 billion in 2009. However, definitions of HF are mainly symptom based and, therefore, may lead to a gross underestimation of the actual prevalence. One study has shown that only 50% of people with echocardiographic evidence of left ventricular (LV) dysfunction are symptomatic.

The limitations of serum creatinine as a blood measure reflecting renal filtration have been extensively debated. Creatinine is a low–molecular-weight (113 Da) protein derived from the breakdown of skeletal muscle creatine phosphate, which is used as an energy substrate (Figure 1). Creatinine is freely filtered by the glomerulus and also undergoes a small amount of tubular secretion. Highly dependent on muscle mass, creatinine levels vary greatly among individuals who differ in age, sex, diet, and race. The first practical test for the determination of creatinine in urine, described more than 100 years ago (1886) by Max Jaffe (1841–1911), involves the formation of the red-yellowish-brown-colored creatinine picate by the bonding of picric acid and creatinine in an alkaline solution. In 1936, the Benedict method of creatinine determination was reported, which involves the reaction of 3,5-dinitrobenzoic acid with creatinine in an alkaline medium. From this point forward, the creatinine assay, unlike other laboratory tests, has not evolved.

Cystatin C is a 122-amino acid, 13,250-Da protein that is a member of the family of cysteine proteinase inhibitors (Figure 2). It is the product of a “housekeeping” gene expressed in all nucleated cells and is produced at a constant rate. Because of its small size, cystatin C is freely filtered by the glomerulus. It is not secreted but is reabsorbed by tubular epithelial cells and subsequently catabolized so that it does not return to the blood flow (Table). This latter property negates calculation of a cystatin C clearance using urine concentrations. The use of serum cystatin C to approximate eGFR is based on the same logic as the use of blood urea nitrogen and creatinine, but because it does not return to the bloodstream and is not secreted, the eGFR obtained may be more reflective of actual renal filtration function.

Endothelial cells, podocytes, mesangial cells, and the glomerular basement membrane are all components of the glomerular membrane and are important for its function. Properties of endothelial cells and their surface layer, the glomerular basement membrane, and podocytes account for variations in glomerular permeability and determine the restriction of solutes based on size, charge, and shape. The glomerular barrier is highly size-selective and charge-selective in qualitative agreement with the classical studies performed 30 years ago. The cellular components are the key players in restricting solute transport, whereas the glomerular basement membrane is responsible for most of the resistance...
to water flow across the glomerular barrier. The sieving coefficient of a solute is a measure of its transport rate in relation to that of water. Interactions between the particle and the wall are mediated by viscous stresses and pressure variations in the fluid. Such hydrodynamic interactions also cause the velocity of a freely suspended particle to deviate from the mean fluid velocity. The finite size of the particle limits the positions that its center can occupy, bringing steric considerations into the calculation of clearance from the blood pool into the urinary space. Activation of the renin-angiotensin system

<table>
<thead>
<tr>
<th>Function</th>
<th>Cystatin C</th>
<th>Creatinine</th>
</tr>
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<tbody>
<tr>
<td>Production</td>
<td>Extracellular cysteine protease inhibitor</td>
<td>Breakdown product of muscle creatine phosphate</td>
</tr>
<tr>
<td>Size, Da</td>
<td>13250</td>
<td>113</td>
</tr>
<tr>
<td>Method of elimination</td>
<td>Glomerular filtration, 100% reabsorption and catabolism by proximal tubules</td>
<td>Glomerular filtration, no reabsorption, active secretion by proximal tubules</td>
</tr>
</tbody>
</table>

Reference values

| Infants/children | 0 to 3 mo: 0.81 to 2.32 mg/L | <2 yr: 0.4 to 0.5 mg/dL |
| 4 to 11 mo: 0.65 to 1.49 mg/L | 2 to 8 yr: 0.5 to 0.7 mg/dL |
| 1 to 17 yr: 0.50 to 1.27 mg/L | 9 to 18 yr: 0.6 to 0.9 mg/dL |

| Adults | 0.59 to 0.91 mg/L | 0.8 to 1.4 mg/dL |

Confounding variables

Increased levels

| Determinants of general cellular metabolism |
| Corticosteroids early after renal transplantation |
| Hyperthyroidism |

Decreased levels

| Dietary protein restriction |
| Muscle wasting |
| Malnutrition |
| Bilirubin (Jaffé)* |
| Advanced age |
| Female gender |

*The impact of some factors on creatinine levels is specific to certain methods of creatinine measurement.

Table. Comparison of Serum Cystatin C and Creatinine

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</tr>
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- Muscle wasting
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- Bilirubin (Jaffé)*
- Advanced age
- Female gender
- Advanced liver disease

Figure 1. Creatinine (molecular formula, C4H7N3O; charge, 0).

Figure 2. Cystatin C (molecular formula, C22H40N8O5; charge, 0).
(RAS) works to increase intraglomerular pressure and thus increase the filtration of creatinine in the setting of normal renal function. Animal studies have shown that the reduction in angiotensin II caused by the initiation of RAS blockers reduces efferent arteriolar pressure and thus reduces intraglomerular pressure by reducing the transcapillary hydrostatic pressure along the glomerular capillary. In addition, there is a small reduction in tubular secretion of creatinine into the urine space and an enhanced proximal tubular reabsorption. These mechanisms may explain the predictable 15% to 30% rise in serum creatinine in patients taking RAS blockers. It is conceivable that creatinine and cystatin C have differing permselectivity functions according to the changes in intraglomerular pressure. The relative size of creatinine is sufficiently small for it to have a high sieving coefficient and, therefore, would have a reduction in filtration in response to a drop in intraglomerular pressure (Figure 3). Cystatin C, a larger-sized protein, is probably situated at a different location on the sieving function curve and is expected to be influenced less by either an increase or reduction in intraglomerular pressure (Figure 3). Thus, it is conceivable that cystatin C is a better indicator of renal filtration function during perturbations of the RAS from early LV dysfunction or use of RAS blocking agents.

Sebekova et al18 studied 12 newly diagnosed individuals with nondiabetic kidney disease (tubulointerstitial nephritis, n = 8; glomerulonephritis, n = 2; polycystic kidney disease, n = 2) and impaired renal function who were subsequently treated with 5 mg daily ramipril (angiotensin-converting enzyme inhibitor) for 2 months. Changes from baseline to follow-up of 1.93 to 1.91 mg/dL for serum creatinine and 1.68 to 1.65 mg/L of cystatin C were found, whereas measured creatinine clearance decreased slightly from 0.72 to 0.76 mL/s, suggesting no differential effect when creatinine clearance is unchanged. In a study by Watanabe et al, 30 patients with nondiabetic hypertension were treated with valsartan for 3 months. Cystatin C decreased (0.63±0.31 mg/L to 0.52±0.27 mg/L, \( P = 0.015 \)) but not serum creatinine (0.75±0.15 mg/dL to 0.74±0.18 mg/dL, \( P = 0.712 \)). In addition, the renal resistive index by Doppler ultrasonography was reduced, suggesting differential changes in renal filtration of creatinine and cystatin C when treated with a RAS blocker, which reduced intraglomerular pressure. In accordance with these studies, eGFR derived from cystatin C equations is more accurate than eGFR from creatinine equations when a reference standard such as iohexol clearance is measured; however, none specifically compared the two with and without RAS blockers.

Finally, cystatin C may be an upregulated and active protein in cardiac remodeling. Cystatin C works to inhibit the activity of cathepsins, which are cysteine proteases that degrade the extracellular matrix proteins via elastolytic and collagenolytic activity. LV remodeling is a complex interaction of matrix assembly and degradation closely regulated by these proteins. Cheng et al22 have demonstrated increased myocardial cathepsins and cystatin C in rats and humans with LV hypertrophy caused by hypertension. In the early stages of LV remodeling and hypertrophy, cystatin C levels may be elevated, potentially indicating preclinical cardiac disease with or without any renal condition.

In summary, cystatin C is an approved marker that can be used in the calculation of eGFR and may give a truer reflection of eGFR in patients where there is dysregulation of the RAS, either with early LV dysfunction or treatment with RAS blocking drugs. Furthermore, cystatin C may be uniquely intimating early disease of both the heart and the kidneys and, therefore, be a superior prognostic marker to serum creatinine or creatinine-based eGFR as an indicator of renal filtration function.

Disclosures

None.

References


**Key Words:** hypertension, renal disease.
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