

The Evaluation of Acute Myocardial Infarction in the Emergency Department: The Role of Cardiac Biomarkers in Patients with Chronic Kidney Disease

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Patients with chronic kidney disease (CKD) who present to the emergency department complaining of chest pain pose a challenge for emergency physicians. These patients are at high risk of developing acute coronary syndromes, and are also at higher risk of developing in-hospital complications, including death. Therefore, a prompt and efficient diagnosis is of the utmost importance. Traditionally, emergency physicians have been dependent upon serial measurements of cardiac biomarkers for the diagnosis of acute myocardial infarction. Myoglobin, creatine kinase-myocardial band isoenzyme, and cardiac troponins are currently the most frequently used biomarkers in the emergency department setting. However, their levels tend to be elevated in patients with CKD even in the absence of any evidence of myocardial ischemia. As a result, the interpretation of cardiac biomarkers in these patients may be difficult. This article reviews the clinical significance of these elevations in this high-risk patient population.

Acute Coronary Syndromes 2003;6(2):42–9.

In the US, approximately 8 million patients with chest pain are seen in emergency departments each year [1]. With the incidence and prevalence of kidney failure increasing in the US, a larger proportion of patient evaluations will involve patients with chronic kidney disease (CKD) [2]. Patients with advanced CKD who present to the emergency department complaining of chest pain are predisposed to higher in-hospital events, 30-day mortality rates, and cardiac-related complications compared with patients with normal renal function [3]. As a result, appropriate and efficient evaluation of this patient population is becoming increasingly important for emergency physicians.

Similar to the population as a whole, cardiac disease is the single most important cause of mortality in patients with CKD in the US. Patients with CKD are more susceptible to accelerated atherosclerosis and have higher rates of coronary artery disease (CAD) than the general population [4]. An acute myocardial infarction (AMI) in this patient population is a devastating event; the 2-year mortality rate for these CAD patients has been reported to be up to

73% [5]. Approximately 44% of patients on long-term dialysis therapy die of cardiovascular causes, and 22% of these deaths are attributable to AMI [6]. This increased risk of AMI and death is evident across the entire spectrum of renal insufficiency, even without a history of CAD [7,8].

Unfortunately, the diagnosis of AMI in patients with CKD is not a simple task. History, physical examination, and the 12-lead electrocardiogram (ECG) have limited sensitivity and specificity [9–11]. As a result, the diagnosis of AMI in patients with nondiagnostic ECGs relies heavily on the measurement of serum cardiac biomarkers of necrosis. As ischemia progresses to infarction, cell death causes disruption of the cell membrane. Subsequently, cytosolic proteins are released into the bloodstream. Due to the release kinetics of cardiac biomarkers, elevations may not be detectable for several hours (Fig. 1) [12]. As a result, single measurements on presentation to the emergency department are of limited diagnostic use. Serial cardiac marker measurements remain the mainstay for the accurate diagnosis of AMI in the ED. The sensitivity of these markers improves over time, thus serial measurements of cardiac troponin T (cTnT) and cTnI, myoglobin, and creatine kinase-myocardial band (CK-MB) isoenzyme are essential for the diagnosis of myocardial necrosis.

Higher levels of cardiac biomarkers have been reported in patients with CKD compared with the general population. There has been controversy regarding the clinical significance of these elevations. Since CKD is a spectrum of disease states, ranging from mild renal insufficiency to end-stage renal disease requiring long-term dialysis, the study of cardiac markers in this patient population remains difficult. The purpose of this article is to examine the evidence that exists to date on the use of these biomarkers in patients with CKD, as well as the clinical impact of this diagnostic tool in this high-risk population.

Myoglobin

Myoglobin is a low-molecular-weight, unbound, cytosolic protein that is found in both the myocardial and skeletal musculature. Its biochemical characteristics allow myoglobin to be elevated in the serum 1–2 h after symptom onset in patients suffering an AMI [13]. Myoglobin gives a positive result earlier than CK-MB for the diagnosis of AMI [14]. Serum levels of myoglobin tend to decrease rapidly, therefore measurements may be normal in AMI patients who present to the emergency department 24–36 h after symptom onset [13]. Gibler et al. found myoglobin to be 100% sensitive and 76% specific at 3 h after symptom onset for the diagnosis of AMI in a study of patients presenting to a community hospital with chest pain who were subsequently hospitalized [14]. Its diagnostic power may be improved when used in conjunction with other markers. McCord et al. found that when used in combination with cTnl, myoglobin sensitivity and negative predictive value for the detection of AMI in consecutive patients presenting to the emergency department was 96.9% and 99.6%, respectively, at 90 min after presentation [15].

The largest criticism of the use of myoglobin is its lack of specificity. Since it is abundant in skeletal muscle, elevations in myoglobin are known to occur in patients with skeletal muscle damage. In addition, myoglobin is cleared through the kidneys, and as a result is elevated in patients with CKD compared with a normal population. McCullough et al. demonstrated elevated myoglobin levels above the diagnostic cut-off across the entire spectrum of CKD patients [16]. As a result, obtaining myoglobin levels even in patients with mild renal insufficiency is of little clinical value.

CK-MB

CK-MB is one of three dimeric CK isoenzymes. As the name suggests, CK-MB is found predominantly in the myocardium. Other isoenzymes exist in the brain (CK-BB) and skeletal muscle (CK-MM). CK-MB is the most specific of the three isoenzymes for the detection of myocardial necrosis, but up to 3% of the total CK in skeletal muscle may contain CK-MB [17,18]. CK-MB appears 4–6 h after the onset of symptoms, remaining elevated for 24–36 h (Fig. 1) [19,12]. Single enzyme measurements have limited sensitivity for diagnosing AMI. Young et al. showed that the initial serum CK-MB measurement during emergency department presentation only yielded a sensitivity of 57% and a specificity of 97%; however, sensitivity improved to 88% at 3 h [20]. Gibler et al. reported that serial CK-MB sampling over a 9-h evaluation period yielded a sensitivity of 100% and a specificity of 98.3% in a chest-pain center population [21]. Serial measurements of CK-MB for the emergency department evaluation of chest pain are therefore a highly sensitive and specific test for the diagnosis of AMI.

Several subforms of CK-MB exist in the plasma. Puleo et al. found that elevated CK-MB₂, and the ratio of CK-MB₂ to CK-MB₁, have better sensitivity (96.6% and 95.7%, respectively) than CK-MB alone (48%) within the first 6 h after onset of symptoms, but have similar specificity [22]. However, this assay is not routinely used in most hospitals.

As mentioned above, CK-MB can be found in trace amounts in skeletal muscle, and has been shown to be elevated in 59% of patients with acute skeletal muscle disease, even in the absence of any myocardial injury [23]. Theoretically, calculating the CK-MB relative index should distinguish myocardial necrosis from skeletal muscle damage. Cappellan et al. showed the CK-MB relative index to be more specific than absolute CK-MB measurements, with a mild decrease in sensitivity [24]. However, Adams et al. suggested that the CK-MB relative index may be nonspecifically elevated in the setting of skeletal muscle injury [23].

Patients with CKD have higher total CK and CK-MB serum levels than patients with normal renal function, although the levels observed are significantly lower than those in patients diagnosed with AMI [16,25,26]. Presumably, these elevations are secondary to a uremic myopathy observed in patients with CKD [27]. The majority of CK elevations are thought to be due to elevated CK-MM, although CK-MB levels are also elevated, but to a much lesser extent [28].

Studies have reported that approximately 4–19% of patients on long-term dialysis have elevated CK-MB levels [25,26]. Fluctuations in serum levels of CK-MB are seen over a prolonged period of time. During a 36-month study period, Green et al. observed at least one CK-MB elevation in 88–100% of asymptomatic patients on long-term dialysis [29]. These fluctuations are not attributable to hemodialysis, as it does not appear to affect serum CK-MB levels acutely [30]. Additionally, CK-MB subforms are also elevated in patients with CKD. Robbins et al. found levels of CK-MB₂ and CK-MB₂/MB₁ to be elevated in 25% of asymptomatic patients on hemodialysis [31]. In CKD patients not on long-term dialysis, elevations in CK-MB levels were less frequently seen [26].

As a result of these fluctuations, the test performance of CK-MB is mildly inconsistent across the entire spectrum of renal dysfunction (Fig. 2) [16]. Using CK-MB, sensitivities and specificities of 44% and 56%, respectively, have been reported in detecting AMI in patients with CKD [32].

Theoretically, the use of the CK-MB relative index may be more useful in this patient population for the diagnosis of AMI, but its clinical utility has been questioned [23]. Lal et al. reported that 7% of long-term dialysis patients had CK-MB levels >5% of their total CK concentrations [33]. Robbins et al. found levels of CK-MB₂ and CK-MB₂/MB₁ to be elevated in 25% of asymptomatic patients on hemodialysis [32].

Thus, CK-MB levels are mildly elevated in patients with CKD, although to a lesser degree than observed in patients with AMI. These elevations appear to be secondary to a uremic myopathy. Because of these chronic CK-MB elevations, some diagnostic power is sacrificed. However, it still appears to have some use in patients with CKD. Theoretically, the calculation of the CK-MB relative index has some clinical use, but its specificity is still in question.

Cardiac troponins

Recently, the definition of AMI has undergone a transformation since the discovery of cardiac troponins [34]. Troponin is a complex of three proteins that regulate muscle contractility. Troponin I and troponin T are two of the three subunits specifically found in cardiac myocytes. Cardiac isoforms are found exclusively in the myocardium in healthy adults, making cTnI and cTnT highly specific. Similar to CK-MB, the cardiac troponins are released within 4–6 h of myocardial necrosis and peak at 24–48 h (Fig. 1) [12,19]. Elevations in troponins may be seen for up to 7–10 days, due to the prolonged breakdown of the cardiac myocyte contractile apparatus [12].

Many studies have demonstrated cardiac troponins to be either equivalent or superior to CK-MB isoforms for the detection of AMI in terms of sensitivity [23,35]. Elevations of both cTnI and cTnT in the context of normal serum CK-MB levels may represent microinfarctions [36]. Approximately 30% of patients who present with chest pain and have a nondiagnostic ECG are diagnosed with non-ST elevation AMI instead of unstable angina based on measurements of cardiac troponins [37]. Cardiac troponin elevations, even in the absence of increased serum CK-MB levels, are also predictive of future adverse cardiac events, including death [38,39].

TnT

There is substantial controversy concerning the interpretation of elevated cardiac troponin levels in patients with CKD. This particular issue has major clinical ramifications in a patient population at high risk of AMI. The majority of the controversy has surrounded cTnT and its use in the ED setting for the diagnosis of AMI [40]. However, most of the literature sampled asymptomatic patients with CKD who underwent long-term dialysis. Initial studies reported that these elevations were nonspecific and did not aid the diagnosis of AMI using the standard cut-off point [40].

It has yet to be determined what causes the raised concentrations of troponins in patients with CKD. It has been shown that cTnT does not cross-react with dialyzable substances [41]. Serum cTnT levels increase after dialysis, presumably secondarily to hemoconcentration [42]. It has been postulated that

cTnT levels increase as a result of re-expression of a fetal isoform of this protein in regenerating skeletal muscle [43]. Four isoforms of cTnT are known to exist [44]. During fetal development, the expression of cTnT is upregulated in skeletal muscle tissue, but usually undergoes downregulation in the post-natal period. Using immunohistochemical and Western blot techniques, cTnT has been detected in the diaphragm and skeletal muscle of patients with polymyositis and muscular dystrophy [45]. Similarly, cTnT has been detected in patients on long-term dialysis [46].

However, the cTnT found in skeletal muscle is structurally different to the cTnT found in cardiac muscle. Current second- and third-generation cTnT immunoassays do not cross-react with the skeletal muscle isoform of cTnT [44,47]. Despite the increased specificity of the newer immunoassays, elevations in cTnT levels have still been reported in 12–20% of asymptomatic patients with CKD [46,48].

Recent studies have shown that elevated troponin levels do have the ability to predict adverse outcomes in asymptomatic patients with CKD on long-term dialysis [49], and also suggests that cTnT elevations are important predictors of mortality [50,51]. Apple et al. followed 733 asymptomatic hemodialysis patients over a 3-year period. They found that serum cTnT elevations >0.01 ng/mL were associated with a 2–4-fold increase in all-cause mortality rates [50]. As serum cTnT levels increased, mortality rates increased in a stepwise fashion (Fig. 3). Similarly, Dierkes et al. reported that cTnT elevations predicted all-cause mortality, including cardiovascular disease, sepsis, tumors, and pulmonary embolisms [51].

The role of elevated cTnT in specifically predicting cardiac morbidity and mortality in patients with CKD is less understood. Ooi et al. initially found no association between raised cTnT levels and cardiac-related deaths, but came to the opposite conclusion after following the patients for 2 years [52,53]. Additionally, they observed that the cTnT levels of some patients fluctuated over time. Increases of >60% were observed in 58% of all patients who died of cardiac-related deaths [53]. In a smaller series of 49 asymptomatic patients with CKD, elevations in cTnT predicted 3-month adverse cardiac outcomes, including death [54]. A sensitivity of 83% and a specificity of 90% was observed when a cut-off level of 0.2 ng/mL was used [54]. However, using a second-generation immunoassay, Lang et al. studied 100 patients with CKD who were asymptomatic during blood sampling and found elevations of cTnT and cTnI in a significant proportion of patients [55]. However, elevated cTnT and cTnI levels were not correlated with adverse events over a 2-year period and had no predictive value [55].

There is minimal evidence available evaluating the diagnostic power the role for serum cTnT levels in patients with possible acute coronary syndromes (ACS) and CKD in the ED. Van Lente et al. evaluated 51 ED patients with renal insufficiency and suspected ACS [56]. Only 9% of the renal cohort was on dialysis. Comparisons were made with healthy controls matched by serum cTnT and cTnI levels. They were unable to predict the in-hospital and 6-month outcomes in the renal insufficiency group, based on these measurements. In contrast, Aviles et al. observed that elevations in serum cTnT increased the risk of myocardial infarction and death within 30 days, regardless of creatinine clearance [57]. However, only 11 patients had severe renal impairment with a creatinine clearance of <10 mL/min.

The predictive role of elevated cTnT levels in patients with CKD and not on dialysis is not well understood. Roppolo et al. reported that 4% of patients with CKD and not on dialysis had elevated levels of troponins, but none of these patients suffered an adverse cardiac event within 6 months [54]. Lowbeer et al. observed increases in the mortality of patients with CKD who were ready to be placed on dialysis with elevated cTnT levels [58]. These elevations also positively correlated with markers of inflammation, such as C-reactive protein and interleukin-6 (IL-6), suggesting an association between inflammation and cTnT levels.

TnI

Elevations in cTnI levels are less frequently observed than cTnT elevations in asymptomatic patients with CKD [50,54]. Embryologically, cTnI is not expressed throughout fetal development and is not seen in the

skeletal muscle of patients with CKD [46]. As a result, increases in cTnl are generally regarded as more specific and secondary to myocardial injury, despite the presence of CKD [23].

Adams et al. reported that only one out of 159 asymptomatic patients with CKD had elevated cTnl levels; however, the patient concerned had echocardiographic evidence of ischemia [23]. Martin et al. reported that the sensitivities and specificities of cTnl for the detection of AMI in renal failure were 94% and 100%, respectively, using a study group consisting predominantly of patients with CKD [59]. In addition, cTnl appeared to maintain its diagnostic power across various creatinine clearance rates compared with myoglobin and CK-MB (Fig. 2) [16]. Elevated cTnl levels were associated with a worse in-hospital prognosis in patients with CKD admitted for ACS evaluation [59].

The ability of cTnl to predict adverse outcomes in both the short-term and long-term is controversial in patients with CKD. The clinical ability to risk-stratify patients with CKD appears to be decreased in patients who are either asymptomatic or have suspected ACS [55,56]. Khan et al. observed 126 asymptomatic hemodialysis patients without a history of chronic angina over a 2-year period and found that elevated serum cTnl levels did not predict all-cause or cardiac mortality, or cardiac hospitalizations [60]. In contrast, Apple et al. found that increased cTnl levels were associated with a 2-fold increase in mortality over a 3-year period [50]. Similarly, Roppolo et al. observed that elevated cTnl levels were associated with adverse cardiac events for up to 6-months of follow-up [54].

Serum measurements of cTnl appear to be more specific than cTnT for diagnosing AMI in patients presenting to the ED with CKD and possible ACS [54]. Nonspecific elevations of cTnl have been reported, although with less frequency than seen with cTnT [50,54]. It has been postulated that the cause of increased serum cTnT level may be a more sensitive marker of myocardial injury than cTnl itself [61]. Elevated serum cTnT levels in patients with CKD should not be discounted as being from a noncardiac source, even in the absence of ACS symptomatology. Though its role in the acute diagnosis of ACS may be limited, cTnT appears to be a more sensitive predictor of long-term mortality [53]. Interestingly, cTnT elevations are predictive of all-cause mortality in addition to cardiac mortality [50,51]. The pathophysiologic basis for these elevations is not fully understood. There is evidence that cTnT is associated with markers of inflammation, such as C-reactive protein and IL-6, which have been implicated in predicting cardiac mortality [58,62]. Therefore, elevations of cTnT or cTnl in the setting of possible ACS in the ED should prompt careful consideration of patient admission for further evaluation.

Conclusion

The evaluation of patients with CKD in the ED is difficult in the setting of renal insufficiency or frank renal failure due to the properties of cardiac biomarkers. Myoglobin has little clinical use in patients with CKD because it is cleared by the kidneys. CK-MB is known to be raised in patients with CKD, but to a lesser extent than the elevations seen in patients with AMI [16,25,26]. cTnT elevations are more frequently encountered than increases in cTnl in patients with CKD. Such elevations should not be called nonspecific since they provide important long-term prognostic information. The

ability of troponins to diagnose AMI and predict short-term events in patients with CKD with chest pain requires further study as the significance of cTnT elevations from baseline values is poorly understood. Elevations in cTnl occur less frequently in patients with CKD and, as a result, may be more useful in the emergency setting. As patients with CKD are at high risk of ACS and death, there is an urgent need to improve evaluation strategies for this patient population in the ED. Further research is needed to understand the pathologic basis of these cardiac marker elevations.

Disclosure

The authors have no relevant financial interests to disclose.

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