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Cardiac Troponin Elevations in Patients Without Acute Coronary Syndrome

Christian W. Hamm, MD; Evangelos Giannitsis, MD; Hugo A. Katus, MD

Cardiac troponin T and troponin I are the most specific and sensitive laboratory markers of myocardial cell injury and therefore have replaced creatine kinase MB as the gold standard.^{1,2} Accordingly, the new definition of acute myocardial infarctions was based on elevations of cardiac troponins in blood in the setting of ischemia.² The compelling clinical value of troponins resides in its superior prognostic potential in predicting the outcome of patients presenting with symptoms of unstable angina.³ Therefore, the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines and the European Society of Cardiology (ESC) Task Force Report on acute coronary syndromes without ST elevation have attributed troponin measurements a central role in the diagnostic work-up and therapeutic decision making.^{4,5} It has been demonstrated that testing for troponins on admission and again after 6 to 12 hours provides better risk stratification than previously used algorithms based on the ECG and creatine kinase MB. The test results should be available within 30 to 60 minutes, because elevated troponins are helpful in identifying the patients who benefit most from early invasive strategies, glycoprotein IIb/IIIa antagonists, and low-molecular-weight heparins.⁵

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Troponins in Cardiology Routine

Since their first introduction in the early nineties, troponin assays have been implemented in most emergency facilities as point-of-care tests or are offered on stat basis by the hospital central laboratories. Initially, there has been some confusion with regard to the correct cut-off values. Particularly irritating to many clinicians was the fact that the results with different troponin I assays were not comparable. This relates to the fact that the antibodies employed in assays of different manufacturers are directed against different epitopes of troponin I. Because circulating troponin I is unstable, some epitopes are lost as a result of degradation, whereas others still remain unaltered, resulting in different recoveries by different assays.⁶ In contrast, there is, because of patent reasons, only one troponin T assay available that has been repeatedly refined, resulting in a lowering of the

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analytical detection limit.^{7,8} The consensus document of the ESC and the ACC, therefore, recommended that each laboratory should determine its cut-offs individually at the 99th percentiles of normals with a <10% variance.²

Aside from patients with renal failure, there should be no difference in interpretation between troponin T and troponin I results, provided the above rules with regard to the analytical quality are followed. Troponin elevations are mostly, but not necessarily always, related to ischemic cell injury in acute coronary syndromes.

Non-Coronary-Related Troponin Elevations

Unexplained elevations of troponins are extremely rare but may sometimes cause confusion. A rise of troponins reflects irreversible myocardial cell necrosis. Accordingly, abnormal values have been described in various conditions not related to acute coronary disease, like myocarditis, pulmonary embolism, acute heart failure, septic shock, and as a result of cardiotoxic drugs as well as after therapeutic procedures like coronary angioplasty, electrophysiological ablations, or electrical cardioversions.

In the emergency room scenario, pulmonary embolism and perimyocarditis represent the most important differential diagnoses associated with elevated troponin levels. In acute pulmonary embolism, troponins probably rise because of acute right heart overload. The release is of shorter duration than in unstable angina, and the peak level is linked to the outcome.^{9,10} In histologically confirmed myocarditis, troponins are regularly elevated but also rise in about half of the patients with only clinically suspected myocarditis.¹¹ In the diffuse myocarditis it is more likely to observe abnormal troponins than in focal disease.¹² However, the link to outcome in these patients, particularly with regard to progressing left ventricular dysfunction, has not yet been convincingly established.

Troponin Elevations Without Overt Cardiac Injury

In patients with severe renal dysfunction troponin T as well as troponin I, elevations are found that cannot be linked to myocardial injury. The reasons for these elevations are not yet convincingly explained. Reexpression of cardiac isoforms in skeletal muscles has been excluded by different analyses and investigators.^{13,14} Loss of membrane integrity and constant outflow from the free cytosolic troponin pool as well as amplified elevation of normal low levels because of impaired renal excretion are more likely. The higher unbound cytosolic pool and higher molecular weight may explain why troponin T is more frequently found elevated than troponin I.

The fraction of troponin-positive patients with end-stage renal disease naturally depends on the assay technology and on the chosen discriminator value. Because of the higher analytical

precision of newer troponin T assays, the discriminator level could be lowered stepwise, and abnormal values in patients with renal dysfunction have become less frequent.⁸

Cardiologists and emergency physicians should not perceive the elevation of troponin T in severe renal dysfunction as a limiting problem. Recently, it was convincingly demonstrated in the Acute Coronary Syndrome Without ST Elevation Trial (GUSTO IV) in patients presenting with chest pain across all creatine clearance levels that troponin T remained predictive for cardiac events.¹⁵ However, confusion may arise when renal patients present with atypical symptoms. For example, a patient with diabetes on dialysis with mild symptoms but elevated troponin T presents to the emergency room. This patient is at increased risk of whatever has caused troponins to rise. If it is an acute coronary syndrome, acute risk is high and the treatment should—on the basis of guidelines—include early angiography and IIb/IIIa antagonists.^{4,5} If this patient has no coronary disease, troponins may be misleading in predicting the acute outcome but still remain predictive for the long-term prognosis. A constellation like this should not be used to discredit troponins as helpful markers but to remind us that troponin measurements, like all other laboratory results, should be seen as pieces in the diagnostic puzzle. They may be helpful, however, if the patient is known to have chronically elevated troponin levels.

Troponins in Nephrology

In asymptomatic patients with renal dysfunction, troponins are not presently part of the routine diagnostic work-up because results with regard to their predictive value based on small series was controversially discussed.^{16–18} Accordingly, the prospective study by Apple et al in 733 patients represents a landmark in support of the clinical role of troponin T in this setting.¹⁹ The documented 2- to 5-fold increase in all-cause mortality is a finding that deserves clinical attention. Of particular interest is the gradual rise in risk with increasing troponin T levels independent of other variables at various discriminator levels. With the use of a 0.10 $\mu\text{g/L}$ versus a 0.03 $\mu\text{g/L}$ discriminator value, the fraction of patients rated positive for troponin T increased from 20% to 53%. The level of troponins was associated with a significant increase in 1-, 2-, and 3-year mortality.

In a prospective way, the present study also confirms previous observations in renal patients that troponin T is superior to troponin I as an indicator of future cardiac events, particularly because more patients can be stratified by troponin T.^{20,21} Accordingly, the disadvantage claimed by cardiologists for troponin T may turn into an advantage for nephrologists. Whether these findings can be extrapolated to patients with compensated renal dysfunction needs to be demonstrated.

The findings of Apple et al provide helpful information for decision making for cardiologists but may have even more of an impact on risk stratification by the nephrologists. The data could imply that this marker should enter routine clinical risk assessment in end-stage renal patients independent of any symptoms or history of coronary artery disease. At the moment, though, it is frustrating that the appropriate therapeutic consequences are not yet established. To achieve this, we must more closely analyze the causes of death to improve our understanding of the underlying pathophysiological mechanisms. The lower troponin levels after kidney transplantation may be an interesting clue because this treatment modality is also associated with improved outcome.¹⁸ In conclusion, a

new marker was born for risk stratification to be used by nephrologists, but there is still more to learn.

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