Prognostic impact of cardiac troponin T in patients with stable coronary artery disease and diabetes

PARADIGM SHIFT OF CARDIAC TROPONINS

Until recently, cardiac troponins (troponin I and T) have been considered markers of myocardial necrosis, especially in the setting of acute coronary syndromes (ACS). Current percutaneous coronary intervention (PCI) guidelines also give a class I recommendation for the measurement of cardiac biomarkers including troponins in ACS patients who underwent PCI. However, more recent observations that very low levels of troponins are found circulating in patients with stable coronary artery disease (CAD), and even in the general population, has changed this paradigm. Alternative mechanisms for low-level troponin release have thus been advocated, including physiological cell turnover and cardiomyocyte apoptosis. Hence, troponin fragments after a short period of myocardial ischemia could be compatible with the chronic and low-grade evaluations of cardiac troponins in patients with stable CAD and even in the general population (Figure 1). Using the conventional assays, troponin can be detected in 0.7% of the population. In contrast, the novel high-sensitivity troponin assay allows identifying the alternative mechanisms, including cardiomyocyte apoptosis, increased cell turnover and reversible increase in cell wall permeability to cardiac troponins, even in the chronic clinical settings.

RELATIONSHIP BETWEEN DIABETES AND MYOCARDIAL INJURY

Various studies have shown associations between hyperglycemia and macrovascular and microvascular complications. Potential mechanisms by which hyperglycemia induces myocardial injury include hyperglycemia-mediated coronary microvascular dysfunction, oxidative stress, advanced glycation end-products and myocardial fibrosis. Hyperglycemia might also be associated with myocardial damage through silent atherosclerotic disease. A previous study reported that higher glycated hemoglobin is associated with elevated high-sensitivity troponin T among persons without clinically evident CAD, suggesting the contribution of hyperglycemia to myocardial injury beyond its effects on the development of clinical atherosclerotic CAD. However, the clinical impact of elevated high-sensitivity troponin T on patients with both type 2 diabetes and stable CAD in terms of the prediction of their outcomes remains elusive.

ROLE OF SERIAL MEASUREMENTS OF TROPONINS

Previous studies have reported an association between increases in troponin levels and adverse outcomes in patients with chest pain, heart failure, and in an elderly community population. In contrast, and death in persons with congestive heart failure, CAD and in the general population. In the acute clinical settings, an early invasive strategy for patients with acute coronary syndrome has been shown to be of benefit only among patients with elevated troponin I concentrations. Meanwhile, it remains uncertain whether the use of high-sensitivity troponin assays facilitates the diagnostic and prognostic value in patients with stable CAD.

Figure 1 | Paradigm shift of cardiac troponins. Traditionally, cardiac troponins have been shown to be the markers of myocardial necrosis, especially in the setting of acute coronary syndrome (ACS). The novel high-sensitivity assay allows identifying the alternative mechanisms, including cardiomyocyte apoptosis, increased cell turnover and reversible increase in cell wall permeability to cardiac troponins, even in the chronic clinical settings. CAD, coronary artery disease.
decreases in troponin levels have been shown to be associated with decreases in the number of events. These findings give rise to the hypothesis that coronary revascularization in patients with stable CAD would lower subsequent measurements of circulation troponin concentrations, thereby reducing the risk of adverse outcomes.

**TROPONIN T IN STABLE CAD AND DIABETES**

Recently, Everett *et al.* reported that using Bypass Angiography Revascularization Investigation in Type 2 Diabetes trial data, the cardiac troponin T concentration is an independent predictor of death from cardiovascular causes, myocardial infarction or stroke in patients who had both type 2 diabetes and stable ischemic heart disease. The study included 2,277 (99.6%) patients who had detectable (≥3 ng/L) troponin T concentrations of the 2,285 patients in the Bypass Angiography Revascularization Investigation in Type 2 Diabetes trial. Of the 2,277 patients, 897 patients (39.3%) had abnormal troponin T concentration (≥14 ng/L) at baseline. The 5-year rate of the composite end-point of death from cardiovascular causes, myocardial infarction or stroke, was 27.1% among the patients who had had abnormal troponin T concentration at baseline, as compared with 12.9% among those who had had normal baseline troponin T concentrations. After adjustment of cardiovascular risk factors, severity of diabetes, electrocardiographic abnormalities and coronary anatomy, the hazard ratio for the composite end-point among patients with abnormal troponin T concentrations was 1.85 (95% confidence interval [CI] 1.48–2.32, *P* < 0.001). These findings suggest that high-sensitivity cardiac troponin T concentration is a powerful prognostic marker in patients who have both type 2 diabetes and stable ischemic heart disease even after adjustment of the possible confounding variables of traditional risk factors.

The study also evaluated whether the addition of prompt revascularization to intensive medical therapy decreases the troponin T concentrations over 1 year of follow up, and reduces the rate of the composite end-point in patients with an abnormal troponin T value of 14 ng per liter or higher. As a result, the authors concluded that despite aggressive medical therapy for type 2 diabetes and stable ischemic heart disease, the median troponin T concentration increased over 1 year of follow-up, and no significant reductions in troponin T concentrations were observed in patients who underwent coronary revascularization. In addition, random assignment to prompt coronary intervention did not improve the outcome in these patients as compared with intensive medical therapy alone (hazard ratio 0.96, 95% CI 0.74–1.25). These results suggest that the factors leading to troponin release in patients with stable ischemic heart disease, including hypertension, diabetes, metabolic abnormalities and chronic kidney disease, might be less responsive to epicardial coronary revascularization than the ischemic injury resulting in troponin release in patients with ACS. Interestingly in the present study, an increase of more than 25% in troponin T concentration at follow up was uncommon. However, the authors found that the patients with this percentage increase, as compared with those with a stable troponin T concentration, were at an increased risk for death from cardiovascular causes, myocardial infarction and stroke, regardless of coronary intervention. These observations raise the possibility that serial measurements of troponin concentration could improve its prognostic value, and might be better predictors of adverse outcomes in patients who have both type 2 diabetes and stable ischemic heart disease.

Finally, various mechanisms might affect the measurements of cardiac troponin concentrations in patients with diabetes, including oxidative stress, metabolic disturbance, diabetic cardiomyopathy, diabetic microangiopathy and diabetic nephropathy. Therefore, it is essential to study the potential differences in chronic release and degradation patterns of cardiac troponin in patients with diabetes as compared with their counterparts, in terms of the assessment of prognostic value of circulating cardiac troponins.

**DISCLOSURE**

The author declares no conflict of interest.

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