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EDITORIAL COMMENT

Low Levels of Circulating Troponin as an Intermediate Phenotype in the Pathway to Heart Failure*

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The current indications for measurement of cardiac troponin T (cTnT) and cardiac troponin I (cTnI) primarily focus on diagnosis and risk stratification in patients with suspected myocardial infarction (MI). Recently, highly sensitive assays for cTnT and cTnI have been developed that can detect troponin concentrations ~10-fold lower than is possible with assays currently in use in the United States.

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These assays improve sensitivity for the detection of MI, particularly early after symptom onset, at a cost of decreased specificity (1,2). Importantly, the ability to detect very low circulating troponin levels with these assays has opened the door for many additional potential applications for troponin measurement, both for clinical and for research purposes. With the highly sensitive cTnT (hs-cTnT) and assay, for example, it is possible to detect circulating cTnT in virtually all patients with chronic coronary artery disease or congestive heart failure (3,4); moreover, 25% to 67% of adults from the general population have detectable troponin levels with this assay (5–7). The augmented sensitivity of these assays has facilitated exploration of the cardiovascular "phenotype" associated with low circulating levels of troponin in asymptomatic individuals, including associations with both subclinical cardiovascular disease as well as future clinical events.

Recent studies have demonstrated that among individuals in the general population and among stable patients with chronic cardiovascular disease, measurable circulating troponin levels reflect chronic sources of myocardial injury, rather than acute processes, and better predict long-term heart failure risk than ischemic risk (3,5–7). In the Dallas Heart study, for example, robust, independent associations were observed between higher cTnT and magnetic resonance imaging-defined measures of abnormal cardiac structure and function, such as left ventricular (LV) hypertrophy and LV dysfunction, but no independent association was seen with coronary artery calcium, a measure of atherosclerosis (5). Furthermore, in 2 large population-based studies, the ARIC (Atherosclerosis Risk in Communities) study and the Cardiovascular Health Study, associations with cTnT were much stronger for incident heart failure than for MI (6,7). Finally, even among patients with a prior MI, higher levels of cTnT predict heart failure events but not recurrent MI (3).

In aggregate, these findings suggest that low circulating levels of troponin, detectable now with highly sensitive assays, may indicate subclinical chronic myocardial injury and thereby identify heightened risk for pathological cardiac remodeling and the development of heart failure. In this issue of the *Journal*, Rubin et al. (8) from the ARIC study capitalize on these observations, utilizing cTnT not as an exposure variable, but rather as an intermediate phenotype of subclinical cardiac injury. The focus of the study is on correlations between chronic hyperglycemia, as measured by the glycated hemoglobin (HbA1c) concentration, and levels of cTnT. HbA1c was measured in almost 10,000 persons free from coronary heart disease (CHD) or heart failure between 1990 and 1992, with cTnT measured from frozen plasma samples collected approximately 6 years later.

"Dose-dependent" associations were seen between HbA1c and cTnT, both among persons who had diabetes and those who did not. After adjustment for traditional cardiovascular risk factors, chronic kidney disease, and prevalent LV hypertrophy, the associations remained significant but were attenuated in magnitude, suggesting that some of the association of chronic hyperglycemia with cardiac injury is likely mediated through shared risk factors. In contrast to HbA1c, fasting glucose did not associate with cTnT after multivariable adjustment.

The major limitation of this study is the 6-year interval between measurement of HbA1c and cTnT. The investigators attempted to account for interval events between the 2 study visits, performing sensitivity analyses excluding participants who had or developed chronic kidney disease, stroke, or atrial fibrillation before the cTnT measurement, which did not alter the findings. These analyses are important because it is clear that variability in cTnT levels in the population is influenced not only by structural heart disease, but also by renal function and other comorbid cardiac and noncardiac conditions (5,9). However, these analyses do not

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completely address other potential issues related to the time delay between measurements. For example, it possible that progression to more mild forms of chronic kidney disease could explain, in part, the associations of HbA1c with troponin elevation. In addition, progression of hyperglycemia between study visits may have led to initiation of glucose-lowering therapy. It is plausible that hypoglycemic medications, most notably sulfonylurea agents (10), could cause or contribute to cardiac injury. It would be useful to investigate further whether specific glucose-lowering therapies cause an increase in troponin among persons without known cardiovascular disease.

Chronic hyperglycemia is commonly believed to contribute to premature cardiovascular disease morbidity and mortality by promoting atherosclerosis development and progression. However, it has not been proven that hyperglycemia accelerates atherogenesis. The current findings (8) provide evidence, albeit circumstantial, to support a role for nonatherosclerotic mechanisms by which chronic hyperglycemia may lead to myocardial injury, and eventually, heart failure. Because prior epidemiologic evidence indicates that cTnT reflects myocardial rather than coronary artery pathophysiology in asymptomatic persons, and because the present analyses excluded participants with CHD and accounted for potential confounding from kidney disease and other potential causes of elevated cTnT, these conclusions appear to be reasonable.

Although diabetes has long been implicated as a predisposing factor for heart failure (11), with greater risk at higher HgA1c concentrations (12), the concept of a specific "diabetic cardiomyopathy" has been more controversial. Other than through promotion of atherosclerosis leading to clinically evident and silent myocardial infarction, the specific mechanisms by which chronic hyperglycemia contributes to myocardial injury remain speculative. Alterations in metabolic substrate for the heart (13), coronary microvascular dysfunction (14), increased oxidant stress (15), enhanced fibrosis (16), and the downstream effects of advanced glycation end products (17) are commonly cited as potential culprits for myocardial dysfunction among patients with diabetes, but less is known regarding the influence of more mild forms of chronic hyperglycemia. The present study (8), which demonstrates that associations of HbA1c with cTnT extend to persons with HbA1c levels below the diabetes diagnostic threshold of 6.5%, suggests that nonatherosclerotic cardiac injury related to hyperglycemia may begin earlier in the disease process, before the onset of clinically evident diabetes.

These intriguing findings should prompt further exploration of the role of chronic hyperglycemia in early pathways leading to heart failure development in both animal and human models. Longitudinal studies, incorporating serial cardiac imaging studies, are needed to evaluate patterns of cardiac remodeling among patients with chronic hyperglycemia and low levels of circulating troponins. Intervention studies, evaluating the influence of glucose control strategies on troponin levels, as well as cardiac structure and function and heart failure outcomes, will provide further insight.

The paper by Rubin et al. (8) is the first of what will likely be many papers considering circulating troponins as intermediate phenotypes or surrogate endpoints for heart failure and mortality risk among asymptomatic persons. The underlying implication of such analyses is that if one could modify the exposure variable, for example, by improving chronic glucose control, it may be possible to prevent subclinical myocardial damage, and thus prevent the development of heart failure. However, while overwhelming evidence supports preventing or minimizing troponin elevation in the setting of suspected ACS, such that troponins are now a cornerstone for MI diagnosis (18), limited data exist suggesting that modifying troponin release among asymptomatic ambulatory persons is associated with benefit. Preliminary findings among patients with chronic heart failure (4) and older adults from the general population (6), suggest that increases in cTnT over a 2- to 3-year period are associated with a higher risk for death and heart failure, whereas a reduction in levels are associated with lower risk. Interpretation of these findings is not straightforward, however, as troponin variation over time may have been influenced by acute and chronic factors other than progression of subclinical myocardial pathology, which were not fully considered in these studies.

Before troponin levels can be considered as a validated intermediate phenotype in the pathway to heart failure, additional studies are needed linking changes in troponins with cardiovascular and noncardiovascular outcomes, and investigating the role of specific therapies on troponin release and subsequent events. These studies should be a high priority, as they will have the potential to facilitate earlier interventions to prevent heart failure.

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