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EDITORIAL COMMENT

Another Piece to the Troponin Puzzle

Better Confirmed, and With a Path Forward*

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There is a tendency to consider biomarkers such as the cardiac troponins as mere diagnostic probes or prognostic markers, rather than important elements of our armamentarium to evaluate the pathophysiology of a variety of disease states. The present paper from Japan by Takashio et al. (1) begins to explore the extent to which the use of high-sensitivity cardiac troponins may provide further pathophysiological insights, which may lead to unique opportunities to intervene in positive ways for patients with cardiovascular diseases, in this instance, congestive heart failure.

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It has been known for years that after an acute ischemic insult or more indolent cases, such as chronic dilated cardiomyopathy, that heart failure often progresses in the absence of clinically detected cardiovascular events. Therefore, there is a degree of subclinical progression of disease, the pathophysiology of which has not totally been elucidated. There are a large number of potential reasons why heart failure could progress in the absence of an additional acute large insult. These could include but are not limited to coronary endothelial dysfunction or microvascular dysfunction, concomitant comorbidities such as anemia and diabetes, autonomic activation, systemic inflammation, acute increases in pre-load causing proteolysis and release of cardiac troponin I (cTnI) due to cell death related to apoptosis via a calpain-mediated mechanism, oxidative stress, abnormal calcium handling, and even autophagia (2). The details related to these processes are beyond the scope of this editorial. However, one common theory in this area, based on prior physiological studies, is that there is relative ischemia in patients with heart failure related to poor subendocardial perfusion at a time when myocardial oxygen consumption is high. One might hypothesize that over time, this subendocardial perfusion–demand imbalance could be responsible for heart failure progression in the absence of overt clinical events. This pathophysiology would also provide at least a partial explanation for the frequent observation of elevated cardiac troponin levels in patients with heart failure, and its potent prognostic influence in patients with both acute and chronic heart failure (3).

Takashio et al. (1) attack this issue of subendocardial supply–demand imbalance directly. First, it is acknowledged that the most important determinant of subendocardial perfusion from the point of view of coronary blood flow is directly related to intracardiac chamber pressure. The reason for this is that the vessels to the subendocardium tend to be straight, making them more vulnerable to high intracavitary pressures. At the same time, hypertrophy reduces the density of blood vessels per gram of myocardium in the subendocardial region. In addition, data suggest that there may be abnormalities in coronary vasoreactivity in these vessels in the setting where hypertrophy further negatively influences subendocardial blood flow. If so, this cascade has the potential to substantially reduce subendocardial blood flow at a time when left ventricular wall stress is elevated. When coupled with reflex-mediated increases in heart rate and contractility, myocardial oxygen consumption will increase dramatically in the face of relative hypoperfusion. This would provide at least 1 mechanism by which heart failure could progress in the absence of an acute event due to relative subendocardial ischemia and its deleterious long-term effects.

The approach taken by Takashio et al. (1) is about as well as can be done to evaluate this difficult issue in humans. The authors use high-sensitivity cardiac troponin T (hscTnT) to evaluate this issue, measuring values across the coronary sinus and systemically in 90 patients with dilated cardiomyopathy and 47 control patients who had clinical indications for cardiac catheterization, but were deemed to have reasonably normal coronary anatomy and cardiac function. Agents that could influence coronary vasomotor tone, if present, were discontinued 72 h before the procedure. This is a critical control issue so that the influence of these agents does not mask the pathophysiology, but the possibility of an accentuated response due to the discontinuation cannot be totally excluded. After the obligatory exclusion of some patients due to an inability to obtain all of the requisite information, 76 patients with heart failure and 28 controls remained. The gradient for hscTnT release across the coronary sinus was significantly greater in those with heart failure, as was the transcoronary gradient for BNP and CRP. Intriguingly, there was a good correlation between the transcoronary gradient and the circulating systemic level, suggesting that peripheral blood levels were reflective of myocardial release and not simply altered clearance. The hscTnT levels were related to numerous other measured

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parameters, but after extensive analysis, the only variable that remained significantly correlated with hscTnT was left ventricular end-diastolic pressure (LVEDP). Importantly, patients who also manifested abnormal coronary flow reserve often were in the highest quartile of hscTnT values. Thus, such dysfunction may be additive and should be considered when the gradient for hscTn is more markedly elevated. This dysfunction also eventually may prove to be a target for additional intervention.

The data appear credible. This author accepts conceptually that evaluation of the left anterior descending territory to get a coronary atrioventricular gradient likely reflects an overall pathophysiological dynamic. One could worry that discontinuation of vasoactive medications to avoid their confounding influences led to some degree of increase in LVEDP that is a reflection of acute withdrawal, and if so, that could introduce some confounding. However, the continuation of these medications would also have been viewed as confounding because it would have left direct effects on this important parameter unopposed. In addition, one could argue that because there are substantial data concerning the importance of endothelial dysfunction in patients with heart failure, and because there are data to suggest that the prognosis of patients with endothelial dysfunction is worse, that this entire cascade that is hypothesized to be based on LVEDP could be based instead on coronary endothelial dysfunction. In this light, the information concerning the relative lack of abnormal vasodilator reserve in controls is an important observation. It does not, of course, eliminate this possibility totally, but from the perspective of providing an important control, it does support the concept that the LVEDP is of mechanistic importance.

This study was done with the high-sensitivity cardiac troponin T assay, but there is little reason to suspect that different results might have been observed with other assays. Assays that have still higher sensitivity are forthcoming, which may hold further promise due to increased sensitivity and precision (4). Most importantly, this study not only confirms an important pathophysiological principle, but it also provides at least the hint that hscTn values may be useable to directly monitor the downstream target of perfusion–demand mismatch. If indeed, LVEDP is the primary contributor to the continuing (albeit subtle) deterioration of cardiac function as marked in this study by hscTnT, one should be able to monitor interventions that reduce LVEDP with these sorts of probes. An aggressive approach to reduce central cardiac pressures was originally advocated 25 years ago based upon the work of Stevenson and Tillisch (5), but some of the enthusiasm for this hemodynamic-tailored approach was lost after the publication of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial (6). Now, with more data and potentially better probes to provide information regarding the causes (perfusion–demand mismatch) and consequences (cardiac myocyte death) of heart failure progression, perhaps acute and chronic interventional studies are again warranted in this important area. Such studies are becoming topical with enthusiasm for the use of more comprehensive biomarker-guided trials (7).

This elegant research from Takashio et al. (1) begins to express in a concrete way the exciting potential of sensitive probes such as high-sensitivity cardiac troponin, not just to our diagnostic armamentarium, but to the panoply of clinical problems that might be addressed in productive ways through proper use of cardiac biomarkers. One can conceive long term of simple, but elegant, algorithms based on sensitive biomarker results predicated on a pathophysiological understanding of the progression of heart failure.

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REFERENCES

1. Takashio S, Yamamuro M, Izumiya Y, et al. Coronary microvascular dysfunction and diastolic load correlate with cardiac troponin T release measured by a highly sensitive assay in patients with nonischemic heart failure. J Am Coll Cardiol 2013;62:632–40.
2. Mann D. Pathophysiology of heart failure. In: Bonow RO, Mann DL, Zipes DO, Libby P, editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th edition. Philadelphia, PA: Elsevier Saunders, 2012;25:487–503.
3. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker G. Troponin elevation in heart failure: prevalence, mechanisms, and clinical implications. J Am Coll Cardiol 2010;56:1071–8.
4. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem 2012;58:1574–81.
5. Stevenson LW, Tillisch JH. Maintenance of cardiac output with normal filling pressures in patients with dilated heart failure. Circulation 1986; 74:1303–8.
6. Binanay C, Califf RM, Hasselblad V, et al., ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA 2005;294:1625–33.
7. Motiwala SR, Januzzi JL Jr. The role of natriuretic peptides as biomarkers for guiding the management of chronic heart failure. Clin Pharmacol Ther 2013;93:57–67.

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