

# Prognostic Value of Circulatory Cardiac Troponins in Heart Failure

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Circulating cardiac troponins (cTn), the proteins that regulate actin and myosin interaction during muscle contraction, are detectable in patients without typical symptoms of acute coronary syndromes. The interpretation for their elevation in this context is challenging to the physician and to the scientist. The clinical potential of measuring the release of myofibrillar cTn into the bloodstream of patients with heart failure (HF) has been suggested more than a decade ago.<sup>1</sup> Due to the minute levels of circulating cTn compared to the limit of detection of the analytical methods available at that time, most of the following clinical investigations were confined to patients with acute decompensation or severe HF since a sizeable fraction of these patients had high (measurable) levels of plasma cTn that were positively correlated to the severity of the disease and unfavorable prognosis. In patients with milder chronic and stable HF, lower levels of cTn should be expected. Previous studies that involved small cohorts of patients with chronic HF have shown that, when detectable, cTn elevation was a negative predictive factor.<sup>2,3</sup> In this context, the study by Pascual-Figal et al<sup>4</sup> extends our understanding of the possible utility of circulating cTn in HF patients. They monitored 80 ambulatory patients with chronic and stable HF of nonischemic origin (NYHA class II-III, left ventricular ejection fraction <40%) for more than 2 years and periodically measured cTnT (as well as NT-proBNP) with a median interval of 3.1 months. Only a minor fraction of these patients (8.7%) were positive for cTnT (>0.01 ng/mL, the limit of detection of the assay used) at an initial visit. However, more than half of the patients had elevated cTnT levels during at least one of the subsequent determinations follow-up. This population

was more severely ill, had more compromised cardiac function (higher plasma NT-proBNP concentrations) and more frequent adverse clinical events (cardiac death by progressive pump failure or sudden death, need for urgent heart transplant) compared to those who never experienced elevation of cTnT.

## Causes for Elevated Circulating Cardiac Troponins in HF

Previous reports, and the present observation by Pascual-Figal et al, raise many questions about the significance of circulating cTn in chronic HF. The main issue regards the origin of circulating cardiac troponins and the mechanisms responsible for their release into the blood stream in chronic HF. A continuous release of troponins from the myocardium might reflect ongoing cardiomyocyte death as seen animal models of post-myocardial infarction LV dysfunction<sup>5</sup> and in patients with chronic HF.<sup>6,7</sup> If ongoing cardiac damage is assumed to be a determinant of circulating troponins, this phenomenon seems to be independent of an ischemic etiology of the disease, as confirmed by Pascual-Figal et al. Stretch of cardiac myocytes might lead to leakage of the cytosolic pool of troponins by transient loss of cell membrane integrity. This reversible damage may contribute to the increase of circulating cTn caused by irreversible injury of cardiac myocytes. It is unknown to what extent, if any, apoptosis contributes to troponin T elevation in chronic HF.<sup>8</sup> There are however alternative causes for elevated cardiac troponin levels including cardiopulmonary disease and chronic renal insufficiency.<sup>9</sup> In addition, several neuroendocrine systems (renin-angiotensin-aldosterone, sympathetic, endothelin) and inflammatory mechanisms are also chronically activated in patients with HF and might contribute to myocyte injury and cell death. Clearly, we need to gain more basic knowledge on the role of these mechanisms. Experimental investigations using well-characterized animal models of cardiac damage (myocardial infarction, cardiac overload, diabetes, renal dysfunction, neuroendocrine activation) and/or cultured isolated myocytes (hypoxia, hyperglycemia, hormonal stimulation) will probably help in deciphering the biological complexity behind the apparently naïve measurement of a cardiac contractile protein in the blood of patients with HF.

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## The Continuum of Cardiac Troponins Release

Though extremely rare, the release of cardiac troponins may be detected in the plasma of apparently healthy subjects with traditional analytical methods. In a population-based study, cTnT was elevated ( $\geq 0.01$  ng/mL) in 0.7% of 3557 residents of the Dallas County and this was statistically associated with a high-risk cardiovascular profile (diabetes mellitus, left ventricular hypertrophy, chronic kidney disease, heart failure).<sup>10</sup> However, this observation might represent only the tip of the iceberg. In fact, new automated assays for circulating cardiac troponins are currently being developed by different manufacturers with much higher sensitivity and limits of detection in the range of few picograms per milliliter.<sup>11</sup> With these new assays, the proportion of subjects with detectable cTn is likely to increase drastically, even in the general population. For instance, circulating cTnI is detectable with a high sensitive immunoassay in 3 out of 4 healthy Caucasian subjects for whom the presence of cardiac or systemic acute or chronic disease was excluded.<sup>12</sup> The impact of high sensitive assay for cTn in patients with chronic HF is even more impressive: in the Valsartan Heart Failure (Val-HeFT) trial, plasma samples were collected at study entry in almost 4000 patients with chronic and stable HF, and cTnT measured both with a traditional (limit of detection 0.01 ng/mL) and a newly developed high sensitive (0.001 ng/mL) assay.<sup>13</sup> Whereas cTnT was detectable in only 10.4% of the population with the traditional assay (a figure in agreement with the data reported by Pascual-Figal et al), the proportion rose abruptly to 92.0% with the high sensitive assay. More importantly, cTnT was able to predict adverse events (mainly death and hospitalization for HF) in a very low range of concentrations that were not detectable with the traditional assay. A striking analogy can be made with brain natriuretic peptides (BNP or NT-proBNP) that show good prognostic performance in patients with cardiovascular diseases at concentrations well below their respective diagnostic threshold for the exclusion of HF.

## Serial Measurement of Cardiac Troponin T in Chronic and Stable HF Patients

Another potentially clinically important observation by Pascual-Figal et al is the fact that repeated measurements of circulating cTn over a rather long period of time may be useful in predicting distant events and helping in the clinical monitoring of patients with chronic HF. They hereby confirm a previous report where persistently elevated cTn in patients with idiopathic dilated cardiomyopathy was a negative prognostic factor.<sup>3</sup> Together, these are promising data but they certainly need to be confirmed in much larger multicenter clinical studies with stronger design. Again, the example of natriuretic peptides in chronic HF tells us that, even if undoubtedly

among the most powerful markers of outcome in HF, early trials of natriuretic peptide-guided therapy have yielded so far mixed results in HF.

In conclusion, the identification of a novel circulating marker of outcome in HF is a relatively frequent event since the seminal study by Cohn et al showing that high plasma concentrations of norepinephrine predicted bad outcomes in moderate to severe chronic HF.<sup>14</sup>

Troponins are now being proposed as markers of outcome in chronic HF by the present study and others. More studies are clearly needed to prove that troponins add substantial prognostic information in patients with HF, when compared with the "gold standard" of natriuretic peptides.

Another potentially relevant and new information from the present study is the observation on beta-blocker-induced decrease in troponin T. If confirmed in larger, controlled cohorts of patients, this would support the use of TnT to titrate and monitor the efficacy of one of the few life-saving therapies in HF. The other candidate surrogate biomarker of efficacy of beta-blockers are natriuretic peptides, though evidences are still contradictory.

Moreover, we need deeper physiopathological insights on the cellular mechanisms leading to the release of cardiac troponin from the stressed myocyte, especially at very low level, to interpret the meaning and appreciate the potential of circulating troponins in HF.

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