Brief Report

# Dancing Cats, Heart Failure, and Circulating Troponin

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In the Japanese town of Minimata in 1950, cats and other wildlife were noted to exhibit abnormal behavior and convulsions and to die without apparent cause, leading to the term "cat dancing disease," which was otherwise not investigated.[1] In 1956, the local inhabitants began to experience progressive neurologic symptoms, which progressed to an epidemic, leaving hundreds dead and thousands permanently disabled. Investigations later determined the cause to be organic methylmercury contamination of the food supply, caused by effluent from a nearby chemical manufacturing plant. It was surmised that investigation of this phenomenon (also caused by methylmercury poisoning) might have led to earlier identification of the risk of methylmercury poisoning and avoidance of human casualties.[2]

What does this a have to do with prediction of the risk of heart failure? Most cases of incident heart failure (HF) in derivation and validation cohorts used in model development occurred outside of the advent of acute coronary ischemia, leading to the lack of emphasis on use of troponins as an important biomarker for prediction of HF. This was reinforced by the lack of highly sensitive troponin assays. More recently, however, small elevations in circulating troponins have been shown to be associated with increased risk of cardiovascular events, even in the absence of acute coronary ischemia.[3] With renewed attention, the concept of low-level cardiomyocyte "micro" injury has gained traction as a mechanism for development of HF.

The current study by Welsh et al assessed the association between high-sensitivity troponin T (hsTnT) and incident heart failure in a population of older men in the British Regional Heart Study.[4] In their analysis, 3851 men were enrolled and followed for a median of 12.6 years, during which 295 incident cases (7.7%) of HF occurred. The study was observational and prospectively performed. The primary end point—a new diagnosis of HF—was sought in primary and secondary care health care records. Results of baseline biomarkers N-terminal pro−B-type natriuretic peptide (NT-proBNP) and hsTnT (lower detectable limit <5 pg/mL) were obtained by means of commercially available tests.

The authors report that hsTnT was predictive of incident heart failure regardless of evidence suggesting coronary artery disease (CAD) at baseline, with each standard deviation increase associated with a 58% higher risk of incident HF after adjusting for clinical factors (34% increase after adjustment for NT-proBNP). A risk-prediction model that included classic clinical risk factors and NT-proBNP yielded a C-statistic of 0.791, which was not increased further with inclusion of hsTnT. Importantly, only 1 case of incident HF occurred in those with no detectable baseline hsTnT.

Although the prospective design, relatively large sample size, inclusion of individuals from a primary care setting, and long duration of follow-up are clearly strengths of the study, weaknesses include a lack of female, younger, and nonwhite participants. In addition, the lack of a "criterion standard" adjudication process for either preexisting CAD or for the primary end point may have led to increased misclassification. Additional study is required to confirm these findings in other populations.

This study is important in 2 ways. First, the results confirm previous work and extend the existing relationship between serum TnT and risk of incident HF to a population of older men in a primary care setting. Perhaps even more important is the observation that elevation of circulating hsTnT is a near prerequisite for progression to HF symptoms.

That observation will serve to refocus our attention to the "troponitis" phenomenon, which clinicians generally ignore. In addition to understanding the risk of elevation of troponin outside of acute coronary syndromes, Lamblin et al have shown that even in patients with CAD, development of HF typically occurs without an incident myocardial infarction.[5] These data support the requirement of ongoing subclinical myocyte injury before symptomatic HF.

Of the many remaining questions, 2 stand out. First, why does the discriminatory value of troponin weaken so

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dramatically when corrected for NT-proBNP, especially since they do not necessarily correlate well with each other? Natriuretic peptides are released from myocardium in response to wall stress (continuous release), whereas troponin is released in response to any myocardial injury (threshold release), whether due to infarction, ischemia, inflammation, or microvascular dysfunction. Perhaps a "threshold" effect occurs whereby mild increases in natriuretic peptides lead to troponin leaks in susceptible individuals but not in others.

A second critical question is whether a change in hsTnT concentration over time is related to outcomes and whether interventions specifically designed to address troponin levels would also change outcomes. For example, therapies such as sacubitril/valsartan, known to improve outcomes in chronic HF, also reduce troponin.[6] Similarly, canagliflozin, a glucose-lowering agent shown to prevent the onset of HF, also has been reported to reduce circulating troponin.[7] Although those studies were not designed to show a cause-effect relationship between reduction of circulating troponin and outcomes, the association is suggestive and supportive.

It is noteworthy that Grodin et al, in a 900-patient substudy of the ASCEND HF trial, showed that both baseline and in-hospital ultrasensitive cTnI (at 48−72 hours) were predictive of outcomes in hospital and at 30 and 180 days, but the short-term change in cTnI was not predictive.[8] Only cTnI measured at 30 days was associated with 180-day death.

Why this apparent lack of near-term prediction with change in troponin? One explanation might be the relatively small number of clinical events, with only 46 in hospital, 105 at 30 days, and 106 (deaths only) at 180 days, which limits statistical power. The confounding effects of treatment may play a role, because at 30 days, we see a reemergence of the predictive association of cTnI. Perhaps myocyte "micro" injury, in contrast to the well known short-term effects of infarction, may lead to ultrastructural change or mRNA expression which manifests over a longer time horizon. This dichotomy is also observed in the case of natriuretic peptides, where short-term associations between change in BNP and filling pressures or in-hospital outcomes are less discriminatory than with longer-term outcomes.[9] Supplementation of current troponin level "snapshots" with repeated levels to allow an area under the curve estimation may provide further insights.

The use of biomarkers for identification of populations at risk of heart failure continues to evolve. Recent data have reminded us of the need to understand mechanisms and treatment options for patients with even small elevations of circulating troponin. During this journey we will undoubtedly uncover new and surprising findings. And if we find any dancing cats, we should not ignore them.

## Disclosures

None.

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