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Editorial

Use of Serial High-Sensitive Troponin T in Patients With Adult Congenital Heart Disease: Enhancing the Detection of Major Adverse Cardiac Events

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See article by Geenen et al., pages 1516–1524 of this issue.

Adult congenital heart disease (ACHD) describes a variety of cardiac and vascular birth defects, with increasing prevalence because of advances in medical therapies and surgical interventions administered in early childhood.[1-5]

Outcomes in Patients With ACHD

As patients with congenital heart disease transition into adulthood, they are at greater risk of adverse clinical outcomes.[6] Furthermore, because of the risk of heart failure (HF) in this aging population,[7] our ability for risk stratification and proper surveillance using cardiac biomarkers in this patient cohort deserves further investigation. N-terminal probrain natriuretic peptide (NT-proBNP) has important prognostic value in ACHD patients; increasing levels are indicative of adverse cardiac remodelling.[8,9] High-sensitivity troponin T (hs-TnT), a biomarker of myocardial injury, represents another promising biomarker for clinical use in the setting of ACHD.[8] Importantly, the change between 2 serial hs-TnT measures is associated with adverse clinical outcomes in the setting of HF,[10] which might be relevant to the ACHD patient population. In this issue of the *Canadian Journal of Cardiology*, Geenen et al. report the results of a prospective study tracking a cohort of patients with ACHD and their clinical outcomes, while simultaneously conducting serial measures of hs-TnT at scheduled follow-up clinic visits, over a 4-year period.[11] From their study, we can conclude that: (1) serial measures of hs-TnT have greater clinical utility than baseline measures of hs-TnT as a prognostic marker for mortality and major adverse cardiac events (MACE) and; (2) ACHD patients with stable measures of hs-TnT are at lower risk of mortality and MACE than patients with dynamic changes (ie, increasing or decreasing) in hs-TnT levels over follow-up. These findings support the clinical utility of serial hs-TnT measures in patients with ACHD, which could potentially improve patient management and surveillance in this patient cohort.[12]

Examining the Prognostic Value of Serial hs-TnT in Patients With ACHD

In their article, Geenen et al. describes a prospective, single-centre study to examine the prognostic value of serial hs-TnT measures, in patients with ACHD, for all-cause mortality and MACE.[11] Six hundred two consecutive patients with moderate to complex ACHD were prospectively included in the study. Patients were excluded if they were younger than 18 years old, were diagnosed with mild ACHD (isolated atrial septal defect [ASD] or ventricular septal defect [VSD]), had impaired renal function (defined as creatinine > 200 μmol/L), or were pregnant. Tetralogy of Fallot was the most prevalent form of ACHD in this study, diagnosed in 30% of the patients; aortic stenosis, aortic coarctation, and transposition of the great arteries repaired with the Mustard operation were diagnosed in 23%, 19%, and 11% of patients, respectively. Patients were managed on the basis of guideline-directed therapy over the follow-up duration. The primary end point was a composite of all-cause mortality, incident HF, cardiac-related hospitalizations, arrhythmias, thromboembolic events, and cardiac intervention or reintervention. The secondary end point was defined as all-cause mortality or incident HF.

Patients were categorized as either having a dynamic change in levels of hs-TnT over a 1-year follow-up period, or as having stable levels (ie, undetectable change) of hs-TnT over the 1-year follow-up period. The median age of all ACHD patients in this study was 32.5 (interquartile range, 24.7-41.2) years. Forty-two percent of the cohort was female; only 26% of female patients had a stable hs-TnT measure. Taken together, this suggests that younger men with ACHD tended to have stable levels of hs-TnT between baseline and a

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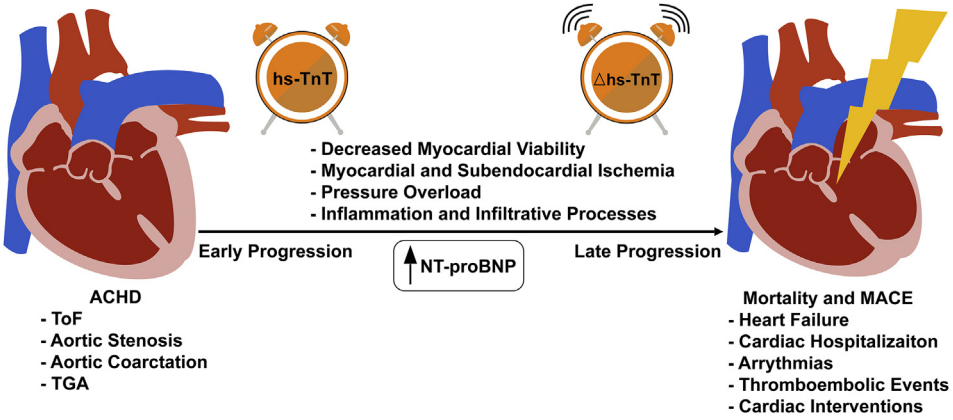

Figure 1. Use of serial high-sensitivity troponin T (hs-TnT) measurements as an indicator of pathological remodelling and as a component in the prognostication of all-cause mortality and major adverse cardiac events (MACE) in patients with adult congenital heart disease (ACHD). NT-proBNP, N-terminal pro-brain natriuretic peptide; TGA, transposition of the great arteries; ToF, tetralogy of Fallot.

1-year follow-up, supported using statistical analyses. Notably, there was a markedly low level of use of cardiac medication in patients (18%) with stable hs-TnT measures from baseline to a 1-year follow-up, suggesting that these patients were clinically stable, as corroborated with lower symptomatic score. Electrocardiography supported these findings, with a significant number of patients with stable hs-TnT measures remaining in sinus rhythm (94%). Echocardiography also showed smaller left atrial and left ventricular volumes and right ventricular dimensions in patients with stable hs-TnT. Geenen et al. conclusively showed that we can identify clinically stable ACHD patients through the observation of stable hs-TnT levels over a 1-year follow-up period. Patients were tracked over 5.8 (interquartile range, 5.3-6.3) years of follow-up, over which time 38.1% and 11.6% of the patients reached the primary and secondary end point, respectively. Geenen et al. noted that the occurrence of the primary end point was associated with older age, cardiac medication use, higher New York Heart Association class, loss of sinus rhythm, and compromised ventricular function. Patients with stable levels of hs-TnT over the first-year follow-up maintained a higher rate of event-free survival. Geenen et al. used a combination of a linear mixed effect model and Cox regression model to assess the association between serial hs-TnT levels and the occurrence of primary and secondary end points, using a joint modelling approach.[13] Their analyses showed that serial hs-TnT measures were more strongly associated with primary end points than single baseline measures (hazard ratio (HR), 1.62 [95% confidence interval (CI), 1.44-1.88] vs HR, 1.38 [95% CI, 1.25-1.52]). A similar trend was shown for the secondary end points (serial hs-TnT measures HR, 2.58 [95% CI, 2.13-3.14]; single baseline measure of hs-TnT HR, 1.92 [95% CI, 1.65-2.24]). Importantly, the analyses conducted by Geenen et al. show that serial measures of hs-TnT have greater clinical utility than baseline measures, because they allow for the adjustment of patient clinical characteristics and levels of NT-proBNP, as shown by statistically significant HRs, not reproducible with baseline measures. Nonetheless, serial hs-TnT measures have clinical utility in the prognostication of ACHD as shown in the current study, allowing for continuous surveillance of disease progression in ACHD patients, with dynamic changes in hs-TnT during follow-up serving as an "alarm" for adverse clinical outcomes (Fig. 1).

Strengths and Weaknesses of the Study by Geenen et al.[11]

The prospective evaluation of serial hs-TnT measures in patients with ACHD is a novel initiative. In previous studies the risk of adverse clinical outcomes in patients with ACHD has been stratified using a single baseline measure of hs-TnT,[14-17] which holds lower prognostic value, and is of limited clinical utility as shown in this study. A major strength of this study is the use of serial hs-TnT measures to identify ACHD patients who are at low risk of mortality and MACE as those with stable levels of hs-TnT. Geenen et al. propose that there might be additional mechanisms of cardiac deterioration to HF in ACHD patients, thus explaining the association of hs-TnT with all MACE and not HF exclusively, unlike NT-proBNP.[18,19] Indeed, although NT-proBNP reflects increased myocardial wall stress, hs-TnT reflects ongoing myocardial injury, thereby providing additional value in assessing heart disease in patients with ACHD. Interestingly, patients classified as having a decrease in hs-TnT levels showed poor clinical outcomes, much like patients with increased levels of hs-TnT. This raises questions about the mechanisms of cardiac injury associated with ACHD, which requires further investigation. As the prevalence of ACHD increases in the clinical population because of advances in medical therapies and surgical interventions, the findings of this study and subsequent investigations will have important prognostic implications for patient management.[1-3]

Although this study was well executed, there are methodological weaknesses that must be recognized. The authors recognize that a larger sample size would be required for subgroup analysis of the value of serial measures. In this study patients with isolated ASD and VSD were excluded, which are the most common forms of ACHD,[2,4] and patients with impaired renal function were also excluded. It is understandable why Geenen et al. chose to exclude patients with renal-failure, because of the effects of troponin T

accumulation, due to diminished renal clearance[20]; however, renal dysfunction is a highly prevalent comorbidity in patients with ACHD.[21,22] The exclusion of these patients limit the external validity of these findings and therefore future investigations should include patients with ASD, VSD, and ACHD patients with renal dysfunction. Future investigations could also use serial cardiac imaging to validate the prognostic value of serial biomarker measures. Additionally, the incorporation of genetic testing could provide a comprehensive evaluation of patient disease etiology and phenotype in conjunction with serial hs-TnT measurements to improve the outcome of these vulnerable patients.

Conclusions

Patients with ACHD are at risk of mortality and MACE. On the basis of the results of the study by Geenen et al.,[11] serial hs-TnT measures serve as a prognostic biomarker of all-cause mortality and MACE, thereby risk-stratifying patients. Hs-TNT levels could be used as a critical indicator of adverse clinical outcomes in patients with ACHD, over and above NT-proBNP measures (Fig. 1). Further research is required to investigate the clinical course associated with ACHD disease progression in which hs-TnT (and NT-proBNP) changes from baseline, the significance of a decrease vs increase in hs-TnT measures, and to define the appropriate changes in management and monitoring.

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