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Clinical Research

Prognostic Value of Serial High-Sensitivity Troponin T Measurements in Adults With Congenital Heart Disease

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ABSTRACT

Background: Single high-sensitivity troponin T (hs-TnT) measurement is predictive of cardiac events in adults with congenital heart disease (ACHD). We aimed to study the prognostic value of serial hs-TnT measurements in stable patients with ACHD.

Methods: In total, 602 consecutive patients with ACHD were enrolled in this prospective study (2011-2013). Blood sampling was performed at enrollment and thereafter yearly during scheduled visits, up to 4 years. Hs-TnT, N-terminal pro B-type natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate (eGFR) were measured. The composite primary endpoint was defined as all-cause mortality, heart failure, arrhythmia, hospitalization, cardiac (re)interventions, or thromboembolic events. The relationship between changes in serial hs-TnT and the primary endpoint was studied by joint models with adjustment for repeated NT-proBNP and eGFR.

Results: In 601 patients (median age, 33 [interquartile range, 25-41] years, 42% women, 90% NYHA I), at least 1 hs-TnT measurement was

RÉSUMÉ

Contexte : Le dosage unique de la troponine T hypersensible (hs-TnT) est prédictif d'événements cardiaques chez les adultes atteints de cardiopathie congénitale. Notre objectif était d'étudier la valeur pronostique du dosage sériel de la hs-TnT chez des patients adultes atteints de cardiopathie congénitale qui présentaient un état stable.

Méthodologie : Au total, 602 patients adultes atteints de cardiopathie congénitale ont été inscrits consécutivement à cette étude prospective (2011-2013). Les prélèvements sanguins ont été effectués au moment de l'inscription et chaque année par la suite au cours des visites prévues, jusqu'à la quatrième année. La hs-TnT, le propeptide natriurétique de type B N-terminal (NT-proBNP) et le taux de filtration glomérulaire estimé (TFGe) ont été mesurés. Le paramètre d'évaluation principal regroupait les décès toutes causes confondues, l'insuffisance cardiaque, l'arythmie cardiaque, les hospitalisations, les (ré)interventions cardiaques et les événements thromboemboliques. La relation entre les variations des taux sériels de hs-TnT et le

Adults with congenital heart disease (ACHD) have a lifelong burden of morbidity and mortality,[1] and therefore they require attentive follow-up over the course of their lives. The recommended frequency and intensity of follow-up are related to the disease complexity;[2] however, follow-up strategies are mostly based on observational studies or expert opinion. Both the need for life-long monitoring and the increased prevalence of patients with ACHD[3] have resulted in an increased health care utilization.[4] To be able to maintain an adequate and sustainable management of patients with ACHD, noninvasive, objective, and accurate methods to monitor patients are needed. Easily accessible blood biomarkers may be useful in this respect.

Over the past few years, several prognostic blood biomarkers in the ACHD population have been identified, among which N-terminal pro B-type natriuretic peptide (NT-proBNP) thus far reveals as most relevant.[5-7] We recently demonstrated the relevance of serial NT-proBNP measurements for risk stratification in patients with ACHD.[8] NT-proBNP is secreted by cardiomyocytes in response to myocyte stretch and stimulated by increased wall stress.[9] However, deterioration of cardiac function in ACHD may include more pathophysiologic pathways. High-sensitivity troponin T (hs-TnT), primarily known for its diagnostic ability in acute coronary syndrome,[10] is also associated with ventricular dysfunction[11,12] and with cardiovascular events in patients with ACHD.[5] Secretion of troponin T in chronic heart failure (HF) can be explained by various postulated mechanisms including myocardial and subendocardial ischemia, inflammation, and myocardial

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performed; a mean of 4.3 hs-TnT measurements per patient were collected. After a median follow-up of 5.8 [interquartile range, 5.3-6.3] years, 229 (38.1%) patients reached the primary endpoint. On average, hs-TnT levels increased over time, and more in patients who reached the primary endpoint ($P < 0.001$). A 2-fold higher hs-TnT was associated with the primary endpoint (unadjusted hazard ratio, 1.62; 95% confidence interval, 1.44-1.82; $P < 0.001$). The association remained after adjustment for repeated eGFR but not when adjusted for repeated NT-proBNP; repeated NT-proBNP remained associated with the primary endpoint.

Conclusion: In stable patients with ACHD, hs-TnT levels increased before the occurrence of an event and repeated hs-TnT was associated with the risk of adverse cardiac events. However, repeated hs-TnT was not superior to repeated NT-proBNP.

paramètre d'évaluation principal a été étudiée à l'aide de modèles conjoints corrigés pour tenir compte de la mesure répétée du taux de NT-proBNP et du TFGe.

Résultats : Chez 601 patients (âge médian : 33 ans [intervalle interquartile : 25-41 ans], 42 % de sexe féminin, 90 % présentant une maladie de classe I de la NYHA), au moins un dosage de la hs-TnT a été effectué; les investigateurs ont effectué, en moyenne, 4,3 dosages de la hs-TnT par patient. Au terme d'un suivi médian de 5,8 ans [intervalle interquartile : 5,3-6,3 ans], le paramètre d'évaluation principal a été atteint chez 229 (38,1 %) patients. En moyenne, les taux de hs-TnT ont augmenté au fil du temps, et davantage dans le cas des patients chez qui le paramètre d'évaluation principal a été atteint ($p <$ 0,001). Un taux de hs-TnT deux fois plus élevé était associé au paramètre d'évaluation principal (rapport des risques instantanés non corrigé : 1,62; intervalle de confiance à 95 % : de 1,44 à 1,82; $p <$ 0,001). L'association a persisté après la correction visant à tenir compte de la mesure répétée du TFGe, mais pas après la correction visant à tenir compte du dosage répété de la NT-proBNP; le dosage répété de la NT-proBNP est demeuré associé au paramètre d'évaluation principal.

Conclusion : Chez des patients adultes atteints de cardiopathie congénitale qui présentaient un état stable, les taux de hs-TnT ont augmenté avant la survenue d'un événement, et le dosage répété de la hs-TnT a été associé au risque d'événements cardiaques indésirables. Toutefois, le dosage répété de la hs-TnT ne s'est pas avéré supérieur au dosage répété de la NT-proBNP.

apoptosis.[13] In chronic HF, the relative change in hs-TnT between 2 measurements has been associated with adverse clinical outcomes.[14] Serial hs-TnT measurements may as well be predictive of cardiac events in the ACHD population.

We assessed the temporal evolution of hs-TnT in stable patients with ACHD over a 4-year period and studied the relation between these longitudinal patterns and the risk of any major adverse cardiac event: all-cause mortality, HF, arrhythmia, hospitalization, cardiac (re)intervention, or thromboembolic event.

Methods

Study design and population

This prospective observational cohort study includes a total of 602 consecutive patients with moderate-to-complex ACHD, who routinely visited the outpatient clinic of the Erasmus MC, a tertiary referral center, between April 2011 and April 2013. We excluded patients aged <18 years, those with mild ACHD (isolated atrial or ventricular septal defect), patients with an impaired renal function (defined as creatinine >200 μmol/L), and pregnant women. The study protocol was approved by the Erasmus MC medical ethics committee, and all research subjects provided written informed consent. The study was performed according to the principles outlined in the declaration of Helsinki.

Patient treatment was according to the discretion of the treating physician, based on current guidelines.[2,15] At baseline, patients underwent physical examination by a cardiologist, 12-lead electrocardiography, echocardiography, and venous blood sampling. Patients returned for yearly follow-up visits during the first 4 subsequent years after study inclusion, in which they received a complete cardiac assessment and venous blood draw. Other aspects of the study protocol have been described previously.[5,16]

Repeated blood sampling and hs-TnT measurements

Venous blood sampling was performed at baseline and all repeated study visits. Blood samples were processed <2 hours after collection and stored at −80°C until batch analysis. NT-proBNP was directly measured in fresh serum samples at the clinical chemistry laboratory, using a commercial electrochemiluminescence immunoassay (Roche Diagnostics, Rotkreuz, Switzerland). Hs-TnT measurements were obtained in 2 batches at the clinical chemistry laboratory of our center. A total of 2574 serum measurements were collected, corresponding to a mean of 4.3 measurements per patient. The first batch analysis of 589 (baseline) samples was performed in 2015[12] and the next batch of 1985 (follow-up) samples in 2018. All hs-TnT measurements were performed with a commercial electrochemiluminescence immunoassay (Roche Diagnostics). The limit of detection was 5 ng/L and the limit of blank was <3 ng/L. For analytical purposes, hs-TnT levels below <3 ng/L were substituted with a level equal to 1.5 ng/L. Hs-TnT level >14 ng/L was considered elevated. The upper limit of normal for NT-proBNP was 14 pmol/L. Samples had not undergone a prior freeze-thaw cycle. Analysts were blinded to patients' characteristics and endpoints.

Definition and assessment of endpoints

The primary study endpoint was a composite of all-cause mortality, incident HF (HF requiring initiation or change in HF medication, or requiring hospitalization), hospitalization for cardiac reasons (eg, endocarditis), arrhythmia

Table 1. Baseline patients' characteristics for all patients and according to the 1-year change in hs-TnT level

		Change in hs-TnT between baseline and 1-y measurement*			
	All patients with ACHD	Decrease	Stable (undetectable)	Increase	*P*-value
No. of patients	601	132	100	326	
Clinical characteristics					
Age, y	32.5 [24.7-41.2]	32.5 [24.1-40.4]	25.8 [21.4-33.1]	34.8 [27.2-44.8]	< 0.001
Sex: women, n (%)	253 (42)	94 (71)	26 (26)	205 (63)	< 0.001
Surgical repair, n (%)	540 (90)	118 (89)	90 (90)	296 (91)	0.893
Age at initial surgical repair, y	3.7 [0.8-11.9]	3.1 [0.5-11.0]	1.9 [0.4-6.3]	5.5 [1.2-14.9]	< 0.001
Cardiac medication use, n (%)†	212 (35)	50 (38)	18 (18)	134 (41)	< 0.001
Body mass index, kg/m^2	24.7 ± 4.4	24.5 ± 4.6	24.3 ± 4.3	25.2 ± 4.3	0.109
Heart rate, beats/min	74 ± 13	73 ± 14	74 ± 13	74 ± 13	0.586
Systolic blood pressure, mm Hg	126 ± 16	127 ± 17	124 ± 16	127 ± 16	0.296
O_2 saturation<90%, n (%)	17 (3)	5 (4)	1 (1)	9 (3)	0.446
NYHA class II/III, n (%)	61 (10)	14 (11)	3 (3)	38 (12)	0.038
Congenital diagnosis, n (%)					
Tetralogy of Fallot	179 (30)	33 (25)	27 (27)	101 (31)	0.398
Aortic stenosis	138 (23)	28 (21)	20 (20)	86 (26)	0.294
Aortic coarctation	112 (19)	26 (20)	27 (27)	51 (15)	0.036
TGA-mustard operation	65 (11)	14 (11)	6 (6)	38 (12)	0.268
TGA-arterial switch operation	24 (4)	6 (5)	10 (10)	5 (2)	< 0.001
Congenitally corrected TGA	20 (3)	8 (6)	1 (1)	11 (3)	0.116
Fontan circulation	36 (6)	7 (5)	8 (8)	20 (6)	0.694
Functionally univentricular heart	7 (1)	2 (1)	0 (0)	5 (2)	0.461
PAH	9 (1)	2 (1)	1 (1)	4 (1)	0.939
REV/Rastelli	11 (2)	6 (5)	0 (0)	5 (2)	0.032
Electrocardiography					
Sinus rhythm, n (%)	520 (87)	108 (82)	94 (94)	282 (87)	0.025
QRS duration, ms	112 [100-137]	118 [105-137]	102 [92-114]	114 [101-145]	< 0.001
Echocardiography					
Left atrial volume, mL/m^2‡	21 [15-29]	22 [15-36]	19 [15-23]	21 [17-30]	0.007
LV end-diastolic volume, mL/m^2‡	64 ± 19	68 ± 20	60 ± 16	63 ± 19	0.017
LV ejection fraction, %‡	56 ± 8	55 ± 9	57 ± 6	56 ± 8	0.077
RV end-diastolic annulus dimension, mm	42 ± 8	43 ± 9	39 ± 7	43 ± 8	< 0.001
RV fractional area change, %	38 ± 11	38 ± 12	42 ± 10	37 ± 11	0.031
Systemic ventricular function, n (%)					0.067
Normal	303 (50)	60 (46)	62 (62)	157 (48)	
Mildly impaired	211 (35)	48 (36)	32 (32)	117 (36)	
Moderately impaired	69 (12)	17 (13)	5 (5)	42 (13)	
Severely impaired	18 (3)	7 (5)	1 (1)	10 (3)	
Laboratory results					
eGFR, mL/min/1.73 m^2	90 [82-90]	90 [83-90]	90 [85-90]	90 [81-90]	0.125
NT-proBNP, pmol/L	15.2 [6.8-33.3]	17.4 [8.3-43.1]	10.7 [6.1-19.6]	16.4 [6.9-36.7]	0.001
Hs-TnT, ng/L	4.3 [1.5-7.2]	7.7 [5.6-11.79]	1.50 [1.5-1.5]	4.4 [1.5-6.5]	< 0.001

ACHD, adults with congenital heart disease; eGFR, estimated glomerular filtration rate; hs-TnT, high-sensitivity troponin T; LV, left ventricular; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; REV, Réparation à l'Etage Ventriculaire; RV, right ventricular; TGA, transposition of the great arteries.

* Includes only patients with hs-TnT measurement at both baseline and 1 year.

† Beta-blocker (n = 90), ACE inhibitor (n = 89), diuretic (n = 71), antiarrhythmic (n = 53), angiotensin receptor blocker (n = 36).

‡ Left-sided volumes were not measured in patients with a systemic right ventricle, univentricular heart, PAH, or a poor acoustic window.

(symptomatic and recorded, or requiring treatment), thromboembolic events (ischemic cerebrovascular accident, pulmonary embolism, or myocardial infarction), or cardiac (re) interventions (surgical or percutaneous). The secondary study endpoint was composed of all-cause mortality or incident HF. All endpoint events were adjudicated by 2 investigators (L.W.G and J.W.R.H) without knowledge of any biomarker level. Patients who did not reach one of the endpoints were censored after January 1, 2018.

Statistical analysis

Continuous data are presented as mean ± standard deviation for normal distributed variables; otherwise the median and interquartile range (IQR) is presented. Normality of continuous variables was examined by visual inspection of histograms and Q-Q plots. Hs-TnT, estimated glomerular filtration rate (eGFR), and NT-proBNP distributions were skewed and 2log-transformed for further analyses. Cox proportional hazard regression was used to investigate the association between baseline hs-TnT and study endpoints. We presented crude hazard ratios (HRs) and HRs adjusted for a range of baseline characteristics including age, sex, congenital diagnosis (aortic stenosis, aortic coarctation, or arterial switch operation vs tetralogy of Fallot (ToF), Rastelli, systemic RV, univentricular heart, or pulmonary arterial hypertension), NYHA class (NYHA I vs NYHA II/III), any cardiac medication use (angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, diuretics, calcium blockers, or antiarrhythmic drugs), loss of sinus rhythm, systemic ventricular function (continuous as 0-3), eGFR, and NT-proBNP.

Table 2. Separate event components of the primary endpoint

Endpoint event	N (%)
Death	25 (4.2)
Heart failure	59 (9.9)
Arrhythmia	127 (21.3)
Hospitalization	181 (30.4)
Cardiac (re)intervention	138 (23.2)
Thromboembolic event	29 (4.9)

Patients were followed until the occurrence of the event of interest and were not censored at the time of another event type.

A linear mixed effect model was used to describe the temporal evolution of hs-TnT.[17] Only measurements that were taken before the occurrence of the study endpoints were used. Joint modelling (combining linear mixed effect models with Cox regression models) was applied to assess the association between individual hs-TnT trajectories and occurrence of study endpoints.[18] We report unadjusted HRs as well as HRs adjusted for baseline characteristics and for repeatedly measured NT-proBNP and eGFR.[19] Furthermore, the absolute change in hs-TnT during the first year was calculated (Δyear 1-year 0), and the Kaplan-Meier method was used to analyse survival according to subgroups based on this change. A subanalysis was performed based on normal vs elevated baseline NT-proBNP levels and also for 3 major diagnosis groups: aortic coarctation, aortic stenosis, and ToF.

Covariates were >99% complete, and missing data were therefore handled by imputation of the mean. SPSS version 24 and R statistical software version 3.5.1 (packages Survival, nlme, JMbayes) were used for the analyses. All statistical tests were 2-tailed, and *P*-values < 0.05 were considered statistically significant.

Results

Baseline characteristics and study endpoints

At least 1 hs-TnT measurement was available in 601 (99.8%) patients, with a median age of 32.5 (IQR, 24.7-41.2) years, 253 (42%) women, and 90% NYHA class I (Table 1). In 47 (8%) patients, hs-TnT was elevated at baseline. In 196 (33%) patients, the baseline hs-TnT level was below the limit of blank (<3.0 ng/L), and patients in whom hs-TnT levels remained undetectable at 1 year (n = 100) were on average younger, less often NYHA II/III, more often in sinus rhythm, and had a shorter QRS duration. Moreover, volumes of the left atrium and end diastolic left ventricle were lower and the right ventricular fractional area change was higher. Follow-up data were available in 596 (99.1%) patients. During a median of 5.8 (IQR, 5.3-6.3) years of follow-up, respectively, 229 (38.1%) and 69 (11.6%) unique patients reached the primary and secondary endpoint. Separate components of the endpoint events are shown in Table 2, and median baseline hs-TnT for achievement of each separate event of interest is given in Supplemental Table S1. The occurrence of the primary endpoint was associated with an older age, cardiac medication use, higher NYHA class, loss of sinus rhythm, worse systemic ventricular function, and higher median baseline hs-TnT (5.7 [IQR, 3.3-9.3] vs 3.8 [IQR, 1.5-6.1 ng/mL]) (Supplemental Table S2).

Baseline hs-TnT was significantly associated with the primary and secondary endpoint. After adjustment for baseline characteristics, hs-TnT remained significantly associated with the secondary endpoint. The association between hs-TnT and the study endpoints was no longer statistically significant after adjustment for NT-proBNP (Table 3).

Evolution of hs-TnT over time and its prognostic value

After omitting measurements that were taken after the occurrence of the study endpoints, 2123 and 2460 hs-TnT measurements were available for analysis concerning the primary and secondary endpoint, respectively. During the entire follow-up period, hs-TnT was on average systematically higher in patients who reached the primary endpoint than those who remained endpoint-free (Fig. 1). Hs-TnT tended to increase during follow-up both in patients with and without the primary endpoint, though a higher increase was observed in patients who reached the primary endpoint. Regarding the secondary endpoint, hs-TnT levels increased during follow-up, but the increase did not differ between patients with and without the endpoint (Fig. 2).

Based on higher HRs obtained from joint models, repeated hs-TnT was more strongly associated with the study endpoints compared with a single baseline hs-TnT measurement (Table 4). The associations between repeated hs-TnT and the study endpoints remained significant after adjustment for baseline NT-proBNP and baseline characteristics separately, but not when these data were combined. In a bimarker model, repeated NT-proBNP, not repeated hs-TnT, was associated with the study endpoints (Table 4).

A stratified analysis based on patients with normal or elevated baseline NT-proBNP showed the absence of prognostic value for a baseline hs-TnT in patients with normal NT-proBNP, while repeated hs-TnT was associated with the primary endpoint (Supplemental Fig. S2). However, in both

Table 3. Associations between baseline hs-TnT levels and endpoints

	Primary endpoint		Secondary endpoint	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Hs-TnT (unadjusted)	1.38 (1.25-1.52)	< 0.001	1.92 (1.65-2.24)	< 0.001
Adjusted for baseline characteristics*	1.12 (0.99-1.27)	0.061	1.51 (1.22-1.86)	< 0.001
Adjusted for baseline NT-proBNP	1.10 (0.99-1.22)	0.084	1.21 (1.00-1.48)	0.050
Adjusted for baseline characteristics* and baseline NT-proBNP	0.99 (0.87-1.12)	0.842	1.23 (0.97-1.56)	0.091

HRs are expressed per 2-fold higher hs-TnT level.

CI, confidence interval; HR, hazard ratio; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide.

*Age, sex, congenital diagnosis, NYHA class, any cardiac medication, loss of sinus rhythm, systemic ventricular function, estimated glomerular filtration rate.

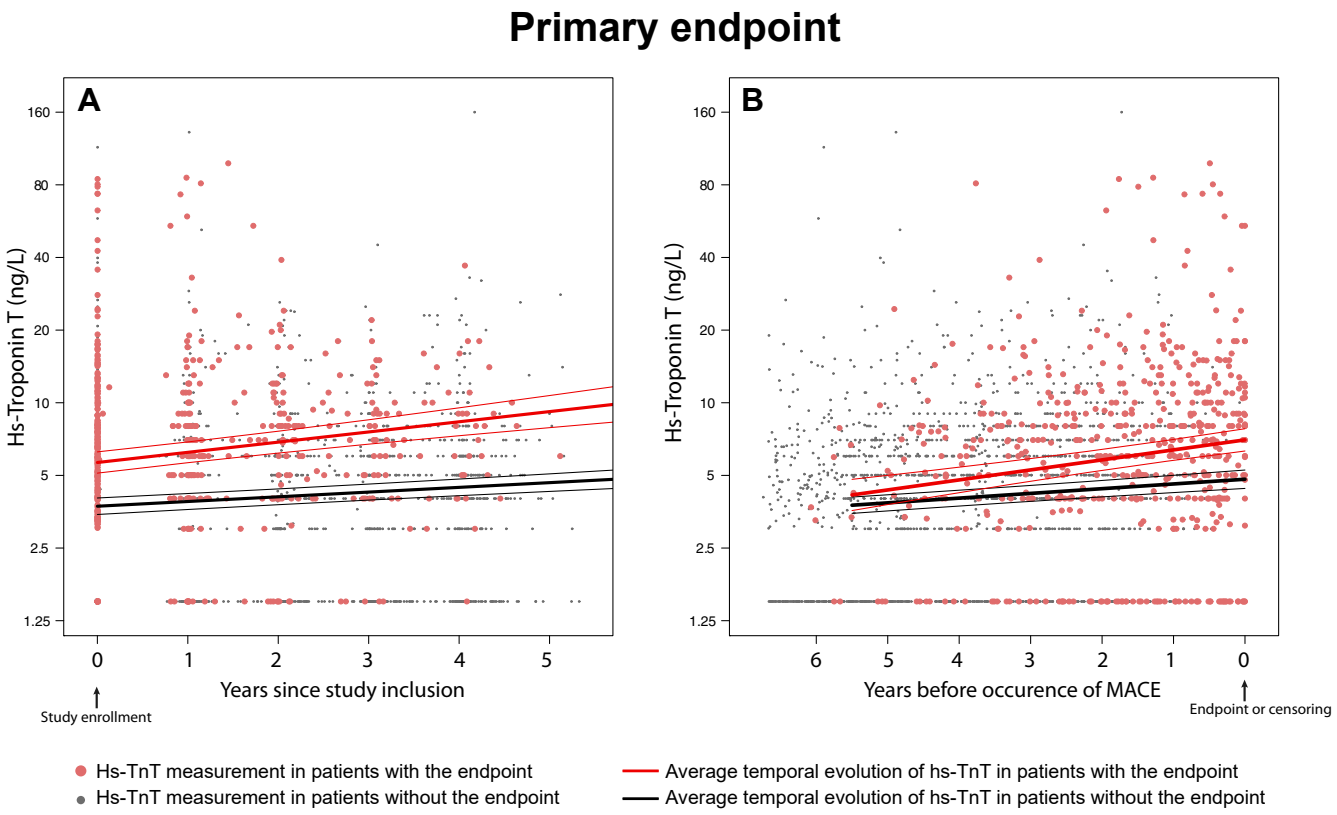

Figure 1. Average evolution of hs-TnT in patients with and without the primary endpoint. Measurements taken after the endpoint were discarded. Time point zero is denoted as the time of study inclusion **(A)** or as the time when the event took place (**B**). hs-TnT, high-sensitivity troponin T; MACE, major adverse cardiac event.

strata, repeated hs-TnT was no longer associated when adjusted for repeated NT-proBNP.

Hs-TnT yielded a stronger association with the endpoints in patients with ToF and aortic coarctation, and a less strong association in patients with aortic stenosis, when compared with estimates from the entire cohort (Supplemental Figure S1).

Hs-TnT change during the first year

In patients with stable, undetectable hs-TnT levels during the first year of follow-up, the event-free survival was significantly higher, compared with patients who had changing hs-TnT levels during the first year (Fig. 3). Of note, interpretation of absolute decreases or increases of hs-TnT in this analysis should be done with caution because of regression towards the mean.[20]

Discussion

Clinically stable patients with ACHD who had an adverse cardiac event within 6 years after inclusion had systematically higher hs-TnT at baseline and during follow-up, and values tended to increase before the occurrence of an adverse cardiac event. This seems to reveal a process of ongoing and enhanced cardiomyocyte loss in mostly asymptomatic patients with ACHD. Particularly undetectable, stable hs-TnT levels (<3 ng/L) were present in patients with a more favourable prognosis. Although repeated hs-TnT yielded prognostic value for adverse cardiac events independently of a single baseline NT-proBNP measurement, repeatedly measured hs-TnT did not yield prognostic value independent of repeated NT-proBNP measurements.

Value of hs-TnT as prognostic biomarker

The prognostic value of hs-TnT was described for the first time in this same cohort of patients with ACHD.[5,12] Meanwhile, several other studies have confirmed the prognostic relevance of hs-TnT in some ACHD diagnoses.[11,21-23] Rybicka et al.[11] investigated hs-TnT levels in 131 stable patients with ACHD and found an association with systemic ventricular dysfunction. In adults with congenitally corrected transposition of the great arteries, hs-TnT was associated with systemic right ventricular function and was even superior to NT-proBNP in detecting systemic ventricular dysfunction.[22] Moreover, hs-TnT was predictive of adverse cardiac events in these patients.[21] These studies indicate that hs-TnT release and its prognostic value are not restricted to patients with systemic left ventricles, or certain types of ACHD. Subgroup analysis in our study further supports this; baseline hs-TnT yields prognostic value in adults with ToF, aortic coarctation, or aortic stenosis. Especially in ToF, the association with death or HF for both a single and repeated hs-TnT measurements was strong.

To the best of our knowledge, this is the first study that investigated repeated hs-TnT measurements in patients with

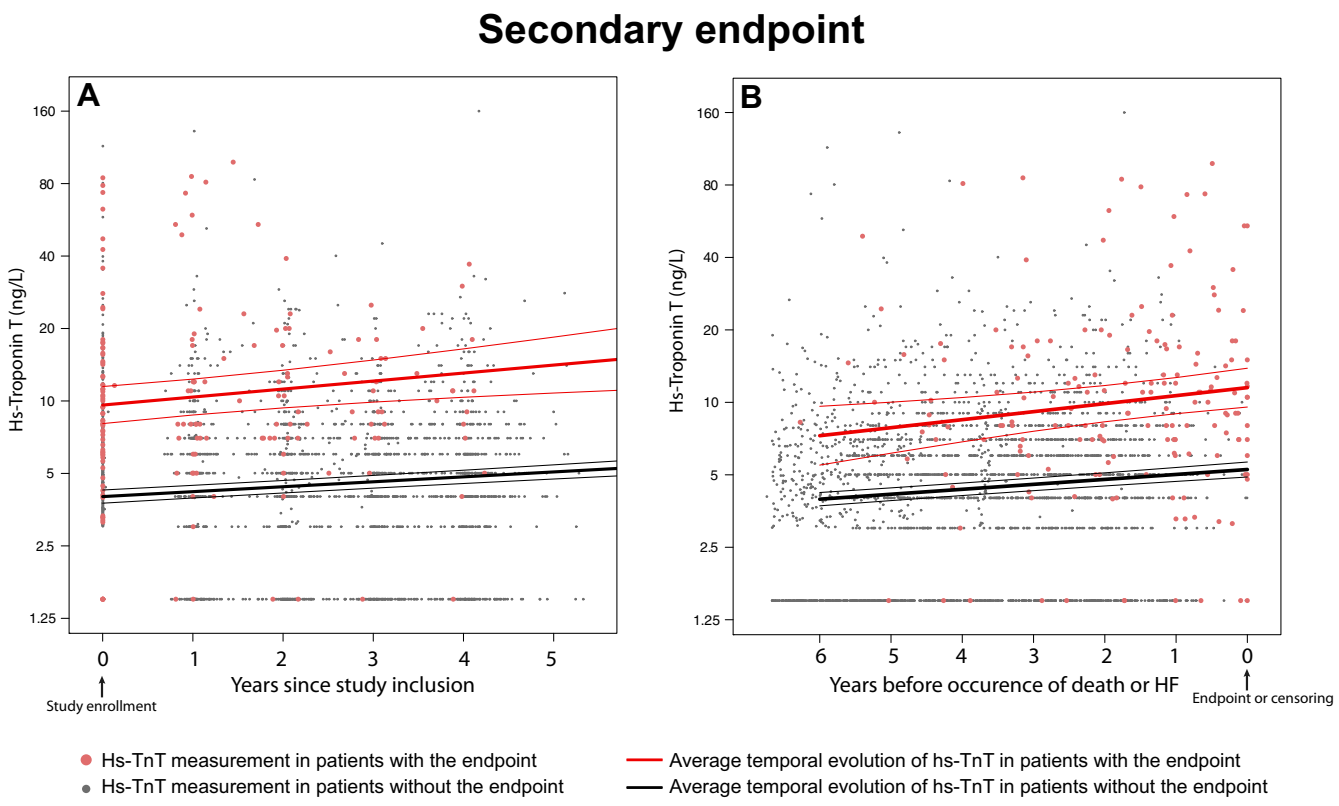

Figure 2. Average evolution of hs-TnT in patients with and without the secondary endpoint. Measurements taken after the endpoint were discarded. Time point zero is denoted as the time of study inclusion (**A**) or as the time when the event took place (**B**). HF, heart failure; hs-TnT, high-sensitivity troponin T.

ACHD. Although data in patients with ACHD are limited, hs-TnT has more extensively been investigated in patients with chronic HF.[24] The relative change between 2 hs-TnT measurements within a 4-month time period was associated with the risk of adverse cardiovascular events in patients with chronic HF.[14] In our study, the absolute change in hs-TnT in the first year was not associated with outcomes. This is most likely due to regression towards the mean; measured values of a random variable fluctuate around a true mean, and extreme values therefore tend to regress towards the mean, becoming less extreme.[20] The median hs-TnT level was highest in patients with a decrease in hs-TnT in the first year, supporting the phenomena of regression towards the mean and subsequently the lack of prognostic value found for the absolute hs-TnT change. Joint modelling, as used in this study, solves this problem by adjusting for the within-subject variation.[18] Temporal hs-TnT patterns investigated in chronic HF using joint modelling showed that repeated hs-TnT was associated with adverse cardiovascular events, but not when adjusted for NT-proBNP and C-reactive protein trajectories.[25] Results of our study are in line with results found in patients with chronic HF,[14,25] suggesting that the role of hs-TnT in the pathophysiology of HF in patients with chronic HF and those with ACHD may be quite similar.

Understanding troponin T release in ACHD

The hs-TnT increase over time found in this study may indicate the existence of a continuous slow troponin T release from the myocardium, which might reflect ongoing subclinical loss of cardiomyocytes. If we assume that the loss of cardiomyocytes is the result of increased wall stress due to HF progression, the hs-TnT increase will be preceded by an increase in NT-proBNP, as NT-proBNP is secreted in response to increased cardiac wall stress.[9] This could explain the prognostic value of serial NT-proBNP independent of serial hs-TnT and not vice versa. In patients with low baseline NT-proBNP, a steeper hs-TnT increase was observed than in patients with elevated NT-proBNP. However, no independent value for hs-TnT was found, supporting the hypothesis that an increase in hs-TnT is preceded by an increasing NT-proBNP.

Besides myocardial cell death, other mechanisms including myocardial and subendocardial ischemia, inflammation, and infiltrative processes may contribute to release of troponin T.[13] This could explain why hs-TnT showed an association with any adverse cardiac event and not only HF. Contrarily, the absence of troponin T release, reflected by patients with undetectable hs-TnT levels, was associated with a low risk of adverse cardiac events. These patients were also characterized by more favourable baseline clinical characteristics. The absence of troponin T release therefore seems to exclude processes provoking cardiac deterioration and may be helpful to detect low-risk patients.

Hs-TnT levels also increase with a worsening renal function, by diminished renal clearance of troponin T.[26,27] Although patients with severe renal dysfunction were not included in this study, hs-TnT levels could have been

Table 4. Associations between repeated hs-TnT levels and endpoints

	Primary endpoint		Secondary endpoint	
	HR (95% CI)	*P*-value	HR (95%CI)	*P*-value
Repeated hs-TnT (unadjusted)	1.62 (1.44-1.81)	< 0.001	2.58 (2.13-3.14)	< 0.001
Adjusted for baseline characteristics*	1.26 (1.09-1.47)	0.004	1.73 (1.31-2.28)	< 0.001
Adjusted for baseline NT-proBNP	1.21 (1.06-1.38)	0.002	1.34 (1.05-1.72)	0.016
Adjusted for baseline characteristics and baseline NT-proBNP	1.07 (0.90-1.26)	0.436	1.31 (0.96-1.80)	0.086
Repeated hs-TnT and NT-proBNP				
Repeated hs-TnT	1.12 (0.98-1.30)	0.102	1.19 (0.89-1.58)	0.262
Repeated NT-proBNP	1.53 (1.38-1.70)	< 0.001	2.42 (1.93-3.04)	< 0.001
Repeated hs-TnT and eGFR				
Repeated hs-TnT	1.50 (1.32-1.70)	< 0.001	2.49 (1.95-3.16)	< 0.001
Repeated eGFR	0.59 (0.39-0.94)	0.028	0.69 (0.39-1.38)	0.240

HRs are expressed per 2-fold higher biomarker level, at any point in time during follow-up.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide.

*Age, sex, congenital diagnosis, NYHA, any cardiac medication, loss of sinus rhythm, systemic ventricular function, eGFR.

influenced by worsening renal function during follow-up. Nevertheless, serial hs-TnT measurements remained predictive of both endpoints, independent of serial eGFR. Therefore, it is likely that the hs-TnT increase is the result of cardiomyocyte loss rather than the effect of a decreased renal clearance of hs-TnT.

Clinical perspective

A single hs-TnT measurement can be used as prognosticator in patients with ACHD besides NT-proBNP to further discriminate between high- and low-risk patients.[5] In addition, this study showed that serially measuring hs-TnT can enhance precision in estimating prognosis in addition to a single measurement. Particularly, stable, undetectable hs-TnT levels seem to identify low-risk patients whom can be reassured. Nonetheless, repeated hs-TnT may not be the biomarker of first choice; repeatedly measuring NT-proBNP for monitoring and risk assessment in clinically stable patients with ACHD over time seems more valuable. However, clinicians should be aware of the biological and analytical variability of biomarkers[28] and the subsequent effect of regression towards the mean, when interpreting repeatedly measured biomarkers.

As previously described, elevated levels of hs-TnT are not uncommon in asymptomatic patients with ACHD.[12] With the ageing ACHD population,[3] coronary artery disease is likely to become more prevalent and a bigger threat to these

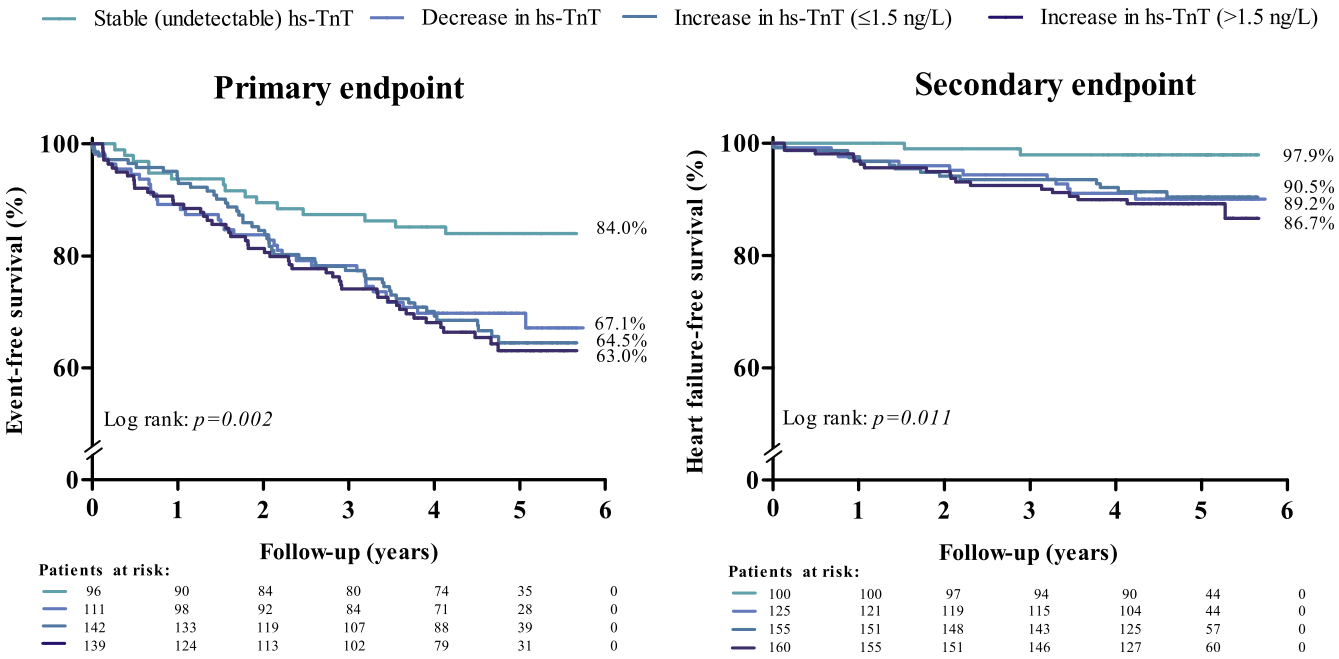

Figure 3. Event-free and heart failure-free survival according to the change in hs-TnT in the first year (Δ year 1-year 0). Log-rank test represents comparison of survival in stable patients vs the other groups. Of note, a subset of the data was used in this analysis; only patients with both hs-TnT measurement at baseline and at 1 year could be included (other hs-TnT measurements were discarded), and the time to event was recalculated from year 1 onwards (patients had to be alive at $t = 1$ year). hs-TnT, high-sensitivity troponin T.

patients. In the management of coronary artery disease in patients with ACHD, it should be taken into account that hs-TnT levels are higher in these patients and increase over time.

Limitations

Hs-TnT was measured in thawed serum samples, which had been stored by −80°C. Hs-TnT is known to be stable up to at least 1 year at −80°C,[29] whereas samples in our study had been stored >1 year. However, we did not find a correlation between storage time within each follow-up moment and hs-TnT levels. Therefore, it is unlikely that levels of hs-TnT have been affected by storage time.

We measured hs-TnT annually, and because of the relatively long time interval between 2 measurements, the time in between biomarker measurement and the onset of a cardiovascular event differs in each case. The last measurement taken before the event may therefore differ from the actual biomarker level prior or at the moment of the actual event. This may also have prevented us to notice more pronounced increases in hs-TnT in anticipation to events. More frequent blood sampling than performed in our study would be needed to more precisely investigate this.

This study consisted of patients with ACHD with different underlying congenital heart defects. Unfortunately, we were restricted by the sample size to perform subgroup analyses for each diagnosis.

Conclusions

In clinically stable patients with ACHD, hs-TnT levels modestly increased over time, indicating loss of cardiomyocytes that might reflect subclinical as well as clinical progression of HF in these patients. Particularly, stable, undetectable hs-TnT levels may identify low-risk patients. However, the additive prognostic value of serial hs-TnT measurements beyond serial NT-proBNP measurements seems limited. Whether hs-TnT could aid guidance of follow-up strategies in specific ACHD diagnoses such as Fontan will require greater sample sizes and needs to be examined in future research.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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