Usefulness of High-Sensitivity Cardiac Troponin T to Predict Long-Term Outcome in Patients with Hypertrophic Cardiomyopathy

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Usefulness of High-Sensitivity Cardiac Troponin T to Predict Long-Term Outcome in Patients with Hypertrophic Cardiomyopathy

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Since the first report of an association between cardiac troponin (cTn) and adverse outcome in hypertrophic cardiomyopathy (HD), there is a paucity in confirmative data. We performed a prospective, prespecified 5-year follow-up cohort study of 135 HC patients who participated in a national multicenter project and underwent clinical evaluation, MRI (cine, LGE and T2-weighted imaging) and biomarker assessment (high-sensitivity cTnT (hs-cTnT), N-terminal pro-B-type natriuretic peptide, soluble tumorgenicity suppressor-2, Galectin-3, Growth differentiation factor-15, C-terminal Propeptide of Type I Collagen (CICP)). An elevated hs-cTnT concentration was defined as ≥14ng/L. Follow-up was systematically performed for the primary endpoint: a composite of sudden cardiac death, heart failure related death, stroke-related death, heart failure hospitalization, hospitalization for stroke, spontaneous sustained ventricular tachycardia (VT) or appropriate ICD discharge, and progression to NYHA class III-IV. Elevated hs-cTnT was present in 33 of 135 (24%) HC patients. During a median follow-up of 5.0 years (IQR: 4.9-5.1) 18 patients reached the primary endpoint. Using Cox regression analysis, elevated hs-cTnT was univariately associated with the primary endpoint (HR: 3.4 (95%CI: 1.4-8.7, p=0.009). Also female sex, previous syncope, previous non-sustained VT, reduced LV ejection fraction (<50%) and CICP were associated with the primary endpoint. In multivariable analysis, elevated hs-cTnT remained independently associated with outcome (aHR: 4.7 (95%CI: 1.8-12.6, p = 0.002). In conclusion, this 5-year follow-up study is the first to prospectively confirm the association of elevated hs-cTnT and adverse outcomes. In addition to established clinical variables, cTn seems the biomarker of interest to further improve risk prediction in HC, which should be evaluated in larger prospective registries. **(Am J Cardiol 2021;152:120−124)**

Hypertrophic cardiomyopathy (HC) is clinically characterized by a very heterogeneous disease presentation ranging from asymptomatic patients with sudden cardiac death (SCD) to progressive heart failure (HF).[1,2] Despite ongoing initiatives to improve risk stratification for SCD, there is limited information on how to discriminate between low and high risk HC patients with regard to the broader spectrum of clinical endpoints.[3] Ischemia as a result of imbalance between increased myocardial oxygen demand in the presence of hypertrophy, and reduced myocardial oxygen supply due to microvascular disease importantly contributes to the clinical presentation of HC.[1,2] In that regard, it is surprising that the role of cardiac troponin (cTn) in HC patients has not been extensively studied.[4-7] Elevated cTn is a common finding and associated with adverse disease characteristics, such as wall thickness and late gadolinium enhancement (LGE).[4-8] In 2013, the first report was published that demonstrated an association between elevated cTnT, assessed with a high-sensitivity assay (hs-cTnT) and adverse long-term outcome in HC.[6] Ever since, however, there is a paucity of confirmatory prospective data.[3,8-10] Therefore, we aimed to validate the association between elevated hs-cTnT and adverse outcomes in a prospective HC cohort with 5 years of clinical follow-up.

Methods

From a Dutch HC multicenter study on biomarkers, MRI and exercise, we selected HC patients of whom baseline hs-cTnT concentration was available.[11] In short, adult HC patients from different hospitals were enrolled at 2 outpatient clinics (Radboud University Medical Center, Nijmegen and Albert Schweitzer Hospital, Dordrecht,

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The Netherlands) between 2008 and 2014. Patients had to fulfill the diagnostic criteria for HC according to the prevailing guidelines and had no history of coronary artery disease or septal reduction therapy. The study complies with the Declaration of Helsinki. The protocol was approved by local ethical committees and conducted accordingly. All participants provided written informed consent.

Blood samples were processed within 60 minutes after phlebotomy, and stored at −80˚C until analysis. Serum samples were used for hs-cTnT. An elevated hs-cTnT concentration was defined as a concentration ≥14ng/L. Our biomarker panel also included: N-terminal-pro-B-type-Natriuretic Peptide, Galectin-3, soluble Tumorigenicity Suppressor2, Growth Differentation Factor-15 and C-terminal Propeptide of Type I Collagen (CICP (Appendix for detailed description of the assays).[5] Variability and performance in healthy controls and patients with heart failure have been published.[12]

CMR imaging with cine, LGE and T2-weighted sequences was performed on 1.5T CMR systems (Philips Achieva (Philips Healthcare, Best, The Netherlands) or (Siemens Avanto (Siemens Health Care, Erlangen, Germany)) according to local imaging protocols, as previously described.[4] Images were analyzed with commercially available software (QMass 7.5, Medis, Leiden, The Netherlands) by three observers unaware of the subjects' clinical information. The extent of LGE was scored visually according to a semi-quantitative score.[4]

Our primary endpoint was a composite of SCD, HF −related death, stroke-related death, HF hospitalization, hospitalization for stroke, spontaneous sustained ventricular tachycardia (VT) or appropriate implantable cardioverter-defibrillator (ICD) discharge, and progression to New York Heart Association (NYHA) functional class III or IV status.[6] As a secondary aim of the previously mentioned multicenter project, prespecified clinical follow-up was systematically performed with telephone follow-up at two and five years. In case the patient reported a potential endpoint, the patients' medical file was reviewed for event adjudication, which was performed by two investigators based on consensus (FG and EC); in case of non-consensus a third investigator provided final adjudication (MK).

Continuous variables are presented as means (± standard deviations) or medians (interquartile ranges (IQR)) and were compared between patients with and without elevated hs-cTnT using a Student's t or Mann-Whitney U test, whichever appropriate. Dichotomous variables were compared using a Chi-square or Fisher exact test, whichever appropriate. As our primary analysis, univariate and multivariate Cox regression survival analyses were performed for the association between elevated hs-cTnT and the first occurrence of the primary endpoint. In addition, analyses were performed for hs-cTnT as a continuous variable. Variables significantly associated with the primary endpoint in univariate analysis were selected for stepwise forward multivariate analysis (p-in: <0.05; p-out: >0.10). A p-value of <0.05 was considered significant (two-sided). Statistical analysis was performed with SPSS Statistics 25 (IBM Corp, Armonk, NY, USA).

Results

For the current analysis, the study population comprised 135 HC patients, in 6 no hs-cTnT concentration was available. Baseline characteristics are stratified to with (n = 33) or without elevated cTnT (n = 102) in Table 1. Median follow-up duration was 5.0 years (IQR: 4.9-5.1) with none lost-to-follow-up. During follow-up 18 patients met the primary endpoint: SCD (n=1), HF-related death (n = 1), stroke-related death (n = 2), HF hospitalization (n = 5), hospitalization for stroke (n = 0); spontaneous sustained VT or appropriate ICD discharge (n = 3), and progression to NYHA functional class III or IV status (n = 9).

In univariate analysis, patients with an elevated hs-cTnT concentration had a more than threefold and significantly higher risk of the primary endpoint (hazard ratio (HR): 3.4 (95%CI: 1.4-8.7, p = 0.009) (Table 2). Other significant univariate predictors were female sex, previous syncope, previous non-sustained VT on Holter monitoring, a reduced left ventricular ejection fraction <50% on echocardiography and serum CICP concentration. In multivariate analysis, elevated hs-cTnT remained independently associated with the primary endpoint; together with non-sustained VT on Holter monitoring (Figure 1 and Table 2). Hs-cTnT as a continuous variable was significantly associated with the primary endpoint in univariate analysis (HR: 1.031(95%CI: 1.004-1.059, p = 0.03), whereas in multivariate analysis the association was no longer significant (p = 0.096); and female sex and non-sustained VT on Holter monitoring were independently associated with outcome (adjusted HRs: 3.1 (95%CI: 1.1-9.0, p = 0.04) and 4.6 (95%CI: 1.7-12.2, p = 0.003), respectively). In an ancillary multivariate analysis restricted to the conventional 5 risk factors for SCD in HC, hs-cTnT remained significantly associated with the primary endpoint (adjusted HR: 1.03 (95%CI: 1.002-1.07, p = 0.04).

Discussion

The present 5-year follow-up study on a well-defined population of participants in a national, multicenter HC study, is the first to reproduce the independent association of an elevated hs-cTnT concentration with adverse clinical outcome in HC. Kubo et al. demonstrated this association for the first time in 2013,[6] and our results underscore the need for more follow-up data on cTn in larger prospective HC registries to investigate the potential for improvement of SCD risk prediction models, but also for prediction of HF-related morbidity and mortality.[3]

Historically, risk prediction has mostly focused on SCD, which is probably the most devastating adverse event for HC patients and their families. Although SCD risk prediction models and the advent of the ICD improved clinical outcome, debate remains on how to optimize current SCD risk stratification schemes. Perhaps even more important, it has become increasingly evident that HC patients suffer from substantial morbidity and mortality related to HF and stroke, for which no specific risk prediction tool is available.[13,14] The mainstay of risk prediction in HC have been the conventional clinical SCD risk factors based on history taking, Holter monitoring and echocardiography.

Table 1
Baseline characteristics

Variable	Total (n = 135)	Elevated hs-cTnT		p
		Yes (n = 33)	No (n = 102)	
Age at participation (years)	54 ± 14	54 ± 16	54 ± 14	0.96
Men	79 (59%)	20 (61%)	59 (58%)	0.78
Age at diagnosis (years)	47 ± 16	45 ± 16	47 ± 16	0.47
Pathogenic mutation present	72 (59%)	16 (53%)	56 (61%)	0.52
Atrial fibrillation	21 (16%)	8 (24%)	13 (13%)	0.11
Hypertension	48 (36%)	14 (42%)	34 (33%)	0.34
Current smoker	23 (17%)	5 (15%)	18 (18%)	0.74
Dyslipidaemia	30 (22%)	6 (18%)	24 (24%)	0.52
Diabetes	7 (5%)	3 (9%)	4 (4%)	0.36
Recent creatinine (μmol/l)	83 ± 16	90 ± 20	81 ± 14	0.008
Systolic blood pressure (mmHg)	129 ± 22	127 ± 18	129 ± 23	0.61
Heart rate (beats/minute)	74 ± 13	78 ± 14	72 ± 12	0.01
Framingham 10-year heart risk (%)	12 (5-25)	14 (5-28)	12 (5-23)	0.65
History of aborted cardiac arrest	3 (2%)	1 (3%)	2 (2%)	0.57
Family history of SCD	18 (13%)	4 (12%)	14 (14%)	1.0
Previous syncope	5 (4%)	3 (9%)	2 (2%)	0.09
History of non-sustained VT	25 (21%)	5 (18%)	20 (21%)	0.69
Abnormal BP response	18 (14%)	6 (19%)	12 (12%)	0.38
Maximal wall thickness ≥30mm	3 (2%)	1 (3%)	2 (2%)	0.57
Symptoms				
Chest pain	22 (16%)	8 (24%)	14 (14%)	0.16
Dyspnea (NYHA class ≥ II)	60 (44%)	23 (70%)	37 (36%)	0.001
Echocardiography				
LV outflow tract gradient at rest ≥30mmHg	20 (15%)	4 (12%)	16 (16%)	0.78
Left atrial diameter (mm)	43 (39-49)	45 (42-53)	42 (39-48)	0.02
Magnetic resonance imaging				
Maximal wall thickness (mm)	17 (14-21)	20 (18-23)	16 (13-20)	0.001
LV mass indexed to BSA (g/m^2)	63 (52-84)	80 (63-115)	60 (51-74)	<0.001
LV ejection fraction	60 ± 7	57 ± 7	60 ± 7	0.04
LGE presence	71 (62%)	23 (85%)	48 (55%)	0.005
LGE extent (% of LV mass)	3 (0-10)	10 (1-18)	1 (0-7)	<0.001
High T2-weighted signal intensity	29 (27%)	16 (59%)	13 (17%)	<0.001
Biomarker panel				
NT-proBNP (ng/l)	138 (76-368)	302 (130-573)	116 (61-250)	0.001
sST2 (ng/ml)	23 (19-32)	26 (21-31)	22 (18-33)	0.17
GDF-15 (ng/l)	800 (481-1007)	967 (573-1322)	706 (475-961)	0.03
Gal-3 (ng/ml)	17 (14-20)	18 (14-21)	16 (13-19)	0.15
CICP (ng/ml)	126 (105-157)	130 (108-167)	125 (100-156)	0.23
Therapy				
Beta-blocker	64 (47%)	18 (55%)	46 (45%)	0.35
Calciumantagonist	20 (15%)	5 (15%)	15 (15%)	1.0

Data are presented as means ± standard deviations, medians (interquartile ranges) or numbers (percentages). Hs-cTnT = cardiac troponin T assessed with a high-sensitivity assay; BP = Blood pressure; LGE = Late gadolinium enhancement; LV = Left ventricle; LVMI = LV mass indexed to body surface area; NYHA = New York Heart Association; SCD = Sudden cardiac death; VT Ventricular tachycardia.

Possible modalities to improve risk stratification are CMR imaging techniques such as LGE, T1- and T2-weighted mapping techniques, but also easily available and patient-friendly serum biomarkers may be attractive.[3,4,11]

In this report, we confirm the independent association of an elevated hs-cTnT with long-term adverse outcome in HC,[6] and the majority of events was related to HF rather than to ventricular arrhythmias. For hs-cTnT as a continuous variable, we also demonstrated a significant association with clinical outcome in univariate analysis, while in multivariate analysis statistical significance was no longer present (p = 0.096), which might be related to limited cohort size and event rate. Yet, the ancillary analysis with hs-cTnT added to the 5 conventional risk factors used in daily practice, shows its promising potential. Acknowledging our cohort size and anticipated event rate, we used a composite of both arrhythmic and HF endpoints, similar to Kubo et al.[6] The composition of observed events in our study is in line with previous reports, which is also true for ventricular arrhythmias in particular.[6,9,10] Our cohort was at relatively low SCD risk (e.g. HC-SCD 5-year risk score was 2.5%), with ventricular arrythmias in only 3% of our patients. Kubo et al. reported this in only 8 out of 181 (4%) patients.[6] Similar to that report, we did not observe a significant association between hs-cTnT and ventricular arrythmias, as single outcome parameter. Apart from statistical

Table 2
Cox regression survival analysis for elevated hs-cTnT and the primary endpoint

	Hazard ratio	95% Confidence interval	p
Elevated hs-cTnT (univariate)	3.4	1.4-8.7	0.009
Independent predictors	**Adjusted hazard ratio**	**95% Confidence interval**	**p**
Elevated hs-cTnT	4.7	1.8-12.6	0.002
Previous NSVT	5.9	2.2-16.2	0.001

Data are presented as means ± standard deviations or medians (interquartile ranges). Female sex, previous syncope, a reduced left ventricular ejection fraction <50% on echocardiography and serum CICP concentration were only univariately and not independently associated with the primary endpoint. Hs-cTnT = cardiac troponin T assessed with a high-sensitivity assay; NSVT = Non-sustained ventricular tachycardia.

considerations, it may also be that cTn better predicts HF outcomes than arrhythmic events, which has previously been demonstrated for the general population as well.[15]

Importantly, our data stress the need for more prospective data on cTn in HC during long-term follow-up. In light of the above, the results of the HC Registry by Kramer et al. are highly awaited.[3] This large cohort study will be the best available data set to evaluate the role of clinical characteristics, serum biomarkers as well as CMR imaging variables in the prediction of arrhythmic and HF endpoints. Regarding the clinical variables, our data confirm associations with outcome for syncope, non-sustained VT on Holter monitoring as well as female sex and reduced left ventricular systolic function on echocardiography. On the other hand, other variables such as LV outflow tract gradient and left atrial size were not significantly associated with outcome in our cohort. As the primary focus of our project was on biomarkers, MRI and exercise, collection of these data was protocol driven, and echocardiography was not.[11] We acknowledge that echocardiographic parameters on diastolic function could be promising for event prediction. In that regard, in future studies it may be considered to include a protocol-driven echocardiographic work-up to assess the potential of these variables. As exploratory analyses, we did consider other serum biomarkers and CMR imaging variables, but none were independently predictive of outcome. We would like to underscore that the absence of an association between these variables (and LGE in particular) and outcome may be merely an issue of lack of statistical power. The limited event numbers are an important restriction to more substantiated analyses. Moreover, at the time of our study design the promising CMR mapping techniques were not yet available. An alternative explanation may be that cTn and CMR imaging markers have different predictive properties. Hypothetically, LGE and other CMR imaging markers may be especially predictive for SCD, while cTn may be more indicative of the risk of HF events. For cTn larger datasets are required to study whether other

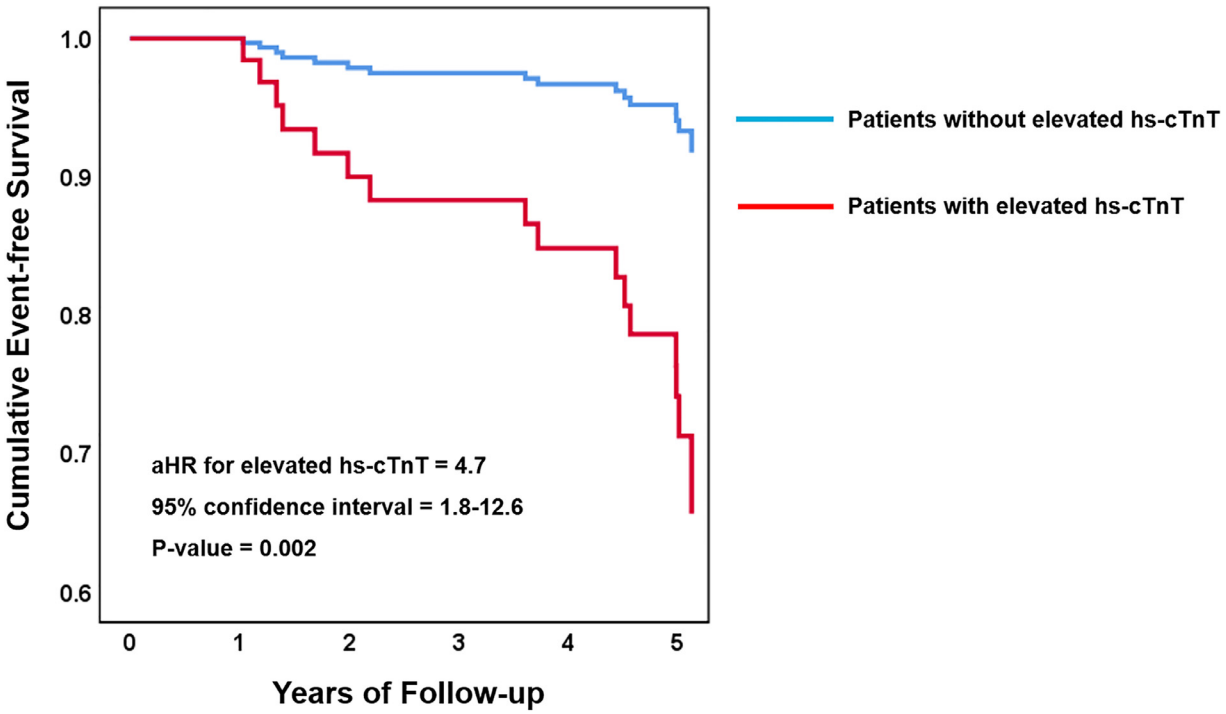

Figure 1. Multivariate Cox regression survival curve for elevated hs-cTnT for the primary endpoint.
Figure 1 demonstrates that HC patients with an elevated hs-cTnT at baseline have a more than 4-fold risk of the composite primary outcome during a 5-year follow-up duration. aHR adjusted hazard ratio; hs-cTnT cardiac troponin T assessed with a high-sensitivity assay.

cut-offs than the 99th percentile may aid in the prediction of adverse events, and HF events in particular.

In conclusion, after more than 5 years after the initial publication on the prognostic impact of cTn in patients with HC, we herein provide the first corroborative evidence that cTn is associated with adverse outcome in these patients. As a biomarker of myocyte injury, cTn may therefore perhaps serve as a future prognostic tool to identify HC-related morbidity such as incident HF.

Author Credit

Frank Gommans: data curation, formal analysis, investigation, writing original draft

Etienne Cramer: conceptualization, data curation, formal analysis, writing review & editing

Michael Fouraux: formal analysis, investigation, resources, writing review & editing

Sanne Heijmans: data curation, formal analysis, investigation

Michelle Michels: resources, formal analysis, writing review & editing

Janneke Timmermans: supervision, writing review and editing

Freek Verheugt: conceptualization, funding acquisition, supervision, writing review & editing

Rudolf de Boer: resources, formal analysis, methodology, writing review & editing

Marcel Kofflard: conceptualization, funding acquisition, supervision, writing review & editing

Marc Brouwer: conceptualization, funding acquisition, investigation, supervision, writing review & editing

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.04.040.

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