Relation of Highly Sensitive Cardiac Troponin T in Hypertrophic Cardiomyopathy to Left Ventricular Mass and Cardiovascular Risk

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Elevated cardiac troponin can be seen in patients with left ventricular (LV) hypertrophy and in asymptomatic subjects with a high a priori risk of cardiovascular disease (CVD). In hypertrophic cardiomyopathy (HC) troponin can be detected as well, but little is known about the contribution of LV mass, on the one hand, and the long-term risk of CVD, on the other. In an observational single-center study of 62 patients with HC, without a history of CVD, we assessed the Framingham Heart 10-year risk score (FH_{10yrs}), LV mass index (LVMI) using magnetic resonance imaging, and highly sensitive cardiac troponin T (hs-cTnT). Hs-cTnT (>3 ng/L) was detectable in 74% of patients (46 of 62). Hs-cTnT was elevated in 26% (16 of 62) of patients (ninety-ninth percentile reference limit of 14 ng/L or more). From 3 to 14 ng/L, patients were older, more often had hypertension, and the FH_{10yrs} was higher. Hs-cTnT correlated positively with LVMI ($p < 0.001$) and maximal wall thickness ($p < 0.001$). In addition, LVMI and hypertension were independently associated with increasing hs-cTnT concentrations in linear regression. Using multivariate binary logistic regression, both LVMI and FH_{10yrs} were independently associated with detectable hs-cTnT levels. In contrast, only LVMI was associated with elevated hs-cTnT levels. In conclusion, hs-cTnT was detectable in 3 quarters and elevated in a quarter of our patients with HC. Although detectable hs-cTnT is associated with both LV mass and CVD risk, elevated hs-cTnT relates to LV mass only. This indicates that hypertrophy more than the risk of CVD seems the most important drive for hs-cTnT to occur in these patients. **© 2014 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2014;113:1240−1245)**

Elevated cardiac troponin has been associated with left ventricular (LV) mass and the a priori risk of cardiovascular disease (CVD) in asymptomatic individuals.[1] In patients with hypertrophic cardiomyopathy (HC), the few reports available demonstrate an association between cardiac troponin and increased LV wall thickness, LV dysfunction, and late gadolinium enhancement (LGE) with magnetic resonance imaging (MRI).[2−6] However, the contribution of mass and the a priori long-term risk of CVD have never been studied. Moreover, previous studies did not address the range of detectable troponin concentrations below the upper reference limit of normal. In the present report, we describe the rate of detectable and elevated troponin (ninety-ninth percentile or more) in a well-defined population of patients with clinical HC, using a highly sensitive assay. Subsequently, we studied the association between troponin and the aforementioned variables, that is, LV cardiac mass measurements—as determined with MRI—and the Framingham Heart 10-year risk score (FH_{10yrs}) as a measure of the predicted CVD risk.[7]

Methods

All participants were patients of a large outpatient clinic that is specialized in HC and performs mutation screening, repeated echocardiographic imaging, and clinical follow-up on a routine basis. Patients with 2-dimensional echocardiographic evidence of LV hypertrophy (maximal wall thickness ≥15 mm, or ≥13 mm in case of an identifying gene mutation and/or compelling factors associated with HC) without another cardiac or systemic cause at the time of HC diagnosis were potential candidates to participate in the present study.[8] For each subject, the HC diagnosis was carefully reviewed. In case of a discrepancy between the treating physician and the investigators, a third opinion of an independent reviewer was decisive. Subjects with known coronary artery disease (previous myocardial infarction, >50% stenosis on coronary angiogram, previous percutaneous coronary intervention, and previous coronary artery bypass grafting), previous stroke, peripheral arterial disease, significant valvular heart disease, previous septal myectomy, or septal alcohol ablation were excluded (Figure 1).

Eligible patients without contraindications for MRI (renal impairment defined as Modification of Diet in Renal Disease estimated glomerular filtration rate <30 ml/min, an implantable cardiac device, or claustrophobia) were invited to the hospital to undergo MRI according to a standard

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See page 1245 for disclosure information.

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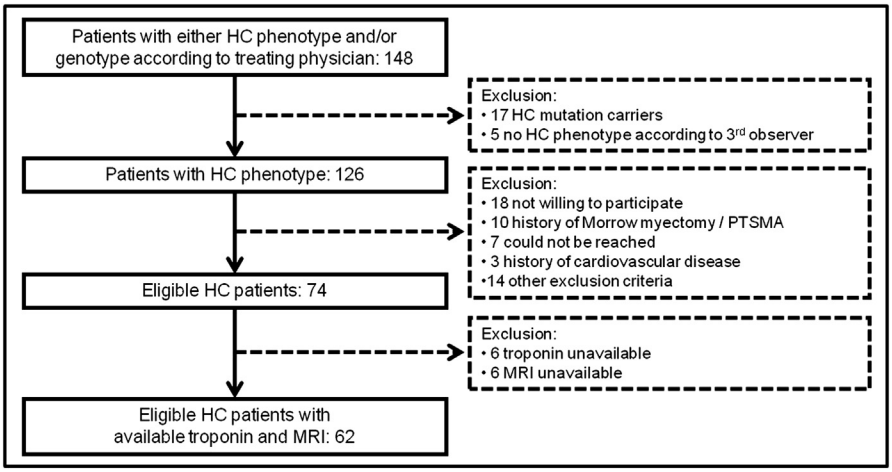

Figure 1. Flow diagram. PTSMA = percutaneous transluminal septal myocardial ablation.

Table 1
Baseline characteristics according to three highly sensitive cardiac troponin T groups of patients with hypertrophic cardiomyopathy

Variable	Total (n = 62)	Undetectable (≤3 ng/L, n = 16)	Detectable Not Elevated (>3 and <14 ng/L, n = 30)	Elevated (≥14 ng/L, n = 16)	p Value*
Age (yrs)	54 ± 16	46 ± 13	59 ± 15	51 ± 19	0.02
Men	36 (58)	8 (50)	18 (60)	10 (63)	0.74
Cardiovascular risk					
Hypertension	24 (39)	1 (6)	16 (53)	7 (44)	0.007
Current smoker	14 (23)	4 (25)	7 (23)	3 (19)	1.0
Systolic blood pressure (mm Hg)	133 ± 24	129 ± 21	138 ± 26	128 ± 23	0.27
Heart rate (beats/min)	74 ± 13	72 ± 8	72 ± 11	81 ± 17	0.05
Body mass index (kg/m^2)	26 ± 3	26 ± 3	26 ± 3	27 ± 4	0.39
History of atrial fibrillation	9 (15)	1 (6)	4 (13)	4 (25)	0.31
Creatinine (μmol/L)	88 ± 16	83 ± 9	88 ± 14	91 ± 22	0.49
Estimated glomerular filtration rate (ml/min)	77 ± 19	81 ± 21	75 ± 18	79 ± 21	0.68
FH_{10yrs} (%)	14 (4–29)	5 (3–11)	21 (9–30)	16 (1–30)	0.005
Symptoms					
Chest pain	13 (21)	4 (25)	5 (17)	4 (25)	0.78
Dyspnea (NYHA class ≥II)	31 (50)	6 (38)	13 (43)	12 (75)	0.06
Therapy					
β Blocker	29 (47)	5 (31)	17 (57)	7 (44)	0.25
Calcium antagonist	13 (21)	3 (19)	8 (27)	2 (13)	0.61
Echocardiography					
LV outflow tract gradient ≥30 mm Hg	15 (24)	2 (13)	9 (30)	4 (25)	0.54
Systolic anterior motion	27 (44)	6 (38)	13 (45)	8 (50)	0.77
Mitral valve regurgitation (mild or more)	40 (65)	11 (69)	19 (63)	10 (63)	0.92
MRI					
Maximal LV wall thickness (mm)	18 (13–21)	15 (13–19)	17 (13–20)	21 (18–24)	0.007
LV mass indexed to body surface area (g/m^2)	65 (52–91)	52 (43–70)	64 (54–89)	101 (67–130)	<0.001
LV ejection fraction (%)	58 (54–65)	61 (55–66)	58 (55–63)	56 (50–65)	0.46
LGE present	31 (50)	7 (44)	13 (43)	11 (69)	0.22

Data are presented as mean ± SD, number (percentage), or median (interquartile range).
NYHA = New York Heart Association.
* p Value for differences across the groups.

protocol. Medical history, New York Heart Association class, medication use, and echocardiographic data were recorded. Echocardiographic LV indexes were derived from an echocardiography performed within a year of the MRI study. At the day of the MRI study, a blood sample was drawn for later assessment of biomarker status and immediate determination of renal function. Whether other clinical investigations had to be performed was left to the discretion of the treating physician, who was blinded for MRI and biomarker results. For each patient, classic risk factors for CVD were collected from hospital records to calculate the FH_{10yrs}.[7] The study protocol was approved by the local ethical committee. All participants provided written informed consent.

Cardiac MRI studies were performed on a 1.5-T cardiac MRI system (Achieva; Philips Healthcare, Best, The

Table 2
Spearman's correlation coefficients of continuous variables with regard to levels of highly sensitive cardiac troponin T

Variable	All Participants (n = 62)	
	Spearman ρ	p Value
Age (yrs)	0.156	0.23
Systolic blood pressure (mm Hg)	0.022	0.86
Heart rate (beats/min)	0.188	0.14
Body mass index (kg/m^2)	0.173	0.18
Creatinine level (μmol/L)	0.148	0.28
Estimated glomerular filtration rate (ml/min)	0.017	0.90
FH_{10yrs} (%)	0.198	0.12
Maximal wall thickness (mm)*	0.348	<0.001
LV mass indexed to body surface area (g/m^2)*	0.513	<0.001
Left ventricular ejection fraction (%)*	−0.194	0.13

* Assessed with MRI.

Netherlands). All images were acquired with electrocardiographic gating and during repeated breath-holds of 10 to 15 seconds, depending on the heart rate, to minimize the influence of cardiac and respiratory motion on data collection. Steady-state free precession cine imaging was used to quantify LV function (short-axis stack with slice thickness of 10 mm from base to apex) and determine myocardial mass by means of standard criteria. Segmented inversion-recovery fast gradient echo imaging was used to assess LGE 10 minutes after the administration of 0.2 mmol/kg contrast medium (Dotarem; Guerbet, Gorinchem, The Netherlands).

Images were analyzed offline using QMass software (version 7.2; Medis, Leiden, the Netherlands) by 2 observers unaware of the subjects' clinical and biomarker information. The endocardial and epicardial borders of the myocardium were manually drawn in end-diastole and end-systole on the short-axis cine images. Volumes were derived by summation of discs, and ejection fraction was calculated accordingly. LV mass was calculated by subtracting endocardial from epicardial volume at end-diastole and multiplied by 1.05 g/cm^3.[9] All volumes and mass were normalized to body surface area. To evaluate maximal wall thickness, the short-axis LV stack was divided into 3 approximately equal levels (basal, mid, and apical). These levels were divided automatically by the software into the standardized 16-segment model—excluding the apex. LV wall thickness was then automatically measured per segment at end-diastole.[10] The greatest thickness measured was recorded as the maximal wall thickness. LGE was visually assessed and determined per segment as either present or absent.

Blood samples were obtained in a standard fashion at the clinical laboratory by trained personnel, processed within 60 minutes after phlebotomy, and stored at −80°C until further analysis. For the determination of troponin T levels, the highly sensitive cardiac troponin T (hs-cTnT) assay was used and performed on the Elecsys 2010 system (Roche Diagnostics; Almere, The Netherlands). The lower measurement range of this test is 3 ng/L, the ninety-ninth percentile reference limit 14 ng/L, and the concentration with a coefficient of variation of <10% is 13 ng/L. All biochemical testing was performed by laboratory personnel who were unaware of clinical information and MRI data.

Baseline characteristics are presented according to 3 groups (troponin ≤3 ng/L, >3 and <14 ng/L, and ≥14 ng/L). For each group, means ± SD, medians (interquartile ranges), or percentages, as appropriate, were calculated. Differences among these 3 groups were analyzed using either Kruskal-Wallis 1-way analysis of variance or chi-square testing. In case of comparisons between 2 groups, either Student's *t* test or the Mann-Whitney *U* test was used; proportions were compared using chi-square test. p Values of ≤0.05 were considered to indicate statistical significance. Spearman's correlation was used to test for associations between continuous variables and linear regression to identify factors that are associated with hs-cTnT (transformed by natural logarithm to approximate a normal distribution). To compare the proportions of patients with detectable (>3 ng/L) and elevated troponin (≥14 ng/L) levels across tertiles of indexed LV mass and FH_{10yrs}, chi-square testing was performed. A similar approach was followed to compare the proportions of patients with a troponin concentration from 3 to 14 ng/L in the respective tertiles. Multivariate binary logistic regression analysis was performed to study the association between LV mass index (LVMI) and detectable and elevated troponin levels independent of the FH_{10yrs}.

Results

Of the cohort of 74 subjects that fulfilled the prespecified inclusion and exclusion criteria, 12 patients were excluded as either the troponin measurement or MRI failed (Figure 1). The hs-cTnT concentration was ≤3 ng/L in 16 (26%), detectable but not elevated above the ninety-ninth percentile in 30 (48%), and elevated (≥14 ng/L) in 16 patients (26%). In total, troponin level above the lower range of measurement of 3 ng/L was seen in 46 patients (74%).

Baseline characteristics are presented in Table 1. Patients with detectable but not elevated troponin concentrations (>3 and <14 ng/L) and those with elevated troponin concentrations (≥14 ng/L) were older (p = 0.02), more likely to have hypertension (p = 0.007), and have a higher FH_{10yrs} (p = 0.005). Patients with elevated troponin levels had a higher heart rate (p = 0.05), higher maximal wall thickness (p = 0.007), and higher LVMI (p <0.001) than patients with undetectable troponin and detectable but not elevated troponin concentrations. In the 24 patients with a history of hypertension, hs-cTnT was undetectable in only 1; without a history of hypertension, 40% (15 of 38) of patients had undetectable levels.

Hs-cTnT as a continuous variable correlated positively with maximal wall thickness and LVMI (Table 2). With linear regression analysis, hs-cTnT, transformed by natural logarithm, was univariably associated with heart rate (p = 0.01), LV maximal wall thickness (p = 0.003), and LVMI (p = 0.001). There was a nearly significant association with hypertension (p = 0.057). In multivariable analysis, only hypertension (p = 0.048) and LVMI (p ≤0.001) were independently associated with increasing levels of hs-cTnT. The median troponin level significantly differed across tertiles of LVMI but not across tertiles of FH_{10yrs} (Figure 2). The percentages of patients with a troponin level of>3 ng/L increased from 50% to 76% and 95% across tertiles of LVMI (p = 0.004) and from 55% to 71% and 95% with

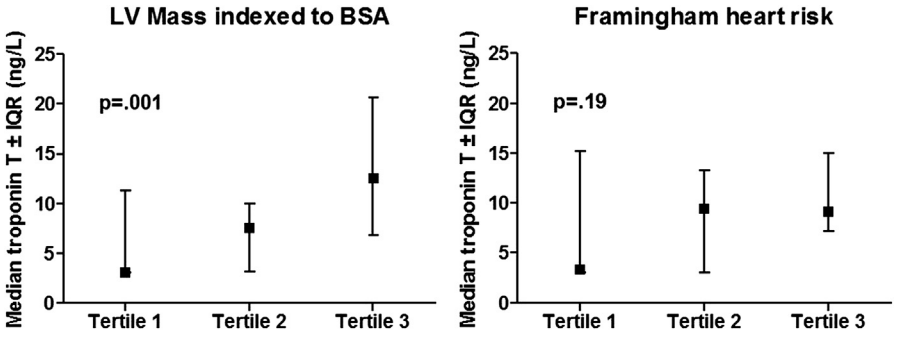

Figure 2. Concentrations (medians and interquartile ranges) of highly sensitive cardiac troponin T across tertiles of indexed LV mass and FH_{10yrs}. p Values for differences across tertiles. BSA = body surface area; IQR = interquartile range.

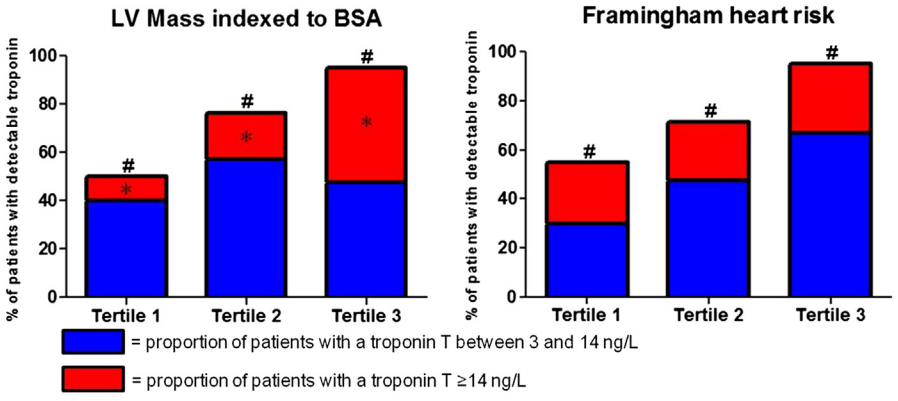

Figure 3. Percentages of detectable and elevated highly sensitive cardiac troponin T across tertiles of indexed LV mass and FH_{10yrs}. Margins of LVMI tertiles: 0 to 54.9 g/m^2, 55.0 to 80.5 g/m^2, and ≥80.6 g/m^2. Margins of FH_{10yrs} tertiles: 0% to 7.4%, 7.5% to 25.2%, and ≥25.3%. #A significant difference across tertiles in the proportion of patients with a troponin level of >3 ng/L ($p \leq 0.01$). *A significant difference across tertiles in the proportion of patients with a troponin level of ≥14 ng/L ($p = 0.02$). BSA = body surface area.

Table 3
Multivariate logistic regression analysis for the association between indexed left ventricular mass (LVMI) and Framingham Heart 10-year risk score (FH_{10yrs}), detectable (>3 ng/L), and elevated (≥14 ng/L) highly sensitive cardiac troponin T (hs-cTnT) in patients with hypertrophic cardiomyopathy

Variable	Detectable (>3 ng/L)			Elevated Hs-cTnT (≥14 ng/L)		
	OR	95% CI	p Value	OR	95% CI	p Value
Unadjusted						
LVMI*	1.68	1.15−2.48	0.007	1.54	1.20−1.97	0.001
FH_{10yrs} †	1.70	1.19−2.43	0.004	NS	NS	NS
Adjusted						
LVMI*,‡	1.93	1.23−3.05	0.005	1.54	1.20−1.97	0.001
FH_{10yrs} †,§	2.09	1.31−3.32	0.002	NS	NS	NS

CI = confidence interval; OR = odds ratio.
* Odds ratios are per 10-g indexed LV mass increase.
† Odds ratios are per 5% FH_{10yrs} increase.
‡ Adjusted for variables univariably associated with troponin values above the lower measurement range of 3 ng/L (i.e., FH_{10yrs}) or elevated hs-cTnT concentrations (i.e., maximal wall thickness and dyspnea New York Heart Association class ≥II complaints).
§ Adjusted for variables univariably associated with hs-cTnT >3 ng/L (i.e., LVMI).

respect to FH_{10yrs} ($p = 0.01$; Figure 3). Across tertiles of LVMI, this increase is explained by the number of patients with elevated hs-cTnT levels (≥14 ng/L) reaching a total of 48% (10 of 21) in the highest tertile. For the FH_{10yrs}, a nearly significant increase in the percentage of patients with a troponin level from 3 to 14 ng/L from 30% in the lowest to 67% in the highest tertile ($p = 0.063$) was observed, whereas for elevated hs-cTnT, proportions were similar. In the absence of hypertension, among patients with a low LVMI (lowest tertile), only 8% (1 of 13) had elevated hs-cTnT levels in contrast to 55% (6 of 11) of patients within the highest tertile of LVMI. In univariate logistic regression analysis, LVMI and FH_{10yrs} were significantly associated with a hs-cTnT of >3 ng/L. Using a stepwise forward method, both FH_{10yrs} and LVMI had an independent association with detectable troponin levels. With respect to hs-cTnT levels ≥14 ng/L, there was a univariable association between troponin level and LVMI, maximal wall thickness, and dyspnea (New York Heart Association class ≥II) complaints. In multivariate analysis, LVMI was the single variable that was independently associated with elevated troponin levels (Table 3).

Discussion

The present study in patients with HC demonstrates that troponin release seems to be related to both cardiac mass and the risk of CVD, with the interesting finding that the contribution of both factors seems to differ in relation to the serum troponin concentration. Both hypertension and LVMI were related to increasing troponin concentrations independent of other variables. Notably, the fact that the FH_{10yrs}

was independently associated with detectable troponin levels (i.e., >3 ng/L) but not with elevated troponin levels (ninety-ninth percentile or more) suggests that LV mass rather than the predicted risk of CVD is the main drive for elevated troponin levels in patients with HC.

In our HC population of 62 patients, troponin was elevated >14 ng/L in 1 of every 4 patients. Previous studies reported elevated troponin levels in 40% to 55% of patients[2,11] and studied associations with concentrations exceeding the ninety-ninth percentile. In the present analysis, we also addressed the more subtle troponin concentrations from 3 to 14 ng/L. In addition, we explored the association not only with cardiac mass but also with the predicted cardiovascular risk, a factor that has consistently been related to measurable troponin concentrations in different study populations of apparently healthy subjects without known structural heart disease.[1,12–15]

Although previous studies in patients with HC have demonstrated that LV indexes correlated with troponin levels,[2–4] this is the first report in which the impact of cardiac mass is described, independent of the predicted CVD risk, making use of MRI. LVMI together with maximal LV wall thickness had the strongest positive correlation with troponin, and a strong association remained after adjustment for all the variables significantly associated with troponin in linear regression analysis, that is, hypertension, heart rate, and maximal wall thickness. Overall, it seems that concentrations of troponin in serum of patients with HC steadily increase with increasing mass and that the same goes for the proportion of patients with detectable and elevated levels, which increases across tertiles of LVMI. The relation between cardiac mass and troponin level has only been described once before in patients with HC. In this particular report, it is shown that echocardiographically determined LV mass is greater in the group with elevated troponin T levels,[16] whereas others reported on associations with maximal wall thickness, myocardial dysfunction, and LGE.[2,4–6]

In populations quite different than patients with HC, ranging from healthy subjects to patients with aortic valve stenosis, a similar relation between increasing LV mass and troponin level was observed.[1,12,17,18] These observations suggest that mass is an important factor in an, as of yet, unknown mechanism of troponin release, independent of the underlying cause and with, as a general rule, an increase in serum troponin levels when LV mass increases. Although it is reasonable to assume that LV mass is the most important factor for troponin release, there are no studies available that have adjusted for CVD risk factors when interpreting troponin results in patients with HC.

Interestingly, it has been demonstrated that troponin is associated with individual risk factors for CVD and the a priori long-term risk of CVD, as expressed by the FH_{10yrs}.[1,12,19] In our population, hypertension has been proved to be associated with increasing troponin levels, even after correction for LV mass measurements. In addition, the FH_{10yrs} was independently associated with detectable troponin levels, suggesting that the predicted cardiovascular risk might also be a factor to consider in patients with HC. This is underscored by the observation that patients with hypertension had detectable troponin levels in almost all patients, whereas in patients without hypertension, troponin level was undetectable in >1/3 of patients. Interestingly, in patients with essential hypertension, troponin was associated with signs of end-organ damage, such as renal dysfunction, and electrocardiographic signs of hypertrophy.[20] With regard to cardiovascular risk factors, patients with hs-cTnT levels >3 and <14 ng/L were older, more likely to have hypertension, and had a higher FH_{10yrs} than patients with undetectable troponin levels. Therefore, besides cardiac mass, the a priori long-term risk of CVD contributes to the number of patients with HC with detectable troponin levels in the low range below the ninety-ninth percentile reference limit.

The phenomenon of cardiac troponin in the circulation of patients with HC may have several underlying mechanisms. Importantly, hypertension and atherosclerotic heart disease share elements of the same pathologic pathways that also occur in patients with HC. Microvascular dysfunction, next to increased pressure load and decreased capillary density, has been reported to cause ischemia in both secondary hypertrophy and HC.[21,22] Hypertrophy plays an important role in this, whereas other mechanisms, less dependent on hypertrophy, may also contribute to the release of troponin. In this respect, myocyte disarray has been mentioned to be the result of myocyte growth due to alterations in myocardial energetics and calcium handling leading to inefficient energy usage.[23,24] Reduced sarcomere responsiveness to stretch has been proposed as a general mechanism of disease-causing myocardial dysfunction with reduced maximal force generation.[25,26] It is quite imaginable that dysfunctional sarcomeres will not be able to adapt sufficiently to the changing circumstances and demands under stressful conditions such as exercise, ultimately leading to cellular injury with release of troponin into the circulation.

The latter mechanisms of disease seem less dependent on phenotype and may already be activated before development of hypertrophy. Likewise, it has been shown that biomarkers of fibrosis can be demonstrated in mutation carriers without the hypertrophic phenotype and without visual evidence of fibrosis on MRI.[27] In these patients, cardiac troponin may also prove to be an interesting early marker of disease for future research, as it may precede the development of cardiac fibrosis. In this respect, exercise-induced troponin release could prove an indicator of disease progression, which might be prevented by β blockade.[28]

There are some limitations to this study that should be recognized. First, we did not study a control group of patients without HC. Especially with controls matched on mass measurements and risk factors for CVD, it would be possible to better elucidate to what extent mass by itself is the important factor, or if the more HC specific characteristics (i.e., sarcomere dysfunction, myocyte disarray, and/or microvascular disease) are also of importance in the process of troponin release. Second, excluding patients with an implantable cardiac defibrillator and with a population of primarily New York Heart Association class II dyspnea, this study population is not representative of the entire HC population. However, even in the absence of higher risk patients, the association between mass and troponin is quite evident. Therefore, we expect the relation to be even stronger in a higher risk population. In addition, it should be appreciated that ideally all patients should have undergone

coronary angiography to exclude important coronary artery disease. Patients included had no clinical and/or imaging evidence of CVD. The FH_{10yrs} that we used is a well-established indicator for the a priori long-term risk of CVD and has been associated with baseline troponin concentrations in asymptomatic subjects.[1,12] Although we used this score as an indicator for "atherosclerotic burden," it should be noted that the prognostic impact for atherothrombotic events has not been studied in patients with HC. Finally, our relatively small sample size precludes adequately powered multivariate analyses.

Disclosures

The authors have no conflicts of interest to disclose.

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