RESEARCH LETTER

Associaton of elevated troponin levels with increased heart rate and higher frequency of nonsustained ventricular tachycardia in hypertrophic cardiomyopathy

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Introduction High-sensitive troponin I (hs-TnI), an ultraprecise biomarker for the detection of myocardial ischemia, has been investigated in patients with hypertrophic cardiomyopathy (HCM) in several studies.[1-4] However, troponin levels were measured only at a resting state and were not synchronized in time with ambulatory electrocardiography (ECG) monitoring (Holter monitoring). So far, no studies have used the following protocol: 24-hour Holter monitoring first and then the measurement of hs-TnI (the biomarker level has a close temporal relationship with findings on Holter monitoring). This protocol seems to be reasonable because hs-TnI levels may be both associated with increased heart rate (potential cause of myocardial ischemia) and be a potential cause of life-threatening ventricular arrhythmias occurring during the previous 24 hours.

As regards the dynamic stress test (under natural conditions and related to a single episode of rapidly increased heart rate) in adults with HCM, there have been only 2 reports of troponin measurement (without the use of high-sensitivity method): one taken after an episode of rapid supraventricular tachycardia in a natural everyday situation,[5] and the other after a physician-controlled exercise stress test.[6] The exercise stress test was performed in a small group of 7 patients, 5 of whom revealed elevated troponin levels after physical exercise, while in the repeated control exercise test after β-blocker use, troponin release was consistently diminished.[6]

There are no unequivocal data regarding the hemodynamic mechanism of myocardial ischemia diagnosed with hs-TnI release in HCM. An elevated troponin level in patients with HCM is probably a common finding during normal everyday physical activity. In particular, we suspect that elevated hs-TnI levels (the high-sensitivity method being particularly useful) are quite common during the daily activities of patients with HCM (even on pharmacotherapy). However, this phenomenon may be underdiagnosed or completely unrecognized. Therefore, we decided to investigate the presence of and potential mechanism underlying the increased hs-TnI levels in relation to findings on Holter monitoring.

Patients and methods Consecutive patients with HCM, treated and monitored at our clinic, were recruited to the study. Most patients received pharmacotherapy (TABLE 1) and underwent regular medical check-ups as part of ambulatory care.

The exclusion criteria were as follows: ST-segment or non-ST-segment elevation myocardial infarction (recent or previous), significant coronary stenosis on coronary angiography, or renal failure. The final sample included 32 patients with HCM (mean [SD] age, 40 [11] years; 20 men and 12 women).

According to the study protocol, echocardiography was performed first. Immediately after the echocardiography, a 24-hour ECG test was started to assess possible tachycardia episodes as a potential trigger of hs-TnI release. Moreover, we searched for possible episodes of nonsustained ventricular tachycardia (NSVT, a risk factor for sudden cardiac death according to the European Society of Cardiology and American Heart Association / American College of Cardiology guidelines) as a potential result of ischemia detected by hs-TnI release. The hs-TnI level was assessed

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Received: May 12, 2017.
Revision accepted: June 12, 2017.
Published online:
Conflict of interests: none declared.
Pol Arch Intern Med. 2017; 127 (6): 445-447
doi:

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TABLE 1 Baseline characteristics of the patients

Ejection fraction, %, mean (SD)		60.9 (13.2)
Maximum LV thickness, mm, mean (SD)		21.7 (4.8)
Resting LVOT gradient, mm Hg, mean (SD)		18.31 (17.23)
Resting LVOT gradient, ≥30 mm Hg, n (%)		7 (21.9)
Left atrial diameter, mm, mean (SD)		49.1 (10.7)
LV end-diastolic diameter, mm, mean (SD)		43.4 (8.8)
NYHA class[a], mean (SD)		2.0 (0.71)
CCS class[a], mean (SD)		1.3 (0.5)
Syncope[a], n (%)		0 (0%)
NSVT[a], n (%)		12 (37.5)
Sudden death in family history, n (%)		11 (34)
Creatinine, μg/l, mean (SD)		87.1 (16.5)
Drugs with negative chronotropic properties[a], n (%)	β-blocker (metoprolol, bisoprolol, sotalol)	24 (75)
	Verapamil	6 (18.75)
	None	2 (6.25)

a Parameters recorded during Holter monitoring in the current study

Abbreviations: CCS, Canadian Cardiovascular Society; LVOT, left ventricular outflow tract; LV, left ventricular; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association

immediately on completing the Holter test. Patients were asked to maintain normal physical activity during the test. The study protocol was approved by a local institutional review board.

Statistical analysis Continuous variables were presented as mean (SD). Categorical variables were assessed using the Fisher exact test and expressed as numbers (percentages). Correlations between hs-TnI levels and ECG parameters were assessed using the Pearson correlation coefficient. A P value of less than 0.05 was considered significant.

Results Baseline characteristics of the patients are presented in TABLE 1. Hs-TnI release was detected in all patients (range, 1.5–38 571 ng/l). Increased levels were revealed for 16 patients (troponin-positive group), and "normal-low" levels, in 16 patients (troponin-negative group). The hs-TnI level was correlated with the maximum heart rate (stronger correlation: r = 0.69, P <0.01) and the mean heart rate (weaker correlation: r = 0.41, P <0.05). There was no correlation between the hs-TnI level and the minimum heart rate (r = 0.21, P = 0.39). The mean (SD) maximum heart rate and the mean (SD) heart rate were higher in the troponin-positive group than in the troponin-negative group: 139 (9) bpm vs 125 (8) bpm and 79 (8) bpm vs 69 (7), respectively (P <0.05 for both comparisons). NSVT episodes were more common in the troponin--positive group than in the troponin-negative group (75% vs 24%; P <0.03).

Discussion Our study suggests a potential risk of myocardial ischemia provoked by exercise-induced or spontaneous tachycardia. Regarding the causal relationship, myocardial ischemia may be associated with NSVT in patients with HCM. In previous experimental studies in patients in a resting supine position, ischemia was provoked by tachycardia, that is, rapid atrial pacing.[7,8] In those studies, the marker of myocardial ischemia was lactate metabolism (myocardial lactate extraction indicated the difference between arterial and great cardiac vein lactate contents). The negative difference was defined as lactate production and precisely indicated myocardial ischemia.

In patients with HCM,[7] the transmural coronary flow reserve was exhausted at a heart rate of 130 bpm. The higher heart rate resulted in a more severe metabolic evidence of ischemia (lactate production instead of consumption), and all patients experienced chest pain. At a heart rate of 150 bpm, most patients demonstrated an actual decline in the coronary flow, which correlated with an increase in the left ventricular filling pressures and more severe metabolic evidence of ischemia.[7]

In a study by Cannon et al,[8] up to 73% of patients with HCM with reversible thallium-201 (^{201}Tl) abnormalities during exercise showed metabolic evidence of myocardial ischemia during rapid atrial pacing (myocardial lactate extraction of 0 mmol/l or less); 31% of the patients with normal ^{201}Tl scans showed myocardial ischemia (detected by metabolic measurement).

In a study by Ogata et al,[9] assessing both invasive lactate measurement and noninvasive exercise test, patients with HCM were shown to be at increased risk of myocardial ischemia during exercise, despite having normal results of coronary arteriograms but with pacing-induced abnormal lactate metabolism.

Currently, hs-Tn in blood sample obtained from the peripheral vein is the best marker of ischemia. Even in apical HCM with a relatively small left ventricular mass, an episode of supraventricular tachycardia with 180 bpm provoked troponin release.[5] Pop et al,[6] in a study on patients with HCM and no abnormalities on coronary angiogram, revealed that increased troponin release may be present before exercise and is temporarily enhanced on exertion and significantly decreased after the administration of a β-blocker.

In a recent study on HCM,[10] mortality was predicted using criteria for detecting ischemia on stress echocardiography. The authors concluded that stress echocardiography has an important prognostic role in patients with HCM, with ischemic endpoints showing a greater predictive accuracy than hemodynamic endpoints.[10]

Although several studies evaluated the role of hs-Tn in patients with HCM, the relationship between Holter ECG parameters and troponin level (measured nearly at the same time but with an adequate delay for the first half of the Holter monitoring, that is, the daily phase) has not been investigated so far.[1-4] In a recent review by McCarthy et al,[11] the utility of troponin assessment in arrhythmic disease was shown only for the the

initial stage, but it was proposed as a valuable screening marker for patients with HCM at high risk of sudden cardiac death.

Regular training exercise has recently been recommended for patients with HCM.[12] In our opinion, based on the association between tachycardia or tachyarrhythmia (NSVT) and elevated troponin levels in patients with HCM, we suggest that any exercise stress test in these patients (performed either for training or diagnostic purposes) should be controlled by troponin level measurements 6 and 12 hours after the test.

Our study has several limitations. First, the current pharmacological treatment was maintained, and particularly β-blockers were not withdrawn. In different patients, 3 β-blockers were used: metoprolol, bisoprolol, and sotalol; therefore, a comparison of the dose of β-blockers between the troponin-positive and troponin-negative groups was statistically impossible because of the small number of patients in the 6 subgroups: metoprolol TnI(+) vs metoprolol TnI(–), bisoprolol TnI(+) vs bisoprolol TnI(–), and sotalol TnI(+) vs sotalol TnI(+). In our pilot study, we aimed to make the first-ever observation on the correlation between hs-TnI release and findings on Holter monitoring. Our preliminary study showed that β-blocker withdrawal might not be safe in this group of patients, and in future studies, we will attempt to increase the dose and use only one type of a β-blocker to minimize an increase in heart rate and, consequently, decrease ischemia burden and the risk of troponin release.

We decided to measure hs-TnI levels only once because our pilot study was conducted in an outpatient setting. The optimal protocol, that is, a 48-hour profile of troponin measurement with the assessment of troponin during the ECG test and every 3 to 6 hours after the test, would require the in-hospital setting and would be more costly. Moreover, only an outpatient-based study provides an opportunity to assess the heart rate during daily routine physical activity of patients.

In conclusion, our study showed that the elevated hs-TnI level correlated with an increased heart rate on Holter monitoring, especially with the maximum heart rate. Moreover, high hs-TnI levels were associated with the presence of NSVT. Moreover, 75% of the patients with positive troponin were shown to have NSVT. Further research is needed to assess the protective role of β-blockers in tachycardia-related troponin release.

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