Usefulness of High-Sensitive Troponin Elevation After Effort Stress to Unveil Vulnerable Myocardium in Patients With Heart Failure

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Elevation of resting high-sensitivity troponin (hs-Tn) holds prognostic value in heart failure (HF), but its pathophysiological meaning is unclear. We aimed to investigate hs-Tn elevation after maximal exercise in patients with systolic HF and its neurohormonal and hemodynamic correlates: 30 patients diagnosed with systolic HF (left ventricular ejection fraction 32 ± 8%, mean ± SD), on guideline-directed medical therapy and not recognized inducible ischemia, underwent maximal cardiopulmonary stress test, with assay of plasma *N*-terminal proB-type natriuretic peptide (NT-proBNP), norepinephrine (NE), and hs-TnT (hs-TnT) at baseline, peak, and 1 and 4 hours after exercise. Cardiac output (CO) was measured during effort, with a rebreathing technique. The natural logarithm of the ratio between percentage (%) increase in CO and NT-proBNP (ln[CO%/NT-proBNP% increase]) was evaluated, as a noninvasive estimate of Frank−Starling adaptation to effort, with NT-proBNP variation considered as a surrogate of end-diastolic left ventricular pressure variation. Hs-TnT increased during exercise with a 4-hour peak ($p = 0.001$); 10 patients had hs-TnT increase >20%. Patients with Hs-TnT increase >20% were more symptomatic at rest ($p = 0.039$) and showed greater NE at peak exercise ($p = 0.003$) and less ln[CO%/NT-proBNP% increase] ($p = 0.034$). A lower ln[CO%/NT-proBNP% increase] correlated with greater NE at peak exercise ($r = -0.430$, $p = 0.018$). In conclusion, acute troponin elevation after maximal exercise was detected in 1/3 of this series. The association of troponin release with NE, CO, and NT-proBNP changes after effort suggests a pathophysiological link among transient hemodynamic overload, adrenergic activation, and myocardial cell damage, likely identifying a clinical subset at greater risk for HF progression. **(Am J Cardiol 2015;116:567−572)**

Neurohormonal activation plays a key role in pathophysiology of heart failure (HF). Activation of adrenergic and renin-angiotensin-aldosterone systems (RAAS) initially supports cardiac output (CO) after damage. Secretion of the B-type cardiac peptides with recognized vasodilator and natriuretic properties reflects either left ventricular filling pressure[1] or the degree of neurohormonal activation.[2] Sustained neurohormonal activation further worsens hemodynamics favoring cardiac remodeling and HF evolution to end stages.[3] Ongoing myocardial damage (OMD) has been proposed as a mechanism of progression of cardiac remodeling and disease likely reflected by long-term troponin release, whose serum levels hold a prognostic value.[4] Adrenergic signaling[5] and mechanical stress due to hemodynamic overload during exercise[6] have been proposed as triggers for troponin release by inducing cardiomyocyte death, with subsequent ventricular remodeling. As a result, further neurohormonal activation may occur, generating a vicious circle with progressive deterioration of cardiac function. A few studies have evaluated in vivo changes in troponin levels and its determinants after exercise,[7] as a tool for the investigation of cardiac vulnerability and of its determinants. We aimed therefore to assess the relation among troponin release, neurohormonal activation, and hemodynamic response to maximal exercise.

Methods

We enrolled 30 stable outpatients with systolic dysfunction (left ventricular ejection fraction, LVEF <50%), diagnosed with HF by history, symptoms, and physical and instrumental findings in accordance to guidelines.[8] Cardiac morphology and function were assessed by 2-dimensional Doppler echocardiography. All patients were on stable guideline-directed medical therapy (GMDT) for HF, with 100% of patients on β blockers and either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In patients with ischemic cardiomyopathy, inducible ischemia was excluded at a recent imaging stress test (i.e., within 3 months before enrollment). Exclusion criteria were New York Heart Association class IV, hospitalization

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See page 571 for disclosure information.

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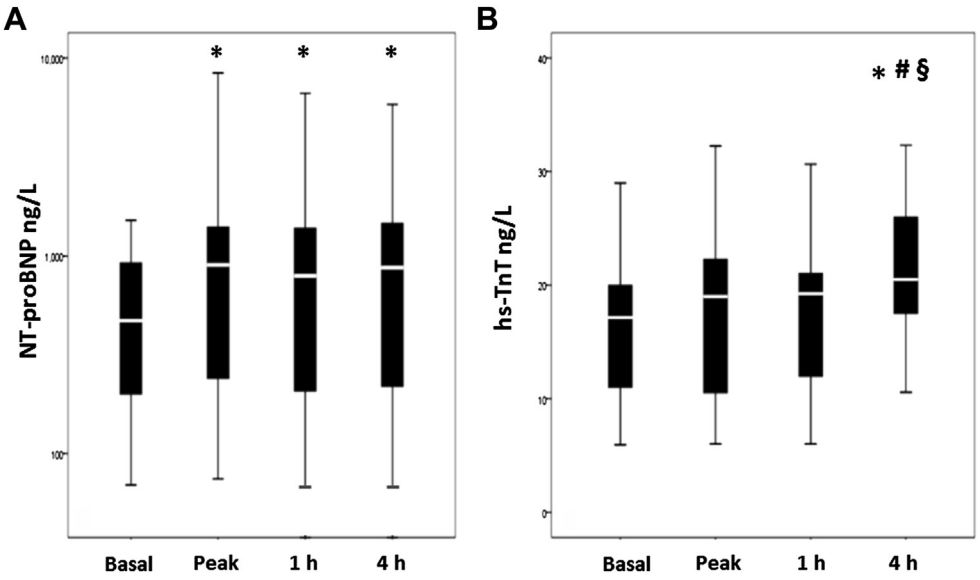

Figure 1. *N*-terminal fragment of NT-proBNP *(A)* and hs-TnT *(B)* values at baseline, peak, and 1 and 4 hours after stress exercise. *p <0.05 versus basal values; #p <0.05 versus peak values; §p <0.05 versus 1-hour values.

Table 1
Clinical, echocardiographic and neurohormonal profile of the study cohort, according to the presence/absence of troponin increase > or < 20% during effort

Variable	All (n =30)	hs-Troponin Increase		*p*
		< 20% (n=20)	>20% (n=10)	
Age (years)	62.5±11.5	63±119	61±11	0.577
Male/female	27/3	18/2	9/1	0.999
NYHA class	1.4±0.5	1.3±0.6	1.6±0.5	0.039
Body mass index (kg/m^2)	25.4±3.2	25±2.8	25±3	0.939
Ischemic etiology	9 (30%)	6 (30%)	3 (30%)	0.999
Diabetes mellitus	10 (33%)	7 (35%)	3 (33%)	0.458
Left bundle branch block	7 (23%)	3 (15%)	4 (40%)	0.049
Atrial fibrillation	3 (10%)	2 (10%)	1 (10%)	0.990
Left ventricular ejection fraction (%)	32.6±8.3	33.2±9	30.1±8	0.091
Left ventricular end diastolic diameter (mm)	62±7	60±7	64±7	0.205
Left ventricular end systolic diameter (mm)	51.4±8	50±7	53±7	0.379
Systolic pulmonary artery pressure (mmHg)	35±9.2	32±11	40±10	0.078
Peak oxygen consumption (ml/Kg/min)	15.9±5	16.2±4	15.4±6	0.654
Ventilation/carbon dioxide production slope	31±7	31±6	30±8	0.721
Watt	99±25	105±20	98±28	0.430
Serum creatinine (mg/dL)	1.06±0.26	1.09±0.3	0.99±0.02	0.355
Hemoglobin (g/dL)	13.7±1.3	13.6±1.2	13.8±0.8	0.713
Basal hs-TnT (ng/L)	17±13	17±12	16±11	0.254
4 hours hs-TnT (ng/L)	22±14	17±13	25±14	0.070
Basal NT-proBNP (ng/L)	592; 207-1324	581;201-754	627; 187-762	0.233
Peak NT-proBNP (ng/L)	902; 240-1455	855;201-1098	949; 250-1158	0.791
Basal norepineprhine (ng/L)	471; 283-864	433;182-815	540; 352-898	0.528
Peak norepineprhine (ng/L)	2955; 1831-4582	2381;1666-3822	4741; 2208-5941	0.035
Basal cardiac output (L/min)	3.8±1.3	3.4±1.2	3.1±1.2	0.105
Peak cardiac output (L/min)	7.8±2.7	8.3±1.9	7.1±1.9	0.220
Cardiac output increase (%)	131±88	146±34	110±96	0.062
lnCardiac output%/lnNT-proBNP % increase	1.4; 0.9-1.9	2.2; 1.9-3.1	0.9; 0.3-1.2	0.034

for acute coronary syndrome or acute HF within 6 months before the enrollment, severe heart valve disease, severe chronic renal failure (estimated glomerular filtration rate <30 ml/min), severe lung disease, limitation to physical exercise other than HF. The study complies with the Declaration of Helsinki, and the protocol was approved by the institutional ethics committee. Informed consent was obtained from all subjects.