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Troponins in Chronic Left Ventricular Dysfunction

D. Anzulović-Mirošević¹, M. Zaninotto², M. Anzulović-Mirošević³, M. Plebani², A. Rozga⁴, S. Dalla-Volta^{1, 3}

<u>Background:</u> Troponins (I and T) are considered a marker of myocardial ischemic damage. We decided to investigate their meaning in patients with left ventricular dysfunction. We studied 59 patients (ranging from 40 to 80 years; mean age 64 years; SD 9) with left ventricular dysfunction from dilated cardiomyopathy, valvular heart disease and chronic ischemic cardiomyopathy. These patients were compared to 30 healthy persons and 15 patients with acute myocardial infarction. Troponins and several biochemical parameters of endothelial dysfunction, of inflammation and of cellular death were analyzed and correlated to echocardiographic index of left ventricular impairment.

<u>Results:</u> I and T troponins were increased in all patients and showed a significantly positive correlation, except in the group of valvular heart disease. Moreover, a statistically significant negative correlation between the levels of troponins and the diastolic blood pressure was observed in chronic patients (TNI: r = -0.235, p = 0.037; TNT: r = -0.223, p = 0.044), contrary to the significantly positive correlation with both systolic and diastolic blood pressure recorded in acute myocardial infarction. Troponins were the only biochemical marker we studied that correlate with diastolic blood pressure.

<u>Conclusions:</u> We believe that an excessively low level of the diastolic blood pressure in chronic patients with left ventricular dysfunction can provoke damage of the myocardium, thus inducing the increase of the circulating troponins. Therefore, we suggest to establish in the protocol of treatment of left ventricular dysfunction with ACE inhibitors, other vasodilators and beta-blockers a cut-off limit for diastolic blood pressure. **J Clin Basic Cardiol 2006; 9 (online): 19–22.**

Key words: left ventricular dysfunction, heart failure, troponin, diastolic blood pressure

The increase of the levels of some cellular enzymes, as CPK and troponins, has been observed and accepted as a sign of cellular death in acute myocardial infarction as well as in other acute coronary syndromes, mainly spontaneous angina. In the latter where, moreover, their level is used in the initial risk stratification of the patients [1, 2].

However, later some investigators [3–7] showed a similar increase, together with the appearance of markers of endothelial dysfunction in a variety of other conditions not necessarily of atherosclerotic origin: dilated and ischemic cardiomyopathies, valvular heart disease, in presence of variable degrees of impairment of the left ventricular function. Their meaning is, therefore, probably not the same and not directly dependent upon the changes induced by atherosclerosis. Actually, in the same chronic heart disease of any cause, several markers of cardiac inflammation and necrosis, of endothelial dysfunction and of neuro-hormonal activation are present. The pertinent data collected by our group are depicted in Figure 1.

For this reason, we decided to analyze the behavior of troponins I and T in a group of patients with left ventricular dysfunction not depending on an acute myocardial infarction, and to investigate the relationship between troponins and some clinical and echocardiographic parameters of left ventricular function.

Materials and Methods

For this study, we recruited a group of 74 patients (62 males, 12 females), ranging from 40 to 80 years (mean age: 64 years; SD 9), with different cardiac diseases, admitted to our department. Inclusion criteria were the presence of dilated cardiomyopathy (according to WHO criteria), valvular heart disease or post-ischemic cardiomyopathy (previous MI older than 6 months). A group of patients presenting acute myo-



Figure 1. Results of previous personal investigations on inflammatory, neurohumoral factors in HF (Note: units are different among parameters; units used are: pg/ml [ADR, BNP, NOR], ng/ml [TNI, TNT], mg/l [CRP], fmol/ml [BIG-ET1])

cardial infarction (AMI), hospitalized in the same period, were also analyzed.

In all patients, systolic LV function, as assessed by echocardiography, was impaired. Other heart diseases were excluded. All patients except those with AMI were admitted for the worsening of their cardiac conditions. The male to female ratio was 5.16. These patients were compared to 30 healthy persons (anamnestically no signs of any disease, negative physical examination and ECG), not age-matched (13 males; 17 females; age: 20–80 years; mean age: 35 years; SD 15). The Ethical Committee of the University of Padova approved the study and informed consent was obtained from each patient.

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From the ¹Department of Cardiology and the ²Laboratory of Medicine, University of Padova Medical School, Padova, Italy, the ³Department of Health Studies, University of Practical Sciences of Split and the ⁴Department of Statistics, University of Split, Split, Croatia. <u>Correspondence to:</u> Dinko Anzulović-Mirošević, MD PhD, Dipartimento di Medicina Clinica e Sperimentale – Clinica Cardiologia, Via Giustiniani 2, I-35128 Padova, Italy; e-mail: cardiopd@unipd.it

For all patients, detailed history, physical examination, ECG, and routine lab analysis were performed. Cardiac functional impairment was graded following the NYHA class; the hemodynamic evaluation was performed by the standard 2D echocardiogram. The diagnosis of left ventricular systolic dysfunction was accepted for an ejection fraction below 45 %, an end-diastolic volume (EDV) more than 100 ml/m² (normal value below 65 ml/m²) and a Suga's contractility index (P/VTS) of less than 3 (normal 3 or more). Patients with relevant liver or kidney dysfunction or other acute major pathology (sepsis, terminal phase tumors etc.) were not included. Chronic patients at the moment of hospitalization were receiving sub-optimal doses of ACE inhibitors and diuretics.

For the biochemical assessment of inflammation and cellular death, a sample of 24 ml of blood was taken in the morning, the patient still lying in bed, using 21G butterfly needles and vacutainer system containers. The sampling was performed within 48 hours of admission for all patients, but in those affected by AMI the samples were taken 4 to 7 days after the acute episode.

The samples were maintained at a temperature of 4 °C during the transport to the central laboratory, where they were processed, frozen to -80 °C and analyzed successively within 6 months after sampling. The time between sampling and processing was in the range from 15 to 45 minutes. Biochemical analyses were performed in the central laboratory of the University Hospital of Padova with proper calibration of instruments (troponin I by one-step enzyme immuno-assay based on the sandwich principle [Rxl dimension analyzer, Dade] and troponin T by two-side third-generation chemio-luminiscent immunoassay [ELECSYS analyzer, Roche]).

The following parameters were analyzed: BNP, endothelin 1, big-endothelin 1, troponin I, troponin T, CRP, adrenalin, and noradrenalin.

The results of the measurements were elaborated with statistical analyses (descriptive statistics, Student's t-test, Mann-Whitney test, Pearson linear coefficient of correlation, linear regression and ANOVA).

Results

Troponins

The levels of the two troponins are summarized in Table 1, and divided according to the different four types of pathology presented: troponins were not detectable in controls.

Troponins I and T increased in a similar way, their values being below the cut-off level for accepting the diagnosis of myocardial infarction (TNI > 0.4 ng/ml; TNT > 0.1 ng/ml). The comparison between these data and the degree of impairment of the left ventricular function demonstrated a statistically significant increase of troponins in patients with left ventricular dysfunction (TNI: 0.34 ng/ml patients vs. 0.00 ng/ml controls, p = 0.004; TNT: 0.19 ng/ml patients vs. 0.00 ng/ml controls, p = 0.003 with T test as shown in Table 1).

Comparing the four groups of patients with the controls, the p-value of the Mann-Whitney test was highly significant in all groups while the t-test was not significant in chronic ischemic cardiomyopathy.

The troponin I and T levels showed a significantly positive correlation for all groups, except in patients with valvular heart disease.

One-way ANOVA showed no statistically significant differences among groups for troponin I and T levels, when patients with acute myocardial infarction were excluded from analysis. Table 1a: Troponin values in four groups: descriptive statistics, troponins

Parameter		Ν	Mean (ng/ml)	Standard Deviation	Range
TNI	Dilated CMP Valvular CMP Ischemic CMP Total Chronic AMI Total patients	24 12 23 59 15 74	0.024 0.034 0.34 0.15 1.02	0.036 0.037 1.22 0.77 1.62	0-0.16 0-0.13 0-5.89 0-5.89 0-2.33
TNT	Dilated CMP Valvular CMP Ischemic CMP Total Chronic AMI	24 12 23 59 15	0.017 0.074 0.22 0.1 0.53	0.022 0.21 0.86 0.55 0.66	0-0.1 0-0.732 0-4.17 0-4.17 0-2.08

 Table 1b: Significant differences between each of the four groups and patients (only p-values of t-test and Mann-Whitney test are reported)

Group	TNI	TNT	
Post-ischemic CMP	t-test n. s. MW test p < 0.0001*	t-test n. s. t-test n. s.	
AMI	< 0.001	< 0.001	
Valvular CMP	< 0.001	0.033	
Dilated CMP	< 0.001	0.006	

*Mann-Whitney test is significant for all sub-groups of patients while t-test is not significant for post-ischemic cardiomyopathy

It is interesting to observe that the mean values of blood pressure for all patients showed, in spite of the normal range of mean values of systolic and diastolic blood pressure, a significantly negative correlation between troponins and diastolic blood pressure in the group of chronic patients (dilated, valvular and ischemic CMP-TNI correlated [0.15 \pm 0.77 ng/ml] to DBP [77.2 \pm 9.79 mmHg] with r = -0.235; p = 0.037 and TNT [0.1 \pm 0.55 ng/ml] to DBP [77.2 \pm 9.79 mmHg] with r = -0.223; p = 0.044 as shown in Table 2). The values of systolic and diastolic pressures are presented in intervals of 5 mmHg. When analyzed by groups, in patients with chronic ischemic CMP significantly negative correlation persisted for TNI (r = -0.374; p = 0.039) and TNT (r = -0.370; p = 0.041), in those with valvular

 Table 2a:
 Correlation of troponins with DBP (all patients excluding AMI group)

TNI:DBP	TNT:DBP	
r = -0.235	r = -0.223	
p = 0.044	p = 0.037	
r = linear coeffici	ent of correlation (Pearson)	

Table 2b: Correlations of troponins with DBP for groups

Dilated	Valvular	Post-ischemic	AMI
CMP	CMP	CMP	
TNI:DBP	TNI:DBP	TNI:DBP	TNI:DBP
r = -0.053	r = -0.495	r = -0.374	r = 0.471
p = 0.402	p = 0.051	p = 0.039	p = 0.038
TNT:DBP	TNT:DBP	TNT:DBP	TNT:DBP
r = -0.183	r = -0.031	r = -0.370	r = 0.436
p = 0.19	p = 0.46	p = 0.041	p = 0.046

r = linear coefficient of correlation (Pearson)

heart disease only TNI was near significance (r = -0,495; p = 0,051) and TNI was not significantly correlated but maintained the negative trend. In dilated cardiomyopathy, the trend towards negative correlation was maintained but it was not significant (TNI: r = -0.053; p = 0.402; TNT: r = -0.183; p = 0.19).

Inversely, the correlation between troponins and diastolic blood pressure was positive in the group of patients with acute myocardial infarction for TNI (1.02 ± 1.62 ng/ml) correlated to DBP (125.93 ± 19.3 mmHg) with r = 0.471; p = 0.038 and for TNT (0.53 ± 0.66 ng/ml) correlated to DBP (125.93 ± 19.3 mmHg) with r = 0.436; p = 0.046.

There were no significant correlations of troponin I and T values with systolic blood pressure in all groups of patients.

Functional Class

There was no significant correlation between the levels of troponins I and T and the NYHA class or the echocardiographic data (EF and others), not even between patients assuming or not ACEI before admission.

Discussion

The rise of troponins in chronic left ventricular dysfunction of different etiologies is of particular interest, even if the magnitude of the cellular death and its mechanisms are not perfectly understood.

Troponin molecules are part of a complex that inhibits interaction of actin and myosin. It is the most widely used marker of cardiomyocite damage and probably the most sensitive test available at the moment. While it is usually believed that an event inducing cell death is necessary to liberate these structural proteins in the circulating blood, it is possible that some troponins escape from suffering but still living myocites [8]. The magnitude of increase of troponin (I or T) levels in patients with heart failure, not necessarily of ischemic origin, seems to correlate with adverse outcomes [5, 6].

The observation that both troponins I and T resulted elevated in patients with left ventricular systolic dysfunction is of relevance, mainly because the result remains statistically significant even when patients with AMI (who by definition have the highest troponin levels) are excluded. The absence of significance of the t-test in chronic ischemic cardiomyopathy in comparison to controls could be the consequence of the relatively wide variations of troponins for this subgroup; notwithstanding, the non-parametric test, like Mann-Whitney, is significant (p < 0.0001) even in the same subgroup. This is the first time, to our knowledge, that the two molecules (I and T) demonstrated an increase in different groups of patients with left ventricular dysfunction, although an isolated increase of one or the other of the two troponins in heart failure was previously published [3-7]. Even if it is likely that the two troponins have the same physiological meaning and the same diagnostic value, it is interesting to stress the lack of significant correlation between troponins I and T in valvular heart disease: the discordance could be the consequence of some differences in the troponin production or degradation or clearance.

An interesting unexpected observation recorded during the study is the negative correlation between diastolic blood pressure and troponins in all patients, except those with the AMI where the correlation is positive. This finding is probably depending on the decreased perfusion of the myocardium, predominant in the diastole [9–12], with special reference to the sub-endocardium. The mechanism could be the combination of lowered aortic and high intracardiac venous pressures, which reduce the effective coronary perfusion gradient [11], and cause cell suffering and death. Previously published data have proved that low perfusion not only hibernates myocites but induces apoptosis [13]. This hypothesis is supported by the higher correlation between diastolic blood pressure and troponin levels in the group of patients with chronic ischemic cardiomyopathy, where the diffuse stenosis of the coronary tree makes the myocardium more vulnerable to the low perfusion pressure [14].

Also the absence of a statistically significant difference for the troponin levels among the three groups of patients with chronic heart disease seems to be relevant, whereas a difference is observed for CRP, a marker of inflammation [15–17], supports the view that the cause of the troponin release in the blood is the low perfusion pressure in the coronary circulation and not the consequence of the inflammatory cell death.

Limitations

Limit of the study is a relatively small number of patients, so it is possible that the statistical significance can be influenced by the dimensions of the sample. The possible role of the inhomogeneous age and sex in the control group could not have significantly influenced the differences of troponins, as controls did not show measurable levels. The hypothesis is corroborated, in the same groups of patients by the behavior of BNP, not reported here, which shows relationship with the age and sex, while was increased thirty fold in the patients compared to the controls.

Conclusions

Troponins I and T, even if their increase is smaller in comparison to observed values in acute myocardial infarction, proved to be a valuable marker of left ventricular dysfunction: nevertheless, the significance of their role needs further research. Both troponins I and T have demonstrated the same value and can be considered equivalent instruments to evaluate left ventricular dysfunction. Only in the valvular group, where the values are both still elevated, they did not show significant correlation between them, so their possible equivalence in this group must be demonstrated.

The negative correlation between the level of the diastolic blood pressure and the increase of troponins suggests that probably an optimal range of diastolic pressure exists, that ensures a more favorable afterload/coronary perfusion ratio and, therefore, the optimal performance of cardiomyocites in patients with left ventricular dysfunction.

Closing this study we propose a multicentric investigation to evaluate:

- a) whether troponin levels vary with changes of diastolic blood pressure;
- b) if it is possible to use troponins in the titration of vasodilator therapy [18] and explore whether there is an individual pressure regimen (systolic and diastolic) for each patient with chronic systolic left ventricular dysfunction.

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