

High Sensitivity Cardiac Troponin T Levels after Elective Cardioversion for Atrial Fibrillation/Flutter

Zaza Iakobishvili MD PhD, Adaya Weissler MD, Kiril Buturlin MD, Gustavo Goldenberg MD, Boris Strassberg MD, Ruth Tur MD and David Hasdai MD FESC

Department of Cardiology and Wiessman Clinical Cardiology Research Center, Rabin Medical Center, Petah Tikva, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** The kinetics of high sensitivity cardiac troponin T (hs-cTnT) levels after elective, biphasic, direct-current cardioversion for persistent atrial fibrillation/flutter remains unknown.

Methods: We examined hs-cTnT kinetics in 24 patients at baseline and at 2, 6 and 24 hours post-cardioversion, and again at 7 and 30 days. We also examined levels of creatine kinase, aspartate aminotransferase, lactate dehydrogenase, brain natriuretic peptide (BNP), and high sensitivity C-reactive protein (hs-CRP).

Results: Median (25th, 75th interquartiles) baseline hs-cTnT concentration was 19.8 (10.4, 35.2) ng/L with 14 patients presenting with levels above the 99th percentile (13 ng/L). Hs-cTnT levels did not change significantly over time although they tended to decrease by 30 days, 18.8 ng/L (12.5, 23.3). There was no significant rise in other markers of myocardial injury. Similarly, BNP and hs-CRP levels were elevated at baseline and tended to decrease over time.

Conclusions: Patients with persistent atrial fibrillation/flutter have elevated hs-cTnT levels, as part of a general rise in biomarkers such as BNP and hs-CRP, without a further rise after cardioversion. After cardioversion, there is a gradual non-significant decrease in biomarker levels over time, and thus a rise in hs-cTnT levels should not be attributed to cardioversion.

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KEY WORDS: high sensitivity cardiac troponin T levels (hs-cTnT), atrial fibrillation, atrial flutter, biomarkers, cardioversion

Cardiac troponins are considered the gold standard biomarker for myocardial injury [1]. Recently, high sensitivity troponin assays were developed, permitting the early measurement of very low concentrations of troponin within the first few hours after an ischemic episode [2,3]. The newer, more sensitive assays detect low level troponin in apparently healthy people, emphasizing the need to discern troponin release kinetics rather than absolute levels when the levels are within the minute range [4]. High sensitivity troponin T is elevated not only in myocardial infarction, but also in other

scenarios such as atrial fibrillation [5,6]. The clinical implications of minute troponin release and its kinetics, as detected by high sensitivity assays, remain unknown in these various clinical scenarios. In particular, it has been suggested that electrical cardioversion may cause myocardial injury [7,8]. When cells are exposed to an external electric field, a voltage is induced across the cell membrane. The amplitude of this transmembrane voltage is proportional to the amplitude of the applied electric field and, with a sufficiently strong field, can cause a large increase in membrane permeability, called electroporation or electropermeabilization [9], with resultant mild troponin leak, even without cardiomyocyte necrosis.

Although several studies have reported that cardiac troponin does not rise after external cardioversion [10–13], others have shown a rise in cardiac troponin levels, depending on the waveform (i.e., monophasic vs. biphasic) [14,15] and energy of direct current applied [14,16]. Most of these studies were performed with older generation troponin assays. One report described the kinetics of high sensitivity cardiac troponin I (hs-cTnI) following external cardioversion, demonstrating a rise in hs-cTnI level at 6 and 12 hours after cardioversion [14]. We therefore sought to characterize the kinetics of high sensitivity cardiac troponin T (hs-cTnT) during the first 24 and up to 30 days following elective, direct-current biphasic cardioversion for persistent atrial fibrillation/flutter.

PATIENTS AND METHODS

We prospectively studied consecutive patients with non-valvular, persistent atrial fibrillation/flutter referred for elective, direct-current electric cardioversion, who gave written informed consent to participate in the study. Patients were excluded if they had the conditions associated with elevated troponin such as recent acute coronary syndrome, overt heart failure or significant left ventricular dysfunction (defined as left ventricular ejection fraction < 40%), significant left ventricular (LV) hypertrophy (defined as LV wall thickness > 15 mm), febrile/active inflammatory state, or severe renal failure defined as estimated glomerular filtration rate (eGFR) < 30 ml/min*1.73m².

External cardioversion was performed using a biphasic cardioverter Lifepak 20e® (Physio-Control Inc., a division of Medtronic, Redmond, WA, USA), under brief general anesthesia induced by midazolam in standard doses. The energy used and number of shocks given was at the discretion of the attending physician.

Circulating hs-cTnT levels were measured at baseline and at 2, 6 and 24 hours post-cardioversion, and again at 7 and 30 days. At these time points we also measured additional markers of myocardial injury, including creatine kinase (CK), lactate dehydrogenase (LDH), and aspartate aminotransferase (AST), as well the marker LV filling pressure, brain natriuretic peptide (BNP), and the marker of inflammation, high sensitivity CRP (hs-CRP).

High sensitivity cardiac troponin T (hs-cTnT) assay was measured quantitatively with the high sensitivity enzyme immunoassay based on electrochemiluminescence technology using the Cobas e 411 instrument (Roche Diagnostics, Penzberg, Germany). Given that the company reported a problem with their calibrator in early batches that were distributed [17], we report the batch numbers that were used (163161, 164773 and 167650). The original values were corrected, as recommended by the company. The limit of quantification (functional sensitivity) was determined as 3 ng/L and the upper reference limit (99th percentile) for myocardial injury hs-cTnT as 13 ng/L.

Creatine kinase was assayed using the Beckman Coulter AU 2700 analyzer, based on the recommendations of the International Federation for Clinical Chemistry (IFCC) using creatine phosphate and ADP as substrates. LDH was assayed using the Beckman Coulter AU 2700 analyzer, based on the recommendation of the Scandinavian Committee on Enzymes. AST was assayed using the Beckman Coulter AU 2700 analyzer, based on the recommendations of the International Federation for Clinical Chemistry (IFCC) but without pyridoxal-5'-phosphate, using L- aspartate and 2-oxoglutarate as a substrates. Plasma BNP concentration was measured using Triage® BNP test (Alere, CA, USA). BNP results ≤ 100 pg/ml are representative of normal values in patients without chronic heart failure. Hs-CRP was measured on Beckman Coulter AU 2700 analyzer (Olympus Germany, Beckman Coulter, Krefeld, Germany) by a particle-enhanced immune turbidimetric method, using latex particles coated with monoclonal anti-CRP antibodies. The test is linear within a concentration range of 0.008–8 mg/dl.

In patients on prolonged anticoagulant therapy and atrial fibrillation/flutter of less than 48 hours duration, transthoracic echocardiography (TTE) was performed before cardioversion. Transesophageal echocardiography (TEE) was performed in patients who had not been on effective chronic anticoagulation therapy and/or the duration of atrial fibrillation/flutter was presumed to be more than 48 hours. TTE was then per-

formed immediately after cardioversion and at 7 and 30 days post-cardioversion. Echocardiography data that were collected included LV ejection function (LVEF) assessed by modified Simpson rule, left atrial dimensions (antero-posterior diameter, area in four-chamber view), and LV diastolic properties (transmitral flow E and A wave peak velocity and lateral wall mitral annular velocity by tissue Doppler imaging).

STATISTICAL ANALYSIS

The baseline clinical and demographic data are expressed as median with 25th–75th interquartile range for skewed distributed quantitative variables and numbers and percentages of patients for categorical data. Other continuous variables are presented as mean and standard error.

A repeated measures ANOVA with Bonferroni correction for multiple comparisons was conducted to determine whether there were statistically significant differences in biomarker levels over the course of a 30 day period after elective electric cardioversion. The significance level was set at 0.05. All data analyses were performed using PASW Statistics for Windows, version 17 (SPSS Inc, Chicago, IL, USA).

RESULTS

Our cohort included 24 patients with 1 month of follow-up after elective cardioversion for persistent atrial fibrillation/flutter [Table 1]. They were predominantly males, mildly overweight, hypertensive, with normal LVEF. About a quarter of the cohort presented with atrial flutter and 70% of the patients were on anti-arrhythmic medications. Mean international normalized ratio (INR) before cardioversion was 2.08 ± 0.79 .

The cardioversion procedure was successful in all patients, and 70% remained in sinus rhythm at 1 month following cardioversion. Median (25th, 75th interquartiles) energy used for cardioversion was 360 J (250, 360). None of the patients underwent repeated cardioversion procedures during the study period.

BIOMARKERS OF MYOCARDIAL INJURY

Median (25th, 75th interquartiles) baseline hs-cTnT levels were slightly above the normal limits at 18.8 ng/L (12.0, 31.9). Fourteen patients presented with hs-cTnT levels above 13.0 ng/L. hs-cTnT levels did not change significantly post-cardioversion, although there was a non-significant decrease in hs-cTnT levels by 30 days [Figure 1]. We attempted to analyze hs-cTnT kinetics for the patients with initially elevated troponin levels (above 99th percentile) versus patients with detectable yet low range initial troponin levels, but no differences were observed, perhaps due to the small number of patients in each group (data not shown). The levels of creatine kinase, AST, and LDH were within the normal range at all time points [Table 2].

OTHER BIOCHEMICAL PARAMETERS

Baseline BNP concentrations were elevated with a non-significant decrease in levels by 30 days after cardioversion [Table 2]. Similarly, hs-CRP levels, which were mildly increased at baseline, decreased over time [Table 2].

Table 1. Demographic data and concomitant medications

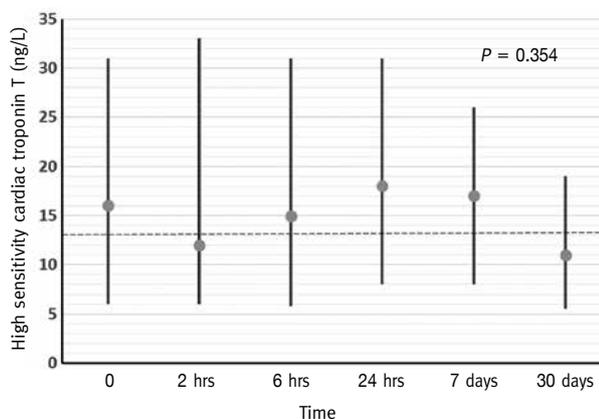
No. of patients	24
Age (years)	69.0 (62.0–76.0)
Male (%)	81.0
Body mass index (kg/m ²)	27.7 (26.3–32.8)
Atrial flutter (%)	23.8
Hypertension (%)	85.7
Diabetes mellitus (%)	42.9
Prior myocardial infarction (%)	33.3
Prior percutaneous coronary intervention (%)	38.1
Prior coronary artery bypass graft surgery (%)	19.0
Left ventricular ejection fraction	58.0 (40.0–60.0)
Concomitant medications	
Antiplatelet (%)	52.4
Anticoagulant (%)	74.1
Beta-receptor blocker (%)	71.4
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (%)	76.2
Calcium channel blocker (%)	33.3
Digoxin (%)	9.5
Diuretic (%)	23.8
Mineralocorticoid receptor antagonist (%)	33.3
Anti-arrhythmic (%)	70.2

Data are presented as frequency (%) or median with 25th–75th interquartile range

ECHOCARDIOGRAPHIC PARAMETERS

LVEF, as a measure of systolic function at baseline, was in the lower limit of normal (52.1 ± 14.7%) and did not change significantly during the study period; the same was seen for end-systolic (36.8 ± 8.5 mm) and end-diastolic (50.1 ± 7.2 mm) dimensions of left ventricle. Left atrial antero-posterior diameter (43.9 ± 5.8 mm) and left atrial area (26.5 ± 4.7 cm²) also did not change during the study period. The only variables that were significantly altered after cardioversion were mitral inflow A wave velocity (35.2 ± 23.7, 50.0 ± 18.9, 62.8 ± 15.9 cm/sec at immediate period after, 7 days and 30 days after cardioversion, respectively) and velocity time integral (4.2 ± 0.8, 5.4 ± 1.7, 7.3 ± 4.2 cm at immediate period after, 7 days and 30 days after cardioversion, respectively).

Figure 1. hs-cTnT kinetics in atrial fibrillation patients after direct current cardioversion presented as median (25th, 75th interquartiles)



Dotted line indicates limit of 99th percentile for troponin assay, 13 ng/L
Hs-cTnT = high sensitivity cardiac troponin T

● = before cardioversion; other values on the x axis indicate time after cardioversion

Table 2. Biomarker levels before and after elective direct current cardioversion

	Baseline	2 hr	6 hr	24 hr	7 days	30 days	P
HscTnT (ng/L) (3–13 ng/L)*	16.0 (6.0, 31.0)	12.0 (6.0, 33.0)	15.0 (5.8, 31.0)	18.0 (8.0, 31.0)	17.0 (8.0, 26.0)	11.0 (5.5, 19.0)	0.354
BNP (ng/L) (5–100 ng/L)*	159.0 (104.0, 206.0)	91.6 (61.6, 175.0)	105.5 (49.4, 180)	177.0 (93.1, 293.5)	164.0 (91.5, 293.5)	77.0 (59.0, 178.0)	0.278
Hs-CRP (mg/L) (0–5 mg/L)*	5.5 (2.1, 8.3)	5.1 (2.2, 6.5)	5.0 (2.5, 5.9)	4.2 (3.2, 5.1)	3.9 (2.5–5.1)	3.5 (1.3, 4.9)	0.732
CK (u/L) (37–167 u/L)*	77.0 (59.0, 178.0)	65.0 (53.0, 161.8)	68.0 (51.0, 159.8)	82.5 (51.3, 159.8)	90.5 (54.5, 161.0)	86.0 (54.0, 170.0)	0.273
LDH (u/L) (230–480 u/L)*	443.0 (366.5, 486.0)	424.0 (377.0, 481.0)	397.5 (306.8, 467.3)	424.0 (338.0, 467.0)	440.5 (351.5, 558.8)	413.0 (364.0, 515.0)	0.132
AST (u/L) (0–35 u/L)*	29.0 (21.0, 34.0)	23.0 (19.5, 31.0)	25.0 (19.0, 29.5)	27.0 (19.0, 29.5)	23.5 (19.3, 29.8)	24.0 (20.0, 35.0)	0.438

Data are presented as median (25th, 75th interquartiles)

*Normal range

BNP = brain natriuretic peptide, Hs-CRP = high sensitive C-reactive protein, CK = creatine kinase, LDH = lactate dehydrogenase, AST = aspartate aminotransferase

DISCUSSION

Our study, to the best of our knowledge, is the first to scrutinize circulating hs-cTnT kinetics over the course of a 30 day period after elective, biphasic, direct-current cardioversion for persistent atrial fibrillation/flutter. The main finding of our study was that hs-cTnT levels, which were slightly elevated at baseline, did not rise after electric cardioversion but tended to decrease over time. There was no rise in other biomarkers of myocardial injury, such as creatine kinase, AST and LDH. However, similar to hs-cTnT, the levels of neuroendocrine and inflammatory biomarkers, such as BNP and hs-CRP, were elevated at baseline and tended to decrease over time.

In a significant portion of our patients (58.3%), hs-cTnT was above the 99th percentile level before cardioversion. The clinical importance of this elevation is not well defined. Some observational data show that elevated baseline troponin levels are associated with increased all-cause and cardiovascular mortality, as well as with increased stroke occurrence [18-20]. Our cohort is too small to explore the prognostic significance of elevated baseline hs-cTnT levels.

Prior studies that examined cardiac troponin I and/or T levels during the first 12–24 hours after external cardioversion showed that the levels do not rise after electrical cardioversion [5-7]. In one study, however, a significant increase in mean serum cardiac troponin I was found 24 hours after cardioversion using monophasic shock, which correlated with total energy used and did not occur using biphasic shock [4]. In the only study that investigated hs-cTnI kinetics after electric cardioversion, hs-cTnI level was measured only during the first 12 hours post-procedure [14]. The authors found that hs-cTnI level increased at 6 and 12 hours after cardioversion, but the levels exceeded the cutoff for myocardial infarction diagnosis according to the manufacturer and the World Health Organization in only one patient [14]. In contrast, we found that hs-cTnT level does not increase significantly during the first 24 hours after cardioversion. Furthermore, we showed that the levels tend to gradually decrease following cardioversion. Given the elevated hs-cTnT levels at baseline in our cohort and the trend for decreased levels after cardioversion, we suggest that the decrease in hs-cTnT level may be attributed to the salutary hemodynamic effects of preserved sinus rhythm.

Pre-procedure BNP levels were also increased, in line with previous studies [9-11]. Prior studies have shown that natriuretic peptide levels decrease rapidly following conversion to sinus rhythm [12,13,15]. Our findings complement these prior studies, demonstrating that BNP levels tend to decrease after sinus rhythm restoration. Several studies found that baseline natriuretic peptide level was an independent predictor for atrial fibrillation recurrence [15], while other studies failed to show a correlation between baseline natriuretic peptides and atrial fibrillation recurrence rate [14,18]. We did not investigate the

correlation between BNP level and the maintenance of sinus rhythm after cardioversion since our population study was too small.

Most studies of hs-CRP kinetics post-cardioversion have shown a decrease in hs-CRP levels after restoring sinus rhythm and found the pre-procedure level to be an independent predictor of atrial fibrillation recurrence [19,20]. We demonstrated a trend for decreased hs-CRP levels after cardioversion, in line with these previous studies.

Altogether, our findings indicate that the hs-cTnT kinetics follow the course of other non-specific neuroendocrine and inflammatory markers and thus most probably reflect a generalized systemic response rather than a localized necrotic process. Possibly, the elevated baseline hs-cTnT levels reflect low grade myocardial injury due to the altered hemodynamic state.

LIMITATIONS

We acknowledge the small sample size of our study, but the comprehensive biomarker surveillance and echocardiographic data that show similar trends lend credence to our findings.

CONCLUSIONS

Patients with persistent atrial fibrillation/flutter have elevated hs-cTnT levels as part of a general rise in biomarkers such as BNP and hs-CRP without further rise after cardioversion and restoration of sinus rhythm in levels of these biomarkers, including hs-cTnT. Thus, a rise in hs-cTnT levels post-cardioversion should not be attributed to the procedure, and other causes should be sought.

Correspondence

Dr. Z. Iakobishvili

Dept. of Cardiology, Rabin Medical Center, Petah Tikva 49100, Israel

Phone: (972-3) 937-7130

Fax: (972-3) 921-3221

email: zaza@o13.net

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