Factors underlying elevated troponin I levels following pacemaker primo-implantation

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Background. Cardiac troponins are routinely used as markers of myocardial damage. Originally, they were only intended for use in diagnosing acute coronary syndromes; however, we now know that raised serum troponin levels are not always caused by ischemia. There are many other clinical conditions that cause damage to cardiomyocytes, leading to raised levels of troponin. However, the specificity of cardiac troponins towards the myocardium is absolute. Our work focuses on mechanical damage to the myocardium and on monitoring the factors that raise the levels of cardiospecific markers after primo-implantation of a pacemaker with an actively fixed electrode.
Aims. (i) To determine whether the use of a primo-implanted pacemaker with an electrode system with active fixation will raise troponin levels over baseline. (ii) To assess whether troponin I elevation is dependent on procedure complexity.
Methods. We enrolled 219 consecutive patients indicated for pacemaker primo-implantation; cardiospecific marker values (troponin I, CKMB, myoglobin) were determined before the implantation procedure and again at 6- and 18-h intervals after the procedure. We monitored duration of cardiac skiascopy, number of attempts to place the electrode (active penetration into the tissue) and intervention range (single-chamber versus dual-chamber pacing), and we assessed the clinical data.
Results. The average age of the enrolled patients was 78.2 ± 8.0 years (median age, 80 years); women constituted 45% of the group. We implanted 128 dual-chamber and 91 single-chamber devices with an average skiascopic time of 38.6 ± 22.0 s (median, 33.5 s). Troponin I serum levels increased from an initial 0.03 ± 0.07 μg/L (median, 0.01) to 0.18 ± 0.17 μg/L (median, 0.13) and 0.09 ± 0.18 μg/L (median, 0.04) at 6 and 18 h, respectively. The differences were statistically significant ($P < 0.001$ or $P < 0.001$). We confirmed a correlation between troponin increase and duration of skiascopy ($P < 0.001$). We also demonstrated a correlation between increased troponin I and number of attempts to place a pacemaker electrode (penetration into the tissue) at 6 h ($P < 0.001$) post-implantation.
Conclusion. We detected slightly elevated troponin I levels in patients with primo-implanted pacemakers using electrodes with active fixation. We demonstrated a direct correlation between myocardial damage (number of electrode penetrations into the myocardium) and troponin I elevation, as well as between complexity (severity) of the implantation procedure (indicated by prolonged skiascopy) and raised troponin I. The described phenomenon demonstrates the loss of the diagnostic role of troponin I early after pacemaker primo-implantation in patients with concomitant chest pain.

Key words: cardiac pacing, troponin, primo-implantation, myocardial damage

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INTRODUCTION

Cardiac troponins are structural proteins in cardiac myofibrils that were first described by Ebasi and Kodama in 1965 (Hartshorne[1]). The structure of the troponin-tropomyosin complex has been discovered gradually, together with advancements in electron microscopy techniques. Initially, troponins were studied to clarify understanding of the contraction and relaxation of cardiac muscle. Since the 1990s, they have been used as markers of myocardial damage, and the need for proper clinical interpretation of troponin elevation has grown as detection methods have increased in sensitivity.

Myofibrils, as the basic building blocks of muscles, consist of thick myosin and thin actin fibres. Mutual interactions between these structures coordinated by myosin heads in combination with energy support leads to the complex mechanism of cardiac contraction[2-3].

Approximately 92% of troponin is found bound to cardiac myofibrils, whereas only ~8% is found within cardiac myocyte cytoplasms in soluble form. The pathological effects associated with injury to cardiomyocytes

generally result in damage to cell wall integrity, leading to the fast release of soluble troponin, which is reflected by a rapid increase in serum troponin levels. This is followed by several hours or days during which myofibrils are gradually proteolytically degraded. In particular, the central, acidic portion of the fast troponin isoform, which is comprised of epitopes that are recognized by antibodies included in diagnostic kits[4], is gradually released from the necrotic portion of the myocardium, explaining its long persistence in serum[5-7]. The actual mechanism of troponin release from cardiomyocytes depends on the mechanism of injury. The most typical mechanism is ischemia, which can be modified by many factors, such as pre-conditioning[8], post-conditioning[9,10], length of ischemic insult, and rate of coronary obturation. Ischemia triggers the apoptotic cascade[11], leading to the presence of detectable troponin fragments in apoptotic bodies[12]. Ischemia also initiates the release of troponin fragments from so-called "myocardial blebs" (ref.[13,14]), which are sarcolemmal evaginations[14]. The development of myocardial blebs may not necessarily result in cell death. It is still disputed whether detectable troponin levels in the serum automatically indicate a loss of myocardial mass[4,15-17]. Mechanisms of troponin release from cardiomyocytes may be further associated with the toxic effects of various substances on the myocardium, i.e., sepsis[18-24] or the administration of "cardiotoxic chemotherapy" (ref.[4,25]), although some authors challenge this[26]. "Catecholamine overload" (ref.[27-29]) or direct mechanical damage[30-39] during skiascopy of the heart (during pacemaker implantation) can be a marker of procedure complexity and may positively correlate with troponin levels[31]. Left ventricular failure[40], right ventricular failure[41-43], or the disparity between physiological degradation of the myocardium and insufficient elimination of its fragments (renal insufficiency) (ref.[44-46]) also lead to slight elevations in serum troponin.

AIMS

(i) To assess the degree of elevation of cardiospecific markers (troponin I, CKMB, myoglobin) in the serum after pacemaker primo-implantation using an electrode system with active fixation in patients with single-chamber and dual-chamber pacing. This serves as a model of direct cardiomyocyte destruction by a fixation system. Additionally, to delineate the dependency between the elevation of cardiospecific markers and other intervention factors, such as duration of skiascopy, number of stimulation electrode penetrations into the tissue, and clinical data.

(ii) To determine the incidence of input-positive findings of troponin I in patients indicated for permanent pacing and coronary angiography and what factors influence this phenomenon.

(iii) To evaluate whether duration of skiascopy in a performed intervention is directly proportional to increases in troponin I after pacemaker primo-implantation.

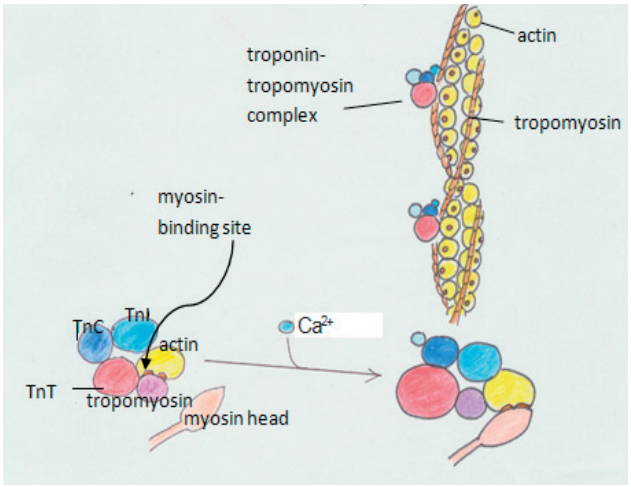

Fig. 1. Troponin-tropomyosin complex.According to Kittnar Otomar. Lékařská fyziologie. 1st edition. Praha: Grada; 2011. p. 92; adapted by Eva Šilerová (ref. [2]).

METHODS

In total, our group included 219 patients indicated for pacemaker primo-implantation. These were consecutive patients registered at the Department of Medicine (Cardiology), 1st Faculty of Medicine, Charles University in Prague, Military University Hospital in Prague.

Indicating diagnoses were based on the Recommendations of the Czech Society of Cardiology on cardiac pacing and resynchronization therapy, 2012 (ref.[47]).

Table 1. Indicating diagnoses.

sick sinus syndrome	93 patients
sick sinus syndrome + AV block	8 patients
sinus rhythm + AV block	41 patients
atrial fibrillation + AV block	77 patients

Exclusion criteria: Previously underwent temporary pacing, poor condition after cardiopulmonary resuscitation, on-going acute coronary syndrome, on-going sepsis or other pathological condition that induces increased levels of troponin. Values of cardiospecific markers in serum were determined using commercially available kits from the following manufacturers: Troponin I (Abbott®), CKMB (Olympus®), and myoglobin (Olympus®). Blood samples from each patient were analysed immediately after collection at the Department of Biochemistry, Haematology and Blood Transfusion in the Central Military Hospital. Troponin I levels were determined using an ARCHITECT analyser with a STAT Troponin I kit (both analyser and kit were manufactured by Abbott®). The detection limit for the kit is 0.01 μg/L, with a range of 0.017-50.0 μg/L (the samples were diluted as necessary). The 99th percentile was 0.06 μg/L. CK-MB enzyme levels were measured using an Aeroset analyser (Abbott®) with a CK-MB test kit (Olympus®; OSR6153). The detection limit for the kit is 0.017 ukat/L, with a range of 0.017-33.3 ukat/L. The 99th percentile was 1.00 ukat/L.

Myoglobin levels were determined using an Aeroset analyser (Abbott®) with a myoglobin detection kit (Olympus®; OSR6168). The detection limit of the kit is 3.14 μg/L, with a range of 3.14-20,000 μg/L. The 99th percentile was 65.0 μg/L. Samples were taken prior to primo-implantation and at 6 and 18 h after the intervention. We monitored duration of skiascopy as a marker of procedure complexity, as well as number of attempts to place the electrode (considering active fixation in the tissue as a sinkhole). Another factor of consideration was the extent of implantation procedure (dual-chamber vs. single-chamber pacing). The implantation procedure was performed in an implantation room using sterile safeguards under skiascopic control. A OEC 9900 device with a rotary C-arm (GE-Healthcare®) was used with a pulse mode of 4 frames/sec. Measured skiascopic time was converted by software into continuous X-ray radiation. We implanted devices from the manufacturers Boston-Scientific® (Guidant®) and Biotronik®; however, the implanted electrodes were mainly from Biotronik® (Siello, Setrox, Safio; Safio electrode is MRI-compatible), while the other electrodes were Flextend 2 (Boston-Scientific®) and Capsurefix (Medtronic®).

The control group consisted of 100 consecutive patients indicated for elective coronary angiography; in this group, only troponin I levels were determined. Data were collected prospectively from patients hospitalized at the Department of Internal Medicine (Cardiology), 1st Faculty of Medicine, Charles University in Prague, Military University Hospital in Prague.

Each of the enrolled patients signed an informed consent, and the project was approved by the local ethics committee.

Standard descriptive statistics was applied in the analysis: absolute and relative frequencies for categorical variables and mean supplemented by standard deviation nad median for continuous variables. Because the assumption of normal distribution was violated for most parameters (Shapiro-Wilk's test), nonparametric analyses were performed. Statistical significance of differences between groups of patients was computed χ^2 test for categorical variables and Mann-Whitney test for continuous variables. The differences of variables in time were tested by paired Wilcoxon test.The Sperman correlation coefficient was used to verify the relationship between studied variables. The level of statistical significance was set at $\alpha = 0.05$. STATISTICA, Stat.Soft, Inc (2013) version 12 was adopted for data analysis.

RESULTS

The following table details the characteristics of the study group, including risk factors.

Table 2. Clinical characteristic.

	Mean ± SD (median)/%
Average age	78.2 ± 8.0 (80)
Percentage of women	45
Implanted devices	128 dual-chamber, 91 single-chamber
Average skiascopic time (s)	38.6 ± 22.0 (33.5)
Hypertension	82
Diabetes	26
Dyslipidaemia	30
ICHS	32
Heart failure	15
Stroke	12

The average age of the study group corresponds to the average age of patients implanted in the Czech Republic; the proportion of women in the group also corresponded to that of implant patients (REPACE register 2010; ref.[48]). Compared to published data, the average duration of skiascopy was short. This may have resulted from the methodology used: a pulse mode of 4 frames/s was applied to all patients, and the time was converted by software into a continuum.

The enrolled patients were quite polymorbid. Their risk factors corresponded to the incidence of risk factors in the population of comparable age[49-50]. In the whole group, the mean baseline value of troponin I was 0.03 ± 0.07 (median is 0.01) μg/L, i.e., normal. As indicated in Table 3, the entire study group showed a significant increase in troponin I 6 h after pacemaker primo-implantation, followed by a gradual decline through 18 h after primo-implantation. This decline, however, was still not within a normal value range. The difference was also statistically significant compared to baseline levels of troponin I prior to implantation. For CKMB, the recorded baseline was 0.45 ± 0.43 (0.33) ukat/L, and at both 6 and

Table 3. Cardiospecific markers.

Entire patient cohort	Troponin I levels (normal range: 0–0.06 ug/L) Mean ± SD (median)	CKMB levels (normal range: 0–1.0 ukat/L) Mean ± SD (median)	Myoglobin levels (normal range: 28–72 ug/L) Mean ± SD (median)
Before primo-implantation	0.03±0.07 (0.01)	0.45±0.43 (0.33)	108.1±59.5 (96.0)
6 h after primo-implantation	0.18±0.17 (0.13)	0.39±0.46 (0.31)	112.1±76.8 (96.4)
18 h after primo-implantation	0.09±0.18 (0.04)	0.32±0.43 (0.27)	99.3±60.6 (92.1)
P (before primo-implantation vs. 6 h after primo-implantation; Wilcoxon test)	1st line against *P* < 0.001	2nd line *P* = 0.001	*P* = NS
P (6 h after primo-implantation vs. 18 h after primo-implantation; Wilcoxon test)	2nd line against *P* < 0.001	3rd line *P* < 0.001	*P* < 0.001

Table 4. Skiascopy.

Parameter	VVI(R) n=91 Mean ± SD (median)	DDD(R) n=128 Mean ± SD (median)	*P* (Mann-Whitney U test)
SKIA time (S.)	29.6±18.6 (23.4)	45.2 ±22.1 (39.0)	< 0.001

18 h after primo-implantation, we observed a statistically significant decline. Myoglobin values before implantation and at 6 and 18 hours after implantation were slightly elevated compared to baseline; however, the differences were not statistically significant.

Subsequently, we studied a group of 91 patients who were implanted with single-chamber systems (VVI) and a group of 128 patients who were implanted with dual-chamber systems (DDD). The single-chamber group required a significantly shorter average skiascopy duration.

We further found that serum levels of troponin I prior to primo-implantation of the single-chamber system differed significantly from those prior to primo-implantation of the dual-chamber system ($P = 0.027$, Mann-Whitney test): they statistically significantly increased by 6 h after primo-implantation in the group receiving dual-chamber pacing versus that receiving single-chamber pacing. A gradual decline followed by 18 h after primo-implantation.

In the entire study group of 219 patients, positive troponin I before pacing was detected in 15 patients (6.8%). Of the entire patient cohort, 46 patients suffered from renal insufficiency. Only 5 patients with renal insufficiency showed input troponin positivity. The other 10 patients with input troponin positivity had normal creatinine levels, and the difference was not significant ($P = 0.25$, χ^2 test). Renal insufficiency was defined as serum creatinine level >110 μmol/L in women and >125 μmol/L in men. Interestingly, a statistically significantly higher level of troponin I was found in patients with single-chamber pacing. After a subanalysis of this group, comprised of 91 patients, we found that 79 patients had an input rhythm of atrial fibrillation, whereas 12 patients had sinus rhythm. In the group with dual-chamber pacing, 1 patient had paroxysmal atrial fibrillation, while the other 127 patients had sinus rhythm. In comparing the troponin levels of the group of patients with atrial fibrillation (n = 80) and the group with sinus rhythm (n = 139), we find the following:

In the group of patients with atrial fibrillation who were indicated for pacemaker primo-implantation, the level of troponin I was higher than in the group with sinus rhythm. However, the average value in the group with atrial fibrillation did not exceed the 99th percentile of the population incidence of serum levels of troponin I. Compared to the group with sinus rhythm, the difference was statistically significant based on the Mann-Whitney U test. When assessing both groups with regard to the number of patients with positive troponin I levels (i.e., values greater than the 99th percentile of the incidence of serum levels in the population), we identified 7 positive patients (8.8%) in the group with input rhythm of atrial fibrillation and 8 positive patients (5.8%) in the group with preserved sinus rhythm. This difference did not reach statistical significance ($P = 0.25$, χ^2 test).

We demonstrated a statistically significant correlation between increased troponin level after primo-implantation and increased skiascopic time (Spearman correlation coefficient = 0.39; $P < 0.001$ and 0.37; $P < 0.001$ after 6 or 18 h). See Fig. 2 and 3.

A pacing electrode is not always placed at the first attempt. Sometimes, it is necessary to make several attempts to place it into the tissue (sinkholes of the fixation system into the myocardium), whereas the electrode must

Table 5. Pacing type.

Paramer	Pacing type: VVI(R) n=91 Mean ± SD (median)	Pacing type: DDD(R) n=128 Mean ± SD (median)	*P* (Mann-Whitney U test)
Tn I (ug/L) before implantation	0.03± 0.10 (0.01)	0.02 ±0.05 (0.01)	$P = 0.027$
Tn I (ug/L) 6 h after implantation	0.12 ± 0.11 (0.08)	0.23± 0.20 (0.16)	$P < 0.001$
Tn I (ug/L) 18 h after implantation	0.08±0.25 (0.04)	0.10±0.11 (0.07)	$P < 0.001$
P (before implantation vs. 6 h after implantation; Wilcoxon test)	1st line against 2nd line $P < 0.001$	1st line against 2nd line $P < 0.001$	
P (6 hours after implantation vs. 18 hours after implantation; Wilcoxon test)	2nd line against 3rd line $P < 0.001$	2nd line against 3rd line $P < 0.001$	

Table 6. Rhythm.

Rhythm	n	Troponin I level (ug/L) mean ± SD	Median (ug/L)	Number of positive Tn I values (%)
Atrial fibrillation	80	0.03±0.10	0.01	7 (8.8)
Sinus rhythm	139	0.02±0.05	0.01	8 (5.8)
P		$P = 0.01$ Mann-Whitney U test		$P = 0.25$ χ^2 test

be repeatedly released. Therefore, the risk of myocardial injury increases.

In our group, the number of performed fixations was low, as we typically managed to place the electrode in the first attempt. See Fig. 4.

After 6 h, we found higher levels of troponin I in the group of patients who underwent more than 1 fixation in myocardial tissue compared to the patients in whom fixation occurred at the first attempt ($P < 0.001$). After 18 h, the difference was not statistically significant ($P = 0.09$; Mann-Whitney U test). We defined a group of 100 patients scheduled for elective coronary angiography as a control group. Positive troponin was detected in 10 patients (10%); the average value was 0.05±0.17 g/L, and the median was 0.01 µg/L. In the control group, renal insufficiency occurred in 5 patients (5%). Of the entire studied group of 219 patients, there were 159 findings of positive troponin I by 6 h after the implantation procedure (73%). Positivity persisted even 18 h post-implantation, at which point we detected 86 positive results (39%). A total of 83 positive samples were taken from patients whose troponin I levels were already elevated after 6 h; 3 positive samples were from patients whose troponin I levels were initially negative after 6 h. Of the whole group of 219 patients, as mentioned above, positive troponin I at input was observed in 15 patients. In one patient, 6 h after primo-implantation, we observed a decline of troponin to within a normal range, and this decline continued even after 18 h. In the remaining 14 patients, the values of troponin I increased by 6 h after implantation; this increase persisted in 11 of the patients even after 18 h.

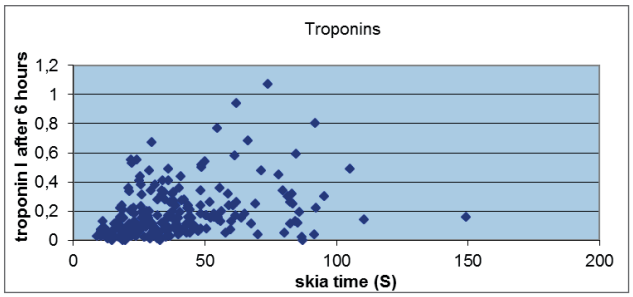

Fig. 2. Relationship between troponin I values 6 h after primo-implantation and skiascopic time (Spearman correlation coefficient = 0.40; $P < 0.001$).

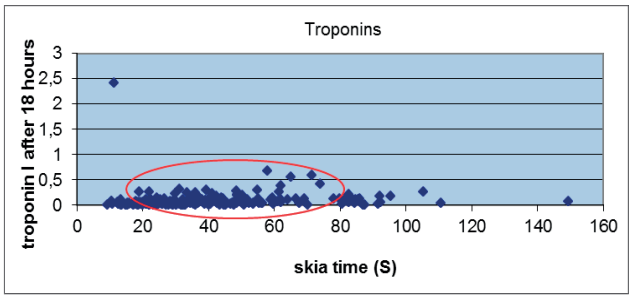

Fig. 3. Relationship between troponin I values 18 hours after primo-implantation and skiascopic time. (Spearman correlation coefficient = 0.37; $P < 0.001$).

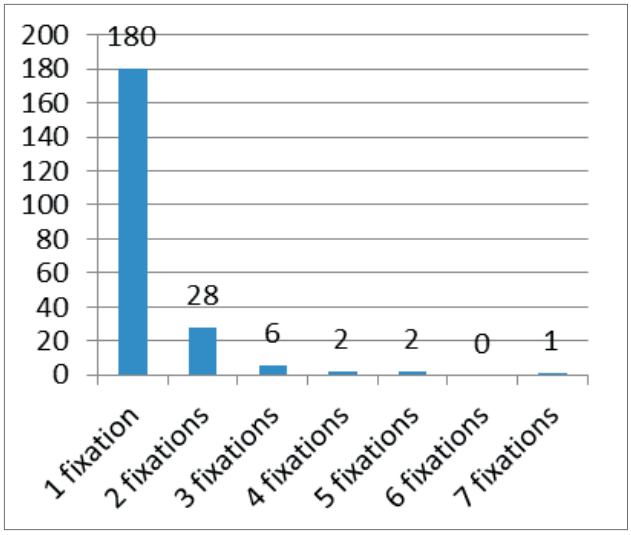

Fig. 4. Number of fixations.

DISCUSSION

In an uncomplicated primo-implantation of a pacemaker with an actively fixed electrode system, purely mechanical damage occurs to the portion of the myocardium subjected to the procedure, including the destruction of a small number of cardiomyocytes and subsequent troponin leakage into the serum. In the current work, we demonstrated a slight elevation in troponin I levels already at input in 15 patients out of the entire cohort (6.8%; n = 219). Subsequently, after performing the primo-implantation procedure, troponin I levels increased; this was more predictable in the group with dual-chamber pacing. In the case of dual-chamber pacing, two electrodes must be inserted, leading to myocardial "wounding" in two places, although the atrial channel implantation is associated with the atrial myocardium. In a study by Martignani, who monitored troponin levels in a group of 70 patients after pacemaker primo-implantation, no significant elevations were found following implantations of atrial electrodes. This result was explained by the reduced content of muscle tissue in the right atrium[30]. Martignani further observed increased troponin I levels in 1/3 of the patients after primo-implantation. The majority of the patients had actively fixed pacing electrodes, and the elevated troponin levels stabilized after 12 h and returned to normal levels after 24 h. In a study published by Boos et al.[31], after the introduction of permanent pacing in 76 patients, positive troponin I levels were found in 21% of the cohort. In our group, we found positive troponin I levels in 73% of patients 6 h after the procedure (159 of 219) and in 39% of patients 18 h after the procedure (86 of 219). The values of input positivity for troponin I were not listed in the studies by Martignani[30] and Boos[31]; we found this positivity in 6.8% of patients. This apparent contradiction can be explained by the use of different diagnostic kits for the detection of troponin I. Kits from different manufacturers are calibrated quite differently, particularly with regard to detection limits and 99th percentile values. The variation

coefficient should not vary considerably (≤10%) with the use of any diagnostic kit[4].

The high rate of positive troponin I following pacemaker primo-implantation in our group can be explained by the application of active fixation to 100% of our patient cohort. Active fixation was not used in the two studies cited above. In the study by Boos, it was even an exclusion criterion (this work was published in 2002, when active fixation was only starting to become a regular part of clinical practice).

In direct mechanical myocardial injuries, compared to ischemic injuries, we found troponin I levels to peak slightly faster; these normalized within 24 h of the procedure[30]. A similar rate for the onset of troponin I elevation was described by Altin[32] after monitoring 30 patients subjected to implantations of different types of pacemakers. In a study by Sbarouni[33], the possibility of myocardial injury during the introduction of passive electrodes was demonstrated. This work evaluated a group of 64 patients and found that after primo-implantation of various devices, both troponin I levels and ischemia-modified albumin (IMA) levels were elevated. According to the author, myocardial damage can be caused in response to the induction of even a very small amount of necrosis from the tip of the electrode.

In a study by Davoodi[34], troponin T levels were compared between patients undergoing pacemaker versus ICD primo-implantations. The group of patients undergoing ICD implantations had higher levels of troponin T. In this case, the aetiology of this phenomenon is polyfactorial. Several studies have attributed serum troponin positivity to the combined use of defibrillation electrode fixation and application of defibrillation discharges in patients with primo-implanted ICDs (ref.[35]). In a study by Hurst that evaluated 49 patients after ICD implantation, troponin I elevation occurred in only 14% of patients, whereas troponin levels were positively correlated with the applied energy during the test discharge as well as with the duration of ventricular tachycardia during ICD testing. However, this study was also relatively small, and individual risk factors related to the studied phenomenon appeared sporadically. In a study by Dworschak[36], elevated troponin T levels were found after the implantation of defibrillation electrodes in 27 patients. Troponin levels were higher when systems with active fixation were implanted, and the levels did not correlate with test discharge energy. There was a positive correlation between troponin T level and length of implantation procedure (in this case, skiascopic time was not used as a marker of procedure complexity). In a study by Schluter[37], 14 patients with indications for ICD implantation were evaluated. Levels of troponin T, troponin I, and CKMB were determined. After implantation, the levels of these markers were elevated in patients who received at least 2 discharges, and an early rise in all of the markers was observed. In ICD implantations, test discharges are always applied. The duration of ventricular tachycardia is generally short. It may vary according to the defibrillator detection scheme, but only on the order of seconds, and therefore does not cause troponin elevation.

In a 2015 study published by Furniss[38], increased levels of troponin T in patients undergoing simple ICD implantations both with and without discharge therapy were observed. There were no differences in troponin T elevation between the two groups and no differences in the dependence on total energy applied during test discharge. Although this study was small (the two groups were comprised of 11 and 13 patients who underwent only 2 troponin samplings, including input sampling and a sampling 6-8 h after ICD primo-implantation), it demonstrated a positive correlation between number of active fixations into myocardial tissue (deployments) and troponin levels, analogous to our group of 219 patients. All of the above-referenced works suffered the limitation of a relatively small number of enrolled patients, which weakens the statistical significance of their conclusions. Nevertheless, troponin positivity has been found in studies on implanted pacemakers and therefore we can extrapolate that the same applies to patients with ICDs. Furthermore, we speculate that troponin levels may slightly increase in response to the use of test discharges during ICD primo-implantations.

The above-referenced studies describing elevated troponin levels following primo-implantation of pacing/defibrillation electrodes with active fixation also demonstrated that troponin levels peak rapidly following these procedures. We confirmed this phenomenon in the present work. This can generally be explained by the rapid release of soluble troponin following cardiomyocyte injury[4]. Interindividually, the rate of troponin release from injured myocardium is modified by lymphatic cardiac drainage capacity when troponin enters the capillary network. After the lymphatic system fills, troponin ultimately flows into the venous system via the ductus thoracicus[4].

Regarding the other evaluated markers, the results were inconclusive. When evaluating CKMB levels, significant decreases of 0.06 and 0.07 ukat/L were noted at 6 and 18 h after primo-implantation, respectively. These decreases do not represent clinically important differences, although they are statistically significant.

A well-known study by Nikolaou[39] found changes in CKMB levels that were statistically insignificant. In contrast, a study by Sbarouni described a statistically significant increase in CKMB after pacemaker primo-implantation. Currently, however, the use of CKMB as a marker of ischemic myocardial damage has been largely abandoned. Current guidelines[51] do not recommend using CKMB levels to diagnose acute coronary syndrome; rather, they are only recommended for the early detection of myocardial reinfarction. Therefore, further studies on this phenomenon have no clinical significance.

In our group of 219 patients, myoglobin levels at 6 and 18 h after implantation varied insignificantly. A similar conclusion was made following pacemaker primo-implantation in the above-mentioned study by Nikolaou[39]. However, the clinical significance of myoglobin is even less than that of CKMB, and myoglobin is no longer used for the diagnosis of acute coronary syndrome. Myoglobin, analogous to CK, is important for diagnosing lesions in striated muscle (e.g., in rhabdomyolysis).

A serious comorbidity affecting the clinical condition of implant patients is atrial fibrillation, which poses a thromboembolic risk and is correlated with a higher incidence of positive serum troponin. In a subanalysis of the ARISTOTLE study, a 9.2% incidence of elevated high sensitive troponin I was found in a group of 14 821 patients. In this analysis, troponin elevation was associated with a worse prognosis and related to a statistically significantly greater incidence of CMP (ref.[52]). In a 2012 study by Roldan[53], troponin T positivity was found in 31% of 930 patients with atrial fibrillation. Roldan's work also indicated that troponin T serves as a marker of worse prognosis (combined objective of cardiovascular events). In this study, a greater predictive value was provided following the combined evaluation of troponin T and interleukin 6 (IL6) (ref.[53]). The combination of these two variables is logical and demonstrates the unsurprising presence of systemic inflammatory responses and high morbidity in patients with atrial fibrillation. In this case, atrial fibrillation represents a secondary manifestation of another commonly encountered disease (sepsis, heart failure, etc.) (ref.[54,55]). However, why "endothelium-stable" patients with atrial fibrillation have higher levels of troponin has not been reasonably explained.

Positive troponin is often found in patients with renal insufficiency. The aetiopathogenesis of this phenomenon is still unclear, despite that low levels of troponin have been repeatedly described in patients with chronic renal insufficiency[45]. The original theory of decreased troponin clearance in patients with renal failure does not seem to be well founded, as the troponin molecule is quite large. However, it is not possible to exclude decreased clearance of troponin fragments (8-25 kDa), which are subsequently detected in the serum[45]. In patients with renal insufficiency, troponin T occurs much more frequently than troponin I (ref.[56]). In a study by Diris[45], the normal clearance of troponin and troponin fragments was evaluated. In a healthy population, the standard serum concentration of troponin T was 0.0002 μg/L, representing a physiological annual loss of myocardium at the level of 27 mg. Therefore, troponin is generally undetectable in the serum of healthy persons (detection limit is 0.005 μg/L). In patients with reduced renal clearance, however, troponin fragments can accumulate in the serum, and their levels may exceed the 99th percentile of the population. The theory of decreased clearance of troponin fragments also corresponds to the fact that patients show reduced levels of troponin after successful kidney transplantation[57-58]. The aetiology underlying troponin elevation in patients with these conditions is probably multifactorial. A significant proportion of patients have chronic ischemic disease. Contributing factors such as tachyarrhythmia, anaemia and acute infection may result in the development of myocardial lesions and the subsequent detection of troponin in the serum. Another probable mechanism is asymptomatic or oligosymptomatic acute coronary syndrome, which can be under-diagnosed, especially in patients with diabetes who are on dialysis[59-60].

In our study, the proportion of patients with renal insufficiency was relatively low, and a correlation between input elevation of troponin and renal parameters was not demonstrated. Nevertheless, troponin elevation in patients with renal insufficiency is positively correlated with higher mortality. However, the reason for this is not the presence of acute coronary syndrome but rather the higher mortality of these patients in general, including from cardiovascular events[44,46]. Cardiology patients usually suffer from a complex of mutually related clinical syndromes, including diabetes, hypertension, dyslipidaemia, nicotinism, and obesity. Therefore, it is expected that patients with renal insufficiency and elevated troponin have a higher risk of cardiovascular mortality[59]. However, the clinical significance of this phenomenon should be interpreted with caution. Certainly, we should perform coronary angiography even in the absence of a straightforward indication for it. The absence of such an indication can ultimately hurt a patient with significant renal insufficiency. Thus, patients should be comprehensively assessed with regard to risk profile.

We do not expect that elevations of cardiospecific markers in response to local damage to the right ventricle would result in worse morbidity or poorer patient prognosis. In considering its mechanism of myocardial damage, we are of the opinion that the small injuries caused by the use of pacing electrodes with fixation systems would not lead to dire consequences, although relevant corresponding studies have not been published. The clinical significance of this phenomenon lies in assessing the informative value of these markers shortly after electrode implantation, which has a crucial diagnostic impact. If clinical suspicion of acute coronary syndrome (chest pain) is expressed, then the diagnosis cannot involve cardiospecific markers or ECGs where the repolarization phase is affected by the mechanism of "cardiac memory" (ref.[61]). The initial examinations of such patients (except for ECG with the mentioned limitation) should therefore be made using echocardiography aimed at excluding the presence of fluid in the pericardial space (tamponades) via possible perforation of the right ventricle. In the case of persistent doubt, it is necessary to perform selective coronary angiography.

CONCLUSION

The fundamental contribution of our work is the demonstration of small elevations in troponin I levels in patients undergoing primo-implantations of pacemakers using electrodes with active fixation. Troponin I levels increase within a few hours of the procedure. Such a finding in an asymptomatic patient is completely normal and does not require increased attention. As such, it probably does not have any prognostic importance for patients. It can be interpreted in the context of pathophysiological changes, supported not only by the mechanism of simple myocardial injury but also by the faster rate of the onset of serum troponin I levels compared to that following classical ischemic myocardial damage. If a patient develops symptoms typical of acute coronary syndrome shortly after primo-implantation of a cardiac pacing system, it is

necessary to consider the diagnostic function of the loss of and to apply other diagnostic methods.

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REFERENCES

1. Hartshorne DJ. Interactions of desensitized actomyosin with tropomyosin, troponin A, troponin B, and polyanions. J Gen Physiol 1970;55(5):585-601.
2. Kittnar O. Lékařská fyziologie. 1st edition. Praha: Grada; 2011.
3. Parmacek MS, Solaro RJ. Biology of the troponin complex in cardiac myocytes. Prog Cardiovasc Dis 2004;47(3):159-76.
4. Engliš M, Šochman J. Srdeční troponiny v klinické praxi. TAC-TAC agency 2009.
5. Filatov VL, Katrukha AG, Bereznikova AV, Esakova TV, Bulargina TV, Kolosova OV, Severin ES, Gusev N. Epitope mapping of antitroponin I monoclonal antibodies. IUBMB Life 1998;45(6):1179-87.
6. Katrukha AG , Bereznikova AV, Filatov VL, Esakova TV, Kolosova OV, Pettersson K, Lövgren T, Bulgarina TV, Trifonov IR, Gratsiansky NA, Pulkki K, Voipio-Pulkki LM, Gusev NB. Degradation of cardiac troponin I: implication for reliable immunodetection. Clin Chem 1998;44(12):2433-40.
7. Wu AH, Feng YJ. Biochemical differences between cTnT and cTnI and their significance for diagnosis of acute coronary syndromes. Eur Heart J 1998;19:N25-9.
8. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986;74(5):1124-36.
9. Na HS, Yang IK, Young WY, Hee Ch H, Sook HN, Seung KH. Ventricular premature beat—driven intermittent restoration of coronary blood flow reduces the incidence of reperfusion-induced ventricular fibrillation in a cat model of regional ischemia. Am Heart J 1996;132(1):78-83.
10. Ostadal B, Ostadalova I, Kolar F, Sedmera D. Developmental determinants of cardiac sensitivity to hypoxia. Can J Physiol Pharmacol 2014;92(7):566-74.
11. Borutaite V, Brown GC. Mitochondria in apoptosis of ischemic heart. FEBS letters 2003; 541(1):1-5.
12. Olah A, Nemeth BT, Matyas C, Horvath EM, Hidi L, Birtalan E, Kellermayer D, Ruppert M, Merkely G, Szabo G, Merkely B, Radovits T. Cardiac effects of acute exhaustive exercise in a rat model. Int J Cardiol 2015;182:258-66.
13. Sage MD, Jennings RB. Cytoskeletal injury and subsarcolemmal bleb formation in dog heart during in vitro total ischemia. Am J Pathol 1988;133(2):327.
14. Armstrong SC, Shivell ChL, Ganote ChE, Stephen C. Sarcolemmal blebs and osmotic fragility as correlates of irreversible ischemic injury in preconditioned isolated rabbit cardiomyocytes. J Moll Cell Cardiol 2001;33(1):149-60.
15. La Gerche A, Connelly KA, Mooney DJ, MacIsaac AI, Prior DL. Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. Heart 2008;94(7):860-6.
16. Chen Y, Serfass RC, Mackey-Bojack SM, Kelly KL, Titus JL, Apple FS. Cardiac troponin T alterations in myocardium and serum of rats after stressful, prolonged intense exercise. J Appl Physiol 2000;88(5):1749-55.
17. Hickman PE , Potter JM, Aroney C, Koerbin G, Southcott E, Wu AHB, Roberts MS. Cardiac troponin may be released by ischemia alone, without necrosis. Clin Chim Acta 2010;411(5):318-23.
18. Ebelt H, Werdan K. Septischer Kreislaufschock und septische Kardiomyopathie. Medizinische Klinik-Intensivmedizin und Notfallmedizin 2012;107(1):24-8.
19. Turner A, Tsamitros M, Bellomo R. Myocardial cell injury in septic shock. Crit Care Med 1999;27(9):1775-80.
20. Arlati S, Brenna S, Prencipe L, Marocchi A, Casella GP, Lazani M, Gandini C. Myocardial necrosis in ICU patients with acute non-cardiac disease: a prospective study. Intensive Care Med 2000;26(1):31-7.
21. Cheng H, Fan WZ, Wang SC, Liu ZH, Zang HL, Wang LZ, Liu HJ, Shen XH, Liang SQ. N-terminal pro-brain natriuretic peptide and cardiac troponin I for the prognostic utility in elderly patients with severe sepsis or septic shock in intensive care unit: A retrospective study. J Crit Care 2014; Dec.18. [Epub ahead of print] doi: 10.1016/j.jcrc.2014.12.008.
22. Landesberg G, Jaffe AS, Gilon D, Levin PD, Goodman S, Abu-Baih A, Beeri R, Weissman C, Sprung CL, Landesberg A. Troponin Elevation in Severe Sepsis and Septic Shock: The Role of Left Ventricular Diastolic Dysfunction and Right Ventricular Dilatation. Crit Care Med 2014;42(4):790-800.
23. Raj S, Killinger JS, Gonzales JA, Lopez L. Myocardial dysfunction in pediatric septic shock. The J pediatr 2014;164(1):72-77.e2.
24. Vasile VC, Chai VC, Abdeldayem D, Afessa B, Jaffe AS Elevated cardiac troponin T levels in critically ill patients with sepsis. Am J Med 2013;126(12):1114-21.
25. Cardinale D, Sandri MT, Martioni A, Tricca A, Civelli M, Lamantia G, Cinieri S, Martinelli G, Cipolla CM, Fiorentini C. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol 2000;36(2):517-22.
26. Horacek JM, Pudil R, Tichý M, Jebavy L, Strasova A, Praus R, Zak P, Maly J. The use of biochemical markers in cardiotoxicity monitoring in patients treated for leukemia. Neoplasma 2004;52(5):430-4.
27. Anders B, Alonso A, Artemis D, Schäfer A, Ebert A, Kablau M, Fluechter S, Findeisen P, Hennerici MG, Fatar M. What does elevated high-sensitive troponin I in stroke patients mean: concomitant acute myoc ardial infarction or a marker for high-risk patients? Cerebrovasc Dis (Basel, Switzerland) 2012;36(3):211-7.
28. Fromm RE jun. Cardiac troponins in the intensive care unit: common causes of increased levels and interpretation. Crit Care Med 2007;35(2):584-8.
29. Mueller M, Biener M, Vafaie M, Doerr S, Keller T, Blankenberg S, Katus HA, Giannitsis E. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. Clin Chem 2012;58(1):209-18.
30. Martignani C, Diemberger I, Biffi M, Ziacchi M, Saporito D, Valzania C, Bertini M, Domenichini G, Branzi A, Boriani G. Troponin I rise after pacemaker implantation at the time of "universal definition of myocardial infarction". Am J Cardiol 2009;103(8):1061-5.
31. Boos CJ, Gough S, Wheather M, Medbak S, More R. Effects of transvenous pacing on cardiac troponin release. Pacing Clin Electrophysiol 2004;27(9):1264-8.
32. Altin T, Akyurek O, Vurgun K, Beton O, Sayin T, Kilickap M, Karaoguz R, Guldal M, Erol C. Effect of transvenous cardiac resynchronization therapy device implantation on cardiac troponin I release. Pacing Clin Electrophysiol 2007;30(11):1356-62.
33. Sbarouni E, Georgiadou P, Panagiotakos D, Livanis E, Theodorakis GN, Kremastinos DT. The Ischemia-Modified Albumin in Relation to Pacemaker and Defibrillator Implantation. Pacing Clin Electrophysiol 2008;31(1):83-7.
34. Davoodi G, Mohammadi V, Shafiee A, Kazemisaeid A, Sadeghian S, Vasheghani-Farahani A, Yaminisharif A. Detection of myocardial injury due to defibrillation threshold checking after insertion of implantable cardioverter/defibrillators. Acta Cardiol 2013;68(2):167-72.
35. Hurst TM, Hinrichs M, Breidenbach C, Katz N, Waldecker B. Detection of myocardial injury during transvenous implantation of automatic cardioverter-defibrillators. J Am Coll Cardiol 1999;34(2):402-8.
36. Dworschak M, Franz M, Khazen C, Czerny M, Haisjackl M, Hiesmayr M. Mechanical trauma as the major cause of troponin T release after transvenous implantation of cardioverter/defibrillators. Cardiology 2001;95(4):212-4.
37. Schlüter T, Baum H, Plewan A, Neumeier D. Effects of implantable cardioverter defibrillator implantation and shock application on bio-

chemical markers of myocardial damage. Clin Chem 2001;47(3):459-63.
38. Furniss G, Shi B, Jimenez A, Harding SA, Larsen PD. Cardiac troponin levels following implantable cardioverter defibrillation implantation and testing. Europace 2015;17(2)262-6.
39. Nikolaou NI, Christou AH, Spanodimos SG, Antonatos DG, Korkonikitas PI, Patsilinakos SP. Marked troponin elevation after implantation of a permanent antibradycardia pacemaker. Hellenic J Cardiol 2011;52(6):489-92.
40. Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation 2003;108(7):833-8.
41. Lualdi JC, Goldhaber SZ. Right ventricular dysfunction after acute pulmonary embolism: pathophysiologic factors, detection, and therapeutic implications. Am Heart J 1995;130(6):1276-82.
42. Giannitsis E, Muller-Bardorff M, Kurowski V,Weidtmann B ,Wiegand U, Kampmann M, Katus HA. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. Circulation 2000;102(2):211-7.
43. Meyer T, Binder L, Hruska N, Luthe H, Buchwald AB. Cardiac troponin I elevation in acute pulmonary embolism is associated with right ventricular dysfunction. J Am Coll Cardiol 2000;36(5):1632-6.
44. Aviles RJ, Askari AT, Bertil L, Lars W, Gang J, Magnus EO, Mahaffey KW, Newby K, Califf RM, Simoons LM, Topol EJ, Berger P, Lauer MS. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. N Engl J Med 2002;346(26):2047-52.
45. Diris JH, Hackeng CM, Kooman JP, Pinto YM, Hermens WT, van Dieijen-Visser MP. Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients. Circulation 2004;109(1):23-5.
46. Herzog ChA, Collins JZ, Poor AJ. Long-term survival after acute myocardial infarction among patients on long-term dialysis. N Engl J Med 1998;339(12):799-805.
47. Taborsky M, Kautzner J. Summary of the 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: Prepared by the Czech Society of Cardiology. Cor Vasa 2014;56(1):e57-e74.
48. Táborský M. REPACE Registr pacemakerů 2010, [online], Brno, Institut biostatistiky a analýz, ©2010. [cited 1.3.2015]. Available from: http://app3.registry.cz/index.php.
49. Vaverková H, Soška V, Rosolová H, Češka R, Cífková R, Freiberger T, Piťha J, Poledne R, Štulc T,Urbanová Z, Vráblík M. Doporučení pro diagnostiku a léčbu dyslipidemií. Cor Vasa 2007;49(3):K73-K86.
50. Widimský J, Špinar J, Vítovec J, Souček M, Cífková R, Filipovský J, Grundmann M, Linhart A. Doporučení diagnostických a léčebných postupů u arteriální hypertenze–verze 2007. Doporučení České společnosti pro hypertenzi. Cor Vasa 2008;50(1):3-16.
51. Hamm ChW, Bassand J-P , Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Sousa Uva M, Widimsky P. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;32.(23):2999-54.
52. Hijazi Z, Siegbahn A, Andersson U, Granger CB, Alexander JH, Atar D, Gersh BJ, Mohan P, Harjola VP, Horowitz J, Husted S, Hylek EM, Lopes RD, Mc Murray JJ, Wallentin L. High-Sensitivity Troponin I for Risk Assessment in Patients With Atrial Fibrillation Insights From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Circulation 2014;129(6):625-34.
53. Roldan V, Marin F, Diaz J, Gallego P, Jover E, Romera M, Manzano-Fernández S, Casas T, Valdés M, Vicente V, Lip GY. High sensitivity cardiac troponin T and interleukin-6 predict adverse cardiovascular events and mortality in anticoagulated patients with atrial fibrillation. J Thromb Haemost 2012;10(8):1500-7.
54. Kucher N, Goldhaber SZ. Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. Circulation 2003;108(18):2191-4.
55. Swinkels BM, Sonke GS, Muller HP, Peters RH. Prevalence and clinical significance of an elevated cardiac troponin I in patients presenting to the emergency department without chest pain. Eur J Intern Med 2006;17(2):92-5.
56. Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. J Am Coll Cardiol 2002;40(12):2065-71.
57. Musso P, Cox I, Vidano E, Zambon D, Panteghini M. Cardiac troponin elevations in chronic renal failure: prevalence and clinical significance. Clin Biochem 1999;32(2):125-30.
58. McNeil AR. Implications of a rapid decrease in serum troponin T levels after renal transplantation. Aust N Z J Med 2000;30(5):638-9.
59. Khan NA, Hemmelgarn BR, Tonelli M, Thompson CR, Levin A. Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease a meta-analysis. Circulation 2005;112(20):3088-96.
60. Deegan PB, Lafferty ME, Blumsohn A, Henderson IS, McGregor E. Prognostic value of troponin T in hemodialysis patients is independent of comorbidity. Kidney Int 2001;60(6):2399-405.
61. Geller JC, Rosen MR. Persistent T-wave changes after alteration of the ventricular activation sequence. New insights into cellular mechanisms of cardiac memory. Circulation 1993;88(4):1811-9.