Troponin I Rise After Pacemaker Implantation at the Time of "Universal Definition of Myocardial Infarction"

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We assessed incidence, magnitude, and time course of cardiac troponin I (cTnI) increase after pacemaker implantation in patients without acute coronary syndromes (ACSs). Seventy patients (mean age 71 years, interquartile range 44 to 92, 38 men) undergoing elective implantation of a single-/dual-chamber pacemaker with active/passive fixation leads were enrolled, excluding subjects with clinical suspicion of ACS, abnormal basal cTnI level, or presenting conditions predisposing to abnormal cTnI. Cardiac TnI concentrations were determined in basal conditions, at the end of the procedure, and after 8, 12, and 24 hours. Single-/dual-chamber devices were implanted in 31 of 39 patients. Cardiac TnI peak concentration occurred within the 12-hour assay in 69 of 70 patients; 26 of 70 had a cTnI above the normal cut-off range. All patients presented normal cTnI at 24-hour assay. In conclusion, pacemaker implantation is associated with increases of cTnI levels in up to 37% of patients. This can affect the specificity of cTnI assessment for ruling out ACS, especially within 12 hours after the procedure. These data deserve consideration in a contemporary setting, in which troponin has gathered a pivotal role in the diagnosis and therapy of ACS, and in particular clinical presentations in which electrocardiogram loses its diagnostic capabilities (due to paced rhythms) and symptoms may be lacking or confusing. © 2009 Elsevier Inc. (Am J Cardiol 2009;103:1061–1065)

The period after pacemaker implantation may constitute a tricky situation in which an acute troponin increase (secondary to the direct myocardial trauma elicited by pacing leads or to other associated clinical conditions) can occur in the context of the loss of information provided by electrocardiograms (ECGs) regarding alterations of ventricular repolarization (commonly considered a marker of ischemia). Moreover, the alteration of the intraventricular and interventricular synchrony induced by right-sided pacemaker stimulation, evaluated at echocardiographic examination, may be consistent with a misdiagnosis of acute coronary syndrome (ACS) evoked by a troponin increase in a setting in which the ECG loses its diagnostic capabilities. The aim of our study was to evaluate the incidence, magnitude, and time course of cardiac troponin I (cTnI) increase after pacemaker implantation and to evaluate its possible impact, as a confounding factor, in the misdiagnosis of serious clinical conditions.

Methods

We enrolled all consecutive patients with standard indications for elective implantation of a permanent pacemaker (single- or dual-chamber pacemaker) according to current guideline indications, on the basis of the leading clinical condition, scheduled in our institution from June 2006 to February 2007. All procedures followed our institutional protocol for pacemaker implantation; all patients gave informed consent for pacemaker implantation and for all clinical and laboratory evaluations described in the following paragraphs. All procedures were consistent with the principles of the Declaration of Helsinki.

Exclusion criteria consisted of clinical or hemodynamic instability, unstable coronary disease, ACS, chest pain suggestive of an ischemic cardiac event within 2 weeks before the procedure, percutaneous coronary intervention or cardiac surgery in the previous month, and blunt chest trauma in the previous month. Patients were also excluded in the event of acute or chronic renal failure, rapidly progressive renal disease, dialysis, cardioversion within the previous month, and basal increase of creatine kinase (CK), myoglobin, alanine aminotransferase, or aspartate aminotransferase.

Patients received active fixation leads (Tendril, St. Jude Medical Inc., Silmar, California or Capsure Fix, Medtronic Inc., Minneapolis, Minnesota) or passive fixation leads (Isoflex, St. Jude Medical Inc., Silmar, CA, USA, or Capsure Sense, Medtronic Inc., Minneapolis, Minnesota) according to the operators' judgment. In any case, patients with previous cardiac surgery underwent implantation with active fixation leads in the atrial and ventricular chambers in consideration of the alteration of the atrial anatomy (e.g., right atrial appendage amputation). In the event of dual-chamber pacemaker implantation, we chose the same fixation system for the 2 pacing leads (atrial and ventricular) to decrease heterogeneity.

Blood samples were drawn before the procedure, immediately after its completion, and after 8, 12, and 24 hours in all patients to evaluate cTnI, CK, and CK-MB concentrations.

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Table 1
Main characteristics of patients who underwent pacemaker implantation

Men/women	70 (38/32)
Age (yrs)	71 (44–92)
Implanted pacemakers (single/dual chamber)	70 (31/39)
Atrial leads (active/passive)	39 (19/20)
Right ventricular leads (active/passive)	70 (34/36)
Basal troponin (ng/ml)	<0.04 (<0.04–<0.04)
Indications for pacemaker implantation	
Sick sinus syndrome	19 (27%)
Atrial fibrillation and bradycardia	8 (11%)
Carotid sinus hypersensitivity	6 (9%)
Atrioventricular block	
Second degree	20 (29%)
Third degree	17 (24%)

Values are expressed as numbers of patients (percentages) or medians (interquartile ranges).

For measurement of cTnI, we used a fluorometric second-generation enzyme immunoassay (cTnI assay Troponin I Flex, Dade Behring, Inc., Newark, New Jersey) measured on the Dade Behring Dimension RxL analyzer (Dade Behring, Inc.). The limit of detection of the immunoassay is 0.04 ng/l. All assays reporting a concentration <0.04 ng/ml were expressed as "<0.04 ng/ml" and not with the assessed value, according to documentation of the manufacturer (Dade Behring, Inc., REF RF421C).

The 10% coefficient of variation at the 99th percentile of a normal reference population[1,2] attending our hospital for cTnI is 0.15 ng/ml; therefore, a cTnI value >0.15 ng/ml was considered abnormal.[3,4]

We also evaluated x-ray exposure for each procedure as an indirect measurement of the complexity of electrode positioning for each patient. We performed this analysis to unmask a possible source of bias that could be connected with the positioning of different types and/or numbers of pacing leads.

Continuous variables are expressed as medians and interquartile ranges. The Shapiro-Wilk test was used to evaluate the distribution of cTnI concentration and x-ray exposure; neither variable showed a normal distribution. Cardiac TnI time-related variations at the end of the procedure and at 8, 12, and 24 hours after pacemaker implantation were analyzed with the Friedman and Student-Newman-Keuls tests. Comparisons of cTnI concentration at baseline, at each of the postprocedure assays, and the peak value reached by the patients were performed using the Wilcoxon test. Chi-square test was used to compare the percentage of patients presenting a peak concentration of cTnI >0.15 ng/ml among different subgroups. X-ray exposure was compared between different subgroups with the Wilcoxon test. We performed binary logistic forward conditional regression analysis to identify a possible relation between the type of device (single- or dual-chamber pacemaker), type of implanted lead(s), and/or x-ray exposure and a peak cTnI level >0.15 ng/ml.

Results

We enrolled 70 consecutive patients. Baseline characteristics are listed in Table 1.

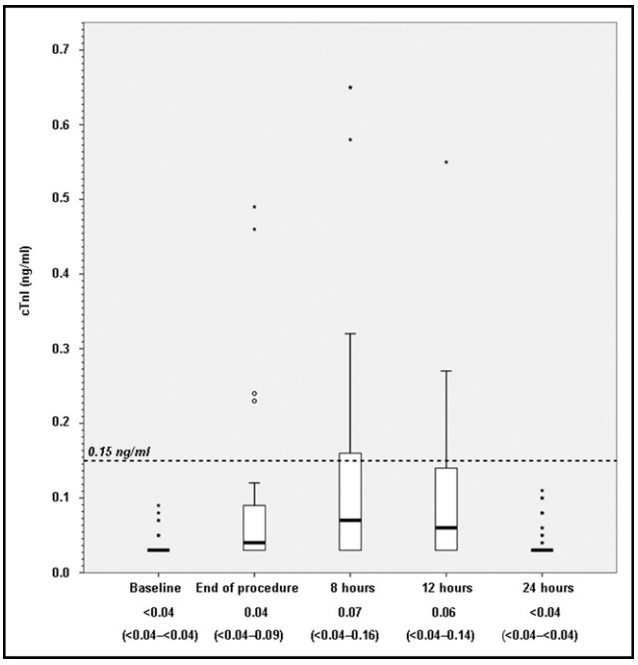

Figure 1. Box plot representation of time course of cTnI concentrations in overall population at baseline, at the end of pacemaker implantation, and after 8, 12, and 24 hours after the procedure, with the cTnI value at the 10% coefficient of variation at the 99th percentile of a normal reference population attending our hospital *(dashed line)*. Median cTnI values (interquartile range) are reported for each assay *(x-axis)*. A significant modification in cTnI concentration was present after comparing all assays with previous assays except for assessments at 8 and 12 hours ($p < 0.001$, Friedman test; all with p values <0.05, Student-Newman-Keuls test). Of note, no statistical difference was present when comparing concentrations at baseline and at 24 hours after pacemaker implantation.

In all patients implantation of the devices was successful and we did not observe any complications. Determination of the main laboratory markers was available before and after the procedure in all patients. No significant variations in terms of CK, CK-MB, creatinine, and hemoglobin were observed during the hospital stay before or after device implantation. There was no clinical suspicion of ACS, expressed by means of chest pain (absent in all cases) or ST-T variations on serial 12-lead ECGs obtained after pacemaker implantation (when a spontaneous rhythm was available for a sufficiently long period) in any patient who underwent implantation. Furthermore, CK levels remained within normal values (<195 UI/dl) in all cases (range 83 to 163) and the CK-MB fraction was 3 to 7 UI/dl and never exceeded 5% in each patient.

In the entire population, the median basal level of cTnI was <0.04 ng/ml (interquartile range <0.04 to <0.04) and no differences were recorded considering the various subgroups of patients with implants, namely dual- versus single-chamber device (<0.04 ng/ml, interquartile range <0.04 to <0.04, vs <0.04 ng/ml, interquartile range <0.04 to <0.04, $p = 0.593$) and active versus passive fixation leads (<0.04 ng/ml, interquartile range <0.04 to <0.04, vs <0.04 ng/ml, interquartile range <0.04 to <0.04, $p = 0.407$). Figure 1 shows the increase in cTnI level in the entire population within 24 hours after the procedure, according to the assays performed (Friedman test, $p < 0.001$). Soon after the pro-

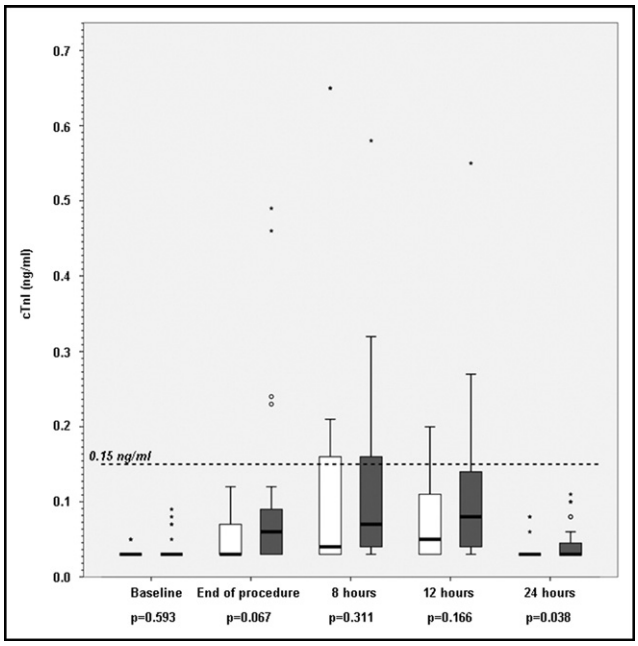

Figure 2. Box plot representation of time course of cTnI concentrations in patients with implanted single-chamber *(white bars)* or dual-chamber *(gray bars)* pacemakers, with the cTnI value at the 10% coefficient of variation at the 99th percentile of a normal reference population attending our hospital *(dashed line)*. No statistical difference was present, except at the 24-hour assay. Of note, cTnI concentration decreased toward normal values at the 12-hour assay after pacemaker implantation despite the number of leads implanted in all patients. The p values refer to patients with single-chamber versus dual-chamber pacemakers at each cTnI assay.

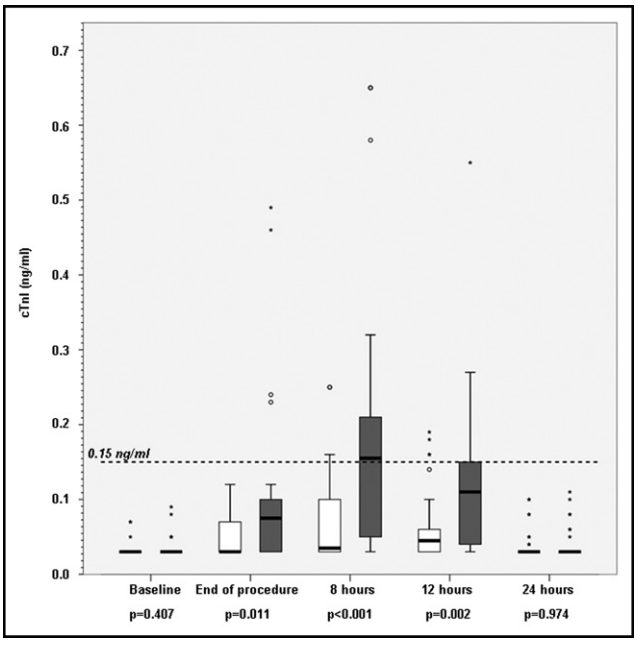

Figure 3. Box plot representation of time course of cTnI concentrations in patients with implanted passive *(white bars)* or active *(gray bars)* leads, with the cTnI value at the at the 10% coefficient of variation at the 99th percentile of a normal reference population attending our hospital *(dashed line)*. A statistical difference between the 2 groups was present at the end of the procedure and after 8 and 12 hours. Of note, cTnI concentration decreased toward normal values at the 12-hour assay after pacemaker implantation despite the type of leads implanted. The p values refer to patients with passive versus active leads at each cTnI assay.

cedure the cTnI concentration significantly increased compared with baseline, reaching the (recorded) peak concentration within 12 hours after the procedure in all patients. Figures 2 and 3 display the time course of cTnI assays in the 2 main sets of subgroups (single vs dual chamber and active vs passive leads). No difference was recorded in patients with implanted dual- versus single-chamber device at baseline, at the end of the procedure, and at 8 and 12 hours; a slight but significant difference was present at the 24-hour assay (<0.04 ng/ml, interquartile range <0.04 to 0.05, vs <0.04 ng/ml, interquartile range <0.04 to <0.04; Figure 2). Of note, no difference was present in terms of peak cTnI concentrations (0.10 ng/ml, interquartile range 0.04 to 0.18, vs 0.05 ng/ml, interquartile range <0.04 to 0.16, p = 0.551). Patients who underwent implantation with active fixation lead(s) presented higher average concentrations of cTnI for each assessment at the end of and at 8 and 12 hours after the procedure (Figure 3). They also presented a higher average peak level (0.16 ng/ml, interquartile range 0.06 to 0.21, vs 0.05 ng/ml, interquartile range <0.04 to 0.16, p = 0.001). Considering the clinical importance of a cTnI value >0.15 ng/ml, we then focused on subjects showing an "abnormal" increase in troponin levels (which could eventually contribute to a false diagnosis of ACS). All patients (n = 27) who presented ≥1 assay of a cTnI level >0.15 ng/ml showed a 24-hour cTnI concentration within the normal range; the peak level occurred within 12 hours after implantation in 24 of 27 patients and only 4 patients (who received a dual-chamber device with active leads) presented a cTnI level >0.15 ng/ml at the end of the procedure. Patients who received active fixation leads (not considering the number of implanted leads) more frequently presented a peak cTnI level >0.15 ng/ml compared with the subgroup of subjects who received passive fixation leads (17 of 34 vs 9 of 36, p = 0.03). When we considered the subgroups of patients with a dual- or single-chamber device, no significant difference was recorded in terms of percentage of patients presenting a cTnI peak level >0.15 ng/ml (14 of 39 vs 12 of 31, p = 0.809).

Patients with implanted dual-chamber devices received higher x-ray exposure compared with patients receiving a single-chamber pacemaker (12 minutes, interquartile range 10 to 13, vs 8 minutes, interquartile range 7 to 10, p <0.001). Of note, no difference was present in patients receiving active versus passive leads (10 minutes, interquartile range 8 to 12, vs 10 minutes, interquartile range 8 to 12, p = 0.873). The only analyzed variable that predicted a peak cTnI concentration >0.15 ng/ml was the use of active fixation leads at univariate and multivariate logistic regression analyses (hazard ratio 3.00, 95% C.I. 1.092 to 8.241, p = 0.033).

Discussion

Cardiac troponin T and TnI represent useful markers for myocardial injury.[5] They have a fundamental role in patients with myocardial ischemia, in particular when other elements (i.e., symptoms or electrocardiographic modifications) may be absent or unclear.[6] Even if cTnI is best known

for its capabilities to unveil myocardial ischemia, many other conditions (pathologic, traumatic, or concerning interventional cardiology) may be responsible for its increase.[3,7] However, as far as we know, few data are available about the extent of troponin increase after pacemaker implantation, its behavior until complete washout, and in particular the differences among different types of pacing systems (single- or multiple-lead insertion, active or passive fixation leads).[8–10] After the implantation of a pacing system, we observed an increase in cTnI over the usual cutoff for the laboratory diagnosis of myocardial infarction in about ⅓ of patients. This finding raises some considerations, such as the possibility that the insertion of "a pacing lead" could affect the specificity of TnI in the identification of ACS. Another interesting aspect is the duration of this possible "interference." When there are conditions in which the ECG loses its sensitivity or specificity (i.e., paroxistic complete atrioventricular block, with the need for temporary or permanent pacing in association with chest pain)[3] or in which the use of symptoms to guide clinical diagnosis is not possible (as in uncompliant patients or in subjects unable to report symptoms properly), the role played by troponin increase in the management of patients with suspected myocardial ischemia is really important in clinical practice.

Considering our series, cTnI increased above the upper limit of the normal range in ⅓ of patients (27 of 70) who underwent pacemaker implantation (i.e., intracardiac insertion of 1 pacing lead or 2 pacing leads), and this observation deserves some consideration. Pacemaker implantation may provoke an increase in cTnI levels because of direct trauma to myocardial cells elicited by endocardial leads.[11] Depending on the difficulties of the implantation, the increase in cTnI might be mild, severe, or, in some cases, not detectable. Due to this extreme variability in cTnI increase after endocardial lead placement, evaluation of further increases due to other subsequent myocardial injury may be really tricky.[8]

Nevertheless, with the limit of a relatively small patient cohort, 2 observations are relevant. First, the type (active vs passive) and not the number (1 or 2) of pacing leads appear to be associated with differences in the release of cTnI. The number of leads "tout court" was related to a statistical difference in cTnI levels only in the blood samples drawn at 24 hours after the procedure, even if still within normal values (Figure 2). As far as type of pacing lead is concerned, active leads caused a greater release of cTnI due to direct trauma caused by fixation inside the myocardium: only about 17% of patients with implanted passive leads showed an increase in their cTnI levels over normal levels, but the active leads led to a release of cTnI in 50% of patients. In contrast, the effect on cTnI increase by means of insertion of the pacing lead at the atrial level was minimal and probably related to the thinner atrial wall and consequently to the small number of myocardial cells damaged by the screw. Second, the increase in cTnI due to pacing lead insertion stopped 12 hours after surgery and returned to normal values after 24 hours in all patients. Other pathophysiologic conditions associated with cTnI increase (namely acute myocardial infarction, pulmonary embolism, congestive heart failure, etc.) cause a longer release of cTnI, with concentrations above the normal range for >1 day and often for weeks (depending on the type and mechanism of myocardial damage).[12,13]

The highest values of cTnI release were observed in patients with implanted single-chamber pacemakers and active fixation leads. No correlation with x-ray exposure time was observed, suggesting that the difficulties in placing the pacing lead correctly (usually related to longer procedures and longer x-ray exposure time) were not significant in cTnI release.

Another consideration can be made regarding the group of patients with implanted single-chamber pacemakers and passive fixation leads in the right ventricle; this kind of implant is similar to those performed for temporary pacing. Because the increase in cTnI levels above the upper cutoff of normal concentrations is detected in about 19% of patients, it could be postulated that the same could happen for temporary pacing lead positioning. Furthermore, and perhaps more interestingly, in all those patients no further increase in cTnI levels was observed after 12 hours and normal values were detected within 24 hours. Thus, in the presence of other conditions causing a potential increase in cTnI levels, we should consider a blind period of $\geq$12 hours because the increase in cTnI levels due to even just a passive pacing lead stops after 12 hours; any other pathologic condition present at the same time of implantation will be able to further increase cTnI levels (in an supplementary fashion).[12]

Normalization of cTnI levels after that time will exclude the coexistence of any other pathologic condition potentially able to favor a cTnI release (i.e., non–ST-elevation myocardial infarction with complete atrioventricular block and the need for pacing—thus zeroing the clinical potentials of ECG for ischemia—in patients unable to express their symptoms—thus exhausting the potential of clinical history in detecting myocardial ischemia—will not be diagnosed with certainty until $\geq$12 hours after pacing lead insertion).[12] Thus, cTnI release after pacemaker implantation may mask, albeit for a short period, other pathologic conditions in which troponin dosage could be crucial for making a diagnosis, for formulating prognosis, for determining clinical management of the patient, and for legal–medical implications. In our study, the "blind period" of cTnI in terms of diagnostic and prognostic capabilities after pacemaker implantation was limited to the first 12 hours.

Not surprisingly, patients with higher increases in cTnI tended to be older ($p = 0.09$); this can be related to a greater cellular fragility at the myocardial level in these subjects, even for mild cardiac trauma.

As previously demonstrated, cTnI increase is associated with a worse prognosis[14–17]; its release could play a prognostic role for clinically relevant events.[18–21] This has been underlined by Babuin et al[22] who reported that admission troponin levels are independently associated with short- and long-term mortalities, even after adjustment for severity of disease.

These data have to be considered when ruling out acute ischemia in patients who have recently undergone pacemaker implantation and in particular when active fixation leads are used. Cardiac TnI increases in patients who have recently undergone implantation of a device may be more challenging when the clinical setting could be characterized

by complete pacemaker dependency and chest pain in the early period after pacemaker implantation; however, no further increase in cTnI is detectable 12 hours after pacemaker implantation. Our study shows that this represents a cutoff in terms of the time beyond which any further increase of cTnI levels has to be attributed to causes other than pacemaker implantation.

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