

Major determinants of myocardial injury after pulmonary vein isolation with radiofrequency ablation

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Abstract

Background: Radiofrequency (RF) current is used as a common energy source to perform pulmonary vein isolation (PVI) in patients with atrial fibrillation. We applied measurements of the blood concentration of cTnI as a surrogate parameter for the injured cell mass.

Aim: To clarify which parameters are major determinants of myocardial injury, estimated by cTnI, after PVI with RF ablation.

Methods: The study population consisted of 82 consecutive patients in whom PVI with RF ablation was performed. In 41 patients, additional linear lesions (LL) were needed. Blood samples were obtained during venous puncture before a procedure and a further one, six and 24 hours after ablation.

Results: Pathological cTnI values were observed in all patients in the first hour and further increased in time. The median of peak cTnI value in the LL group was significantly ($p < 0.05$) higher than the respective value in patients without LL made: 1.16 (0.85;1.98) and 0.94 (0.65;1.14) ng/mL, respectively. Significantly higher cTnI values ($p = 0.043$) were observed in patients who maintained sinus rhythm in long term follow-up.

Conclusions: The only independent predictor of myocardial injury after PVI with RF ablation, expressed as an increase in cTnI level, is cumulative energy applied. The larger the myocardial injury, the greater the PVI effectiveness.

Key words: atrial fibrillation, radiofrequency ablation, troponin

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INTRODUCTION

Radiofrequency (RF) current is used as a common energy source to perform percutaneous transluminal catheter based pulmonary vein isolation (PVI) in the vast majority of patients with atrial fibrillation (AF). Many authors have tried to implement different biomarkers in order to evaluate and quantify the size of effective ablation lesions [1–9].

Tissue ablation creates immediate myocardial necrosis and the process is usually slower in ischaemic events. As a result, the release of myocardial injury markers starts earlier [2, 3]. An additional problem, which appears when analysing release of biomarkers after ablation-related injury, is the influence of low or high temperature on their stability.

The published studies used creatinine kinase (CK), myocardial bound for creatinine kinase (CK-MB) and cardiac troponins I (cTnI) and T (cTnT) to evaluate the myocardial cells injury after ablation [1–9]. Some of the results produced concerns about the reliability of measurements showing inadequately small rises in CK and CK-MB after effective RF ablation (RFA). In 1995, Haines described inactivation of CK, in biopsies of canine hearts, at a temperature of 65°C after RF energy ablations or direct heating [10]. We recently reported that only troponins can be evaluated in patients after RFA of AF, as both CK and CK-MB levels suddenly drop down to nearly 50% of their base values at 50°C and 40°C, respectively [11]. Therefore we applied measurements of the blood con-

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centration of cTnI only, before and after ablation, as a surrogate parameter for the injured cell mass. The aim was to clarify which parameters are major determinants of myocardial injury, estimated by cTnI, after pulmonary vein isolation with RFA.

METHODS

Patients

The study population consisted of 82 consecutive patients with symptomatic and drug refractory AF, documented in at least two ECGs in the three month period preceding an ablation procedure. The indication for ablation was based on the guidelines [12]. Patients with primarily unknown, or known to be elevated, levels of cTnI at baseline were excluded from the study. The procedural-related risk was presented in detail, and written informed consent was obtained from all patients before the ablation. The study was approved by the local ethical committee.

Ablation procedure

Left atrium was reached via double trans-septal approach. Selective angiography of all PVs was made. RFA was performed with a 3.5 mm irrigated 7 F Thermo-cool catheter (Bio-sense Webster, Diamond Bar, CA, USA). We used the MESH catheter (high density mesh mapper, Bard Electrophysiology, Lowell, MA, USA) placed at ostium of each PV. The cut-off temperature of the generator was 42°C; energy delivery was limited to a maximum of 35 W. Successful PVI was defined as complete elimination of all fragmented signals at PV ostium. In case of failure of sinus rhythm restoration during PVI, additional linear lesions (LL; roof line and/or mitral isthmus line) were performed (in 41 patients). Numbers of application, cumulative RF energy were collected and calculated.

Measurement of biomarkers in RFA patients

Blood samples were obtained during venous puncture before a procedure and a further one, six, and 24 hours after ablation. All serum samples were analysed with standard laboratory kit (STAT Troponin I, Abbott®). Cardiac TnI cut-off values for diagnosis of myocardial infarction (MI) (0.01 ng/mL) was treated as pathologically increased.

Statistical analysis

Parametric data was expressed as median values and interquartile range (25;75). The Mann-Whitney U-test was used to analyse parametric data. Multi-variable regression analysis and linear regression analysis was also performed. A p values < 0.05 were considered statistically significant.

RESULTS

Patient characteristics

Patient characteristics are presented in Table 1. Pulmonary vein isolation with RFA was performed in 48 patients with paroxysmal AF (PAF), and 34 with persistent or permanent AF (CAF). Significantly ($p < 0.001$) larger left atrium (LA) and lower left ventricular ejection fraction (LVEF) was observed, as could be expected, in CAF patients.

None of the patients complained about symptoms suggestive of ischaemia or had clinical signs of coronary ischaemic episodes either prior to or at the end of the procedure. We did not find any changes of the ST-segment comparing ECG tracings before, during or after the procedure.

Procedure characteristics

Procedure characteristics are presented in Table 2. The end-point (electrical isolation of all PVs) was achieved in all patients. Total time of procedure and total fluoroscopy time was significantly ($p < 0.0001$) longer in LL patients. Similarly, the

Table 1. Patients characteristics

	1 Whole group			2 No linear lesions group			3 Linear lesions group			2 vs 3 P
	Median	25%	75%	Median	25%	75%	Median	25%	75%	
Whole group	82			41			41			NS
Paroxysmal AF	48			28			20			NS
Male	61			31			30			NS
Hypertension	53			26			27			NS
CAD	10			4			6			NS
BMI	27	25	29	27	25	29	27	25	30	NS
Age	57	49	65	58	49	66	56	49	64	NS
Long axis	56	51	61	54	49	59	59	52	62	0.021
Short axis	40	37	42	40	35	42	40	38	43	NS
LVEF	60	55	62	60	56	63	60	55	62	NS

AF — atrial fibrillation; CAD — coronary artery disease; BMI — body mass index; LVEF — left ventricular ejection fraction

Table 2. Procedural characteristics

	1 No linear lesions group			2 Linear lesions group			1 vs 2 P
	Median	25%	75%	Median	25%	75%	
Procedure time [h]	4.3	3.5	5.0	5.0	4.3	6.0	< 0.0001
Fluoroscopy time [min]	74.6	57.1	94.0	98.0	76.3	123.0	< 0.0001
Total energy [J]	126476	85000	168011	173028	131764	225768	< 0.0001
No of radiofrequency applications	48	35	68	65	50	82	< 0.0001

number of RF applications and cumulative energy applied was significantly ($p < 0.0001$) higher in LL patients.

Predictors of high levels of cTnI

The first step was clarifying which parameters predicted high levels of cTnI after RFA. Performed multi-variable regression analysis showed that the only independent predictor was cumulative energy applied during RFA ($p < 0.0001$). The maximum value of cTnI significantly depended on the cumulative energy applied during RFA (Fig. 1) and the correlation was linear (Fig. 2).

Myocardial lesions and cTnI

The rise in cTnI levels was highly significant in both groups after ablation and was observed at each hour of collection compared to baseline measurement (Fig. 1). Pathological cTnI values, defined as higher than cTnI cut-off value for diagnosis of MI (0.01 ng/mL), were observed in all patients in the first hour, and further increased in time. The median of peak values in the LL group was 1.16 (0.85;1.98) ng/mL. It was significantly ($p < 0.05$) higher than the respective value in patients without LL made, i.e. 0.94 (0.65;1.14) ng/mL.

Myocardial lesions and effectiveness of PVI

The effectiveness of PVI, measured as maintenance of sinus rhythm in a long follow-up of median 13 months (6;16), was higher in patients in whom PVI resulted in greater myocardial injury (measured by cTnI values). It was true both for the whole population (Fig. 3A) as well as for the subgroups of CAF (Fig. 3B) and PAF (Fig. 3C) patients. Significantly higher cTnI values ($p = 0.043$; $p = 0.055$; $p = 0.033$, respectively) were observed in patients who maintained sinus rhythm in long-term follow-up.

DISCUSSION

As we have reported previously, the detected levels of CK-MB and CK activity suddenly drop down to nearly 50% of its base value at 40°C and 50°C, respectively [11]. These intra-tissue temperatures are usually targeted by RFA operator to produce locally irreversible cell injury. As a result, only cardiac troponins, which are stable in higher temperatures, can serve as a surrogate marker of myocardial injury [11]. We focused on troponin I as it is more specific and temperature-stable than troponin T [13, 14].

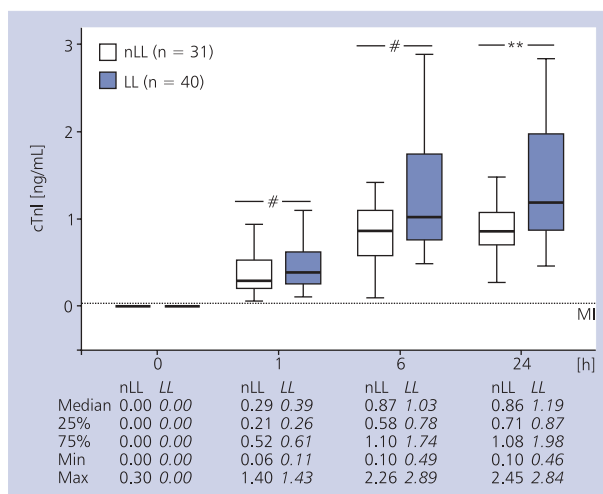


Figure 1. Comparison of kinetics of cardiac troponin I (cTnI) after radiofrequency ablation in patients without (nLL) and with additional linear lesions (LL) performed. Data is depicted as box plots with minimum, maximum and median values as well as interquartile range; MI — dotted line expresses our laboratory routine value of cTnI (0.01 ng/mL) for detection of myocardial infarction; #not statistically significant difference ($p \geq 0.5$) between LL and nLL; **statistically significant difference ($p < 0.05$) between LL and nLL

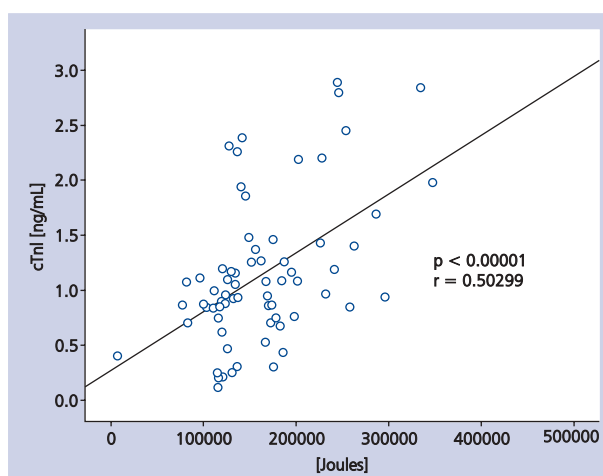


Figure 2. The correlation of maximum values of cardiac troponin I (cTnI) with the cumulative energy applied during radiofrequency ablation

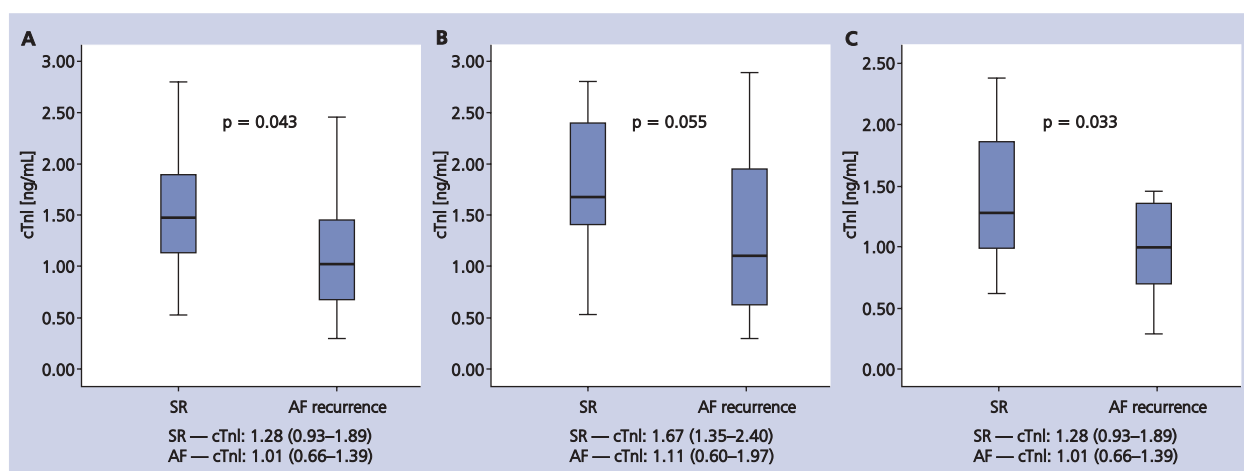


Figure 3. Maximum values of cardiac troponin I (cTnI) and long term outcome after pulmonary vein isolation (PVI). Data is depicted as box plots with minimum, maximum and median values as well as interquartile range; **A.** CAF+PAF. The whole studied population of patients; **B.** CAF. Patients with persistent or permanent atrial fibrillation (AF); **C.** PAF. Patients with paroxysmal AF; SR — patients who maintain sinus rhythm in long term follow-up; AF recurrence — patients with recurrence of AF after PVI

To the best of our knowledge, this is the first report which shows that the only independent determinant of myocardial injury after PVI is cumulative energy applied. Additionally, we show that the larger the myocardial injury (measured by cTnI), the higher the long-term effectiveness of PVI (measured by clinical outcome).

Our observations are similar to those reported by others [1–5]. Hirose investigated the increase of different biomarkers (CK-MB, hFABP and cTnT) after RFA [1]. The study was limited by four different target arrhythmias with highly different numbers of applications needed for ablation in these 34 patients. He observed a significant rise in cTnT levels immediately, and at the third, sixth and 24th hours after RF delivery. Peak cTnT was significantly correlated with the cumulative amount of RF energy applied ($r = 0.641$, $p < 0.001$) but also the number of applications and delivery duration. Both Madrid et al. [2] and del Rey et al. [3] also reported superior diagnostic accuracy of cTnI in a non-homogeneous group of patients after RFA. Level of cTnI was elevated in 92% of patients. They observed a correlation between peak level of cTnI and the total time of application ($r = 0.67$, $p < 0.0001$) and the number of applications ($r = 0.688$, $p < 0.0001$). Manolis et al. [5] published results from a cohort of 118 patients who were ablated for six different types of arrhythmias. After performing a sophisticated analysis for dependencies of localisation (atrial or ventricular ablation, neighbourhood to the mitral annulus) and number of applications, they could only find good correlations with cTnI concentration changes. Levels of cTnI correlated with number and site of RFA lesions. Bednarek et al. [15] analysed a non-homogeneous group of 53 patients. They found correlation of cTnI and RF energy applied and cTnI values were elevated regardless of the site of RFA

[15]. In a larger cohort of 108 patients, they further confirmed the usefulness of cTnI as a marker of myocardial injury after RFA [16].

We cannot discuss correlations between cTnI levels and the number, site and time of each application reported by cited authors. All the above studies were focused on focal lesions. Only Carlsson et al. [6] differentiated focal and linear lesions. They reported strong correlations ($p < 0.001$) of peak cTnT levels with cumulative energy (both for focal and linear lesions) and number of RFA applications (for focal lesions only). In contrast to the abovementioned studies, the location of ablation lesions and the target arrhythmias were much more homogenous in our cohort. Our lesions were linear, i.e. catheter was moved from one point to another every 30 s to produce continuous line lesions. That type of lesion results in larger myocardial injury [6]. We observed pathological cTnI values in all patients. Similar observations were made by Carlsson et al. [6], who described elevated cTnT levels in 100% of patients with linear lesions in contrast to 50% of patients after focal ablation, and Brueckmann et al. [17] who reported elevated cTnI in 100% and 25% of patients, respectively.

We observed that cTnI showed earlier peak values than expected in the setting of ischaemic heart disease, as described by previous authors [3, 18, 19]. Ablation procedure results in immediate myocardial necrosis, whereas ischaemic events develop more slowly, sometimes over hours. The peak concentration of cTnI can be expected 12–24 h after MI [18, 20, 21]. In our study group, cTnI crossed its pathological values for detection of MI in the first hour and further increased to reach its maximal values in the sixth and 24th hours for patients without LL and with LL made, respectively. This could have a practical application in the differential diagnosis of

chest pain or suspected acute MI after RFA, especially in pacemaker-implanted patients with active ventricular pacing in whom we can mostly judge on clinical manifestation and biomarkers behaviour but limited help from ECG tracings.

Limitations of the study

We cannot comment on the detailed kinetics of cTnI after PVI as no blood collection was performed between the sixth and 24th hours and further on.

CONCLUSIONS

The only independent predictor of myocardial injury after PVI with RFA, expressed as an increase in cTnI level, is cumulative energy applied. The larger the myocardial injury, the greater the PVI effectiveness.

Conflict of interest: Maciej Wójcik — supported by European Heart Rhythm Association (2-years EHRA Clinical Electrophysiology Fellowship, 2007–2009); Sebastien Janin — supported by French Federation of Cardiology 2008–2009.

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Ablacja migotania przedsionków prądem o wysokiej częstotliwości: główne wyznaczniki uszkodzenia mięśnia sercowego przy elektrycznej izolacji ujścia żył płucnych

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Streszczenie

Wstęp: Izolacja elektryczna ujścia żył płucnych (PVI), przy użyciu prądu o wysokiej częstotliwości (RF), jest coraz częściej stosowaną metodą inwazyjnego leczenia pacjentów z migotaniem przedsionków (AF). W badaniu zmierzono koncentrację troponiny I (cTnI) jako odpowiednika masy uszkodzonych komórek mięśnia sercowego.

Cel: Celem pracy było wyjaśnienie, jakie parametry są głównymi wyznacznikami uszkodzenia mięśnia sercowego po ablacji RF PVI.

Metody: Badaniem objęto 82 kolejnych chorych z AF, u których wykonano ablację RF PVI. W 41 przypadkach, oprócz PVI, przeprowadzono dodatkowe linie (LL) w dachu i cieśni mitralnej lewego przedsionka. Próbkę krwi żyłnej pobrano przed procedurą oraz w 1., 6. i 24. godzinie po zabiegu.

Wyniki: Patologiczne wartości cTnI obserwowano u wszystkich pacjentów, zarówno w 1. godzinie, jak i ich narastające wartości w godzinach kolejnych. Mediana maksymalnych wartości cTnI była istotnie wyższa ($p < 0,05$) w grupie chorych z LL w porównaniu z pacjentami bez LL, odpowiednio: 1,16 (0,85; 1,98) i 0,94 (0,65; 1,14) ng/ml. Istotnie wyższe wartości cTnI ($p = 0,043$) zanotowano u chorych, którzy pozostawali na rytmie zatokowym w długim okresie obserwacji.

Wnioski: Jedynym niezależnym czynnikiem uszkodzenia mięśnia sercowego po ablacji RF PVI, wyrażonym jako wzrost stężenia cTnI, jest łączna wartość zastosowanego prądu RF. Im większy jest uraz mięśnia sercowego, tym większa jest skuteczność ablacji RF PVI.

Słowa kluczowe: biomarkery, uszkodzenie mięśnia sercowego, ablacja, migotanie przedsionków, CK, CK-MB, troponina

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