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Which standard biomarkers are useful for the evaluation of myocardial injury after pulmonary vein isolation with cryoballoon?

Maciej Wójcik[1, 2], Sebastien Janin[1], Thomas Neumann[1], Malte Kuniss[1], Alexander Berkowitsch[1], Damir Erkapic[1], Sergey Zaltsberg[1], Katherina Madlener[1], Andrzej Wysokiński[2], Christian W. Hamm[1], Heinz F. Pitschner[1]

[1]Kerckhoff Heart Centre Department of Cardiology, Bad Nauheim, Germany
[2]Department of Cardiology, Medical University of Lublin, Lublin, Poland

Abstract

Background: Many studies have used creatinine kinase (CK), myocardial bound for CK (CK-MB), and cardiac troponin I (cTnI) and T (cTnT) to evaluate myocardial cells injury after ablation. We applied measurements of the blood concentration of cardio-specific biomarkers as surrogates for the injured cell mass.

Aim: To clarify which of the standard biomarkers are useful in the evaluation and quantification of lesions produced by cryoballoon ablation (CBA) during pulmonary vein isolation.

Methods: The CBA was performed in 33 patients with atrial fibrillation. Blood samples were obtained before CBA and one, six, and 24 h after CBA. We analysed CK, CK-MB and cTnI.

Results: A significant increase of all biomarkers was observed at each hour of collection as compared to the baseline measurement. Maximum median peak levels occurred at 6 h. Pathological values of CK, CK-MB and cTnI were observed in 94%, 100% and 100% of patients, respectively. Both maximum CK and CK-MB values correlated with median temperature ($p < 0.05$) reached during CBA. Additionally, CK-MB correlated with total cryo-time ($p < 0.03$).

Conclusions: The CK-MB is the best biochemical marker for the evaluation of myocardial injury after CBA. The cTnI can be useful as an additional parameter of myocardial injury after CBA.

Key words: biomarkers, myocardial injury, cryoballoon ablation

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INTRODUCTION

Different energy sources have been used to perform percutaneous transluminal catheter-based pulmonary vein isolation (PVI) in patients with atrial fibrillation (AF). In recent years, the cryoballoon (CB) technique has offered a new way of accomplishing PVI [1–3].

Several markers have been shown to be useful in the diagnosis and evaluation of the size of myocardial injury after an acute ischaemic episode. Tissue ablation creates immediate myocardial necrosis. As a result, the release of myocardial injury markers starts earlier than in ischaemic events [4–6]. Many authors have tried to implement different biomarkers so as to evaluate and quantify the size of effective ablation lesions [4–12]. Both past and recently published studies have used creatinine kinase (CK), myocardial bound for CK (CK-MB), and cardiac troponins I (cTnI) and T (cTnT) to evaluate myocardial cells injury after ablation [4–12].

We applied measurements of the blood concentration of cardio-specific biomarkers, before and after ablation, as surrogate parameters for the injured cell mass. The aim was to clarify which of the standard biomarkers are useful in the evaluation and quantification of lesions produced by CB (CBA).

Address for correspondence:
Maciej Wójcik, MD, PhD, Department of Cardiology, Medical University of Lublin, ul. Jaczewskiego 8, 20–954 Lublin, Poland, e-mail: m.wojcik@am.lublin.pl
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METHODS

Patients

The study population consisted of 33 consecutive patients with symptomatic and drug refractory AF. The arrhythmia was documented in at least two ECG, during three months preceding an ablation procedure. The indications for ablation were based on the relevant guidelines [13]. Patients with an elevated level of any of the investigated markers (CK, CK-MB, or cTnI) at baseline were excluded from the study.

The procedural-related risk was fully explained and written informed consent was obtained from all patients before the ablation. The study was approved by the local ethics committee.

Ablation procedure

Left atrium was reached via double trans-septal approach. We made selective angiography of all PVs. The CBA was performed with a double-walled balloon (Arctic Front, Cryocath). The degree of balloon occlusion was judged using a semi-quantitative grading: from grade 4 = excellent (full retention of contrast medium without visible outflow) to grade 1 = very poor (immediate rapid outflow from the PV). We aimed for at least one CBA with occlusion of grade 4 on every targeted PV. Additional delivery of cryoenergy was applied after the guidewire was placed in different branches of the PV with early branching, which usually allowed for better contact of the balloon at different sites of the PV antrum. One application lasted 240–360 s per freeze and complete PVI was confirmed using a Lasso catheter (Biosense Webster). During CBA of the antrum of the right-sided PVs, phrenic movement was monitored by either continuous phrenic nerve stimulation via a right atrial stimulation catheter or by continuous monitoring of spontaneous breathing. In all patients, PVI of all targeted PVs was the therapeutic aim with the primary use of a CB only. Each PV was estimated as successfully isolated if no recurrence of conduction 20 min since the last CBA was observed. This procedure has been described recently in detail [3]. The number of applications, the lowest temperature of each cryo-application, and the cumulative time of each CBA application were also recorded.

Measurement of biomarkers

Blood samples were obtained during venous puncture before ablation, and 1, 6 and 24 h after ablation. All serum samples were analysed using standard laboratory kits (CL NAC, CKMBL and STAT Troponin I Abbott®). The CK, CK-MB and cTnI cut-off values for diagnosis of myocardial infarction (MI) (167 U/L, 25 ng/mL, 0.01 ng/mL, respectively) were used.

Statistical analysis

Parametric data are expressed as median values and interquartile range (i.e. 25–75). The median temperature was calculated as the median of the lowest temperature reached for each cryo-application performed in the patient. The Mann-Whitney U-test was used to compare parametric data, and the χ^2 — for non-parametric, data. The association of the biomarkers concentration with temperature and cryotime was tested using linear regression analysis. Multivariable regression analysis of each biomarker was performed for adjusting on other clinical variables such as age, gender and left atrial size. A p value < 0.05 was considered statistically significant.

RESULTS

Patients and procedural characteristics

The studied sample consisted of 33 patients, 20 males, median age 55 (48–61) years. Thirty two patients had paroxysmal AF and one patient had persistent AF. Transthoracic echocardiography was performed in all patients. Median value of left ventricular ejection fraction was 62% (57–67). Median diameters of short and long left atrium were 50 mm (48–55) and 37 mm (35–40), respectively. None of the patients complained of symptoms suggestive of ischaemia or had clinical signs of a coronary ischaemic episode either before or during the procedure. We did not find any changes of the ST-segment comparing ECG tracings before, during or after the procedure. The median number, time and temperature of applications were 14 (12–16), 74 min (64–86) and –40°C (–36 to –45), respectively.

Biomarkers of myocardial injury

A significant increase of all biomarkers was observed at each hour of collection compared to baseline measurement (Fig. 1). Maximum median peak levels occurred at 6 h. Abnormal values of CK, CK-MB and cTnI were observed in 94%, 100% and 100% of patients, respectively.

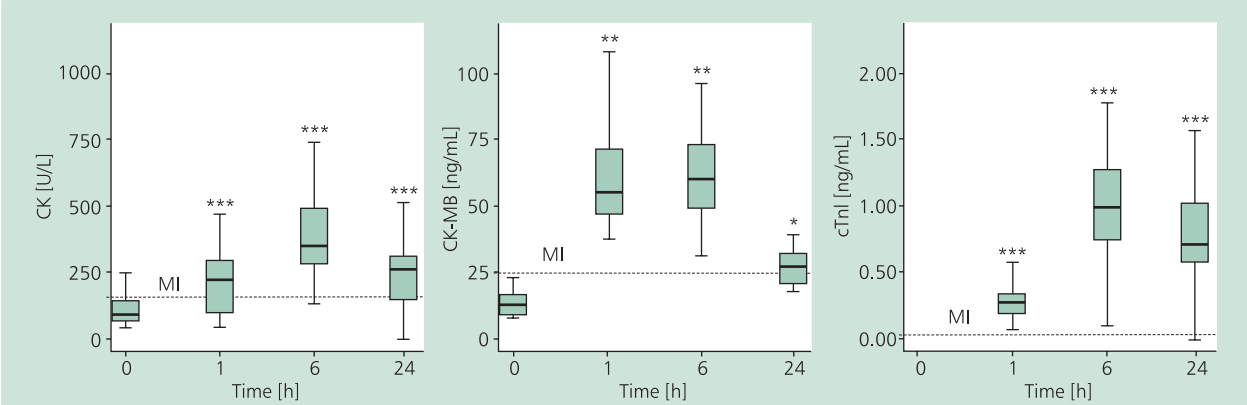
Both maximum CK and CK-MB values correlated with median temperature ($p < 0.01$, $r = 0.39$ and $p < 0.05$, $r = 0.25$, respectively) reached during CBA (Fig. 2A, B). Additionally, CK-MB correlated (Fig. 2C) with total cryo-time ($p < 0.03$, $r = 0.36$). No correlation was found for cTnI.

DISCUSSION

We found that all studied biomarkers can be used for evaluating myocardial injury after PVI performed with CBA. The most useful biomarker for evaluating CBA — induced myocardial injury was CK-MB.

Cardiac biomarkers and low temperature

Previous reports have confirmed the *in vitro* stability of biomarkers in low temperatures [14, 15], suggesting that analysis of these markers is reliable after CBA. The lowest median temperature in our group was –40°C. This temperature was low enough to assume cell death, with rupture of the cell membranes, due to ice crystal formation which starts much earlier — at –10°C [16]. Buttery et al. [14] confirmed stability of CK-MB at –20°C. Woltersdorf et al. [15] froze serum samples at –70°C: the intra-tissue temperature hardly reached during CBA. They described no significant change in serum cTnT or cTnI concentration. The CK activity was almost unchanged.



Mean	145	239	383	258	15	59	62	28	< 0.01	0.37	1.01	0.85
Median	91	223	351	263	13	55	60	28	< 0.01	0.28	1.01	0.78
Min	43	46	132	43	8	37	31	8	< 0.01	0.08	0.11	0.01
Max	250	735	743	514	32	107	108	54	< 0.01	2.23	1.81	1.85

Figure 1. Comparison of the kinetics of creatine kinase (CK), myocardial bound for CK (CK-MB), and cardiac troponin I (cTnI). Data are depicted as box plots with median values and interquartile range; MI — laboratory routine value of CK (167 U/L), CK-MB (25 ng/mL) for detection of myocardial infarction (MI); *p < 0.05; **p < 0.005; ***p < 0.0001

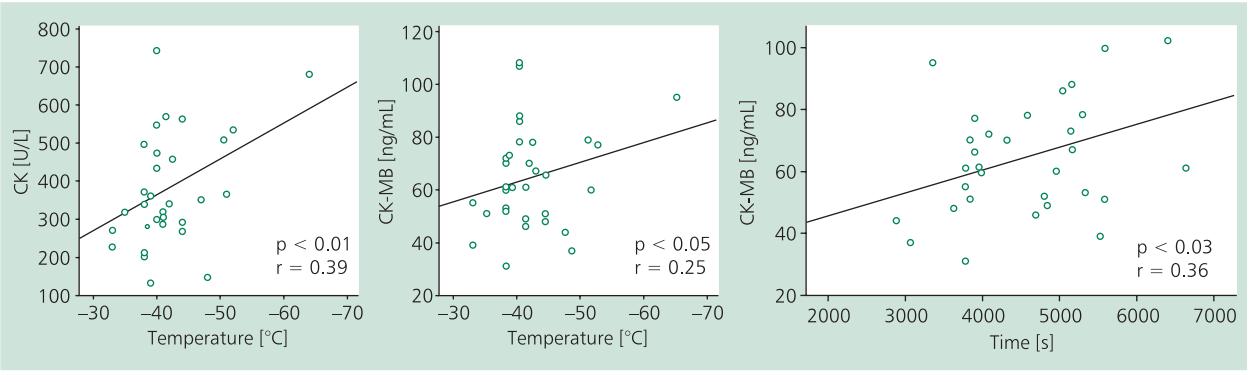


Figure 2. Correlation of maximum values of creatine kinase (CK) (**A**) and myocardial bound for CK (CK-MB) (**B**) with median temperature reached during cryoballoon ablation; **C**. Correlation of maximum values of myocardial bound for creatine kinase (CK-MB) with total time of applications during cryoballoon ablation

A statistically significant decrease (2.6% of CK base-line activity, $p < 0.01$) was reached after 14 days of sample storage at –70°C. Surprisingly, CK-MB concentration significantly (14.8%, $p < 0.01$) increased in frozen samples. However, this storage temperature was almost twice as low as that of the median temperature reached in our patients.

Measurement of biomarkers

Only a single report has described myocardial injury biomarkers after cryo-ablation [6]. It evaluated a small sub-group of ten patients after cryo-ablation of atrial flutter (AFL). Oswald et al. [6] observed significantly higher peak values both for CK and CK-MB at 6 h after cryo-ablation (356 U/L and 27 ng/mL, respectively) than after radiofrequency ablation of AFL (84 U/L and 19 ng/mL, respectively). These results accord with our observations. The authors argued that higher levels of CK and CK-MB in the cryo-group reflect different lesions formation, as compared to radiofrequency lesions. Bigger sheaths used in the cryo-group led to higher CK values.

In our opinion, the significant rise in biomarkers levels reflects effective myocardial death caused by CBA. Both CK and CK-MB are quantitative parameters, and their peak values depend on the number of irreversibly destroyed myocardial cells [17]. The CK is not as specific as CK-MB with regards to myocardial cells injury. Therefore, we should focus on CK-MB rather than on CK. A significant correlation between maximum values of CK-MB and total CBA time as well as median temperature reflects the effectiveness of CBA in annihilating myocardial cells. This observation is important in clinical settings. The CBA parameter which can be directly controlled by the operator is the time of application. After setting the time of application as constancy, only lowering

the temperature can further influence the effectiveness of myocardial injury. The achieved temperature during CBA depends on the quality of CB contact with myocardial issue. The better the CB contact, the lower the temperature that can be achieved as the blood flow between myocardial tissues and balloon surface is stopped or at least significantly decreased. In such settings, CK-MB reflects mass of cells death.

Oswald et al. [6] also described a significant increase in cTnT concentration, especially in the cryo-group, with the cTnT highest levels 6 h after procedure. Although we measured cTnI and not cTnT, we also observed the highest cTnI values at 6 h blood collection from CBA patients. The values of cTnI did not correlate with duration and temperature of CBA, as early cardiac troponins are a qualitative marker of myocardial injury [18]. Their peak value is related to injury *per se* rather than reflecting mass of myocardial death.

We observed that the kinetics of myocardial injury markers showed earlier peak values then expected in the setting of ischaemic heart disease, as described by previous authors [19–21]. The ablation procedure results in immediate myocardial necrosis, whereas ischaemic events develop more slowly, even over hours. Peak concentrations of CK, CK-MB and cTnI can be expected 12, 24 and 12–24 h after MI respectively [20, 22, 23]. In our study group, all the biomarkers crossed their pathological values for detection of MI at the first hour, and further increased to reach their maximal values at the sixth hour. This could have practical application in the differential diagnosis of chest pain or suspected acute MI after CBA, especially in pacemaker-implanted patients with active ventricular pacing in whom we can mostly judge on clinical manifestation and biomarkers behaviour, but in whom we receive only limited help from ECG tracings.

Limitations of the study

The detailed kinetics of biomarkers cannot be commented on, because no blood collection was performed between 6 h and 24 h. We cannot exclude the possibility that reaching a temperature of –70°C and below could lead to an increased value of measured CK-MB concentration.

CONCLUSIONS

The CK-MB is the best biochemical marker for the evaluation of myocardial injury after CBA. The cTn I can be useful as an additional parameter of myocardial injury after CBA.

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Conflict of interest: *none declared*

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Które ze standardowo dostępnych biomarkerów są użyteczne w ocenie uszkodzenia mięśnia sercowego po krio-balonowej izolacji żył płucnych?

Maciej Wójcik[1, 2], Sebastien Janin[1], Thomas Neumann[1], Malte Kuniss[1], Alexander Berkowitsch[1], Damir Erkapic[1], Sergey Zaltsberg[1], Katherina Madlener[1], Andrzej Wysokiński[2], Christian W. Hamm[1], Heinz F. Pitschner[1]

[1]Kerckhoff Heart Centre Department of Cardiology, Bad Nauheim, Niemcy
[2]Katedra i Klinika Kardiologii, Uniwersytet Medyczny, Lublin

Streszczenie

Wstęp: W dotychczas opublikowanych badaniach dotyczących oceny uszkodzenia mięśnia sercowego po zabiegach ablacji oznaczano aktywność kinazy kreatynowej (CK), izoenzymu sercowego CK (CK-MB) i stężenie sercowych troponin I (cTnI) oraz T (cTnT). Dokonano pomiarów koncentracji kardio-specyficznych biomarkerów jako odpowiednika masy uszkodzonych komórek mięśnia sercowego.

Cel: Celem pracy było wyjaśnienie, który ze standardowo dostępnych biomarkerów jest użyteczny w ocenie uszkodzenia komórek mięśnia sercowego po krio-balonowej izolacji żył płucnych (CBA).

Metody: U 33 pacjentów z migotaniem przedsionków wykonano CBA. Próbki krwi pobrano przed CBA oraz w 1., 6. oraz 24. godzinie po CBA. Analizie poddano CK, CK-MB i cTnI.

Wyniki: W próbkach pobranych po CBA zaobserwowano istotny wzrost koncentracji wszystkich badanych biomarkerów w stosunku do poziomu wyjściowego. Maksymalny wzrost zanotowano w 6. godzinie; CK, CK-MB i cTnI osiągnęły wartości patologiczne u, odpowiednio, 94%, 100% i 100% pacjentów. Maksymalne wartości CK i CK-MB korelowały ($p < 0.05$) z medianą temperatury osiągniętej w czasie CBA.

Wnioski: Okazało się, że CK-MB jest najlepszym standardowym biomarkerem do oceny uszkodzenia mięśnia sercowego po CBA. Sercowa troponina I może być użyteczna jako dodatkowy parametr oceny uszkodzenia po CBA.

Słowa kluczowe: biomarkery, uszkodzenie mięśnia sercowego, krio-balonowa ablacja, CK, CK-MB, troponina

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Adres do korespondencji:
dr n. med. Maciej Wójcik, Katerda i Klinika Kardiologii, Uniwersytet Medyczny, ul. Jaczewskiego 8, 20–954 Lublin, e-mail: m.wojcik@am.lublin.pl
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