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A retrospective study: elevation of cardiac troponin T after transcatheter closure of the interatrial septum is related to device size and procedural duration

Joanna Hlebowicz*, Johan Holm, Nazim Isma and Ulf Thilén

Abstract

Background: Limited data are available on the increase in cardiac troponin after transcatheter closure of interatrial septal defects, and the mechanism is not fully understood. The aim with the study was to examine retrospectively whether transcatheter closure of the interatrial septum leads to myocardial injury, and to determine the mechanism.

Methods: Troponin T (TnT) serum concentrations were determined before and 1 day after transcatheter closure of an atrial septal defect (ASD) or patent foramen ovale (PFO) in a retrospective study in adults. Fifty-one patients were included, 36 ASD and 15 PFO (female/male 35/16), mean age 52 ± 16 y (range 17–80 y).

Results: An increase in TnT was observed 1 day after the procedure ($p = 0.000$) in 44 patients (92%). The increase in TnT was significantly correlated to the size of the ASD ($r = 0.424$, $p = 0.010$), as well as to the size of the implanted ASD device ($r = 0.542$, $p = 0.001$), and the duration of the ASD intervention ($r = 0.348$, $p = 0.035$). In cases of PFO, the increase in TnT was not correlated with the size of the PFO or the PFO device, or the duration of the intervention. No correlations were found between the increase in TnT and the patient's age, body weight or body surface area.

Conclusions: Transcatheter closure of the interatrial septum causes an increase in TnT indicating a minor and clinically insignificant myocardial injury. The findings indicate that mechanical trauma caused by inserting the ASD device may play an important role in this elevation. The impact of the size of the device on the degree of TnT elevation reflects the amount of myocardium affected by the device.

Trial registration: NCT03099967. Registered 4 April 2017, retrospectively registered.

Keywords: Congenital heart disease, Atrial septal defect, Patent foramen ovale, Transcatheter closure, Troponin T

Background

Percutaneous closure is a safe and effective treatment for the closure of an atrial septal defect (ASD) and patent foramen ovale (PFO) [1]. The increase in cardiac troponin T (TnT) is a sensitive and specific marker of myocardial damage. It has been found that the increase in TnT level after elective percutaneous coronary intervention predicts future cardiac events [2]. Limited data are available on the increase in TnT after transcatheter closure of interatrial septal defects, and the specific mechanism of myocardial damage is not yet fully understood [3–6].

The aim of this study was to investigate whether transcatheter closure of interatrial septal communications leads to myocardial injury, by measuring the serum concentration of TnT before and after catheter closure in adults, and to try to determine the cause of such an elevation.

Methods

Fifty-one patients who had undergone transcatheter ASD and PFO closure at the University Hospital in Lund, Sweden, from 2010 to 2016, were studied retrospectively. The characteristics of the patients are given in Table 1. Electrocardiograms were obtained before the procedure and 1 day after the procedure. Cardiac

* Correspondence: Joanna.Hlebowicz@med.lu.se
Department of Cardiology, Skåne University Hospital, Lund University, SE-221 85 Lund, Sweden

Table 1 Clinical characteristics of the 51 patients before and 1 day after transcatheter closure of an atrial septal defect (ASD) or patent foramen ovale (PFO). The three patients who only underwent diagnostic balloon sizing of the defect are included in the ASD group. Differences in age, BSA, degree of TnT elevation, the procedural duration, defect size and device size between the subjects who underwent transcatheter ASD and PFO closure were evaluated with the Mann–Whitney U-test. Chi-squared analysis was used to examine the distribution of the cardiovascular risk factors and sex across the groups

	ASD	PFO	*p*-value
Number of patients, n (%)	36 (71)	15 (29)	
Age, years (mean/range)	52 / 22–80	52 / 17–74	ns
Female, n (%)	29 (81)	6 (40)	0.004
BSA (m^2)	1.86 ± 0.21	1.97 ± 0.22	ns
Cardiovascular risk factors (%)			
Hypertension	33	33	ns
Smoking	6	7	ns
Dyslipidemia	3	7	ns
Impaired renal function	0	0	ns
Procedural data			
Device size: ASD waist/PFO disc (mean ± SD, mm)	22.8 ± 5.4	24.9 ± 3.9	ns
Defect size: stretched diameter (mean ± SD, mm)	22.8 ± 6.2	11.9 ± 3.2	0.000
Procedural duration (mean ± SD, min)	58.9 ± 11.5	48.1 ± 11.7	0.006
Biochemical results			
TnT increase ≥5 ng/, n (%)	32 (89)	15 (100)	ns
TnT increase (mean ± SD, ng/L)	18 ± 23	13 ± 10	ns

ns not significant

rhythm was monitored during the procedure and the day after. Transthoracic echocardiography was performed before, and 1 day after, the procedure. Blood samples were taken for the analysis of TnT 1 day before the intervention and 1 day after the intervention. All laboratory analysis was carried out at the laboratory of the University Hospital in Lund, using the commercial version of the TnT assay [7]. The lower detection limit for TnT was 5 ng/L. The interassay coefficient of variability was 2% at 16 ng/L, and 2.0% at 240 ng/L. The intraassay coefficient of variability was 0.6% at 16 ng/L and 0.6% at 100 ng/L.

In one patient, transcatheter closure was performed under general anesthesia with propofol. All other patients were awake, receiving midazolam for sedation if needed. Six of the patients with ASD and one of the patients with PFO were receiving antithrombotic treatment with warfarin before and after the procedure. One of the patients with ASD and eight of the patients with PFO were receiving Novel Oral AntiCoagulants (NOAC) before and after the procedure. All of the other patients ($n = 35$) received routinely antithrombotic treatment with aspirin the day before the procedure and this was maintained at a dose of 160 mg daily for at least 6 months after ASD (or PFO closure. If PFO closure because of cryptogenic stroke aspirin was prescribed lifelong, however, in a lower dose of 75 mg after 6 months.

Vascular access was obtained via the femoral vein. Heparin (100 IU/kg) and a single dose of prophylactic antibiotics (cloxacillin) were given. A sizing balloon was positioned in the ASD or PFO in all cases to measure the stretched diameter of the defect. The procedure was guided by transesophageal echocardiography in all cases, and was used to measure the defect diameter, the position in the interatrial septum, surrounding structures, the position of the sizing balloon, the device position and stability, and to detect any residual shunt. An Amplatzer Septal Occluder was used in 46 cases, and an Occlutech Figulla septal occluder in 2 cases. Periprocedural complications were limited: two patients exhibited transient (< 5 min) inferior ST elevation during the procedure, and two patients suffered from atrial arrhythmia during the procedure.

The study was approved by the Ethics Committee at Lund University, and performed according to the Declaration of Helsinki.

Statistical analysis

Results are given as mean values and SD, unless otherwise stated. Changes in the level of TnT were calculated as the difference between the level before the intervention (baseline) and 24 h after the intervention. The elevation of TnT was evaluated with the Wilcoxon t-test. Differences in the degree of TnT elevation, the procedural time, defect size and device size between the

subjects who underwent transcatheter ASD and PFO closure were evaluated with the Mann–Whitney U-test. Chi-squared analysis was used to examine the distribution of cardiovascular risk factors and sex across the groups. Possible relations between TnT elevation and age, body weight, body surface area (BSA), duration of the intervention, or size of the implanted device were analyzed with the Pearson correlation.

All statistical calculations were performed using SPSS for Windows (version 22.0, 2016). Values of $p < 0.05$ were considered to indicate statistically significant differences.

Results

Catheter closure was performed in 48 of the 51 patients (94%). In the other three patients (all ASD) only diagnostic balloon sizing of the defect was performed, and no attempt was made to close the defect. These three patients were included in the ASD group. A TnT level ≤ 5 ng/L (i.e. the lower detection limit) was found at baseline in 37 of the 51 patients (73%), and 1 day after the procedure in 5 of the patients (10%). The level of TnT was ≥15 ng/L at baseline in three patients (6%, one ASD closure, one ASD balloon sizing only, and one PFO closure), and an increase in TnT was found in 47 patients (92%) 1 day after the procedure (Table 1). The age, BSA, TnT elevation and cardiovascular risk factors did not differ between the ASD and the PFO groups (Table 1). There were significantly more women in the ASD group ($p = 0.004$). The mean procedural duration of ASD closure was 58.9 ± 11.5 min, which was significantly longer ($p = 0.006$) than that of PFO closure, 48.1 ± 11.7 min. The mean stretched diameter of the ASD was 22.8 ± 6.2 mm; significantly larger ($p = 0.000$) than the diameter of the PFO, 11.9 ± 3.2 mm.

The mean TnT level at baseline in the ASD group ($n = 33$) was 6.8 ± 4.9 ng/L, and increased significantly, to 26.4 ± 23.3 ng/L ($p = 0.000$), 1 day after ASD closure. The increase in TnT was significantly correlated to the stretched diameter of the ASD ($r = 0.424$, $p = 0.010$), as well as to the size (waist) of the implanted ASD device ($r = 0.542$, $p = 0.001$), and the duration of the procedure ($r = 0.348$, $p = 0.035$) (Fig. 1). The TnT elevation after ASD closure was not correlated with the patient's age, body weight or BSA.

The mean TnT level at baseline in the PFO group ($n = 15$) was 7.1 ± 3.2 ng/L, and increased significantly, to 19.7 ± 12.0 ng/L ($p = 0.001$), 1 day after PFO closure. The TnT elevation was not correlated with the balloon-stretched size of the PFO, the duration of the intervention, the size (largest disc) of the PFO device nor with the patient's age, body weight or BSA.

Three patients (all in the ASD group) underwent diagnostic balloon sizing of the defect without any attempt to close it. However, an increase in TnT was observed in one of these patients 1 day after the procedure (TnT 2 ng/L, 1 ng/L, and 49 ng/L, respectively).

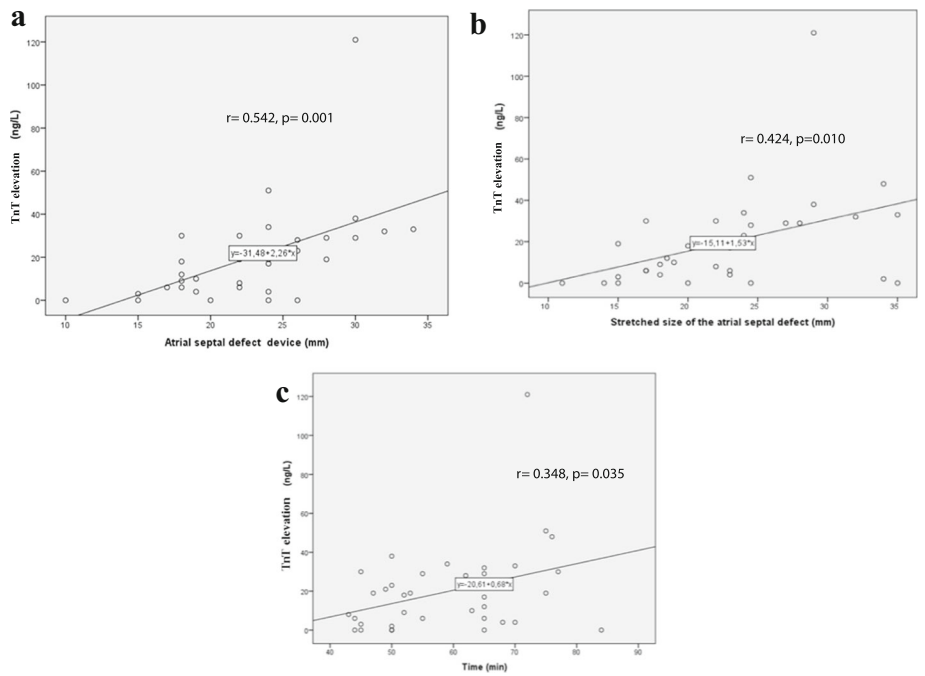

Fig. 1 Correlations between TnT elevation and (**a**) the size (waist) of the implanted ASD device, (**b**) the stretched size of the ASD, and (**c**) the duration of the procedure, evaluated with the Pearson correlation. Each data point represents an individual patient

The mean TnT level at baseline in the group receiving warfarin or NOAC (n = 16) was 9.0 ± 6.9 ng/L, and increased significantly, to 29.8 ± 31.9 ng/L (p = 0.001) 1 day after PFO or ASD closure. The mean TnT level at baseline in the group receiving aspirin (n = 35) was 5.1 ± 2.5 ng/L, and increased significantly, to 22.3 ± 12.7 ng/L (p = 0.000), 1 day after PFO or ASD closure. The TnT elevation was not significantly different between the group receiving warfarin and NOAC or aspirin (p = 0.474).

Discussion

The aim of this study was to determine whether catheter closure of an atrial septal defect leads to myocardial injury, and to determine the cause. Our finding, that catheter closure of an ASD or PFO causes a minor myocardial injury, is in accordance with earlier studies using troponin I (TnI) as a marker of myocardial damage [3–6]. The number of patients in these studies was about the same as in the present study. We also found that in patients with ASD, the extent of myocardial damage, expressed as the increase in TnT, was related to the waist size of the implanted ASD device. As the choice of device is based on balloon sizing, the size of the device is related to the stretched ASD diameter. It has also been found in previous studies on both children and adults that the elevation of TnI was related to the size of the implanted device [3, 6]. The larger the device, the greater the number of myocytes affected by mechanical stress, and it is thus logical to assume that a larger device will lead to a greater increase in TnT. In one of the studies mentioned above it was suggested that the increase in TnI was caused by transient, reversible myocardial membrane instability caused by the device, however, the relation to device size was not analyzed in that study [4]. In a study on children, the ratio of the device size to BSA was reported to be correlated to the magnitude of the myocardial injury [6]. This was not the case in our study. One reason for this may be that the variation in BSA in adults is much lower than in children, making correlations more difficult to identify.

We found an increase in TnT in one of the three patients undergoing balloon sizing only, in contrast to a previous study on diagnostic balloon sizing in seven patients, where no significant elevation of TnI was seen [4]. However, the small number of patients undergoing this procedure in the present study makes statistical analysis of this group impossible. Nevertheless, is appears that stretching the interatrial septum may cause mild myocardial injury. An increase in TnI has also been reported after other transcatheter interventions such as balloon dilation and the insertion of a stent in the pulmonary artery in one child aged 1.6 years and in the descending aorta in another aged 13.4 years [8]. However, in these cases this was explained by the acute obstruction of cardiac output by the balloon, causing ventricular strain and myocardial injury [8]. Cardiac catheterization alone has been reported not to lead to an increase in TnI in children [3], however, it is unclear whether balloon sizing was performed in that study.

An increase in TnT was also seen after PFO closure, but this was not correlated with the balloon-stretched size of the PFO or the size of the PFO device. However, PFO devices have a very narrow waist, and the designated size of PFO devices reflects the size of the largest disc; thus the strain on the rim/edge of the defect would be lower. Nevertheless, TnT was elevated after PFO closure, suggesting that the discs of the device may contribute to the release of TnT. However, a slight increase in TnT level can be caused by balloon sizing alone.

The increase in TnT in the ASD and PFO groups was not statistically significantly different, although a somewhat greater increase in TnT was seen after the ASD intervention. The duration of the ASD procedure is significantly longer than in PFO closure, and TnT elevation was related to the procedural time in the ASD group. This finding is in contrast to the study mentioned above, on ASD closure in children and adults, where no such relation was found [3]. PFO closure is usually straightforward, while the closure of ASDs, particularly large ones, may require more or longer manipulation. If so, the larger device size and repeated minor trauma caused by the catheter may explain our findings.

When the patient is in the supine position, air bubbles from the long sheaths may reach the right coronary artery due to the anterior position of the right sinus of Valsalva, and coronary air embolism has been reported in the systemic circulation during ASD catheter closure [9, 10]. In the present study, transient inferior ST elevation occurred in two patients during the ASD procedure and an increase in TnT level was observed. The one with the highest TnT increase observed in this study was 121 ng/L. This increase could be explained by coronary air embolism and a minor ventricular injury. If the patients had level of TnT was ≥15 ng/L the TnT was controlled to return to baseline. Unfortunately, lower levels TnT between 5 and 15 ng/L were not followed up. Therefore we cannot exclude leakage of low TnT elevels for a longer time. Transthoracic echocardiography was performed 1 day after closure, and no changes were observed in the left ventricular ejection fraction or wall motion, thus significant myocardial injury appears unlikely.

In our study 16 patients with ASD or PFO were receiving antithrombotic treatment with warfarin or NOAC before and after the procedure. All of the other patients received treatment with aspirin the day before the procedure and after the ASD or PFO closure. In our study the TnT elevation was not significantly different

between the group receiving warfarin and NOAC or aspirin. After transcatheter closure of an ASD defect a mild increased coagulation activation has been observed with increased prothrombin fragments after device implantation up to 3 months after the device implantation [11, 12]. However, no platelet activation was observed [11, 12]. Therefore the question has been raised whether we should use anticoagulant instead of antiplatelet therapy after closure of ASD defects. In our study the nitinol wire devices might have activated the coagulation in a short period causing microvascular myocardial injury. Unfortunately the troponin levels were only measured 1 day before the intervention and 1 day after the intervention. Therefore can a longer leak of troponin not be excluded. The coagulation returns to normal levels after 1–3 months [11, 12] and this has been explained caused by endothelialization of the ASD devices within 1–3 months after implantation [13, 14]. In our study the TnT elevation did not differ between those receiving warfarin or other antithrombotic treatments. The one with the highest TnT increase observed in this study had ST elevation during the procedure was treated with warfarin. However, the results did not differ if this patients was included or excluded in the statistical analysis. This study was not designed to measure the changes in the coagulation and the small numbers make statistical sub analysis uncertain with low statistical power.

Conclusions

The most important finding of this study is that patients undergoing uncomplicated catheter closure of an ASD or PFO experience minor and clinically insignificant myocardial injury as evidenced by the levels of TnT following the procedures. From the point of differential diagnoses, this knowledge is important when dealing with complications after ASD and PFO catheter closure. The mechanical trauma caused by insertion of the device appears to be the main mechanism responsible for this increase, as the circumference of the waist of the device is directly related to the affected area of the myocardium. The ASD devices seem to have a greater effect than PFO devices probably due to their larger waist.

Abbreviations

ASD: Atrial septal defect; PFO: Patent foramen ovale; TnT: Troponin T

Availability of data and materials

The datasets generated during the current study are not publicly available but are available from the corresponding author on reasonable request.

Authors' contributions

The authors' contributions were as follows: JH and UT contributed to the design of the study; JH performed the statistical calculations and wrote the first draft of the manuscript. JH, UT, JH and NI critically revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee at Lund University, Sweden, Dnr 2016/525.

Competing interests

The authors declare that they have no competing interests.

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