Clinical impact and predictors of periprocedural myocardial injury among patients undergoing left bundle branch area pacing

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ORIGINAL RESEARCH

Clinical impact and predictors of periprocedural myocardial injury among patients undergoing left bundle branch area pacing

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Abstract

Background The clinical impact of Periprocedural myocardial injury (PMI) in patients undergoing permanent pacemaker implantation with Left Bundle Branch Area Pacing (LBBAP) is unknown.

Methods 130 patients undergoing LBBAP from January 2020 to June 2021 and completing 12 months follow up were enrolled to assess the impact of PMI on composite clinical outcome (CCO) defined as any of the following: all-cause death, hospitalization for heart failure (HHF), hospitalization for acute coronary syndrome (ACS) and ventricular arrhythmias (VAs). High sensitivity Troponin T (HsTnT) was measured up to 24-h after intervention to identify the peak HsTnT values. PMI was defined as increased peak HsTnT values at least > 99th percentile of the upper reference limit (URL: 15 pg/ml) in patients with normal baseline values.

Results PMI occurred in 72 of 130 patients (55%). ROC analysis yielded a post-procedural peak HsTnT cutoff of fourfold the URL for predicting the CCO (AUC: 0.692; $p = 0.023$; sensitivity 73% and specificity 71%). Of the enrolled patients, 20% ($n = 26$) had peak HsTnT > fourfold the URL. Patients with peak HsTnT > fourfold the URL exhibited a higher incidence of the CCO than patients with peak HsTnT ≤ fourfold the URL (31% vs. 10%; $p = 0.005$), driven by more frequent hospitalizations for ACS (15% vs. 3%; $p = 0.010$). Multiple (> 2) lead repositions attempts, the use of septography and stylet-driven leads were independent predictors of higher risk of PMI with peak HsTnT > fourfold the URL.

Conclusions PMI seems common among patients undergoing LBBAP and may be associated with an increased risk of clinical outcomes in case of more pronounced (peak HsTnT > fourfold the URL) myocardial damage occurring during the procedure.

Keywords Periprocedural myocardial injury · Left bundle branch area pacing · High sensitivity troponin · Lumen less lead · Stylet-driven lead · Septography

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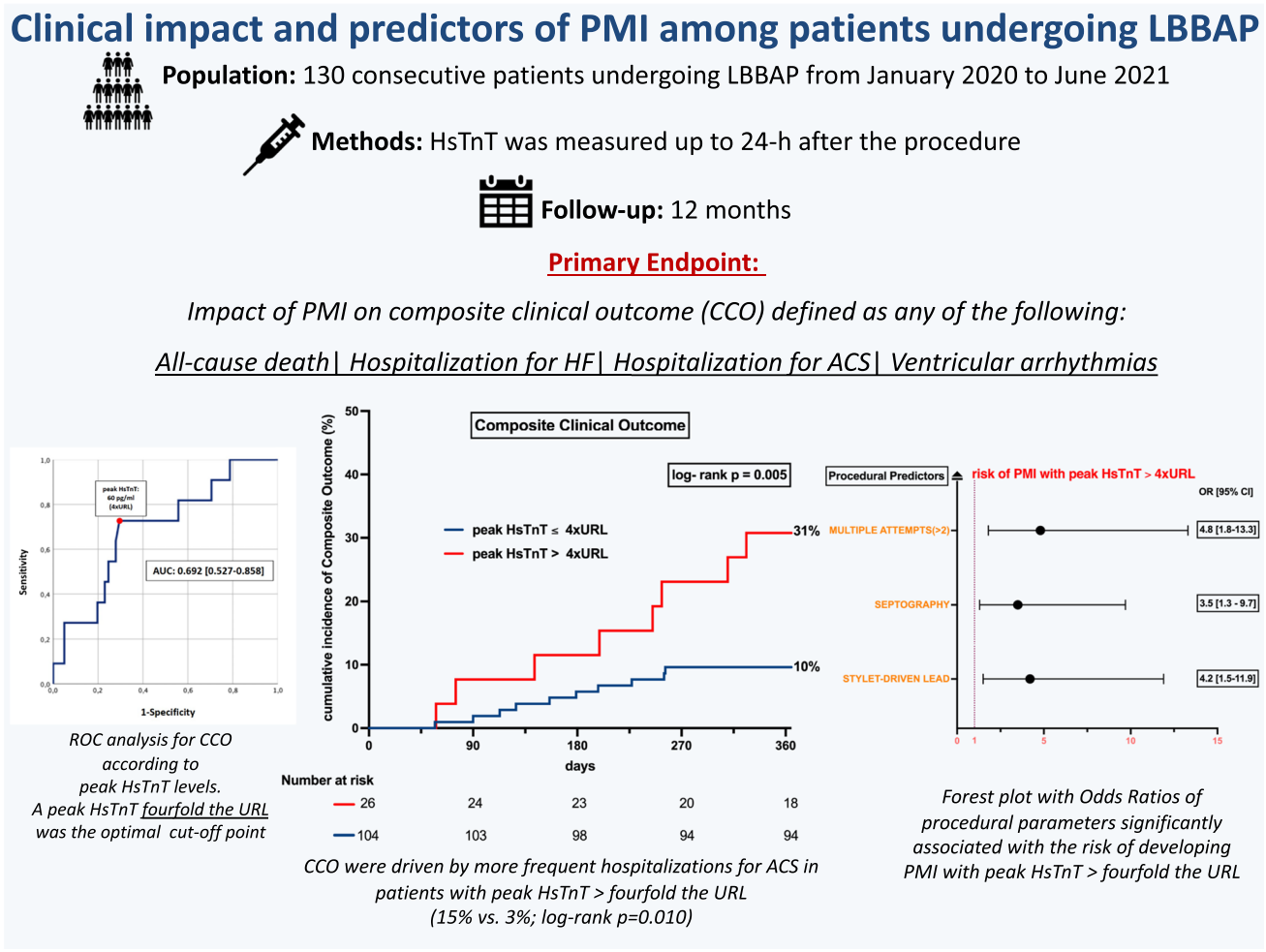
Graphical Abstract



1 Introduction

Periprocedural myocardial injury (PMI) is a well-recognized entity characterized by a transient increase in cardiac biomarkers signifying myocardial damage occurring in relation to an invasive cardiovascular or non-cardiovascular procedure [1, 2]. Though often subclinical, PMI has garnered increasing attention as a prognostic index in various clinical scenarios, especially in the case of extensive myocardial injury [1, 2]. Accordingly, the latest guidelines recommend routine perioperative assessment of cardiac biomarkers (i.e., high-sensitivity troponins) to identify PMI and facilitate risk stratification and management of patients undergoing cardiac and non-cardiac interventions [3].

Across the spectrum of cardiac interventions, cardiac pacing has significantly evolved over recent years from conventional right ventricular pacing (RVP) to physiological pacing techniques such as Left Bundle Branch Area Pacing (LBBAP) [4–7]. LBBAP has shown considerable potential benefits in preventing pacing-induced cardiomyopathy with favourable procedural parameters and safety profiles [4]. As this procedure gains popularity, elucidating its potential risks along with beneficial effects remains of paramount importance [8–10]. Namely, the investigation of PMI and the mechanisms underlying this phenomenon are still uncharted in patients undergoing LBBAP.

Pivotal observational studies reported less frequent troponin release following HBP and traditional RV pacing when compared to LBBAP [11]. Indeed, apart from localized myocardial edema, commonly advocated with conventional pacing, deep lead screwing through the interventricular septum in LBBAP might lead to amplified myocardial damage and inadvertent harm of the coronary arteries (e.g., septal branches) due to their anatomical proximity [12]. Some reports describe isolated cases of septal hematoma, coronary vasospasm leading to transient ST-elevation myocardial infarction and the rare occurrence of coronary fistulae or extrinsic coronary artery compression during LBBAP [12, 13]. In this new and more complex scenario,

myocardial injury associated with LBBAP deserves an in-depth standardized appraisal of its features and impact on patient outcomes. This study aimed to analyze the incidence of PMI in patients undergoing LBBAP implantation and determine the extension of PMI impacting on clinical consequences.

2 Methods

In this prospective observational study, consecutive patients undergoing LBBAP implantation from January 2020 to June 2021 for bradycardia or CRT indications and completing a clinical follow-up at 12 months were enrolled.

Patients with < 18 years old or with any of the following characteristics were excluded: abnormal levels of pre-operative cardiac biomarkers, acute myocarditis, acute myocardial infarction, coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) within the last three months; cardiac surgery, transcatheter aortic valve replacement (TAVR), ventricular septal myectomy and ablation for any atrial or ventricular arrhythmias within the last three months; history of complex congenital heart disease (i.e., surgically corrected ACHD); severe reduction in glomerular filtration rate (GFR < 30 mL/minute/1.73 m^2); metastatic cancer or unable to undergo the planned follow-up for any reason.

Baseline demographic characteristics and relevant clinical variables were collected for each patient, including comorbidities, medication history, and left ventricular ejection fraction (LVEF).

Pacing indication and electrocardiographic parameters were also recorded.

Each patient underwent a clinical follow-up visit at 12 months after the implantation procedure.

All patients provided written informed consent regarding LBBAP as a novel alternative pacing approach.

2.1 Biomarker assessment

Blood samples were drawn in all patients within 12 h prior to implantation and at 6, 12 and 24 h after the procedure and were analyzed with an immunoassay system COBAS PRO (Roche International Ltd) for HsTnT assessment. The upper reference limit (URL) for HsTnT was 15 pg/ml.

2.2 Procedural aspects

LBBAP was performed using either the 4.1F 3830 SelectSecure (Medtronic, Minneapolis, MN) lumen-less lead (LLL) with exposed-helix delivered through the C315HIS (Medtronic, Minneapolis, MN) sheath or the 5.6F Biotronik Solia S60 (Biotronik, Berlin, Germany) stylet-driven lead (SDL) with extendable-helix delivered via the Biotronik Selectra 3D sheath (Biotronik, Berlin, Germany).

A 12-lead ECG and intracardiac electrograms (EGMs) were continuously recorded with an electrophysiology recording system (Lab SystemTM PRO-EP, Boston Scientific).

The deployment of the lead in the subendocardial area of LV septum was performed as previously described [14]. Left bundle branch (LBB) capture was confirmed in case of demonstration of QRS transition with differential output or with morphological criteria [7]. Left ventricular septal pacing (LVSP) was defined by terminal R-wave in V1 lead, deep septal position of the pacing lead and absence of criteria for conduction system capture [7].

The decision to use a LLL or SDL or to perform septography (i.e., contrast injection through the sheath) to assess lead depth within the interventricular septum was left to the discretion of the individual operator.

All electrophysiological measurements were performed at a 100 mm/s scroll speed. QRS duration was measured from the first initial deflection to the final QRS component in any of the 12 ECG leads.

2.3 Study endpoints

The primary endpoint was the incidence of PMI classified according to the fourth universal definition of myocardial infarction (UDMI) [15]: increased HsTnT values at least > 99th percentile of the upper reference limit (15 pg/ml) in patients with normal baseline values.

HsTnT values at baseline (prior to implantation), 6, 12 and 24 h after intervention were measured to identify the peak HsTnT values which were then used to classify patients with PMI.

The clinical endpoint was the incidence of composite clinical outcome within 12 months of follow-up. The composite clinical outcome was defined as any of the following: all-cause death, hospitalization for heart failure (HHF), hospitalization for acute coronary syndrome (ACS), and ventricular arrhythmias (VAs).

HHF was defined as hospital admission for clinical symptoms and signs of HF with objective evidence of elevated levels of natriuretic peptides or the need for loop diuretics to reduce fluid overload.

Hospitalizations for ACS were considered admissions for abnormal levels of cardiac troponins associated with symptoms (such as chest pain/discomfort and/or shortness of breath) and/or electrocardiographic alterations suggestive of acute myocardial ischemia.

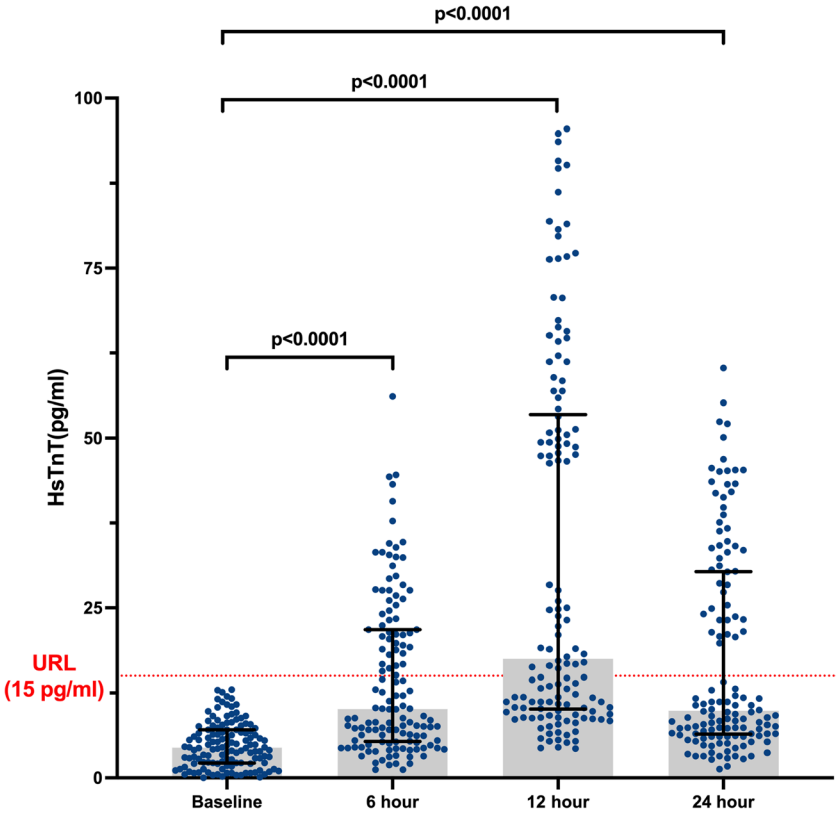


Fig. 1 Periprocedural variations of high sensitivity cardiac troponin T (HsTnT) levels from baseline to 6-h, 12-h, and 24 h after LBBAP procedure. URL: upper reference limit = 15 pg/ml. Data are presented as median and interquartile ranges

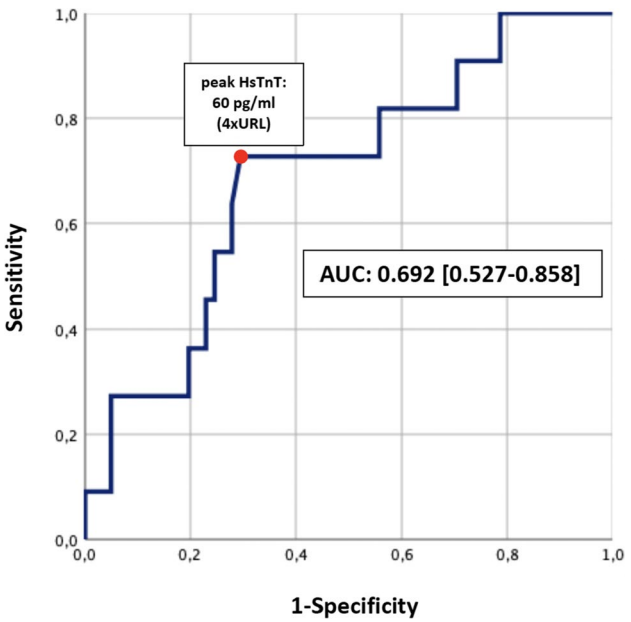


Fig. 2 Receiver-operating characteristic (ROC) analysis for composite clinical endpoint according to peak HsTnT levels. A peak HsTnT value of 60 pg/ml (fourfold the URL) was the optimal cutoff point to predict adverse events, with a sensitivity of 73%, and specificity of 71%. AUC: area under the curve; 95% CI: confidence intervals

VAs referred to documented episodes of ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) characterized by consecutive ventricular beats at a rate of more than 100 beats per minute for a duration of over 30 s as registered by the device or requiring hospital admission and medical intervention for termination. ECG and EGM device tracings were independently reviewed and analyzed by 3 board-certified cardiac electrophysiologists. An event was classified as a ventricular arrhythmia if there was concordant adjudication by at least 2 out of the 3 electrophysiologists.

2.4 Statistics

Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test or the Mann–Whitney U test, depending on the data distribution. Categorical variables were expressed as frequency (percentage) and compared using the Chi-square test or Fisher's exact test, as appropriate.

A Receiver-Operating Characteristic (ROC) analysis was constructed to find the cut-off of peak HsTnT value that could significantly discriminate between groups of patients with and without the composite clinical outcome.

Table 1 Clinical characteristics

	Total ($n=130$)	HsTnT ≤ 4xURL ($n=104$)	HsTnT > 4xURL ($n=26$)	*P* value
Age, yrs	77 ± 11	76 ± 10	78 ± 12	0.383
Male, n (%)	87(67)	67(65)	20(76)	0.226
Body mass index, kg/m^2	26 ± 4	27 ± 4	26 ± 5	0.281
Diabetes mellitus, n (%)	23(18)	17(16)	6 (23)	0.403
Hypertension, n (%)	94(72)	75(72)	19 (73)	1.000
Hyperlipidemia, n (%)	72(55)	58(56)	14(53)	0.860
Chronic Kidney disease, n (%)	60(46)	49 (47)	11(44)	0.661
COPD, n (%)	36(28)	29(28)	7 (27)	0.922
Atrial fibrillation, n (%)	23(18)	16(15)	7(27)	0.248
Ischemic heart disease, n (%)	48(37)	39(38)	9(35)	0.786
Medications				
ACEi/ARBs/ARNI, n (%)	104(80)	83 (80)	21(82)	0.913
Beta blockers, n (%)	107(82)	87(84)	20(80)	0.423
Diuretics, n (%)	84(65)	68(66)	16(60)	0.725
CCBs, n (%)	55(42)	45(43)	10(42)	0.658
AADs, n (%)	87(67)	70(68)	17(67)	0.515
Statins, n (%)	75(58)	61(59)	14(54)	0.658
Pacing indications				0.177
SSS, n (%)	6(5)	5 (5)	1 (4)	
AVB, n (%)	69(53)	51(49)	18(69)	
CRT, n (%)	55(42)	48(46)	7(27)	
ECG parameters				
PR interval, msec	266 ± 48	260 ± 43	271 ± 55	0.273
Native QRS duration, msec	150 ± 38	151 ± 39	148 ± 36	0.677
Echocardiographic parameters				
LVEF (%)	44 ± 13	44 ± 14	45 ± 12	0.471
IVS diameter, mm	11 ± 4	11 ± 5	11 ± 2	0.595

COPD chronic obstructive pulmonary disease, *ACEi* ace-inhibitors, *ARBs* angiotensin II receptor blockers, *ARNI* angiotensin receptor -neprilysin inhibitors, *CCBs* calcium channel blockers, *AADs* antiarrhythmic drugs, *SSS* sick-sinus syndrome, *AVB* atrio-ventricular block, *CRT* cardiac resynchronization therapy, *LVEF* left ventricle ejection fraction, *IVS* interventricular septum

Survival analysis with Kaplan–Meier curves to evaluate the relationship between peak HsTnT groups and the occurrence of clinical events during follow-up was analyzed using the log-rank test.

Predictors of PMI were assessed using univariable and multivariable logistic regression analysis. Risk estimates were expressed as Odds Ratio (OR) and 95% confidence intervals (CI).

For the multivariable logistic regression analysis all variables with $p < 0.05$ at univariable analysis were included in the final model and adjusted for potential confounders (i.e., sex and renal function). A P value < 0.05 was considered statistically significant.

All statistical analyses were performed using STATA version 17.0 (StataCorp LLC, TX—USA) and Prism GraphPad (GraphPad Software, Boston, MA—USA).

3 Results

A total of 130 patients (age 77 ± 11 years, 67% male) were enrolled and all patients completed the clinical follow-up at 12 months.

3.1 Primary endpoint

HsTnT values at baseline were 4.5 [2.2–7.1]pg/ml and showed a significant post-procedural increase to 10.1[5.4–21.8]pg/ml at 6 h, 17.5[10.1–53.5]pg/ml at 12 h, and 6.5[9.9–30.3]pg/ml at 24 h, ($p < 0.0001$) (Fig. 1). PMI occurred in 72 patients (55%) after LBBAP. None of these patients developed electrocardiographic changes

Table 2 Procedural parameters

	Total ($n=130$)	HsTnT ≤ 4xURL ($n=104$)	HsTnT > 4xURL ($n=26$)	*P* value
Fluoroscopy time, min	9 ± 6	10 ± 6	8 ± 6	0.797
Procedure duration, min	80 ± 23	82 ± 24	78 ± 22	0.441
Multiple attempts (> 2), *n* (%)	46 (35)	31 (30)	15 (58)	**0.011**
Septography, *n* (%)	44 (34)	30(29)	14(54)	**0.021**
Stylet driven leads (SDL), *n* (%)	42 (32)	29(28)	13(50)	**0.037**
Type of capture				
LBBP, *n* (%)	37(28)	29(28)	8(31)	0.770
LVSP, *n* (%)	34(26)	28 (27)	6 (23)	0.689
LBFP, *n*%	59(46)	47 (45)	12 (46)	0.929
Pacing parameters				
Threshold, V*	0.9 ± 0.5	0.9 ± 0.6	0.8 ± 0.4	0.137
R wave, mV	9.8 ± 4.3	9.7 ± 4.6	10.7 ± 3.1	0.245
Impedance, ohms	598 ± 191	593 ± 200	614 ± 152	0.190
Paced QRS duration, msec	146 ± 23	145 ± 24	146 ± 22	0.570
LVAT, msec	80 ± 19	81 ± 18	77 ± 20	0.664

*Threshold values were considered with a pulse width of 0.5 ms

LBBP left bundle branch pacing, *LVSP* left ventricular septal pacing, *LBFP* left bundle fascicular pacing, *LVAT* left ventricular activation time (measured as the interval from stimulus to peak of the R wave in leads V6)

Table 3 Clinical outcomes

	Total ($n=130$)	HsTnT ≤ 4xURL ($n=104$)	HsTnT > 4xURL ($n=26$)	*P* value
Composite outcome, *n* (%)	18 (14)	10(10)	8(31)	**0.010**
Death, *n* (%)	0 (0)	0 (0)	0 (0)	/
Hospitalizations HF, *n* (%)	5 (4)	3(3)	2(8)	0.261
Hospitalizations ACS, *n* (%)	7 (5.5)	3(3)	4(15)	**0.029**
Ventricular Arrhythmias, *n* (%)	6(4.5)	4(4)	2(8)	0.345

Data are presented as number (percentage). *P* values reported for χ^2 or Fisher's exact test

HF heart failure, *ACS* acute coronary syndrome

and symptoms suggestive of acute myocardial ischemia or required acute urgent coronary angiography.

3.2 Clinical endpoint

In patients with PMI, the ROC analysis showed that peak HsTnT values could significantly discriminate between patients with and without composite clinical outcome. The value of 60 pg/ml (fourfold the URL) was the optimal cut-off point with a sensitivity of 73% and specificity of 71% (area under the curve [AUC]: 0.692; 95% CI: 0.527 to 0.858; $p=0.023$) (Fig. 2).

Based on these results, we divided our study population into 2 groups based on the distribution of post-procedural peak HsTnT ≤ fourfold the URL ($n=104$ patients, 80%) or peak HsTnT > fourfold the URL ($n=26$ patients, 20%), respectively.

The clinical and procedural characteristics of both groups are presented in Tables 1 and 2, respectively. No significant differences in baseline clinical characteristics, medications or pacing indications were detected between the groups. Also, there were no significant procedural differences in terms of pacing electrical parameters. However, a significantly higher rate of multiple (> 2) attempts, use of septography, and use of stylet-driven leads were noted in the group that developed post-procedural peak HsTnT release > fourfold the URL.

Compared to patients with peak HsTnT ≤ fourfold the URL, those with peak HsTnT > fourfold the URL had a significantly higher incidence of the composite clinical endpoint during follow-up (31% vs. 10%; log-rank $p=0.005$). No deaths were documented during the follow-up; a higher incidence of hospitalizations for ACS occurred in the peak HsTnT > fourfold vs. ≤ fourfold the URL group (15% vs. 3%,

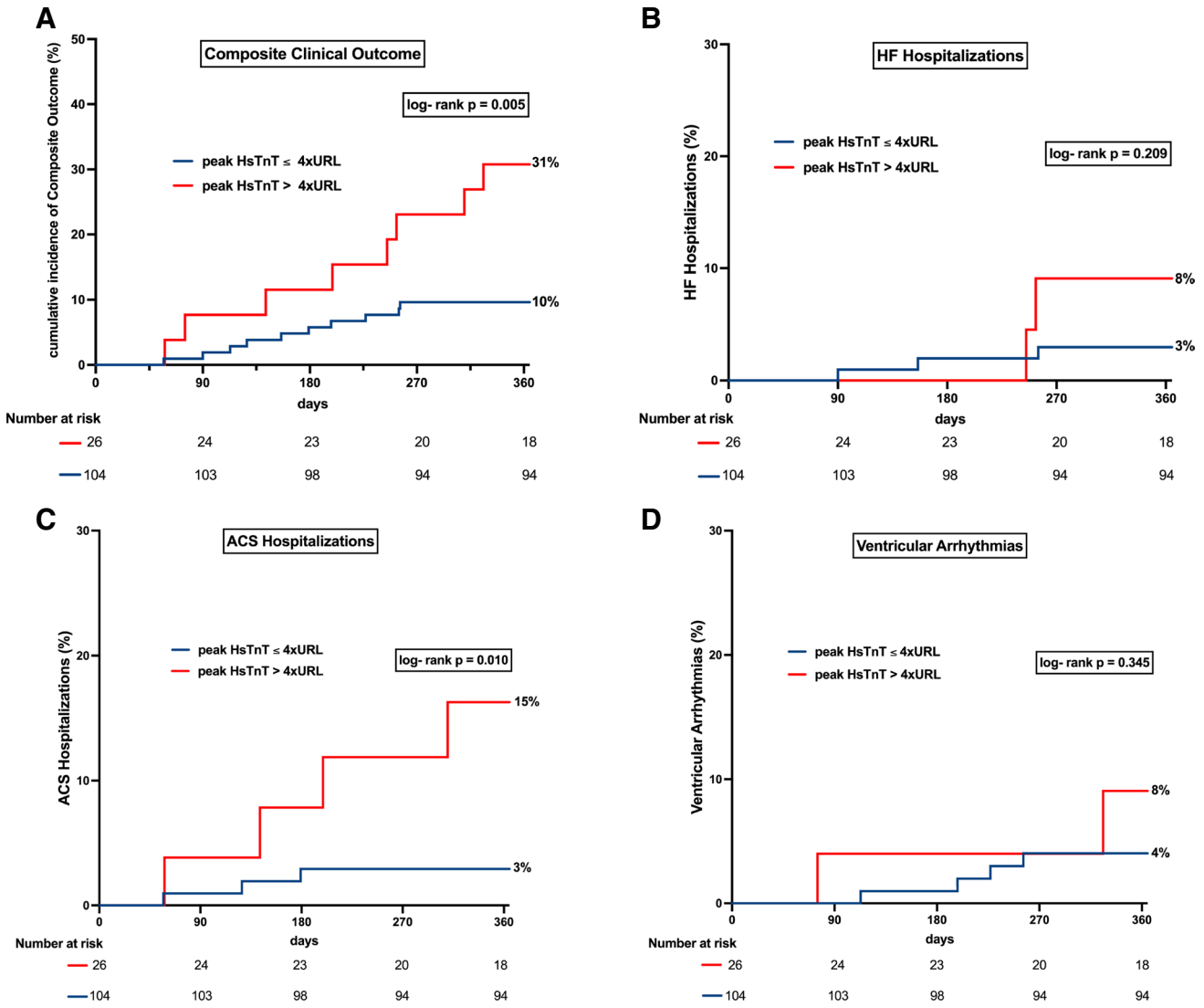


Fig. 3 Kaplan–Meier estimates at 12-months follow-up of composite clinical outcome (panel **A**), hospitalizations for heart failure (HHF) (panel **B**), hospitalizations for acute coronary syndrome (ACS) (panel **C**) and ventricular arrhythmias (VAs) (panel **D**) according to peak HsTnT groups [peak HsTnT ≤ fourfold the URL (blue) versus peak HsTnT > fourfold the URL (red)]

Table 4 Predictors of PMI with peak HsTnT release > fourfold the URL

	Univariable analysis			Multivariable analysis		
	OR	95%CI	*p* value	OR	95%CI	*p* value
Sex	0.5	0.2–1.5	0.214			
Renal function	0.3	0.04–2.7	0.282			
Multiple attempts (> 2)	3.2	1.3–7.8	**0.010**	4.8	1.8–13.3	**0.002**
Septography	2.9	1.2–6.9	**0.019**	3.5	1.3–9.7	**0.014**
SDLs	2.6	1.1–6.2	**0.035**	4.2	1.5–11.9	**0.006**

Univariable and multivariable logistic regression analysis of clinical and procedural parameters with their risk estimates of developing PMI with a peak HsTnT release > fourfold the URL. The multivariable logistic regression analysis was adjusted for sex and renal function (creatinine clearance)

PMI periprocedural myocardial injury, *HsTnT* High sensitivity Troponin T, *URL* upper reference limit, *OR* odds ratio, *CI* confidence interval, *SDLs* stylet-driven leads

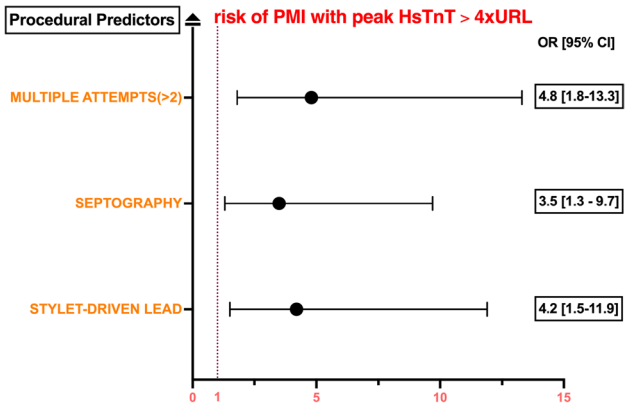


Fig. 4 Forest plot of Odds Ratios (ORs) for procedural parameters significantly associated with the risk of developing PMI with peak HsTnT > fourfold the URL: multiple attempts (> 2), the use of septography and the use of stylet-driven extendable-helix lead (SDLs). The multivariable logistic regression analysis was adjusted for sex and renal function (creatinine clearance)

log-rank $p = 0.010$), while no significant differences were recorded between the groups in the rates of HHF (8% vs. 3%, log-rank $p = 0.209$), and ventricular arrhythmias (8% vs. 4%, log-rank $p = 0.344$) (Table 3, Fig. 3).

3.3 Procedural predictors of PMI

Univariable and multivariable logistic regression analysis of clinical and procedural parameters with their risk estimates of developing PMI with a peak HsTnT release > fourfold the URL are reported in Table 4.

At univariable analysis, multiple (> 2) LBBAP lead implantation attempts, the performance of septography, and the use of SDLs were parameters significantly associated with increased risk of PMI with peak HsTnT release > fourfold the URL.

A multivariable logistic regression analysis including univariable predictors and adjusted for factors known to influence troponin levels (sex and renal function) was then performed.

In this multivariable model, multiple (> 2) LBBAP lead implantation attempts [OR:4.8, 95%CI:1.8–13.3; $p = 0.002$], the use of septography [OR:3.5, 95%CI:1.3–9.7; $p = 0.014$] and the use of SDLs [OR:4.2, 95%CI:1.5–11.9; $p = 0.006$] were independent predictors of a higher risk of PMI with peak HsTnT release > fourfold the URL (Fig. 4).

4 Discussion

The key findings of this study are the following:

1. PMI was common in patients undergoing LBBAP, occurring in 55% of the patients.
2. PMI with a more extensive myocardial damage (peak HsTnT increase > fourfold the URL) occurred in 20% of the patients and was associated with an increased risk of clinical outcomes at 12 months.
3. Multiple (> 2) LBBAP lead repositioning attempts, the performance of septography, and the use of SDLs were factors associated with a higher risk of developing a more extensive PMI with peak HsTnT increase > fourfold the URL.

4.1 Primary endpoint: incidence of PMI

Cardiac troponins are routinely used as standard markers of myocardial injury. Originally, their application was confined to diagnosing or ruling out an acute coronary syndrome [16]. However, their prognostic significance in various clinical scenarios is now widely recognized [17].

One of the first descriptions of isolated troponin elevation after traditional cardiac pacing traces back to the work of Martignani and colleagues, who demonstrated elevation in cardiac Troponin I levels in nearly 37% of patients within 12 h following pacemaker implantation [18]. Subsequently, many studies described the mechanical effects of lead-tissue interactions and its relation to the extent of myocardial inflammation and injury, which was influenced by the pacing lead fixation types and the number of positioning attempts during implantation [19, 20].

Recently, Castellanos and colleagues documented histopathological alterations occurring at the ventricular sites of pacing leads insertion, including myocardial compression, fibrosis, and calcifications [21].

With the evolution of cardiac pacing and a shift towards physiological pacing, epitomized by LBBAP, there might be concerns about the potential risk of more pronounced myocardial injury due to the lead screwing and positioning deep within the interventricular septum to reach the left bundle branch area [22].

Our study confirms that subclinical PMI is not an uncommon issue in patients undergoing LBBAP, aligning with the data of a retrospective study by Ponnussamy and colleagues, which described asymptomatic troponin release of threefold the URL in almost 50% of cases at 6 -12 h following LBBAP[11]. In contrast with that study, in which the authors used both high sensitivity troponin T and I assays and set an arbitrary threshold of cardiac troponins rise > threefold the URL within 12 h from intervention to classify a significant PMI, we used only the HsTnT assay for PMI assessment.

Moreover, we categorized the PMI according to the fourth universal definition of myocardial infarction [15] and monitored the troponin for up to 24 h from the index procedure, providing a more thorough characterization of troponin kinetics and reliable representation of peak troponin values

post-intervention. At the same time, given that a uniform PMI definition related to LBBAP and data on its clinical relevance is still lacking, our research suggests a potential HsTnT cut-off that warrants further investigation to confirm its predictive value for clinical events at 12 months.

4.2 Secondary endpoint: composite clinical outcome

Our study highlights that the risk of developing clinical adverse outcomes at 12 months is commensurate to the magnitude of PMI occurring at the time of implantation. Patients exhibiting a > fourfold URL rise in troponin levels post-LBBAP had a significantly higher rate of clinical adverse events driven by hospitalization for acute coronary syndromes during follow-up. The exact pathophysiological mechanisms remain unexplored, but our findings suggest that extensive PMI might be a forerunner or unveil patient propension to subsequent coronary events. A plausible speculation is that PMI secondary to LBBAP lead position across the interventricular septum, beyond the potential direct myocardial and coronary damage, could predispose to coronary vasospasm or microvascular dysfunction, rendering the myocardium susceptible to future ischemic insults.

Nonetheless, further investigations are required to delineate causal connections, especially for events occurring moderately downstream from the implantation timeframe.

Moreover, as no patient required coronary angiography acutely post-implantation, we cannot entirely speculate whether LBBAP lead placement and position within the septum was linked with the increased risk of hospitalization for ACS per se or if these events observed during follow-up were unanticipated manifestations of an underlying coronary artery disease.

Despite the aforementioned increase in ACS hospitalizations, extensive PMI did not translate in increased risk of mortality, heart failure hospitalizations, or ventricular arrhythmias. This might be attributed to the beneficial and protective effect exerted by LBBAP, in which ameliorating the adverse cardiac remodeling and dyssynchrony could offset the detrimental impact of PMI [23, 24].

Alternatively, the nature and extent of myocardial injury with LBBAP might differ from other invasive procedures and may not be significant enough to precipitate heart failure or fatal arrhythmias [11].

4.3 Procedural predictors of PMI

Since the precise mechanism of PMI in LBBAP remains uncertain, our study also focused on concurrent factors associated with an increased risk of more extended myocardial damage during LBBAP lead implantation.

Preliminary evidence described a higher incidence of PMI in those patients who required multiple attempts to achieve a successful lead position or needed repositioning due to acute septal perforation [11, 12]. We found that patients who required more than two attempts were at risk for more pronounced PMI. Multiple attempts might indicate procedural challenges due to anatomical obstacles or difficulties in obtaining optimal pacing parameters. Therefore, the repetitive manipulations of the lead within the septum could portend to further myocardial traumas, increase the likelihood of mechanical stress, septal injury or perforation, and trigger an exaggerate inflammatory response. Lead placement optimization during the first or second attempt, by standardized procedural protocols, the guidance of electrophysiological and electrical parameters, and the support imaging techniques (e.g., Ultra High-Frequency ECG), could potentially help blunt this risk [25–27].

Our study also indicates a potential deleterious association between septography and PMI.

The performance of septography has become a default approach in many centers to guide LBBAP lead placement and assess lead depth into the interventricular septum [4, 28].

However, the forceful-pressure exerted from a sheath tip tenting the interventricular septum during contrast injections, especially if performed once the lead has been screwed deep inside the septum, might induce localized myocardial trauma portending to endothelial dysfunction and inflammatory response with further cardiomyocyte injury [29]. The routine use of septography should be reframed especially when there are validated electrophysiological criteria and electrocardiographic step-wise approaches to guide LBBAP lead implantation without the need of contrast [27, 30–32].

Given our findings, septography benefits should be balanced against its potential risks (e.g., PMI or nephropathy/allergy) and it should be used judiciously in selected and more challenging procedures [12].

Notably, in our study, SDLs were linked with a higher incidence of significant PMI than LLLs.

With expansion of CSP techniques and the advent of different marketed delivering tools, also commercially available stylet-driven leads with extendable-helix are becoming widely adapted to perform LBBAP in addition to LLLs [33].

In this regard, the Multicenter European Left Bundle Branch Area Pacing Outcomes Study (MELOS) reported slightly higher procedural success but at the expenses of higher complications rate with SDLs when compared to LLLs [34]. In detail, the MELOS registry displayed a higher overall complication rate (16.4% vs. 9.4%, $p < 0.001$) and higher LBBAP-specific complication rate (11.9% vs. 6.9%, $p < 0.001$), driven by higher post-implantation lead displacement (3.8% vs. 1.1%, $p < 0.001$) and a trend in higher acute

septal perforation (4.8% vs. 3.5%, $p=0.19$) with SDLs compared with LLLs [34].

The higher rate of complications in the aforementioned registry as well as the higher risk of PMI with SDLs found in our study may be explained by the larger diameter of the SDL and the mechanical stiffness provided by the stylet, which might increase the chances of myocardial trauma or perforation, especially during repeated attempts [35].

Furthermore, cases of lead deformations, fractures and entanglement in the septum are more frequently documented with SDLs, most of which occur during repetitive screwing maneuvers for lead repositioning [35–37]. Conversely, the LLLs, consisting of an isodiametric and smaller diameter due to the absence of an inner lumen, might be less irritative of the myocardial tissue and less prone to deformations than SDLs [35].

Nonetheless, as most of the procedures were performed with a LLL in our study, we cannot exclude the higher risk of extensive PMI associated with SDLs might not be solely related to the structure of the SDL but also reflect the operators' learning curve. Cano and colleagues, indeed, describe higher rates of acute lead-related complications in LBBAP practice with SDLs than LLLs (15.9% vs 6.1%, respectively; $P<0.001$) which downtrends over time with acquired experience [38].

Starting from these observations, a potential area of future investigation could be developing a lead design that combines the advantages of both LLL and SDL technologies to facilitate successful implantation while preventing possible complications.

Finally, all these elements also underline awareness of the risk of each procedural step and that adequate specific training (e.g., simulation sessions) should be crucial to enhance technical skills for those in their early phases of cardiac pacing career or those transitioning from traditional pacing methods to LBBAP [5, 39].

5 Limitations

The results of this study should be interpreted with several limitations acknowledged.

Firstly, this was a prospective observational study and its findings may not be generalizable to all patient populations or procedural settings. Residual influence from unaccounted covariates or potential pre-selection and selection biases also cannot be excluded. Secondly, our study relied on a single cardiac biomarker used as a surrogate for myocardial injury. Although the HsTnT is widely used and validated for this purpose, additional biomarkers and imaging modalities, including CCT or cardiac magnetic resonance (CMR), might provide further insights into the mechanisms and the extent of the myocardial injury detected in this study and prove causation with the clinical consequences observed during the follow-up. Finally, we cannot exclude that the higher risk of troponin release may also reflect the operator's different expertise and be contingent on multiple repositioning attempts required in those initially gaining more proficiency in the LBBAP procedure.

6 Conclusions

In this study, PMI emerges as a common issue among patients undergoing LBBAP associated with an increased risk of clinical consequences in case of more extended myocardial damage (peak HsTnT increase > fourfold the URL) arising during implantation.

Until a standardized classification validates the clinical relevance of PMI related to LBBAP, it may be advisable to refine some procedural technicalities preventing more significant myocardial injury.

Future research is, therefore, warranted to elucidate the myocardial injury phenomenon occurring during LBBAP and explore potential management strategies to improve patient outcomes.

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Data availability All data are available for research purposes as encrypted anonymous files upon request.

Declarations

Ethics approval The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the local ethics committee.

Consent to participate Written informed consent of all subjects had been acquired.

Consent for publication All authors read the final version of the manuscript and agreed on submission to the JICE.

Conflicts of interest/Competing interests KC—consultancy agreements with Medtronic, Abbott, speaker honoraria Medtronic, Biotronik.
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