



Advantages and disadvantages of drug challenge during electrophysiological study in patients with new left bundle branch block after transaortic valve implantation

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ABSTRACT

Aims: Electrophysiological study (EPS) is recommended in case of new-onset persistent left bundle branch block (NOP-LBBB) after transaortic valve implantation (TAVI) to identify patients at high risk of delayed atrioventricular block (D-AVB). We evaluated the added value of drug challenge, after normal baseline EPS, to predict D-AVB in such patients.

Methods: We conducted a comparative single-centre study of two successive periods, during which we used baseline EPS alone (first period) or drug challenge in case of normal baseline EPS (second period), for patients with NOP-LBBB after TAVI. The primary endpoint was a composite of pacemaker use, documented D-AVB, cardiac syncope, sudden death, or delayed pacemaker implantation.

Results: Among 736 patients with TAVI implantation between January 2016 and September 2019, 64 with NOP-LBBB were included. During the first period, 4/22 (18.2%) presented with a positive baseline EPS. After a mean (standard deviation [SD]) of 15.6 (8.3) months, 7/22 (31.8%) reached the primary endpoint. During the second period, 19/42 (45.2%) presented with a positive EPS. After a mean (SD) of 12.8 (3.5) months, 8/42 (19.0%) reached the primary endpoint. There was a tendency to increased sensitivity (42.9–87.5%; $P = 0.12$) and negative predictive value (77.8–95.7%; $P = 0.15$) of the EPS, respectively during the first to the second period. However, the specificity decreased (93.3–64.7%; $P = 0.04$).

Conclusion: Diagnostic yield improved with drug challenge in case of normal baseline EPS. However, the decrease in specificity led to a high rate of unnecessary pacemaker implantation.

1. Introduction

New-onset persistent left bundle branch block (NOP-LBBB) is the most frequent conduction disturbance observed after transaortic valve implantation (TAVI), being observed in 13–37% of cases [1]. Concerns regarding NOP-LBBB after TAVI include potential delayed high-degree atrioventricular (AV) block (D-AVB) [2], left ventricular dysfunction, and long-term mortality [2–5]. In recent consensus document on post-TAVI conduction disturbance management [6] and European guidelines on cardiac pacing [7], best strategies to identify patients at risk of

developing D-AVB are still debated and include electrophysiological study (EPS) or prolonged electrocardiographic monitoring. However, baseline EPS is known to have a low sensitivity for detecting patients at risk of D-AVB [8–12]. Drug challenge is recommended for increasing the sensitivity of EPS to detect infra-nodal conduction disturbances in patients with syncope and bundle branch block [13]. It has rarely been reported in patients with new conduction abnormalities after TAVI [14]. At our tertiary centre, all patients with NOP-LBBB underwent an EPS before discharge and, since January 2016, drug challenge was performed in case of normal baseline EPS. We assessed the added value of

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drug challenge during the EPS through a two-period study.

2. Methods

2.1. Study population

All consecutive patients, with no prior pacemaker, requiring an EPS for NOP-LBBB after TAVI between January 2016 and September 2019 at our tertiary centre were retrospectively included in the study. All data were retrieved from our institutional cloud where they are anonymized and systematically recorded in a dedicated file.

During this period of time, per institutional practice, all patients who had successful TAVI in accordance to current guidelines [15] had continuous electrocardiographic monitoring for at least 24 h after TAVI and a daily 12-lead electrocardiogram (ECG) until discharge. NOP-LBBB was defined as a new left bundle branch block (LBBB) diagnosed on the daily 12-lead ECG that lasted for more than 24 h. LBBB was defined according to the American Heart Association consensus [16].

In case of NOP-LBBB after TAVI, ECG monitoring was continued until LBBB resolved or an EPS was carried out. The NOP-LBBB was deemed transient if it resolved before hospital discharge.

The total cohort was divided into two groups. Group A included patients who were investigated between January 2016 and December 2017, who had baseline EPS only. Group B included patients who were investigated between January 2018 and September 2019, who eventually received drug challenge with ajmaline (Cardiorhythmine®, Carinopharm GmbH, Elze, Deutschland) in case of normal baseline EPS.

Inclusion criteria were: age ≥ 18 years; implantation with a percutaneous aortic biological valve according to European Society of Cardiology (ESC) recommendations [15]; EPS for infra-nodal conduction evaluation; and presentation with a NOP-LBBB after TAVI. Exclusion criteria were: contraindication to ajmaline injection (underlying moderate or severe left ventricular dysfunction [left ventricular ejection fraction {LVEF} < 45%] or chronic severe kidney disease); presence of a pacemaker before TAVI; presence of a LBBB or right bundle branch block (RBBB) before TAVI; and transient LBBB.

2.2. Electrophysiological study protocol

For patients in Group A (baseline EPS only; January 2016 to December 2017): all consecutive patients with NOP-LBBB after TAVI had an intracardiac EPS performed under local anaesthesia (via the femoral vein) before hospital discharge. Two quadripolar catheters were used to measure baseline atrio-hisian (AH) and his-ventricular (HV) intervals and evaluate AV conduction through incremental atrial pacing and single atrial extra stimulus. In patients with atrial fibrillation, only the HV interval measurement was performed. The EPS was considered positive in case of HV interval > 70 ms or induction of infra-hisian second- or third-degree AV block during atrial pacing. Patients with a positive EPS were implanted with a dual-chamber (or single-chamber in case of atrial fibrillation) pacemaker according to current guidelines [7]. Patients with a normal EPS were discharged without further monitoring.

For patients in Group B (baseline EPS and eventual drug challenge; January 2018 to September 2019): patients with a normal baseline EPS had a repeated HV measurement after drug challenge. Ajmaline was infused intravenously at 1 mg/kg over 1 min. Pacing manoeuvres and HV interval measurements were repeated, starting 1 min after the injection and ending when the HV interval returned to its basal value. Drug challenge was considered positive in case of HV interval prolongation > 100 ms or twice its basal value, or induction of infra-hisian second- or third-degree AV block spontaneously or by atrial pacing [14,17]. Patients with a positive EPS, either at baseline or after drug challenge received a dual-chamber pacemaker (or single-chamber in case of atrial fibrillation). Other patients were discharged without further monitoring.

2.3. Endpoints

The two strategies were compared for the prediction of bradycardia-related events. The primary endpoint was a composite of bradycardia-related events including: pacemaker use, D-AVB, syncope, or sudden death. Pacemaker use was considered present in case of pacemaker dependency or a percentage of ventricular pacing $> 1\%$ at pacemaker interrogation [12]. Pacemaker dependency was defined as asystole or complete AV block with or without escape rhythm > 40 bpm after turning the ventricular pacing off. D-AVB was defined as the occurrence of complete or second-degree Mobitz II AV block (documented on 12-lead ECG or recorded in the pacemaker memory), or the need for delayed pacemaker implantation. Necessity for a delayed pacemaker implantation was defined as the implantation of a pacemaker in a patient previously discharged from hospital without a pacemaker. Syncope was defined as cardiac or unexplained syncope. Hypotensive or reflex syncope were not considered in the primary outcome. They were identified by a trained cardiologist (MB, ND, BM) according to the ESC guideline definition [13]. Sudden death was defined as an unexpected death from a presumptively cardiac cause that occurred in a short period of time, generally within 1 h of symptom onset or without prior symptoms [6].

In patients who received a pacemaker, in the absence of AV block at the time of programming, the lower rate was programmed to 40 bpm and unnecessary right ventricular pacing was avoided by programming long AV intervals or specific algorithms to minimize the ventricle pacing rate.

Secondary endpoints were: new hospitalization for heart failure; all-cause syncope; all-cause mortality; and adverse events related to pacemaker implantation or EPS (including pocket infection, pocket haematoma, pneumothorax, bleeding, tamponade, mechanical AV block, infective endocarditis, and death).

2.4. Follow-up

The clinical follow-up of patients was conducted in person or by telemedicine, according to clinician and patient choice. Clinical and functional status, including New York Heart Association (NYHA) status, occurrence of syncope, need for delayed pacemaker implantation, and hospitalization for heart failure, were collected at 1 and 12 months. A 12-lead ECG was performed in case of in-person evaluation. When a pacemaker was implanted, the following information was collected at each pacemaker interrogation: percentage of pacing pulses per chamber; episodes of D-AVB in the pacemaker memory (number, time to onset, type); and intrinsic rhythm after turning the ventricular pacing off. Systematic prospective recording of anonymized data was performed through a dedicated file in our institutional cloud.

2.5. Statistical analyses

Quantitative variables are presented as means (standard deviations [SDs]); categorical variables as numbers (percentages). For continuous variables, comparisons were made using Student *t* test, or Mann-Whitney *U* test, as appropriate. Discrete variables were compared using Fisher exact test. Exact logistic regression to determine univariate predictors for the occurrence of the composite primary endpoint was performed. Receiver-operating characteristic (ROC) curves were constructed to identify the optimal threshold (cut-off value) to identify patients at risk of a bradycardia-related event with a high specificity. The area under the ROC curve (AUC) was calculated, along with 95% confidence intervals (CIs). Diagnostic yield values were compared using Chi [2] test, or Fisher exact test as appropriate.

All analyses were performed using R software, version 3.6.3. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

3. Results

Among 736 patients who underwent TAVI implantation between January 2016 and September 2019, 91 developed NOP-LBBB. Of these, 27 had drug challenge contraindications, due to renal insufficiency ($n = 19$) and/or LVEF $< 45\%$ ($n = 12$) (Fig. 1). The 64 remaining NOP-LBBB patients underwent an EPS, a mean (SD) of 4.3 (1.6) days after TAVI. Group A consisted of 22 patients who had EPS only. Group B included 42 patients who had EPS with an eventual drug-challenge approach. Patient characteristics are summarized in Table 1.

3.1. Group A

Four of 22 patients (18.2%) presented with an HV interval > 70 ms and therefore required pacemaker implantation. No adverse events occurred after pacemaker implantation or EPS and there were no sudden deaths. After a mean (SD) of 15.6 (8.3) months, 7/22 patients (31.8%) reached the primary bradycardia-related endpoint: three patients had pacemaker use (all had a ventricular pacing rate $> 1\%$, and none of them were pacemaker dependent), one of them had also D-AVB documented on the pacemaker memory; two other patients had delayed pacemaker implantation because of documented D-AVB; and one patient experienced unexplained syncope. One patient had pacemaker implantation despite a normal EPS, due to physician choice. Pacemaker follow-up showed a 6% ventricular pacing rate, but no high-degree AV block was documented in the pacemaker memory.

The diagnostic accuracy of baseline EPS only for the identification of NOP-LBBB patients who will develop an arrhythmic event after TAVI is detailed in Table 2 and illustrated in Fig. 2A.

3.2. Group B

Out of 42 patients, 13 (31.0%) had a baseline HV interval > 70 ms and therefore underwent pacemaker implantation without drug challenge. Among the 29 patients with normal baseline EPS who therefore required a drug challenge, six patients (20.7%) had a positive drug challenge (four because of induced high-degree AV block and two

because of HV interval prolongation > 100 ms). These six patients received pacemaker implantation before hospital discharge. Therefore, a total of 19 patients were implanted with a pacemaker in group B (45.2%). No adverse events occurred during or after the EPS (including drug challenge) or pacemaker implantation.

After a mean (SD) of 12.8 (3.5) months, 8/42 patients (19.0%) in Group B reached the primary arrhythmic endpoint. Five of the 19 patients (26.3%) implanted after a positive EPS had pacemaker use (all had a ventricular pacing rate $> 1\%$, and none of them were pacemaker dependent) and two others (10.5%) had D-AVB documented on the pacemaker memory. Among the 23 patients with normal EPS and no pacemaker implantation before hospital discharge, only one (4.3%) reached the primary endpoint, due to sudden death that occurred 14 months after TAVI.

The diagnostic accuracy of EPS with eventual drug challenge for the identification of NOP-LBBB patients who will develop an arrhythmic event after TAVI is detailed in Table 2 and illustrated in Fig. 2B.

3.3. Secondary endpoints

After a mean (SD) of 13.7 (5.7) months, the hospitalization rates for acute heart failure were 27.3% (95% CI 10.7–50.2%) and 9.5% (95% CI 2.7–22.6%), in Groups A and B, respectively ($P = 0.08$), and the syncope rates were 18.2% (95% CI 5.2–40.3%) and 4.8% (95% CI 0.6–16.2%), respectively ($P = 0.17$). Only one patient in Group A experienced unexplained syncope, all other syncope events were hypotensive or reflex. A total of 43 patients (67.2%) had an in-person evaluation 1 month after TAVI. Univariate analysis showed that NOP-LBBB at 1 month was an independent predictor of arrhythmic events (odds ratio 6.40; 95% CI 1.22–65.09; $P = 0.03$). The other independent predictors of arrhythmic events are presented in supplemental Table 1.

4. Discussion

This is the first study to compare the diagnostic yield of EPS with drug challenge to EPS alone for predicting bradycardia-related events in NOP-LBBB patients after TAVI. Compared to EPS alone, drug-challenge

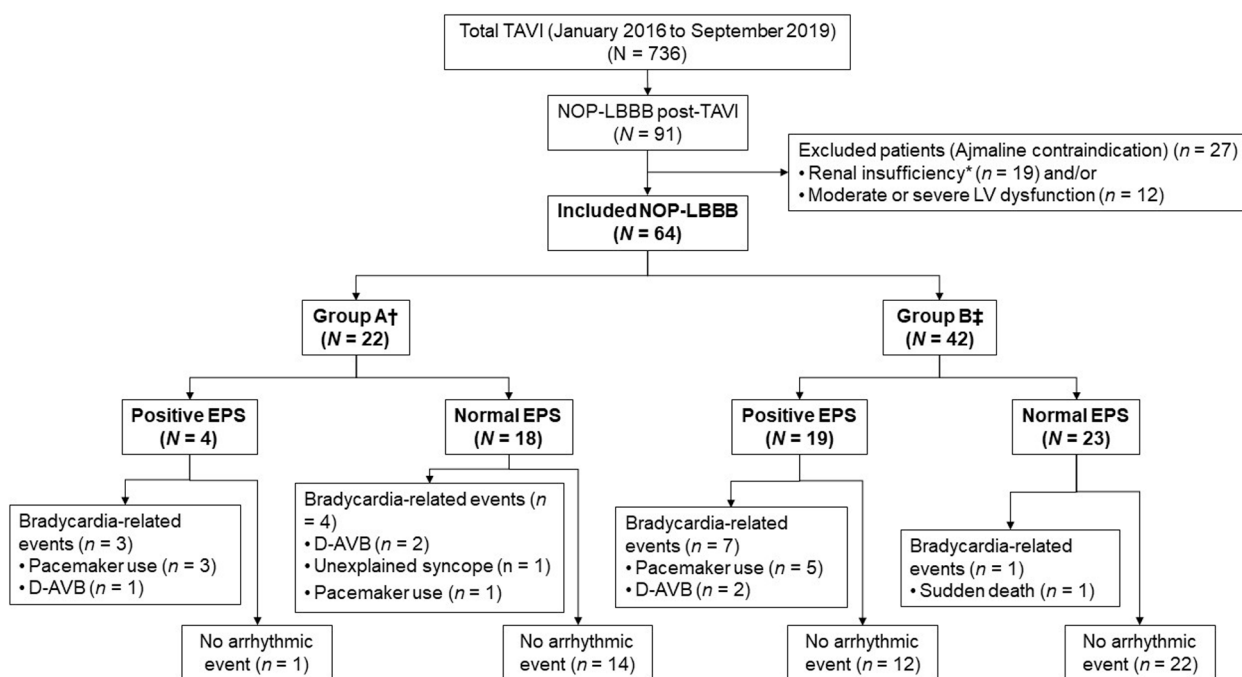


Fig. 1. Flowchart of the study population. D-AVB, delayed atrioventricular block; EPS, electrophysiological study; LV, left ventricular; MDRD, modification of diet in renal disease; NOP-LBBB, new-onset persistent left bundle branch block; TAVI, transaortic valve implantation. *MDRD clearance < 30 mL/min. †Group A: baseline EPS only. ‡Group B: baseline EPS with eventual drug challenge.

Table 1
Clinical and TAVI procedural characteristics of the study population.

	Total cohort (N = 64)	Group A ^a (N = 22)	Group B ^b (N = 42)	P value
Age (years), mean (SD)	82.3 (6.5)	82.6 (5.9)	82.0 (6.8)	0.7
Female, n (%)	38 (59.4)	11 (50.0)	27 (64.3)	0.3
Diabetes mellitus, n (%)	10 (15.6)	3 (13.6)	7 (16.7)	1.0
Hypertension, n (%)	54 (84.4)	21 (95.5)	33 (78.6)	0.1
Moderate CKD, ^c n (%)	23 (35.9)	12 (54.5)	11 (26.2)	0.02
Coronary artery disease, n (%)	26 (40.6)	9 (40.9)	17 (40.5)	0.8
Atrial fibrillation, n (%)	21 (32.8)	10 (45.5)	11 (26.2)	0.2
NYHA class, median (Q1–Q3)	2 (2–3)	2 (2–3)	2 (2–3)	0.3
Pre-procedural ECG, mean (SD)				
PR interval (ms)	175.8 (36.8)	182.8 (34.6)	172.4 (37.8)	0.3
QRS duration (ms)	84.9 (10.9)	85.5 (10.6)	84.6 (11.1)	0.7
Pre-procedural echocardiography, mean (SD)				
LVEF (%)	63.3 (7.9)	61.8 (8.6)	64.0 (7.6)	0.3
Mean aortic gradient (mmHg)	56.6 (14.7)	54.2 (14.2)	57.9 (14.9)	0.4
Indexed aortic valve area (cm ² /m ²)	0.40 (0.1)	0.40 (0.1)	0.40 (0.1)	0.7
Aortic outflow tract diameter (mm)	21.6 (2.7)	22.2 (3.3)	21.3 (2.3)	0.5
TAVI procedural characteristics, n (%)				
Transfemoral access	62 (96.9)	20 (90.9)	42 (100)	NS
Balloon Pre-dilatation	12 (18.8)	5 (22.7)	7 (16.7)	0.6
Balloon Post-dilatation	1 (1.6)	1 (4.5)	0 (0)	0.3
Valve type				
Edwards Sapien®	49 (76.6)	16 (72.7)	33 (78.6)	NS
Medtronic Corevalve®	13 (20.3)	5 (22.7)	8 (19.0)	NS
Accurate®	2 (3.1)	1 (4.5)	1 (2.4)	NS
Device success	64 (100)	22 (100)	42 (100)	NS
Per-procedural high- degree AV block, n (%)	5 (7.8)	1 (4.5)	4 (9.5)	0.7
Post-procedural characteristics, mean (SD)				
PR interval (ms)	214.9 (43.4)	219.9 (45.9)	212.6 (42.2)	0.6
QRS duration (ms)	148.9 (16.3)	149.0 (14.0)	148.8 (17.5)	0.9
Time to EPS (days post- TAVI)	4.3 (1.6)	5.2 (1.6)	3.8 (1.4)	0.001
Hospitalization length (days)	11.9 (5.6)	13.3 (5.0)	11.2 (5.8)	0.02
Clinical follow-up				
NOP-LBBB persistent at 1 month, ^d n/N (%)	25/43 (58.1)	7/14 (50.0)	18/29 (62.1)	0.5
Mortality at 1 year, ^d % (95% CI)	11.6 (3.0–18.9)	18.7 (0.3–33.7)	7.3 (0–14.8)	0.3

AV, atrioventricular; CI, confidence interval; CKD, chronic kidney disease; ECG, electrocardiogram; EPS, electrophysiological study; LVEF, left ventricular ejection fraction; MDRD, modification of diet in renal disease; NOP-LBBB, new-onset persistent left bundle branch block; NS, not significant; NYHA, New York Heart Association; Q, quartile; SD, standard deviation; TAVI, transaortic valve implantation.

^a Group A: baseline EPS only.

^b Group B: baseline EPS with eventual drug challenge.

^c MDRD clearance 30–60 mL/min.

^d Data were only available for 43, 14, and 29 patients in the total cohort, group A, and group B, respectively.

EPS showed a tendency to increase sensitivity (87.5% vs. 42.9%; $P = 0.12$) and negative predictive value (95.7% vs. 77.8%; $P = 0.15$). However, the specificity significantly decreased (64.7% vs. 93.3%; $P = 0.04$). There was also a tendency to a decreased positive predictive value (36.8% vs. 75.0%; $P = 0.28$). In the drug-challenge group, 7/8 patients who experienced a bradycardia-related event during follow-up were

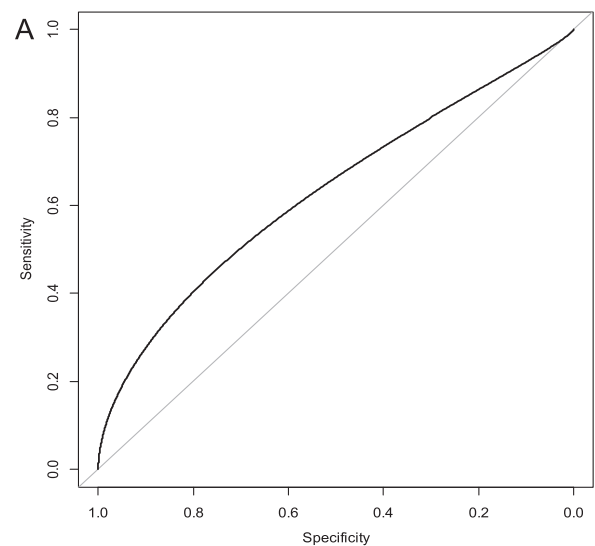
Table 2
Diagnostic yield for predicting the primary endpoint of baseline EPS only and of EPS with eventual drug challenge.

	Group A ^a (N = 22)	Group B ^b (N = 42)	P- value
Sensitivity, % (95% CI)	42.9 (9.9–81.6)	87.5 (47.4–99.7)	0.12
Specificity, % (95% CI)	93.3 (68.1–99.8)	64.7 (46.5–80.3)	0.04
Positive predictive value, % (95% CI)	75.0 (19.4–99.4)	36.8 (16.3–61.6)	0.28
Negative predictive value, % (95% CI)	77.8 (52.4–93.6)	95.7 (78.1–99.9)	0.15

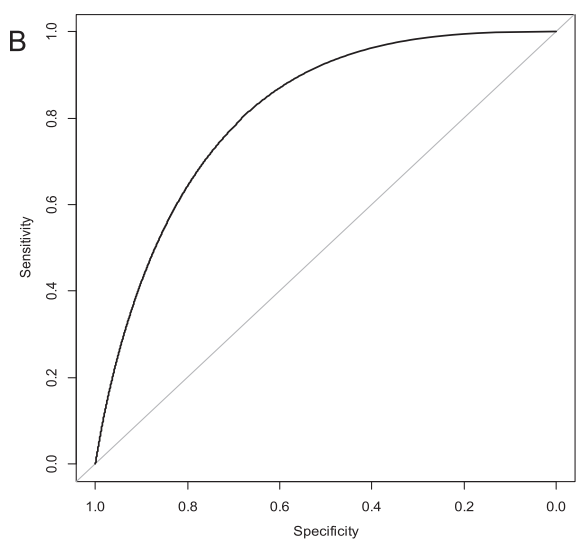
CI, confidence interval; EPS, electrophysiological study.

^a Group A: baseline EPS only.

^b Group B: EPS with eventual drug challenge.



AUC: 0.622 (95% CI 0.439–0.805)



AUC: 0.814 (95% CI 0.574–1.055)

Fig. 2. ROC curves demonstrating the accuracy of HV measurement (A) at baseline and (B) after drug challenge to predict arrhythmic events. AUC, area under the receiver-operating characteristic curve; CI, confidence interval; HV, his-ventricular; ROC, receiver-operating characteristic.

correctly identified.

As shown in previous studies [8–12], baseline EPS alone has a relatively poor diagnostic yield, particularly a poor sensitivity. In our Group A, 4/18 patients with a normal baseline EPS experienced a bradycardia-related event during follow-up and < 50% of the patients who eventually experienced a bradycardia-related event had positive EPS. Regardless of the cut-off value of HV interval for pacemaker implantation, other studies showed similar diagnostic value [8–12]. As emphasized by the latest guidelines, choice of pacemaker implantation or not in case of NOP-LBBB can be guided by infra-hisian conduction evaluation by standard HV interval measurement. However, because of its poor sensitivity and imperfect negative predictive value, it may incorrectly answer that patients need pacemaker implantation while they will not use it and that the conduction system is preserved in patients which subsequently will experience bradycardia related event. Therefore, improvement of the EPS sensitivity and negative predictive value with drug challenge could be a preferred option in daily practice to improve safety management of NOP-LBBB after TAVI.

We chose a threshold of 1% pacing rate for defining pacemaker use, but we acknowledge that this value is arbitrary and may not reflect true pacing use. Scarce and variable data have been published regarding such a cut-off value for pacemaker use [8–12]. A bradycardia-related event including a higher ventricular pacing rate would probably have decreased EPS sensitivity in both groups. Moreover, these criteria are strongly dependent on pacemaker programming.

A previous study has already described the safety of class IA anti-arrhythmic drug challenge in case of NOP-LBBB after TAVI [14], but did not assess the improvement in diagnostic yield obtained with drug challenge. Our study shows that, when used in patients without drug contraindications (i.e. underlying moderate or severe LV dysfunction, renal insufficiency), drug challenge is safe even in patients who received TAVI in the previous few days. Most (22/23 patients) with normal drug-challenge EPS remained free from bradycardia-related events, and 7/8 patients with a bradycardia-related event had a positive drug-challenge EPS. These results are comparable with EPS drug challenge in syncope patients [13,17]. In a large cohort of NOP-LBBB after TAVI, 20% of NOP-LBBB patients developed a paroxysmal bradycardia event, with half on them requiring pacemaker implantation at 1 year due to a symptomatic bradycardia-related event [18]. Drug-challenge EPS would limit these paroxysmal AV block consequences after TAVI.

Our study shows that drug challenge increased the sensitivity of EPS, but it also decreased the specificity of the test. This might be related, not only to the test itself, but to the transient nature of conduction abnormalities after TAVI. Half of post-procedural NOP-LBBB are known to disappear before hospital discharge and only 60% of the remaining are still present 30 days after TAVI [2–5]. Most D-AVB episodes have been shown to occur in the first month after TAVI [5,18,19], with this proportion remaining stable at 1 year. In our study, persistence of LBBB at 1 month was associated – in univariate analysis – with the occurrence of bradycardia-related arrhythmic events during follow-up. Only 1/18 patients with narrow QRS at 1 month after TAVI experienced bradycardia-related arrhythmic events, while 4/18 had an abnormal EPS (three at baseline and one after drug challenge). This is a strong limitation of the pre-discharge EPS, and drug challenge cannot overcome this difficulty.

Another important aspect to consider is that when a pacemaker is implanted early after TAVI because of a positive EPS (i.e. in order to decrease the risk of D-AVB), it is likely to be a conventional pacemaker, even in case of LBBB. This was the case in our study in all of the patients, mostly due to the inclusion criteria of our study, which excluded patients with underlying severe or moderate LV dysfunction (i.e. drug challenge contraindication). However, over time, cardiac resynchronization therapy (CRT) may become indicated, due to LBBB and heart failure symptoms, and upgrading the patient becomes necessary. It is well known that upgrading procedures carry a risk in themselves, and this may be avoided when an unnecessary early implant is avoided. An

implantation strategy considering an indication for CRT may be considered in patients with LBBB and heart failure, several weeks after TAVI [20].

4.1. Limitations

Owing to the small study sample size, the statistical power of our study is low. However, our results are similar to other published studies on the same topic [8–12]. Methodological aspects, such as only including patients in a single centre and the comparison of patients during two different time periods add also some bias. Our results have also yet to be proven in a larger multicentre, prospective study.

5. Conclusions

Our study shows the feasibility and added value of drug-challenge EPS over EPS alone to identify the long-term risk of a bradycardia-related arrhythmic event. However, the decreases in specificity and positive predictive value leads to a high rate of unnecessary pacemaker implantation. Other strategies should be developed in order to better identify patients who eventually will need antibradycardia pacing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The data that support the findings of this study are available from the corresponding author (BM), upon reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2022.100961>.

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