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Randomized comparison of balloon aortic valvuloplasty performed with or without rapid cardiac pacing: The pacing versus no pacing (PNP) study

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Objectives: To compare the effectiveness and safety of balloon aortic valvuloplasty (BAV) performed with or without rapid ventricular pacing (RP).

Background: BAV technique is poorly standardized.

Methods: One hundred consecutive patients were randomly assigned 1:1 between BAV performed with or without RP. Exclusion criteria were an immediate indication for surgical or transcatheter aortic valve replacement, presentation in cardiogenic shock or pulmonary edema refractory to medical stabilization.

Results: There were 51 patients in the BAV group performed with RP, 49 in the BAV group without RP (noRP). Procedural success (50% hemodynamic gradient reduction) was achieved in 37.3% and 55.1%, respectively ($P = 0.16$). Fewer people in the noRP group complained of poor tolerance to the procedure (16% vs 41%). The primary efficacy endpoint, a 50% reduction in the mean echocardiographic trans-aortic gradient, was met in 21/49 patients in the noRP group compared to 20/51 in the RP (42.9% vs 39.2%; $P = 0.84$). No significant difference between the groups was observed in the primary safety endpoint, a 30-day composite of death, myocardial infarction, stroke, acute aortic regurgitation, and BARC bleeding ≥3 (8.2% noRP vs 13.7%; $P = 0.53$). The noRP group required fewer bailout temporary pacemakers ($P = 0.048$) and had a lower incidence of moderate/severe renal function worsening (4.1% vs 17.6%; $P = 0.052$).

Conclusions: Rapid ventricular pacing did not influence BAV efficacy or safety and tolerance was slightly worse.

KEYWORDS
aortic valve stenosis, aortic valvuloplasty, randomized trial, rapid ventricular pacing

1 | INTRODUCTION

In the last decade, alongside the development and consolidation of transcatheter aortic valve replacement (TAVR), we witnessed a renewed interest in percutaneous balloon aortic valvuloplasty (BAV), demonstrated by a considerable increase in the number of procedures performed worldwide.[1,2] Recent data suggest a lower incidence of complications during BAV in comparison to the initial experiences dating

back to the eighties.[3,4] However, several technical aspects of BAV have never been standardized and are currently left to the operator's preference.[5] Variability includes, among others, balloon sizing, vascular sheath size and hemostasis, and the definition of procedural success.

Rapid ventricular pacing (RP) is commonly used during balloon inflation to obtain temporary circulatory arrest and help stabilize the balloon within the valve orifice. Yet, in expert hands, BAV can be performed without RP with an overall less invasive and possibly better tolerated approach. To date, there are no direct comparisons between BAV performed with or without RP in terms of safety and effectiveness. Registry data suggest similar procedural safety in the two techniques but less efficacy in the RP technique, in terms of a smaller post-procedural aortic valve area (AVA), despite easier balloon stabilization.[6]

Our study sought to compare the effectiveness and safety of BAV in a randomized setting performed with or without RP in an unselected patient population.

2 | MATERIALS AND METHODS

2.1 | Patient population

This is a prospective, open-label, randomized study with the purpose of enrolling 100 consecutive patients with severe degenerative aortic stenosis (AS) undergoing BAV at the S.Orsola-Malpighi University Hospital in Bologna. The study protocol was approved by the local Ethics Committee (CE41/2015/O/Sper) and published on clinicaltrials.gov (NCT02498639). Patients 70 years of age or older, affected by severe symptomatic AS and with an indication for BAV were eligible. The indication for BAV was independent from the present study and preceded enrollment. Exclusion criteria were an immediate indication for surgical aortic valve replacement (AVR) or TAVR, clinical presentation in cardiogenic shock or pulmonary edema refractory to medical stabilization. Before enrollment, all patients were required to sign an informed consent to adhere to the study procedures and allow their personal data to be processed. They were then 1:1 randomly assigned to undergo BAV with or without rapid cardiac pacing. Randomization was done using specific software after patients signed the informed consent.

Of note, enrollment in the study did not exclude a subsequent final treatment of the aortic valve disease via TAVR or AVR.

Before BAV, all patients received an echocardiography scan to specifically check, among other parameters, the left ventricle ejection fraction (LVEF), the left ventricle outflow-tract diameter (LVOT), the aortic annulus, the maximum and mean trans-aortic gradients (ΔP), the aortic valve area (AVA) calculated by the continuity equation, the indexed AVA (AVA/BSA), and the aortic regurgitation grade. Ultrasound measurements were collected according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations.[7]

2.2 | Balloon aortic valvuloplasty procedure

Percutaneous balloon aortic valvuloplasty was performed through the left or right femoral artery, where a 9 or 10 Fr vascular sheath (Cordis Corporation, Fremont, CA) was placed, depending on the size of the selected balloon catheter. All procedures were performed with the semi-compliant Cristal Balloon™ (BALT Extrusion SAS, Montmorency, France). All patients received a low dose bolus of intravenous unfractioned heparin (30-50 IU/kg). The retrograde crossing of the aortic valve was achieved with a 0.035″ straight wire within an Amplatz AL1 catheter. After crossing the valve orifice, a 0.038″ extra stiff wire with a handmade loop at its distal tip was placed into the left ventricle. To minimize the pressure recovery phenomenon when measuring the hemodynamic gradient, instantaneous mean hemodynamic trans-aortic gradient (ΔP) was measured with two 4 Fr pigtail catheters, one in the left ventricle and the other in the ascending aorta (central ΔP). Additionally, the instantaneous gradient between the ventricular pigtail and the side port of the vascular sheath (peripheral ΔP) was available and collected to check for possible differences with the central measurement, but was not considered for interruption criteria (see below). Both pigtails, by virtue of their small size, were inserted within the same femoral vascular sheath.

After gradient measurement, the balloon was advanced within the valve over the extra stiff wire and inflated with a mixed solution of contrast dye and saline. The same inflation system was used in both groups, consisting of a "volumetric" syringe (50 mL), which initially fills the balloon, and a "pressure" syringe (10 mL), both connected to a manometer through a deflection valve. In the group randomized for RP, a temporary flow-directed unipolar pacing catheter (Pacel™, St. Jude Medical Inc., St Paul, MN) was positioned in the right ventricle through a 6 Fr vascular sheath (St. Jude Medical) placed in the ipsilateral femoral vein. Ventricular pacing at 180-200 bpm rate was started just before balloon inflation and stopped at the time of deflation, for a maximum duration of 10 s. In the group randomized for BAV without RP, the ventricular contractions compromise the stability of the balloon during inflation, facilitating slippage towards the aorta or the ventricle chamber. Balloon stabilization at the level of the valve orifice was obtained by balancing the thrust forces exerted on the extra stiff wire inside the left ventricle and those exerted on the balloon pushed over the wire.

The pressure line connected to the side port of the vascular sheath allowed systemic pressure to be monitored during the entire procedure. Generally, when rapid pacing is not used, normal pressure wave oscillations become damped during balloon inflation. In the event of complete aortic pulse abrogation, the operator can infer that the inflated balloon almost completely seals off the valve orifice, and can thereby avoid further increasing inflation volume and pressure (Figure 1A). Likewise, for safety reasons, the operator is discouraged from upgrading balloon size even in the presence of a suboptimal procedural result. When rapid pacing is applied, the pressure curve is abolished due to deliberately ineffective contractions and so the operator cannot rely on the sealing concept (Figure 1B).[8]

To prevent possible bias from influencing the efficacy or safety of either technique due to potentially applying different inflation pressures, three inflations were planned for each patient in both branches of the trial, always at nominal balloon pressure (checked via manometer), after which the trans-aortic gradient was measured again.

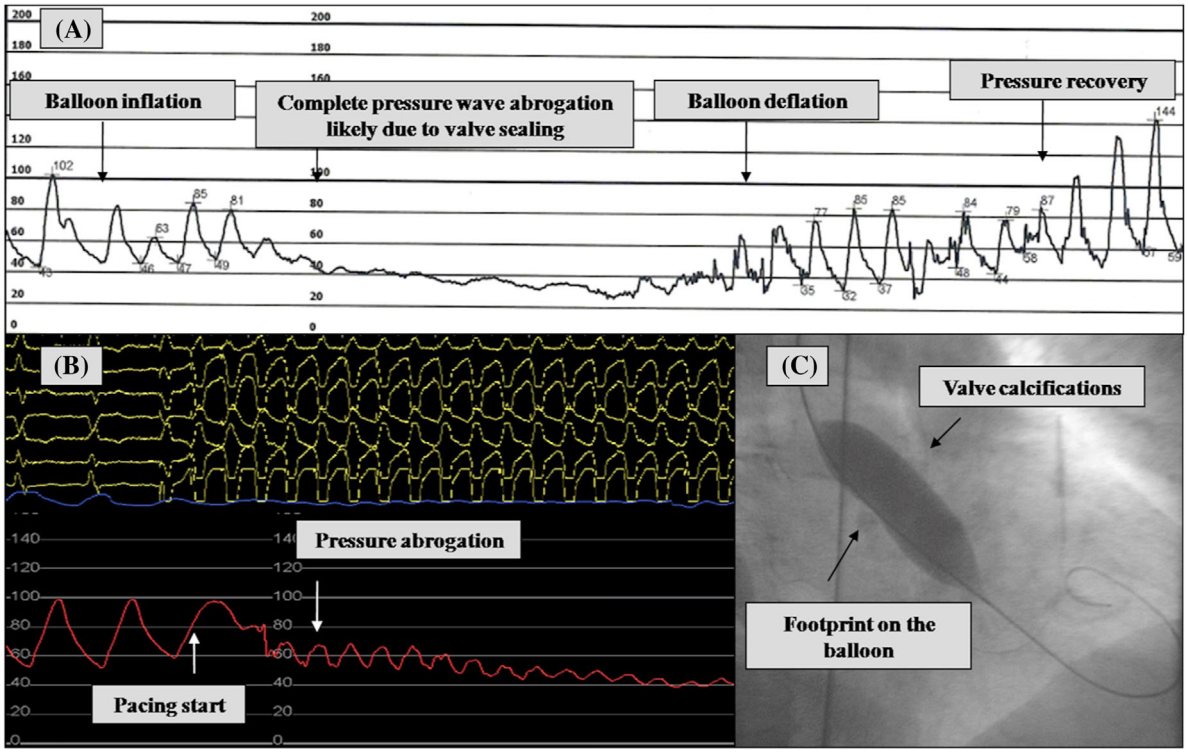

FIGURE 1 (A) Printing of the pressure curve during aortic valvuloplasty at the moment of balloon inflation; (B) image from the polygraph at the time of rapid ventricular pacing preceding balloon inflation; (C) inflated balloon at the valve orifice level, with a visible footprint on its sides given by the calcified valve annulus and leaflets

Moreover, the duration of iatrogenic hypotension, due to valve sealing or RP, per protocol was sustained for 10 s (less only if poorly tolerated) in both branches of the study. Balloon size was initially chosen according to the aortic valve annulus measured at echocardiography:[7]

- annulus ≤ 19 mm → balloon diameter 18 mm
- annulus 20-23 mm → balloon diameter 20 mm
- annulus ≥ 24 mm → balloon diameter 23 mm

After the first sequence of three inflations, the procedure was terminated if one of the following criteria was met:

1 Procedural success, defined as 50% reduction of the mean trans-aortic gradient (hemodynamic measurement);
2 Procedural complication (ie, cardiac tamponade, acute aortic insufficiency, etc.)
3 Poor patient tolerance to the procedure (malaise, overt intolerance), in particular during balloon inflation and rapid pacing, or worsening of the vital parameters (ie, changes in pressure wave, electrocardiogram, O_2 arterial saturation).

Additional interruption criteria were:

4 In case of BAV without RP, aortic pressure drop due to the inflated balloon sealing off the valve annulus (confirming achievement of a 1:1 balloon-to-annulus ratio, hence no benefit expected from upgrading balloon size) as shown in Figure 1A;
5 In case of BAV under RP, observing the aortic annulus footprint on the balloon profile during full balloon expansion (confirming achievement of at least a 1:1 balloon-to-annulus ratio, hence no benefit expected from a larger balloon) as shown in Figure 1C.

When none of the above criteria was met, a second series of three inflations was performed with a larger diameter balloon. Only one balloon upgrade was allowed per protocol. An 8 Fr Angio-Seal™ (St. Jude Medical, St. Paul, MN) was used for arterial hemostasis, whereas manual compression was applied to the venous access site. All patients received a compressive bandage for 24 h of bed rest. This study was conducted according to the Declaration of Helsinki.

2.3 | Endpoints and definitions

The primary efficacy endpoint, in an intention to treat analysis, was a 50% reduction in the mean trans-aortic gradient measured by echocardiography 30 min after BAV.

Valve Academic Research Consortium-2 definitions were used to classify the in-hospital and follow-up complications, whereas Bleeding Academic Research Consortium (BARC) definitions were specifically applied for bleedings.[9,10] The primary safety endpoint was the composite of death, myocardial infarction (MI), stroke, acute aortic regurgitation, and BARC bleeding ≥3 collected at 30-day follow-up.

Secondary endpoints were: a 50% reduction in the mean transaortic gradient measured via echocardiography 30 min after BAV in a per-treatment analysis; a gradient reduction of 30-49%; reduction of the mean invasive hemodynamic gradient ≥ 50% and in the 30-49% range; the 30-day rate of all-cause death, cardiovascular death, stroke, myocardial infarction, major bleeding (BARC ≥3), evaluated individually; all vascular complications (VARC-2 definitions); procedural acute aortic insufficiency, procedural acute kidney injury (VARC-2); length of hospital stay; increase in AVA echocardiography post-BAV; poor tolerance to the procedure subjectively reported by the patient; comparison of Numeric Rating Scale for Pain (NRS) questionnaire data.[11] Outpatient clinic visits were scheduled for 30-day follow-up and data were collected via telephone if the visit was not possible.

2.4 | Statistical analysis

Continuous variables are illustrated as mean ± standard deviation and compared via the *t*-Student test. Categorical variables are shown as absolute number and percentage. The differences between the groups were analyzed using the Chi-square tests or the Fisher's Exact test when appropriate. A *P*-value <0.05 was considered statistically significant. All analyses were performed with SPSS Statistic, version 17.0 (SPSS Inc., Chicago, IL).

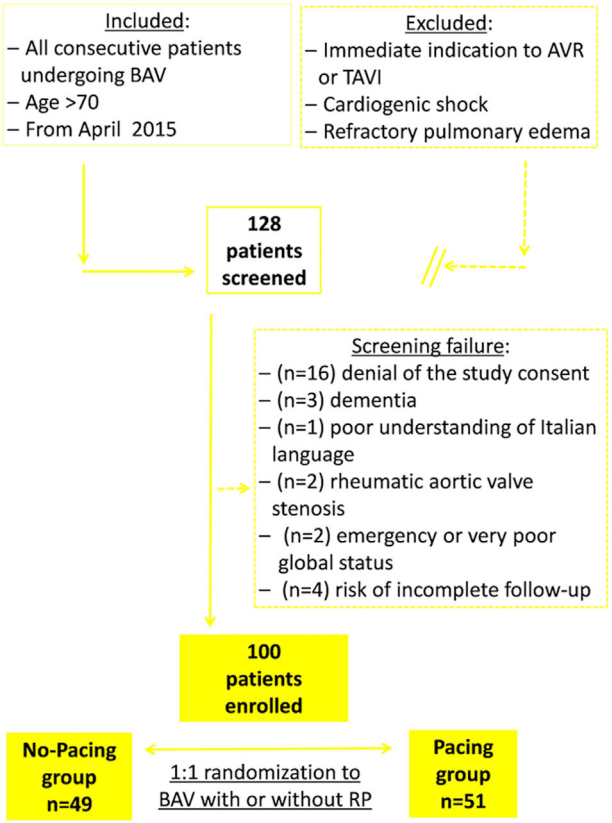

FIGURE 2 Study flow chart

3 | RESULTS

Starting in April 2015, 128 consecutive patients with severe symptomatic aortic valve stenosis referred to our hospital were evaluated for study eligibility. Figure 2 shows the study flow chart. We collected 28 cases of screening failure mainly due to denial of consent for the study (*n* = 16), while some cases failed screening because of dementia (*n* = 3), difficulty in comprehending Italian (*n* = 1), rheumatic aortic valve stenosis (*n* = 2), emergency procedure or very poor global status (*n* = 2), patients coming from other hospitals with risk of incomplete follow-up (*n* = 4). One hundred patients were enrolled in the study and randomized 1:1 so that 49 were assigned to the No-RP group and 51 to the RP group. All patients underwent the assigned procedure, resulting in the "intention-to-treat" and "per-treatment" analysis coinciding. Baseline characteristics, clinical presentation and echocardiography data did not differ between the groups (Table 1).

3.1 | Procedural data

The main baseline hemodynamic parameters at univariate analysis were similar between the groups as well at the end of the entire procedure (Figure 3). Furthermore, this picture shows that the mean aortic and femoral pressure values were similar, hence in our population the pressure recovery phenomenon was trivial. Because the baseline mean gradient between aortic and femoral artery pressure was between 5 and 4.3 mmHg in the two groups, we assumed that our decision to rely on the LV-Aortic (for the hemodynamic endpoints and decision making) did not bring to different results in comparison to the eventual use of the LV-femoral artery gradient. As reported in Table 2, the first series of inflations was more frequently performed with a 20 mm balloon both in the No-RP (38/49, 77.6%) and in the RP group (41/51; 80.4%). Of note, the balloon/annulus diameter ratio, calculated as the ratio between the nominal balloon size and the echocardiographic measurement of the aortic annulus, was equivalent (0.92 vs 0.93; *P* = 0.12).

After the first series of inflations, procedural success was achieved in 15 out of 51 patients in the RP population compared with 20 out of 49 among those without RP (29.4% vs 40.8%; *P* = 0.30) (Table 3).

In the latter group, despite mean gradient halving not being met in 29 (59.2%) patients, only 10 underwent a second series of inflations with a bigger size balloon. The upgrade to a bigger balloon was not performed 16 times because aortic valve sealing was obtained (predefined no upgrade criterion), whereas in the remaining three cases, the reasons were: balloon rupture and entrapment at the vascular sheath requiring recapture by a lazo; ventricular fibrillation treated by DC-shock; subjective intolerance to the procedure. When the balloon upgrade was performed, aortic valve sealing was always met. In the RP group, the upgrade to a bigger balloon size was required in 36 cases (70.6%), but only actually performed in 19. Lack of balloon upgrade in 17 patients was due to: very poor patient tolerance (*n* = 6); prolonged hypotension after RP (*n* = 4); severe bradycardia or high grade A-V block (*n* = 3); atrial fibrillation with fast ventricular rate (*n* = 1); transient acute aortic regurgitation (*n* = 1); chest discomfort

TABLE 1 Baseline characteristics

	No Pacing $n = 49$	Pacing $n = 51$	P
Age,years	82.5 ± 5.5	83.3 ± 7.2	0.52
Male gender	23 (46.9)	25 (49.0)	0.84
BSA,m^2	1.8 ± 0.2	1.7 ± 0.2	0.23
Diabetes mellitus	11 (22.5)	14 (24.4)	0.38
Hypertension	41 (83.7)	41 (80.4)	0.80
COPD	9 (18.4)	8 (15.7)	0.79
Peripheral artery disease	4 (8.2)	12 (23.5)	0.06
Carotid disease	6 (12.2)	9 (17.6)	0.58
Previous TIA/stroke	4 (8.1)	6 (11.8)	0.79
Previous MI	11 (22.4)	13 (25.5)	0.82
Previous PCI	6 (12.2)	7 (13.7)	1.00
Previous CABG	1 (2.0)	3 (5.9)	0.33
Previous valve surgery	3 (6.1)	4 (7.8)	0.74
Previous BAV	8 (16.3)	6 (11.8)	0.57
Significant CAD	23 (46.9)	22 (43.1)	0.84
Hemoglobin,g/dL	12.2 ± 1.7	11.7 ± 1.7	0.12
GFR <30mL/min	8 (16.3)	14 (28.0)	0.23
Dialysis	0 (0.0)	2 (3.9)	0.16
Clinical presentation			
NYHA III-IV	33 (67.3)	33 (64.7)	0.84
Pulmonary edema	2 (4.1)	8 (15.7)	0.09
Angina pectoris	6 (12.2)	8 (15.7)	0.78
Acute coronary syndrome	4 (8.2)	4 (7.8)	0.95
Syncope	11 (22.4)	12 (23.5)	1.00
Asymptomatic	1 (2.0)	3 (5.9)	0.33
ECG			
Atrial fibrillation	14 (28.6)	7 (13.7)	0.09
PR interval, msec	192.2 ± 46.0	175.2 ± 36.0	0.08
QRS interval, msec	118.0 ± 34.8	118.4 ± 28.3	0.89
LBBB	7 (14.3)	10 (19.6)	0.60
RBBB	4 (8.2)	9 (17.6)	0.24
Permanent pacemaker	6 (12.2)	3 (5.9)	0.27
Echocardiography			
LVEDV, mL	102.3 ± 41.2	99.5 ± 39.2	0.71
LVEF, %	56.9 ± 14.7	54.2 ± 14.8	0.38
Aortic annulus, mm	22.6 ± 1.6	22.0 ± 1.2	0.07
Aortic mean	44.5 ± 16.0	45.2 ± 16.2	0.77
ΔP, mmHg	73.5 ± 24.0	72.5 ± 24.8	0.84
Aortic max ΔP, mmHg	0.7 ± 0.1	0.7 ± 0.2	0.73
AVA, cm^2	1 (2.0)	3 (5.9)	0.33
Moderate-severe AR	2 (4.1)	0 (0.0)	0.15
Moderate-severe MR	47.1 ± 16.7	40.7 ± 10.7	0.06
PAP, mmHg			
STS-PROM score, %	4.6 ± 3.7	6.6 ± 6.5	0.06
EuroSCORE II, %	6.0 ± 5.7	6.1 ± 3.6	0.92

Continuous variables are expressed as mean ± SD; categorical variables as number (%). AR, aortic regurgitation; AVA, aortic valve area; BAV, balloon aortic valvuloplasty; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass graft; CAD, coronary artery; COPD, chronic obstructive pulmonary disease; ΔP, pressure gradient; GFR, glomerular filtration rate; LBBB, left bundle branch block; LVDEV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PCI, percutaneous coronary intervention; RBBB, right bundle branch block; STS-PROM, Society of Thoracic Surgeons—probability of mortality; TIA, transient ischemic attack.

($n = 2$). The balloon/annulus ratio remained comparable between the groups after diameter upgrade (1.0 vs 1.0; $P = 0.30$).

Final halving of the hemodynamic gradient was met in 26/49 patients in the No-RP and 19/51 in the RP group (55.1% and 37.3%, respectively; $P = 0.16$). Mean trans-valvular gradient decreased similarly and did not differ between the groups either before or after the first or second series of inflations (Figure 4).

Overall, significantly fewer patients who underwent BAV without RP complained of poor tolerance to the procedure than those with RP (16% vs 41%, respectively, $P < 0.05$). No differences in the sensation of pain were collected with the NRS questionnaire. Use of procedural antithrombotics was similar between the two groups. Equivalent percentages of patients underwent concomitant angiographies and percutaneous coronary revascularization procedures and, as such, the total amount of contrast dye was also equivalent between the two populations.

3.2 | Primary endpoints

The primary efficacy endpoint, given by a 50% reduction of the echocardiographic mean trans-valvular gradient, was met in 21/49 patients in the No-RP group compared to 20/51 in the RP group (42.9% vs 39.2%; $P = 0.84$). The primary safety composite endpoint given by the sum of death, myocardial infarction, TIA/stroke, acute aortic regurgitation, BARC bleeding ≥3 did not differ between the groups (8.2% for No-RP vs 13.7% for RP; $P = 0.53$) or any of its individual components (Table 4).

3.3 | In-hospital clinical complications

Table 4 reports the overall safety outcomes. Of note, we found there was a significantly higher frequency in the RP population to maintain the temporary pacemaker post-BAV as compared to the No-RP population, while no one required a bailout implantation ($P = 0.048$). Likewise, albeit not statistically relevant, more permanent pacemakers were implanted in the RP group (0% vs 5.9%; $P = 0.09$). No differences appeared regarding the other main in-hospital complications, in particular any bleeding, vascular access complications, TIA/stroke, acute MI, acute aortic regurgitation, pericardial effusion. Moderate to severe worsening of renal function was similar, but numerically fewer patients in the No-RP group suffered from transient mild worsening (4.1% and 17.6% respectively; $P = 0.052$).

Finally, two patients died during hospital admission in the RP group, none in the No-RP ($P = 0.17$). One death was due to cardiac

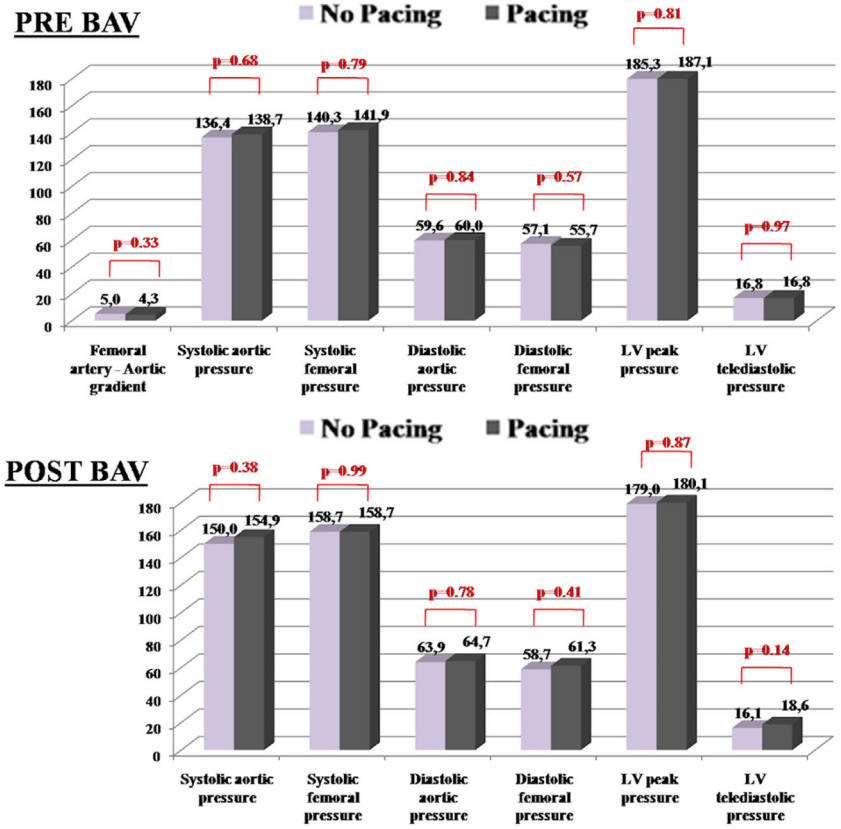

FIGURE 3 Comparison between the groups of aortic, femoral, and ventricular pressures. At the superior level, the first comparison on the left is between aortic and femoral pressure, showing no significant difference between central and peripheral arterial pressure: this means that both values could have been used to calculate the trans-aortic gradient with respect to the left ventricular pressure (in the study we refer to the difference between LV and aortic pressure as the mean hemodynamic gradient)

arrest in an 88-year-old woman admitted with pulmonary edema, severe renal failure and severe left ventricle dysfunction, a EuroSCORE II of 16% and STS risk of mortality of 38%. The second patient who died was an 84-year-old frail diabetic man, admitted in NYHA functional class IV, with a EuroSCORE II of 7% and STS of 7%. BAV was preceded by PCI and then complicated by procedural MI with prolonged bradycardia and hypotension. In comparison to the in-hospital outcome, at 30-day follow-up, we collected one death in the No RP group about 2 weeks after discharge, and one stroke in the RP group.

3.4 | Other echocardiographic results

After BAV, no differences appeared between the groups regarding final AVA ($P = 0.34$), average AVA increase (0.27 vs 0.24 mm; $P = 0.39$), as well as the absolute value of the mean trans-valvular gradient and its reduction percentage (44.8% vs 44.3%, $P = 0.87$).

4 | DISCUSSION

This study shows no significant differences in the efficacy of percutaneous balloon aortic valvuloplasty performed either with or without rapid cardiac pacing. Moreover, the primary safety endpoint was similar between the two techniques.

We decided to focus on the BAV technique, aware that TAVR has clearly demonstrated its superiority over BAV in the treatment of aortic valve disease.[12] On the other side, we believe that BAV will maintain a role in the management of some patients with aortic stenosis in particular those with: hemodynamic instability at presentation, relevant frailty, doubtful symptoms (COPD, reduced mobility, etc. . .) and so a weak initial indication for TAVR. The incoming extension of TAVR indication to moderate risk patients, and its not negligible costs, will maintain BAV an option for very old, frail, and high-risk patients.[13] Furthermore, we confirm that enrollment in this study did not prevent patients from accessing a future TAVR or AVR treatment.

The BAV procedure has received renewed interest in the last decades.[14] Despite the fact that the first cases date back to about 30 years ago, several aspects of the procedure itself are not well defined or standardized.[5,15,16] The concomitant use of rapid cardiac pacing to help balloon stabilization has been adopted in most centers, while BAV is performed without in others. In the absence of a direct comparison between the two techniques, we sought to evaluate the influence of RP on procedural efficacy and safety in a randomized and rigorous study. As the design of the study enrolled a mere 100 patients

TABLE 2 Procedural and hemodynamic data

	No pacing $n = 49$	Pacing $n = 51$	P
Balloon size at 1st inflations, mm	20.7 ± 1.3	20.5 ± 1.2	0.46
18 mm	0 (0.0)	1 (2.0)	
20 mm	38 (77.6)	41 (80.4)	
23 mm	11 (22.4)	9 (17.6)	
Balloon/annulus ratio at 1st inflations	0.92 ± 0.04	0.93 ± 0.05	0.12
Sealing yes	33 (67.3)		
Sealing/pacing duration			
First inflation, sec	10.6 ± 2.6	10.3 ± 1.0	
Second inflation, sec	10.2 ± 2.6	10.0 ± 0.8	
Third inflation, sec	9.7 ± 1.8	9.5 ± 1.1	
Balloon size at upgrade, mm	23.4 ± 0.8	23.3 ± 0.7	0.79
23	8/10 (80.0)	16/19 (84.2)	
25	2/10 (20.0)	3/19 (15.8)	
Balloon/annulus ratio at upgrade	1.0 ± 0.1	1.0 ± 0.0	0.30
Sealing yes (upgrade)	10/10 (100.0)		
Sealing/pacing duration (upgrade)			
First inflation, sec	9.4 ± 1.7	10.3 ± 1.0	
Second inflation, sec	9.7 ± 1.0	10.0 ± 0.8	
Third inflation, sec	9.0 ± 2.1	9.5 ± 1.2	
Concomitant iliac and aortic study	33 (67.3)	30 (58.8)	0.41
Concomitant PCI	8 (16.3)	8 (15.7)	1.0
Total contrast dye,ml	60.9 ± 47.9	56.3 ± 47.6	0.63
Procedure duration, min	87.2 ± 24.5	89.3 ± 27.5	0.68
Procedural drugs			
ASA	23 (47.9)	30 (58.8)	0.32
Clopidogrel	7 (14.6)	5 (9.8)	0.55
Clopidogrel Load	7 (14.6)	6 (11.8)	0.77
OAT	17 (35.4)	13 (25.5)	0.38
Heparin	48 (98.0)	51 (100.0)	0.55
Poorly tolerated BAV	8 (16.3)	21 (41.2)	<0.05
NRS questionnaire	2.5 ± 2.4	3.1 ± 2.5	0.58

Continuous variables are expressed as mean ± SD; categorical variables as number (%). ASA, acetylsalicylic acid; BAV, balloon aortic valvuloplasty; OAT, oral anticoagulant therapy; NRS, Numeric Rating Scale for Pain; PCI, percutaneous coronary intervention.

at a single center (the number is only relatively small for a single center study, in consideration of the amount of BAV performed worldwide per center), this analysis can be considered hypothesis generating and a potential basis for sample size calculation in a larger, multi-center trial, enrolling more patients with shorter recruitment time.

We defined an echocardiographic endpoint as primary efficacy comparison, obtained by measuring the trans-aortic gradient about

TABLE 3 Hemodynamic success in BAV

	Overall	No pacing	Pacing	P
Success after 1st inflations	35/100 (35.0)	20/49 (40.8)	15/51 (29.4)	0.30
Success after balloon upgrade	10/29 (34.5)	6/10 (60.0)	4/19 (21.1)	0.051
Final success	45/100 (45.0)	26/49 (55.1)	19/51 (37.3)	0.16
Final 30-49% gradient reduction	35/100 (35.0)	14/49 (28.6)	21/51 (41.2)	0.19

Categorical variables as number/total (%). BAV, balloon aortic valvuloplasty.

30 min after the end of the procedure. We believe that this parameter, collected shortly after BAV, may be more reliable than the procedural success evaluated via hemodynamic measurement immediately after balloon inflation. In fact, BAV generates short phases of hypotension and stress in patients, which can lead to a reaction characterized by a release of catecholamines, tachycardia, and increased contractility. This is often evident when transient phases of high blood pressure are observed just after the maneuver and, as such, the mean trans-aortic gradient may be acutely overestimated. Thirty minutes was elected as a reasonable time frame to allow for full hemodynamic stabilization after procedural stress or transient complications.

In this study, we must acknowledge a slightly smaller percentage of success compared to previous reports, defined as a 50% reduction of the trans-aortic gradient.[2] We would like to highlight that the study protocol mandated balloon inflation at a nominal pressure, so as not to determine any bias between the groups. At our institute, BAV was usually performed without RP, allowing the operator to adapt inflation pressure upon aortic valve sealing, at times even over-expanding the balloon.[8] The predefined less aggressive approach adopted in this trial might have influenced the final efficacy outcome.

Although not significantly, success in terms of both hemodynamics and echocardiography was numerically more frequent in the No-RP group. This trend is in line with a previous observation by Witzke et al.[6] A contribution to the final result may have come from the more

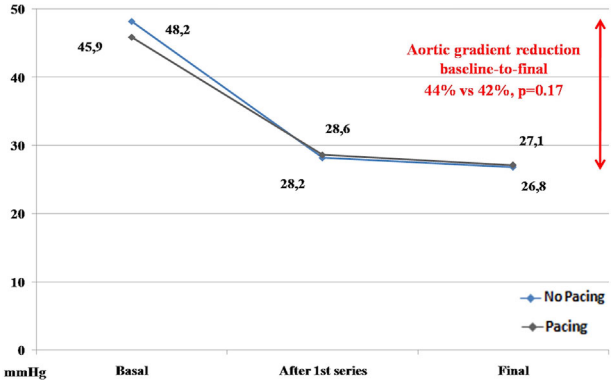

FIGURE 4 Comparison between the groups of the hemodynamic gradient across the procedural steps

TABLE 4 Primary endpoints and safety outcome

	No Pacing *n* = 49	Pacing *n* = 51	*P*
Primary efficacy endpoint (50% gradient reduction)	21 (42.9)	20 (39.2)	0.84
Primary safety composite endpoint (30-day)	4 (8.2)	7 (13.7)	0.53
Death	1 (2.0)	2 (3.9)	0.58
Myocardial infarction	0 (0.0)	2 (3.9)	0.16
TIA/stroke	0 (0.0)	1 (2.0)	0.31
Acute aortic regurgitation	3 (6.1)	2 (3.9)	0.61
BARC bleeding ≥3	0 (0.0)	2 (3.9)	0.16
In-hospital complications/ events			
TIA/Stroke	0 (0.0)	0 (0.0)	
AMI	0 (0.0)	2 (3.9)	0.16
AAR	3 (6.1)	2 (3.9)	0.61
Pericardial effusion	0 (0.0)	2 (3.9)	0.16
Cardiac tamponade	0 (0.0)	1 (2.0)	0.33
Emergency surgery	0 (0.0)	0 (0.0)	
Temporary PM implantation bailout	0 (0.0)	4 (7.8)	0.048
Bleedings			
BARC ≥3	0 (0.0)	2 (3.9)	0.16
RBC transfusion	0 (0.0)	1 (2.0)	0.33
BARC 1-2	5 (10.2)	2 (3.9)	0.22
Access site complications			
Hematoma	3 (6.1)	3 (5.9)	0.96
Arterial-venous fistula	0 (0.0)	0 (0.0)	
Pseudoaneurysm	1 (2.0)	0 (0.0)	0.31
Femoral dissection	0 (0.0)	0 (0.0)	
Peripheral embolization	0 (0.0)	0 (0.0)	
Angio-Seal failure	1 (2.0)	1 (2.0)	0.98
Acute kidney injury			
AKI 1	2 (4.1)	9 (17.6)	0.052
AKI 2	0 (0.0)	0 (0.0)	
AKI 3	0 (0.0)	2 (3.9)	0.16
Heart rhythm			
New onset atrial fibrillation	1 (2.0)	1 (2.0)	0.98
Permanent PM implantation	0 (0.0)	3 (5.9)	0.09
New LBBB	1 (2.1)	2 (4.1)	0.57
New RBBB	0 (0.0)	1 (2.0)	0.32
Death	0 (0.0)	2 (3.9)	0.17
Other echo data post BAV			
Max gradient, mmHg	39.1 ± 13.4	40.8 ± 16.2	0.57
Mean gradient, mmHg	24.4 ± 8.7	25.3 ± 11.0	0.68
Delta mean gradient reduction, %	44.8 ± 13.4	44.3 ± 12.0	0.87
30-49% gradient reduction	24 (49.0)	26 (51.0)	0.84
AVA, cm^2	0.98 ± 0.2	0.94 ± 0.2	0.34
AVA improvement, cm^2	0.27 ± 0.2	0.24 ± 0.1	0.39

Continuous variables are expressed as mean ± SD; categorical variables as number (%). AAR, acute aortic regurgitation; AKI, acute kidney injury; AMI, acute myocardial infarction; AVA, aortic valve area; BARC, Bleeding Academic Research Consortium; BAV, balloon aortic valvuloplasty; LBBB, left bundle branch block; PM, pacemaker; RBBB, right bundle branch block; RBC, red blood cells; TIA, transient ischemic attack.

frequent balloon upgrade in the population without pacing, justified by a better tolerance to the procedure both in terms of perceived feeling (patient-reported), and in terms of fewer hemodynamic and rhythm disorders. Yet, we believe that the perception of annular sealing when no rapid pacing is used may be helpful in achieving the best benefit-to-risk ratio for potential balloon upgrades. In fact, due to its frequently elliptical shape, accurate aortic annular sizing would require a CT scan, which is rarely used before BAV.

Our data did not show any differences in terms of significant safety outcomes between the techniques. However, some individual parameters slightly favored the No-RP group, such as the need for pacing support after BAV and a trend towards a lower incidence of transient acute mild kidney injury. These episodes might incur a more pronounced hemodynamic imbalance during RP rather than the controlled hypotensive phases observed during BAV without pacing. In any case, in the absence of any compelling evidence in favor of either technique, interventional cardiologists are encouraged not to change their usual BAV procedural practice.

4.1 | Other limitations

At our center, operators more frequently perform BAV without RP, thus we cannot completely exclude that this may have influenced the procedural outcome. In this case, multi-center enrollment would also prevent this potential bias. A primary safety composite endpoint was chosen to collect a sufficient number of events in consideration of the overall population enrolled. In particular, we included bleedings to study whether the different vascular access approach in each group (a single artery puncture in the No-RP group, a systematic venous plus arterial puncture in the RP group) could have influenced the outcome.

The semi-compliant balloons used in this study are widely used in Europe. Comparing other available devices with different characteristics (ie, non-compliant, 8-shaped) and/or dedicated to BAV without RP is certainly a source of further study in this field.

5 | CONCLUSION

In this randomized pilot trial, rapid ventricular pacing did not influence BAV efficacy or safety. However, BAV without RP would seem to

confer a slight advantage in terms of patient comfort and lower incidence of secondary safety outcomes.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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