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**Rapid right ventricular pacing for balloon valvuloplasty in congenital aortic stenosis: A systematic review**

Mylonas KS *et al*. RRVP for balloon valvuloplasty

Konstantinos S Mylonas, Ioannis A Ziogas, Charitini S Mylona, Dimitrios V Avgerinos, Christos Bakoyiannis, Fotios Mitropoulos, Aphrodite Tzifa

**Konstantinos S Mylonas,** Department of Cardiothoracic Surgery, Yale New Haven Hospital, New Haven, CT 06510, United States

**Ioannis A Ziogas,** Department of Surgery, Vanderbilt University Medical Center, Nashville, TN 37232, United States

**Charitini S Mylona,** Department of Pediatrics, Trikala General Hospital, Trikala 42100, Greece

**Dimitrios V Avgerinos,** Department of Cardiothoracic Surgery, New York Presbyterian Hospital, New York, NY 10065, United States

**Christos Bakoyiannis,** Division of Vascular Surgery, First Department of Surgery, Laiko General Hospital, National and Kapodistrian University of Athens, Athens 11527, Greece

**Fotios Mitropoulos,** Department of Pediatric Cardiac Surgery, Mitera Children’s Hospital, Athens 15123, Greece

**Aphrodite Tzifa,** Department of Pediatric Cardiology and Adult Congenital Heart Disease, Mitera Children’s Hospital, Athens 15123, Greece

**Author contributions:** Mylonas KS did conception/design of the study, acquisition, analysis and interpretation of data, manuscript drafting, critical revision, final approval; Ziogas IA did acquisition, analysis and interpretation of data, manuscript drafting, critical revision, final approval; Mylona C did acquisition of data, critical revision, final approval; Avgerinos DV, Bakoyiannis C, Mitropoulos F and Tzifa A did conception/design of the study, critical revision, final approval.

**Corresponding author: Konstantinos S Mylonas, MD, Doctor,** Department of Cardiothoracic Surgery, Yale New Haven Hospital, 20, York Street, New Haven, CT 06510, United States. konstantinos.mylonas@yale.edu

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**Abstract**

BACKGROUND

Balloon aortic valvuloplasty (BAV) is a well-established treatment modality for congenital aortic valve stenosis.

AIM

To evaluate the role of rapid right ventricular pacing (RRVP) in balloon stabilization during BAV on aortic regurgitation (AR) in pediatric patients.

METHODS

A systematic review of the MEDLINE, Cochrane Library, and Scopus databases was conducted according to the PRISMA guidelines (end-of-search date: July 8, 2020). The National Heart, Lung, and Blood Institute and Newcastle-Ottawa scales was utilized for quality assessment.

RESULTS

Five studies reporting on 72 patients were included. The studies investigated the use of RRVP-assisted BAV in infants (> 1 mo) and older children, but not in neonates. Ten (13.9%) patients had a history of some type of aortic valve surgical or catheterization procedure. Before BAV, 58 (84.0%), 7 (10.1%), 4 (5.9%) patients had AR grade 0 (none), 1 (trivial), 2 (mild), respectively. After BAV, 34 (49.3%), 6 (8.7%), 26 (37.7%), 3 (4.3%), patients had AR grade 0, 1, 2, and 3 (moderate), respectively. No patient developed severe AR after RRVP. One (1.4%) developed ventricular fibrillation and was defibrillated successfully. No additional arrhythmias or complications occurred during RRVP.

CONCLUSION

RRVP can be safely used to achieve balloon stability during pediatric BAV, which could potentially decrease AR rates.

**Key Words:** Congenital aortic stenosis; Rapid right ventricular pacing; Balloon aortic valvuloplasty; Congenital heart disease; Systematic review; Aortic regurgitation

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**Core Tip:** Balloon aortic valvuloplasty (BAV) for congenital aortic valve stenosis is well established. Rapid right ventricular pacing (RRVP) is helpful in achieving balloon stability in children undergoing aortic valve dilatation. Our findings demonstrate that RRVP is an effective and safe procedure that helps stabilize the balloon during BAV and decreases the rate of aortic regurgitation in the pediatric population. No reports of severe aortic regurgitation after RRVP-assisted BAV have been published to date.

**INTRODUCTION**

Congenital aortic valve stenosis (AS) is the most frequent type of left ventricular outflow tract obstruction in the pediatric population and accounts for more than three-fourths of the left ventricular outflow tract obstruction cases in children[1,2]. The severity of obstruction and symptoms typically guide the management of valvar AS, while a peak-to-peak systolic gradient > 50 mmHg is associated with an increased likelihood of ventricular arrhythmias and sudden death mandating immediate intervention[3]. Treatment modalities focus on adequately relieving the obstruction, while simultaneously avoiding valvular damage and regurgitation. The two most commonly implemented modalities include balloon aortic valvuloplasty (BAV) and surgical aortic valvotomy (SAV), which have demonstrated an equivalent incidence of aortic regurgitation (AR), gradient reduction, and survival outcomes[4]. However, the invasiveness and long recovery period associated with SAV render BAV a more appealing first-line treatment option. On the other hand, BAV is also not a risk-free intervention because cardiac contractions and pulsatile blood flow can lead to balloon displacement during aortic valve dilation. Additionally, damage to vessels or intraluminal structures may also result from increased wall stress during cardiac contraction against an inflated balloon[5-12]. Overall, moderate to severe AR develops in about 15% post-BAV even if the balloon diameter does not oversize the aortic valve annulus[13-16].

To increase stability during balloon placement and to minimize the risk of AR, several techniques have been implemented, including extra-stiff wires, long balloons, long sheaths, compliant balloons in the inferior and superior vena cavae or in the main pulmonary artery[17,18]. Bolus adenosine is a considerably safe and effective method to achieve transient, pharmacologic cardiac standstill; however, periods of asystole may occur, which are variable and cannot be easily controlled or predicted[19]. Moreover, adenosine does not prevent ventricular contractions, which may occur spontaneously or be triggered by the balloon itself during inflation[20].

Another mode of balloon stabilization during BAV includes rapid ventricular pacing, which decreases stroke volume, pulse pressure, and blood pressure without causing cardiac standstill and without the limitations associated with other techniques. Rapid right ventricular pacing (RRVP) was initially reported in 2002 and has since been broadly implemented throughout the world[5-12]. Rapid left ventricular pacing has also been reported but is less widely implemented[21,22]. RRVP is commonly utilized during BAV in older children and adults, but there is a scarcity of data regarding neonates and infants. We aimed to systematically review the literature and assess the safety and efficacy of RRVP-assisted BAV in children.

**MATERIALS AND METHODS**

***Study design and inclusion/exclusion criteria***

We conducted the present systematic review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (Supplementary Table 1)[23]. Since this study utilized only already published data, no patient written consent or Institutional Review Board approval was required.

The study selection criteria were defined by applying the PICO (Population/Participants, Intervention, Comparison, and Outcome) framework: Participants: Children (< 18 years) of any sex or race with congenital aortic stenosis; Intervention: RRVP-assisted balloon aortic valvuloplasty; Comparison: Not applicable; Outcomes: Aortic valve gradient reduction, incidence of AR, freedom from re-intervention, arrhythmias, and other procedure-related complications; Study design: Original randomized clinical trials, non-randomized prospective or retrospective clinical studies (*i.e.*, cohort, case-control, case series, case reports).

Exclusion criteria for the present systematic review were: (1) Non-English articles and (2) Narrative or systematic reviews and meta-analyses, animal and in-vitro studies, errata, comments, perspectives, letters to the editor, and editorials that did not provide any primary patient data. No publication date, sample size restrictions or any other search filters were applied.

***Literature search strategy***

Two independent researchers (Mylonas KS, Ziogas IA) identified eligible studies through a systematic search of MEDLINE (through PubMed), the Cochrane Library, and Scopus (end-of-search date: July 8th, 2020). The search was executed using the following algorithm: (rapid ventricular pacing OR cardiac stimulation) AND aortic valvuloplasty AND (balloon OR transcatheter OR percutaneous) AND (pedi\* OR child\* OR adolescent OR neonat\*). The reference lists of eligible articles were hand-searched for potentially missed studies[24]. All eligibility concerns were addressed via consensus with the senior author (Tzifa A).

***Data tabulation and extraction***

A pre-specified spreadsheet was utilized to perform data tabulation and extraction for evidence synthesis and assessment of study quality. Two reviewers (Mylonas KS, Ziogas IA) extracted the data independently, and any disagreements were addressed via consensus with the senior author (Tzifa A). We extracted the following data from the eligible articles: Study characteristics (PubMed identification number, first author, publication year, country, study design, study sample), patient demographics (sex, age in years, weight in kg, length in cm), cardiac pathology, past cardiac intervention history, timing of RRVP, pacing mode, pacing rate in beats/minute, pacing time in seconds, balloon length and diameter in mm, balloon displacement, pre-/post-BAV peak systolic gradient in mmHg, pre-BAV AR, aortic valve gradient post-BAV, incidence of AR after dilatation, freedom from re-intervention sustained arrhythmias, and other procedure-related complications.

***Assessment of study quality***

The quality of the included case series was assessed using the National Heart, Lung, and Blood Institute (NHLBI) scale[25]. The NHLBI scale ranges from 1 to 9; with a score of 1-3 denoting poor quality, 4-6 fair quality and 7-9 suggesting good quality. In the item assessing whether the follow-up period was long enough for outcomes to occur, the cut-off value was a priori set at one year after BAV. The mean and standard deviation for the NHLBI score of the entire review were calculated.

The Newcastle-Ottawa scale was utilized to evaluate the quality of case-control studies[26]. In the item assessing whether the follow-up period was long enough for outcomes to occur, the cut-off value was a priori set at 1 year after BAV. In line with standard practice, adequacy of follow-up was set at the 90% rate.

***Statistical analysis***

Continuous variables were reported as medians and ranges or as means and standard deviations, while categorical variables as frequencies and percentages. All relative rates were estimated according to the available data for each variable of interest, and all data were handled based on the Cochrane Handbook principles[27].

**RESULTS**

***Study selection and characteristics***

Five publications reporting on RRVP-assisted BAV for congenital aortic stenosis fulfilled our predetermined literature search criteria (Figure 1)[5-9]. All included eligible studies enrolled a total of 72 patients from September 1999[5] until August 2009[9]. Median patient age ranged from 10 to 13.4 years (1 mo-32 years) and median weight at the time of the intervention ranged from 14 to 48.5 kg (range: 4.4-79 kg). No neonates were treated with RRVP-assisted BAV in any of the published studies. Only 10 (13.9%) patients had a history of some type of aortic valve surgical or catheter-based procedure (Table 1).

***Assessment of study quality***

According to the NHLBI scale, all published case series[5-8] were studies of good quality, and the mean NHLBI score of the review was 7.5 ± 1.0. The case control study by Gupta *et al*[9] comparing RRVP alone to RRVP plus controlled transient respiratory arrest also showed high quality according to the Newcastle-Ottawa scale (score: 6). Detailed quality assessment for each study is provided in Supplementary Tables 2 and 3.

***RRVP-assisted BAV outcomes***

Published studies have evaluated the use of rapid pacing for transcatheter valvuloplasty in infants (over 1 mo of age) and older children, but not in neonates. Daehenert *et al*[6] used RRVP after the failure of an initial non-paced balloon placement attempt. All other teams utilized rapid pacing from the outset of the procedure. Although initial pacing rates varied, most protocols employed RRVP until a 50% reduction in systolic aortic blood pressure was achieved.

Median pacing rates ranged between 209-240 (200-260) beats per minute. On average, pre-BAV peak systolic gradient was in the upper 60 s (mmHg), whereas after the procedure, it typically dropped below 20 mmHg (three-fold reduction). To accurately quantify the impact of RRPV on post-BAV AR rates, we had to exclude 3 patients from the Mehta *et al*[8] series since they had “mixed aortic valve disease” of unknown severity.

Prior to BAV, 58 (84.0%), 7 (10.1%), and 4 (5.9%) patients respectively had AR grade 0 (none), 1 (trivial), 2 (mild). After BAV, 34 (49.3%), 6 (8.7%), 26 (37.7%), 3 (4.3%), patients respectively had AR grade 0, 1, 2, and 3 (moderate). No patient developed severe aortic insufficiency after BAV with RRVP.

Gupta *et al*[9] compared RRVP alone to RRVP plus controlled transient cessation of positive-pressure ventilation and found no statistically significant difference in terms of peak systolic gradient reduction (*P* = 0.25) and post-BAV aortic insufficiency rates (*P* > 0.05). Lastly, among 72 reviewed patients, only one (1.4%) developed ventricular fibrillation and was cardioverted successfully[8]. No additional arrhythmias or other complications occurred after RRVP (Table 2).

**DISCUSSION**

BAV constitutes the treatment of choice for severe congenital AS in several centers worldwide, as there is no requirement for cardiopulmonary bypass, the length of hospital stay is shorter, and its outcomes are comparable to that of SAV. However, patients treated with BAV are at risk of developing AR, which can be moderate to severe in about 15%[13-16] and may progress over time[14]. Several approaches have been implemented to stabilize the balloon and decrease the risk of post-BAV AR, including the use of special equipment (extra-stiff guidewires and double balloons)[5,28] or bolus intravenous adenosine. The latter is generally considered to be safe and effective in decreasing cardiac output and generating a transient state of asystole by inducing sinoatrial and atrioventricular block[19,20,29]. Nevertheless, adenosine needs to be titrated on a patient-by-patient basis, and the onset and duration of pharmacologic the transient cardiac standstill is dose-dependent and variable among patients. As RRVP can decrease stroke volume, blood pressure, and transvalvular flow without causing asystole and can be modified according to the needs of the procedure, a growing number of centers began using this approach as the method of choice for balloon stabilization in children and adults[5-9]. In the present systematic review, we sought to summarize all published literature assessing the safety and efficacy of RRVP-assisted BAV for congenital aortic valve stenosis.

Our findings suggest that the maximum aortic valvular gradient after aortic dilatation with pacing decreases significantly[5-9]. In children, RRVP is typically implemented from the beginning of the intervention, since even a single balloon displacement event can be enough to damage the aortic valve[7,8]. However, it should be emphasized that according to our systematic review, no cases of severe AR after rapid pacing have ever been reported. Despite its well-known benefits, RRVP has not been broadly employed in neonates and infants, and thus the outcomes of RRVP-assisted BAV in congenital AS patients < 1 year are largely unknown. The absence of a unified pacing approach during BAV in this population is based on the hypothesis that the low stroke volumes (1.0-1.5 mL/kg), higher heart rates, and low ejection fractions are unable to cause uncontrolled balloon movement and valvar damage. However, this theory cannot explain the need for a surgical bailout for severe AR post-BAV, which has been repeatedly reported for neonates and infants subjected to BAV without rapid pacing. Decreasing the risk and extent of post-BAV AR is vital in this population, in whom the performance of bailout Ross (with or without Konno) has been associated with poor prognosis[30]. Therefore, future studies should explore the role of RRVP-assisted BAV in neonates and infants. Nonetheless, RRVP does have certain pitfalls, including a prolongation in operative time and a potentially higher risk of cardiac perforation and pneumothorax (if performed *via* the jugular/subclavian vein)[18]. It has also been suggested that rapid ventricular pacing may increase the risk of sustained ventricular arrhythmias compared to the baseline risk of cardiac catheterization (< 1%)[31]. According to our findings, only one (1.4%) case of ventricular fibrillation has been described, which was still successfully defibrillated[8].

Nonetheless, certain limitations inherent to the nature of the included studies should be considered when interpreting the results of the present systematic review. Three of the five included studies were retrospective in nature, and thus may impart a degree of selection bias; albeit, upon rigorous quality assessment, all studies were deemed to be of high-quality. Additionally, to accurately quantify the impact of RRPV on post-BAV AR rates, in the study by Mehta *et al*[8] we excluded three patients from the pooled analysis since their pre-BAV pathology was “mixed aortic valve disease” of unknown severity. Lastly, as with all systematic reviews, some of the eligible studies did not report on all characteristics or outcomes of interest, and thus the relative rates were estimated accordingly based on the availability of data.

**CONCLUSION**

In conclusion, RRVP is an effective and safe procedure that can help stabilize the balloon during BAV and decrease subsequent AR rates. No reports of severe AR after RRVP-assisted BAV in children have been published to date.

**ARTICLE HIGHLIGHTS**

***Research background***

Congenital aortic valve stenosis is the most frequent type of left ventricular outflow tract obstruction in the pediatric population and accounts for more than three-fourths of the left ventricular outflow tract obstruction cases in children. The two most commonly implemented modalities include balloon aortic valvuloplasty (BAV) and surgical aortic valvotomy, which have demonstrated an equivalent incidence of aortic regurgitation (AR), gradient reduction, and survival outcomes.

***Research motivation***

Another mode of balloon stabilization during BAV includes rapid ventricular pacing, which decreases stroke volume, pulse pressure, and blood pressure without causing cardiac standstill and without the limitations associated with other techniques. Rapid right ventricular pacing (RRVP) was initially reported in 2002 and has since been broadly implemented throughout the world. Rapid left ventricular pacing has also been reported but is less widely implemented. RRVP is commonly utilized during BAV in older children and adults, but there is a scarcity of data regarding neonates and infants.

***Research objectives***

RRVP is commonly utilized during BAV in older children and adults, but there is a scarcity of data regarding neonates and infants. We aimed to systematically review the literature and assess the safety and efficacy of RRVP-assisted BAV in children.

***Research methods***

A systematic review of the MEDLINE, Cochrane Library, and Scopus databases was conducted according to the PRISMA guidelines (end-of-search date: July 8, 2020). The National Heart, Lung, and Blood Institute and Newcastle-Ottawa scales was utilized for quality assessment.

***Research results***

Five studies reporting on 72 patients were included. The studies investigated the use of RRVP-assisted BAV in infants (> 1 mo) and older children, but not in neonates. Ten (13.9%) patients had a history of some type of aortic valve surgical or catheterization procedure. Before BAV, 58 (84.0%), 7 (10.1%), 4 (5.9%) patients had aortic regurgitation (AR) grade 0 (none), 1 (trivial), 2 (mild), respectively. After BAV, 34 (49.3%), 6 (8.7%), 26 (37.7%), 3 (4.3%), patients had AR grade 0, 1, 2, and 3 (moderate), respectively. No patient developed severe AR after RRVP. One (1.4%) developed ventricular fibrillation and was defibrillated successfully. No additional arrhythmias or complications occurred during RRVP.

***Research conclusions***

RRVP is an effective and safe procedure that can help stabilize the balloon during BAV and decrease subsequent AR rates. No reports of severe AR after RRVP-assisted BAV in children have been published to date.

***Research perspectives***

Future studies should explore the role of RRVP-assisted BAV in neonates and infants.

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**Footnotes**

**Conflict-of-interest statement:** The authors have no conflict of interest and no financial ties to declare.

**PRISMA 2009 Checklist statement:** We conducted the present systematic review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.

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Grade E (Poor): 0

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**Figure Legends**

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**Figure 1 PRISMA flow diagram of the search strategy and study selection.**

**Table 1 Study and patient characteristics**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| PMID | Ref. (year of Publication) | Country | Study type | Study period | Patient sample | Male:female | Patient age(years) | Age groups | Weight(kg) | Length(cm) | Cardiac pathology | Past cardiac intervention history |
| **Neonates** | **Infants** | **Children** | **BAV** | **SAV** |
| 20826965 | Gupta *et al*[9] (2010) | India | Retrospective case series | June 2006-August 2009 | A: 5B: 5 | A: 5:0B: 4:1 | A: 5.04B: 5.04 | 0 | 0 | 10 | A: 20.04B: 14.04 | NR | AS NYHA II & III | 0 | 0 |
| 20465717 | Mehta *et al*[8] (2010) | United Kingdom | Retrospective case series | NR | 25 | NR | 11.61,4(1.0 mo-32.0)5 | NR | NR | NR | 38.81,4(4.4-67.1)5 | NR | Isolated AS: 18/25 (72%) | 7/25(28%)2 |
| Mixed aortic valve disease: 3/25 (12%) |
| Other associated lesions: 4/25 (16%) |
| 16889846 | David *et al*[7] (2007) | Mexico | Non-randomized, prospective | September 2004-July 2005 | 10 | 6: 4 | 10.04(3.0-16.0)5 | 0 | 0 | 10 | NR | NR | Untreated AS with gradient ≥ 50 mm Hg or less, with obstructiveand ARgrades I– II or without insufficiency. | 0 | 0 |
| 15310698 | Daehnert *et al*[6] (2004) | Germany | Prospective pilot | September 2001-August 2003 | 14 | 9: 5 | 13.44(0.3-20.2)5 | 0 | 1 | 13 | 48.54(7.0-79.0)5 | 158.04(65.0-180.0)5 | AS: 14/14(100%) | 1(7.6%) | 2/14 (14.3%) |
| N/A3 | Ing *et al*[5](2002) | United States | Retrospectivecase series | September 1999-June 2001 | 13 | NR | 9.96 | NR | NR | NR | 31.7 6 | NR | AS: 13/13(100%) | 0 | 0 |

1David *et al*[7] reported on 25 patients who underwent balloon aortic valvuloplasty and 4 patients who had stenting of coarctation (these demographics were not grouped according to type of cardiac pathology).

2Seven patients had previous interventions either in the form of surgery of catheterization.

3Ing *et al*[5] was the first group to describe rapid right ventricular pacing for balloon aortic valvuloplasty in an abstract at the Journal of the American College of Cardiology.

4Median.

5Range.

6Mean.

A: Rapid right ventricular pacing (RRVP); B: RRVP + controlled transient respiratory arrest. PMID: PubMed identification number; BAV: Balloon aortic valvuloplasty; SAV: Surgical aortic valvotomy; AS: Congenital aortic valve stenosis; AR: Aortic regurgitation; CTRA: Controlled transient respiratory arrest; NYHA: New York Heart Association.

**Table 2 Outcomes of rapid right ventricular pacing-assisted balloon aortic valvuloplasty**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| PMID | Ref. (year of Publication) | Timing of RRVP | Pacing mode | Pacing rate(bpm) | Pacing time (sec) | Balloon length(mm) | Balloon diameter (mm) | Balloon displacement | Pre-BAV PS gradient(mmHg) | Post-BAV PS gradient(mmHg) | Pre-BAVAR | Post-BAVAR | Sustained arrhythmias | Other procedure-related complications |
| 20826965 | Gupta *et al*[9] (2010) | Pacing untilSBP dropped by 50% | NR | NR | NR | Balloon:aortic annulus size = 1:1 | A: 1/5 (20%)B: 0% | Gradient reduction (%):A: 52.2%B: 70.1%; *P* = 0.25 | G0: 10/10 (100%) |  | A | B | None | None |
| G0 | 0% | 2/5(40%) |
| G1 | 0% | 0% |
| G2 | 4/5(80%) | 3/5(60%) |
| G3 | 1/5(20%) | 0% |
| G4 | 0% | 0% |
| 204657174 | Mehta *et al*[8] (2010) | Initially180 bpm.Pacing rate wasincreased by 20 bpm until SBP dropped by 50% ± pulse pressure by 25% | AAI/AO | 2405(200-260)6 | NR | NR | NR | 1/25 (4%) | Gradient reduction:205(0-60)6 | G0: 22 (88%) | G0: 16/22(72.7%) | 1/25 (4%) VFib which was successfully cardioverted | None |
| G1:0% | G1:0% |
| G2:0% | G2: 6/22(27.8%) |
| G3:0% | G3:0% |
| G4:0% | G4: 0% |
| 16889846 | David *et al*[7] (2007) | Initially at a frequency slightly higher than the spontaneous patient's frequency. Pacing rate was increased until SBP dropped by 50% | NR | 2097 (170-250)6 | NR | 40(40-40) | 185(14-22)6 | NR | 68.57 ± 208 | 19.77 ± 8.38 | G0: 6/10(60%) | G0: 5/10(50%) | None | None |
| G1: 4/10(40%) | G1: 5/10(50%) |
| G3: 0% | G3: 0% |
| G4: 0% | G4: 0% |
| 15310698 | Daehnert *et al*[6] (2004) | After failure of first non-paced dilatation attempt | VVI | 2202 | 12.77 (7-16)6 | 605(30-60)6 | 205(10-25)6 | 3/14(21.4%)1 | 82.55(60-110)6 | 28.65(10-50)6 | G0: 7/14(50%) | G0: 1/14(7.1%) | None | None |
| G1: 3/14(21.4%) | G1: 0 |
| G2: 4/14(28.6%) | G2: 11/14(78.6%) |
| G3: 0% | G3: 2/14(14.3%) |
| G4: 0% | G4: 0% |
| N/A3 | Ing *et al*[5] (2002) | Pacing just prior to balloon inflation. HR increased by an average of 80 ± 29% &LV systolic pressure decreased by 36 ± 12%. | NR | NR | NR | NR | NR | 1/13(20.1%) | 67.87 ± 18.68 | 19.47 ± 9.18 | G0: 13/13 (100%) | G0: 10/13(76.9%) | None | None |
| G1: 1/13(7.7%) |
| G2: 2/13(18.4%) |
| G3: 0% |
| G4: 0% |

1Two in the aorta and 1 in the left ventricle.

2In 2 patients the balloon continued to move and rapid right ventricular pacing (RRVP) was increased to 240 bpm.

3Ing *et al*[5] was the first group to describe rapid right ventricular pacing for balloon aortic valvuloplasty in an abstract at the Journal of the American College of Cardiology.

4To accurately quantify the impact of RRPV on post-balloon aortic valvuloplasty (BAV) aortic regurgitation (AR) rates, we had to exclude 3 patients since pre-BAV they had “mixed aortic valve disease” of unknown severity.

5Median.

6Range.

7Mean.

8Standard deviation.

G0: No AR; G1: Grade 1 AR (trivial); G2: Grade 2 AR (mild); G3: Grade 3 AR (moderate); G4: Grade 4 AR (severe); A: RRVP; B: RRVP + controlled transient respiratory arrest; NR: not reported; PMID: PubMed identification number; RRVP: Rapid right ventricular pacing; PS: Peak systolic; AR: Aortic regurgitation; SBP: Aortic systolic blood pressure; VFib: Ventricular fibrillation; CTRA: Controlled transient respiratory arrest.