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SYSTEMATIC REVIEWS

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

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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.

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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.

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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. Daehener *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 RRVP 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,

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 <i>et al</i> ^[9] (2010)	India	Retrospective case series	June 2006-August 2009	A: 5 B: 5	A: 5:0 B: 4:1	A: 5.0 ⁴ B: 5.0 ⁴	0	0	10	A: 20.0 ⁴ B: 14.0 ⁴	NR	AS NYHA II & III	0	0
20465717	Mehta <i>et al</i> ^[8] (2010)	United Kingdom	Retrospective case series	NR	25	NR	11.6 ^{1,4} (1.0 mo-32.0) ⁵	NR	NR	NR	38.8 ^{1,4} (4.4-67.1) ⁵	NR	Isolated AS: 18/25 (72%) Mixed aortic valve disease: 3/25 (12%) Other associated lesions: 4/25 (16%)	7/25 (28%) ²	
16889846	David <i>et al</i> ^[7] (2007)	Mexico	Non-randomized, prospective	September 2004-July 2005	10	6: 4	10.0 ⁴ (3.0-16.0) ⁵	0	0	10	NR	NR	Untreated AS with gradient \geq 50 mm Hg or less, with obstructive and AR grades I- II or without insufficiency.	0	0
15310698	Daehnert <i>et al</i> ^[6] (2004)	Germany	Prospective pilot	September 2001-August 2003	14	9: 5	13.4 ⁴ (0.3-20.2) ⁵	0	1	13	48.5 ⁴ (7.0-79.0) ⁵	158.0 ⁴ (65.0-180.0) ⁵	AS: 14/14 (100%)	1 (7.6%)	2/14 (14.3%)
N/A ³	Ing <i>et al</i> ^[5] (2002)	United States	Retrospective case series	September 1999-June 2001	13	NR	9.9 ⁶	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 or 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: RRVF + 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.

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 RRVF can decrease stroke volume, blood pressure, and transvalvular flow without causing

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

PMID	Ref. (year of Publication)	Timing of RRVF	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
									Pre-BAV PS gradient (mmHg)	Post-BAV PS gradient (mmHg)	Pre-BAVAR	Post-BAVAR				
20826965	Gupta et al ^[9] (2010)	Pacing until SBP 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%						
20465717	Mehta et al ^[8] (2010)	Initially 180 bpm. Pacing rate was increased by 20 bpm until SBP dropped by 50% ± pulse pressure by 25%	AAI/AO	240 ⁵ (200-260) ⁶	NR	NR	NR	1/25 (4%)	Gradient reduction: 20 ⁵ (0-60) ⁶	G0: 22	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	209 ⁷ (170-250) ⁶	NR	40 (40-40)	18 ⁵ (14-22) ⁶	NR	68.5 ⁷ ± 20 ⁸	19.7 ⁷ ± 8.3 ⁸	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	220 ²	12.7 ⁷ (7-16) ⁶	60 ⁵ (30-60) ⁶	20 ⁵ (10-25) ⁶	3/14 (21.4%) ¹	82.5 ⁵ (60-110) ⁶	28.6 ⁵ (10-50) ⁶	G0: 7/14 (50%)	G0: 1/14 (7.1%)	None	None		
									G1: 3/14 (21.4%)	G1: 0						

N/A ³	Ing et al ^[5] (2002)	Pacing just prior to balloon inflation. HR increased by an average of $80 \pm 29\%$ & LV systolic pressure decreased by $36 \pm 12\%$.	NR	NR	NR	NR	1/13 (20.1%)	$67.8^7 \pm 18.6^8$	$19.4^7 \pm 9.1^8$	G2: 4/14 (28.6%)	G2: 11/14 (78.6%)	None	None
										G3: 0% G4: 0%	G3: 2/14 (14.3%) G4: 0%		
										G0: 13/13 (100%)	G0: 10/13 (76.9%) 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 RRVP 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.

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

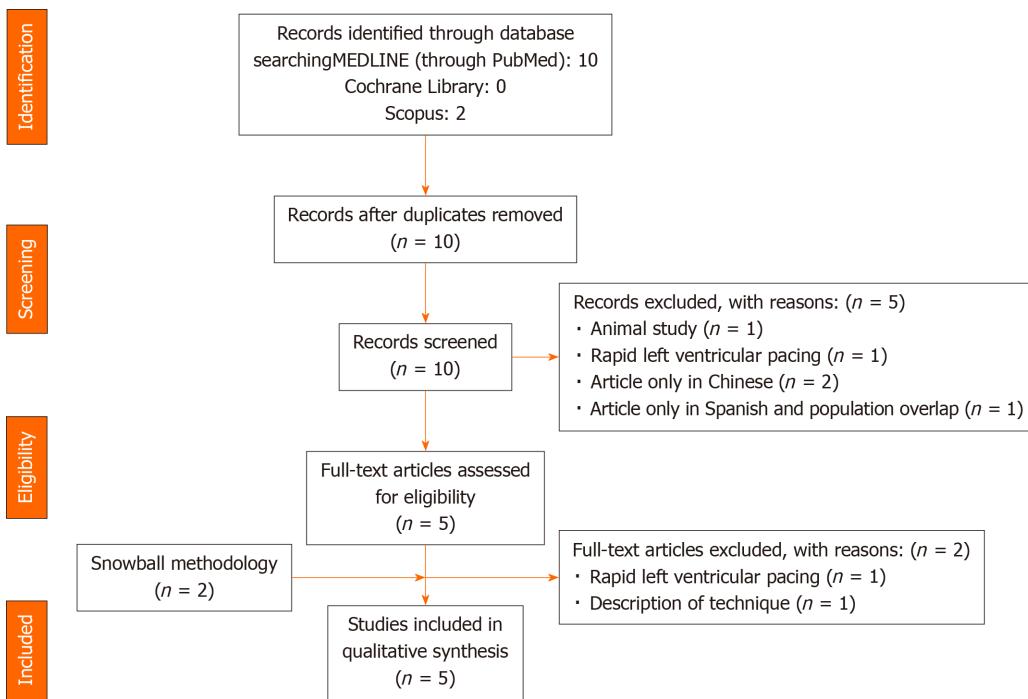


Figure 1 PRISMA flow diagram of the search strategy and study selection.

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 RRPV-assisted BAV in neonates and infants. Nonetheless, RRPV 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, RRPV 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 RRPV-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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