Cardiology in the Young

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Percutaneous pulmonary valve implantation in children and adults with an age and gender-specific analysis

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Original Article

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Abstract

Background: There are limited studies with medium-term follow-up following percutaneous pulmonary valve implantation and no studies with a gender-specific analysis. *Aims:* To report clinical outcomes up to five years following percutaneous pulmonary valve implantation using the two most common balloon expandable valves in a mixed population of paediatric and adult patients with an age and gender-specific analysis. *Methods:* This was a single-centre retrospective observation study. Relevant data were obtained retrospectively from the case files. Age and gender- specific analysis was performed using SPSS. *Results:* Totally, 58 patients (13 children, 45 adults) underwent percutaneous pulmonary valve implantation. Statistically significant reduction in median right ventricular outflow tract flow velocity following valve implantation was maintained for the whole five years in adults but not in children. There were no gender-specific differences despite the study being adequately powered. Independent of valve type used, there was significant reduction of the right ventricular outflow tract flow velocity in the immediate post valve implantation period (Edwards $P = 0.001$, Melody $P = 0.013$). There was a significant negative correlation between implanted valve Z-score and subsequent right ventricular outflow tract gradient during the first two years following valve implantation. *Conclusion:* Gender does not significantly affect valve function following percutaneous pulmonary valve implantation. It is important to consider patients' age and body surface area in relation to existing right ventricular outflow tract size during decisions for percutaneous pulmonary valve implantation.

Percutaneous pulmonary valve implantation is an established alternative to the surgical approach to treat right ventricular outflow tract dysfunction in patients with CHD. Percutaneous pulmonary valve implantation randomised controlled trials are not considered feasible anymore according to Chatterjee et al..[1] Moreover, patient heterogeneity because of background diagnosis, age, and previous procedures renders a randomised controlled trial even more difficult.[1] Finally, most of the previous studies report small number of patients with mainly short- and mid-term outcomes and meta-analysis is needed to reach generalisable conclusions.[2] Percutaneous pulmonary valve implantation is increasingly used in paediatric patients, but reports are scarce and nowadays percutaneous pulmonary valve implantation is not infrequently used in native right ventricular outflow tracts.[3,4] There is limited evidence comparing Medtronic and Edwards valves in pulmonary position[5,6] and although there is guidance from funding bodies in the European Union to include gender-specific analysis in clinical research[7] to the best of our knowledge there are not such reports relevant to percutaneous pulmonary valve implantation. This is in contrast to the growing evidence of gender-specific differences in patients undergoing transcatheter aortic valve implantation.[8] A recent large study with real-world data reported that female patients have similar in-hospital death rates to male patients who underwent transcatheter aortic valve implantation.[9] However, subgroup analysis demonstrated differences between genders for the need of post procedural pacemaker implantation and risk of all-cause readmission. Our aim was to report clinical outcomes up to five years following percutaneous pulmonary valve implantation in a mixed population of paediatric and adult patients with CHD from a single centre in UK. Furthermore, we assessed the clinical outcomes of the two most used balloon expandable valves (Medtronic Melody or Edwards Sapien (XT, s3 and s3 Ultra valves) and performed a gender-specific analysis.

Materials and methods

This was a retrospective observational study with up to five-year follow-up in a mixed population of paediatric and adult patients, who underwent percutaneous pulmonary valve implantation between January 2013 and January 2022 in East Midlands Congenital Heart Centre, Leicester, UK. The study was approved by the University Hospitals of Leicester as part of a clinical audit (University Hospitals of Leicester audit registration number 10,615), and

patients' consent was not required. Patients' clinical data (demographics, New York Heart association classification according to symptoms and/or exercise test and echocardiography) and cardiac MRI data were retrieved from case notes and electronic database before and after percutaneous pulmonary valve implantation. All patients referred for percutaneous pulmonary valve implantation following a multidisciplinary team meeting were included in the study.

All percutaneous pulmonary valve implantation procedures were performed under general anaesthesia following standard procedures.[10] Valve size and type decision was left to the operator discretion. Further data capture occurred at follow-up which was at the discretion of the named consultant, but usually occurred and clustered at one, six and twelve months and then annually up to five years. Unfavourable clinical outcome following percutaneous pulmonary valve implantation was considered any case needing reintervention due to restenosis (right ventricular outflow tract maximum velocity > 4m/sec) or severe pulmonary regurgitation

Transthoracic echocardiography was performed on a General Electric machine (Vivid E9, London, UK) using standard methods.[11] Z-scores were calculated using Lopez et al. nomograms.[12] The tricuspid regurgitation jet velocity was measured using continuous wave Doppler. Right ventricular outflow tract gradient was calculated using continuous wave Doppler from parasternal views. The degree of pulmonary regurgitation was evaluated using established methods.[13] For comparison, the patient population was divided as following: pulmonary stenosis, mixed pulmonary valve disease, or pulmonary regurgitation. Pulmonary stenosis was defined as right ventricular outflow tract maximum velocity above 4m/sec with pulmonary regurgitation less than moderate. Pulmonary regurgitation was defined as severe or free pulmonary regurgitation with right ventricular outflow tract maximum velocity < 3m/sec. All the other cases were classed as mixed pulmonary valve disease.

Cardiac MRI

MRI was performed on a 1.5 T SOMATOM force MRI system (Siemens Medical Solutions, Erlangen, Germany) using a standard protocol and was reviewed by an MRI specialist blinded to the study objectives. As this was a retrospective study, the follow-up MRI was performed at variable time points depending on clinician discretion, but majority were performed on second year following implantation.

Statistical analysis

Statistical analysis was performed using SPSS (version 27). Demographics were described using median, interquartile range, frequencies, and percentages as appropriate. Analysis was performed on the full cohort as well as 2 subgroups based on gender, age above and below 18 years of age and type of valve used. Five years follow-up data were analyzed. Comparison between groups was performed with Student t test or Mann–Whitney U test depending on distribution. Pearson correlation analysis was used to compare pulmonary valve Z score to right ventricular outflow tract and tricuspid regurgitation velocity. Power calculation was performed using standard methods.[14] Statistical significance was set at $P < 0.05$.

Results

Totally, 76 patients were referred for percutaneous pulmonary valve implantation (61 adults and 15 children). Eighteen patients (24%) were deemed unsuitable for percutaneous pulmonary valve implantation. These patients did not have statistically significant different background demographics compared to those who underwent percutaneous pulmonary valve implantation (data not shown). Nine patients (50%) of this group had previously known borderline right ventricular outflow tract size for percutaneous pulmonary valve implantation and found to have even larger right ventricular outflow tract at balloon sizing. Four patients did not proceed for percutaneous pulmonary valve implantation because of coronary artery proximity to right ventricular outflow tract. Three patients with severe narrowing of the right ventricular outflow tract had technically challenging outflow tract in order to create a landing zone for the valve. One patient had a previous right ventricular outflow tract stent, which was already fractured. During the haemodynamic assessment and the attempt to stabilise the fractured part of the stent, this was snapped and dislodged to the tricuspid valve apparatus requiring an urgent operation. Finally, one patient with a mobile mass on pulmonary valve was referred for surgical repair.

Totally, 58 patients underwent a percutaneous pulmonary valve implantation, and their background demographics are shown in Table 1. There were 125 patient years of follow-up with mean 2.5 years per patient. Nine patients (15%) had percutaneous pulmonary valve implantation in native right ventricular outflow tracts. Almost half of the cohort population had mixed pulmonary valve disease and equal number of patients ($n = 16$) had pulmonary stenosis and pulmonary regurgitation. Five adults were lost on follow-up. Eight patients (14%) had mild pulmonary regurgitation and one patient had severe pulmonary regurgitation at three years follow-up and three patients developed moderate pulmonary regurgitation at five years follow-up. Three adults died from non-cardiac reasons during follow-up. One patient had residual right ventricular outflow tract stenosis requiring right ventricular to pulmonary artery conduit replacement four years post percutaneous pulmonary valve implantation. Two patients, one received a Melody and one an Edwards valve, were treated for endocarditis (1.6% per patient years) and two for suspected endocarditis (both received Melody valve). 78% ($n = 45$) of the whole cohort of patients had NYHA 2 or above. Overall, 38 (66%) patients, 7 children (54%) and 31 adults (69%), improved exercise tolerance (reported NYHA status or following exercise test).

All patients received post procedural antiplatelet treatment with aspirin for six months. However, long-term use of antiplatelet treatment was variable: eight patients (14%) stopped antiplatelet during follow-up; 42 patients (71%) remained on aspirin throughout the follow-up. Two patients were on clopidogrel or clopidogrel and aspirin. Seven patients (12%) were already on warfarin prior to the procedure and remained on this thereafter. There was no statistically significant difference on right ventricular outflow tract velocity of patients with interrupted and continuous antiplatelet treatment.

There was a significant reduction in median right ventricular outflow tract flow velocity following percutaneous pulmonary valve implantation in all patients with previous pulmonary stenosis or mixed pulmonary valve disease [median (interquartile range), 4.1 (0.5) versus 2.8 (1.0) m/sec, ($P < 0.001$), and this effect persisted up to five years follow-up (4.1 (0.5) versus 2.8 (1.1) m/sec, $P = 0.012$)] (Fig. 1). Independent of valve type used for percutaneous pulmonary valve implantation there was significant reduction of the right ventricular outflow tract velocity in the immediate post-implantation period [Edwards: pre-implantation 4.1 (0.5), post-implantation 3 (1.1), $P < 0.001$,

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Table 1. Baseline characteristics. Numbers represent median and interquartile range or number of patients and percentage as appropriate

	Children	Adults	Male	Female	All patients
Num. of patients	13	45	33	25	58
Age (years)	13 (5)	32 (13)	26 (22)	34 (16)	29 (19)
Weight (kg)	36 (23)	68 (27)	64 (34)	60 (24)	64 (31)
BSA	1.16 (0.39)	1.78 (0.43)	1.72 (0.56)	1.62 (0.43)	1.71 (0.44)
Primary diagnosis					
TOF	9 (69%)	24 (53%)	15 (45%)	17 (68%)	33 (57%)
PA with VSD	1 (8%)	5 (11%)	4 (12%)	3 (12%)	6 (10%)
TAC	2 (15%)	3 (7%)	2 (6%)	3 (12%)	5 (9%)
Other	1 (8%)	13 (29%)	12 (27%)	2 (8%)	14 (24%)
NYHA					
1	5 (38%)	8 (18%)	6 (18%)	7 (28%)	13 (22%)
2	8 (62%)	33 (73%)	23 (70%)	18 (72%)	41 (71%)
3	0 (0%)	3 (9%)	4 (12%)	0 (0%)	4 (7%)
Indication					
Regurgitation	1 (8%)	15 (33%)	7 (21%)	9 (36%)	16 (28%)
Stenosis	3 (23%)	13 (29%)	10 (30%)	6 (24%)	16 (28%)
Mixed	9 (69%)	17 (38%)	16 (49%)	10 (40%)	26 (44%)
Valve type					
Edwards	7 (54%)	34 (76%)	22 (67%)	19 (76%)	41 (71%)
Melody	6 (46%)	11 (24%)	11 (33%)	6 (24%)	17 (29%)
Valve size (mm)	22 (3)	23 (3)	23 (1)	23 (4)	23 (2)
Z-score	−0.16 (2.47)	−0.75 (1.25)	−0.72 (1.53)	−0.44 (1.8)	−0.66 (1.55)

BMI = body mass index; NYHA = New York Heart Association functional classification; PA = pulmonary atresia; TAC = truncus arteriosus communis; TOF = Tetralogy of Fallot; VSD = ventricular septal defect.

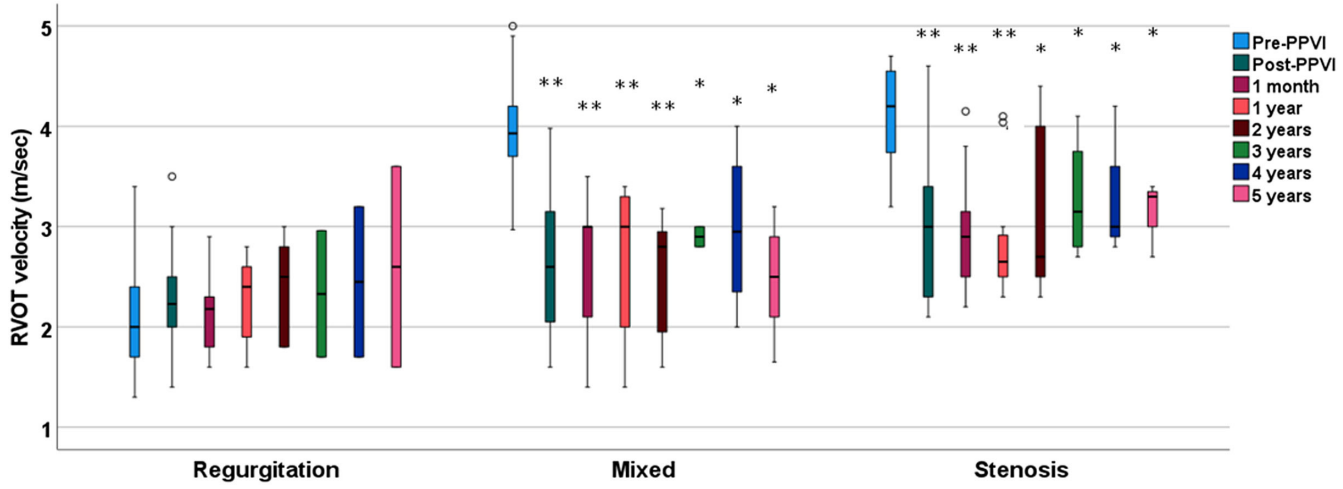

Figure 1. Right ventricular outflow tract flow velocity at baseline and during a five-year follow-up period with subgroup analysis according to percutaneous pulmonary valve implantation indication. Patients with pulmonary regurgitation have low baseline right ventricular outflow tract gradient which does not significantly increase in the subsequent years. Patients with mixed pulmonary valve disease have significant right ventricular outflow tract gradient reduction following percutaneous pulmonary valve implantation which maintained for the whole five years of follow-up. Patients with pulmonary stenosis have significant right ventricular outflow tract gradient reduction following percutaneous pulmonary valve implantation with a trend to increase after 3 years. *: P-value < 0.05, **: P-value < 0.005, PPVI: percutaneous pulmonary valve implantation, RVOT: right ventricular outflow tract.

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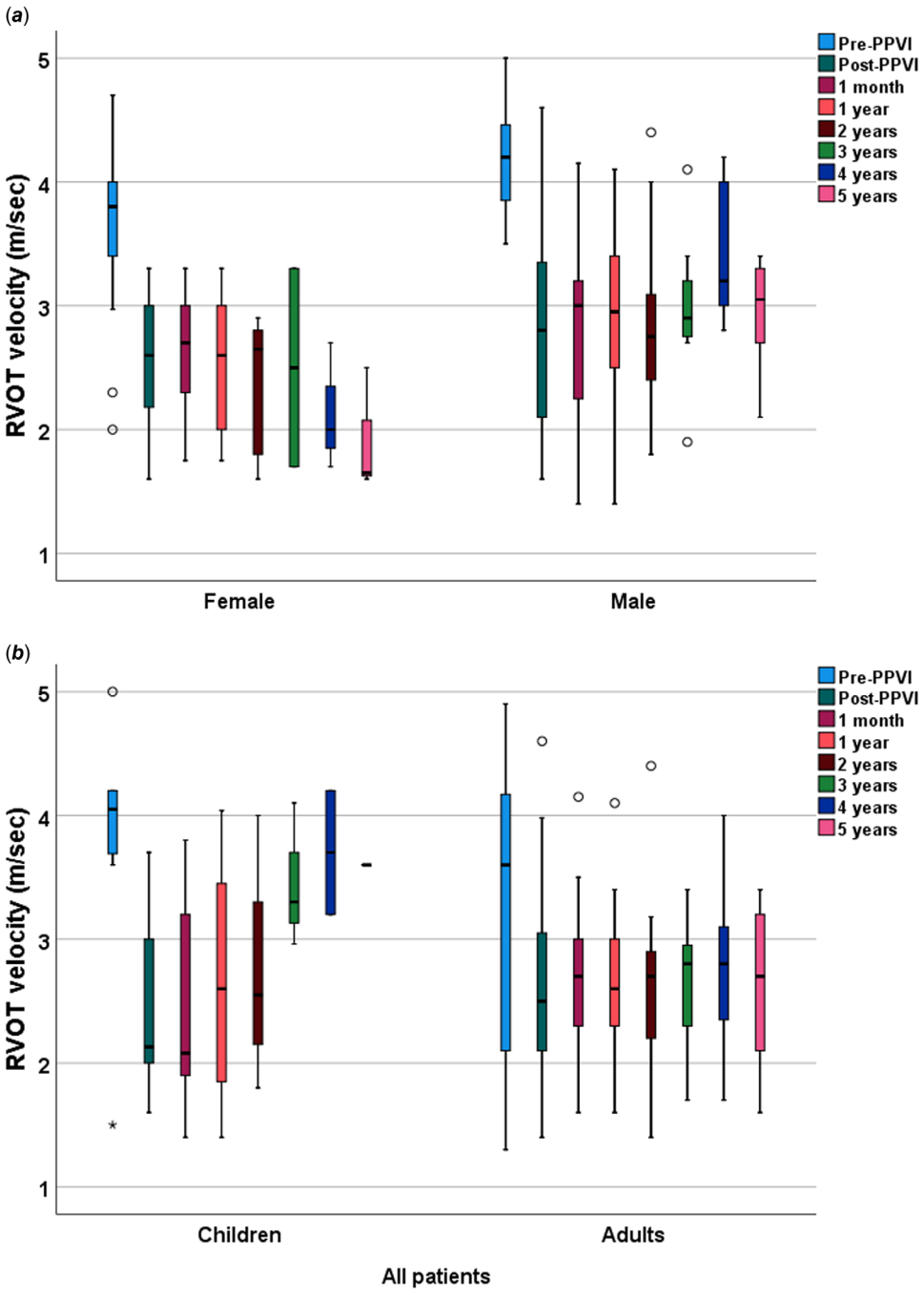

Figure 2. ***a***. Subgroup analysis right ventricular outflow tract velocity according to age in the whole cohort. Children had a significant right ventricular outflow tract velocity reduction up to 1 year following percutaneous pulmonary valve implantation with subsequent increase, whereas the adult population maintained a statistically significant right ventricular outflow tract velocity reduction up to five years (for specific right ventricular outflow tract velocity and P values please refer to Table 2). This is possibly attributed to the rapid body growth during puberty, which renders the implanted valve relatively smaller as children grow. ***b***. Gender-specific analysis of right ventricular outflow tract flow velocity at baseline and during a five-year follow-up period post percutaneous pulmonary valve implantation in patients with mixed pulmonary valve disease and pulmonary stenosis. There is no significant difference of the right ventricular outflow tract gradient between genders at any time point during the follow-up. PPVI = percutaneous pulmonary valve implantation; RVOT = right ventricular outflow tract.

Melody pre-implantation 4.1 (0.5), post-implantation 3 (1.1)m/sec, P = 0.004) as well as in the five-year follow-up (Edwards: 1.88 (1.4) P = 0.024, Melody 2.9 (0.7) m/sec, P = 0.003) (Supplementary Figure s1). No difference between the two groups (Edwards vs. Melody) was observed at any time point during follow-up. Moreover, there was no statistically significant restenosis during the five years following percutaneous pulmonary valve implantation in patients with pulmonary regurgitation (Fig. 1).

In the paediatric population, there was a statistically significant right ventricular outflow tract flow velocity reduction up to one year following percutaneous pulmonary valve implantation, which was not sustained thereafter. In contrast, the adult cohort maintained a statistically significant right ventricular outflow tract flow velocity reduction throughout the five years follow-up (Table 2, Fig. 2b). Furthermore, when we assessed tricuspid regurgitation velocity for both paediatric and adult population independent from the type of the pulmonary valve disease, there was a statistically significant reduction of tricuspid regurgitation velocity up to one year post-implantation, which subsequently became non-significant, but still reduced. There was a statistically significant negative correlation between the implanted pulmonary valve Z-scores and tricuspid regurgitation velocity (post-implantation: r = −0.43, P = 0.017, one month: r = −0.46, P = 0.015, one year: r = −0.38, P = 0.035) and right ventricular outflow tract velocity (post-implantation: r = −0.30, P = 0.041, one month: r = −0.49, P < 0.001, one year: r = −0.43, P = 0.008 and two years: r = −0.45, P = 0.032) in the first years following percutaneous

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Table 2. RVOT and TR velocity at baseline and during a five-year follow-up period post PPVI in children and adults. Values expressed as median and interquartile range. Mann–Whitney U test was performed for comparison between pre-PPVI and follow-up measurements

	Children		Adults	
	RVOT	TR	RVOT	TR
Pre-PPVI	4.1 (0.5)	4.2 (0.5)	3.6 (2.1)	3.3 (1.3)
Post-PPVI	2.1 (1.0)*	2.9 (0.7)*	2.5 (1.0)**	3.0 (1.3)*
1 month	2.1 (1.4)*	2.9 (1.0)*	2.7 (0.8)**	2.8 (0.8)**
1 year	2.6 (2.5)	2.9 (1.3)*	2.6 (0.8)**	2.8 (0.6)**
2 years	2.6 (1.7)	2.9 (–)	2.7 (0.8)*	3.1 (3.7)
3 years	3.3 (–)	–	2.8 (1.1)*	3.7 (1.8)
4 years	3.7 (–)	–	2.8 (1.1)*	4.1 (2.3)
5 years	–	–	2.7 (1.4)*	3.7 (1.7)

PPVI = percutaneous pulmonary valve implantation; TR = tricuspid valve regurgitation velocity (m/sec).
*P - value<0.05.
**P - value<0.005, (–): not enough patients to perform statistics. RVOT: right ventricular outflow tract velocity (m/sec).

pulmonary valve implantation. There was reduction in MRI measured median right ventricular volumes following percutaneous pulmonary valve implantation, but this did not reach statistical significance (end diastolic volume 194 (110) versus 142 (80), P = 0.051 and end systolic volume 113 (117) versus 95 (56) ml/m^2, P = 0.061, N = 5).

We performed a gender-specific analysis and found no statistically significant difference between men and women on measured right ventricular outflow tract and tricuspid regurgitation velocity at any time point during follow-up (Fig. 2a). Our study seems to be well powered for this analysis as a two-armed study aimed to find a clinically significant right ventricular outflow tract velocity would need 23 patients on each arm [total of 46 patients, power: 95%, P-value: 0.05 when the clinically significant effect size of 0.5m/sec was standardised by the upper limit of the 95% confidence intervals for mean and standard deviation of right ventricular outflow tract velocity found at 2 years in the present study (2.4 and 0.47 m/sec, respectively)].

Complications

No procedural deaths or major complications occurred. One patient had perioperative severe pulmonary regurgitation during an Edwards valve balloon dilation with a high pressure balloon and underwent conduit change on the next day. One patient had minor bleeding in right ventricular outflow tract, one left pulmonary artery perforation with transient electrocardiogram changes, one minor pulmonary haemorrhage, and one developed atrial fibrillation during stenting.

Discussion

Our study reports outcomes up to five years following percutaneous pulmonary valve implantation from a mixed population of 58 adults and children using the two most common balloon expandable valves (Medtronic Melody and Edwards Sapien). To the best of our knowledge, this is the first study to perform a gender-specific analysis following percutaneous pulmonary valve implantation. This is in contrast to the extensive gender-specific research in patients following transcatheter aortic valve implantation.[15] We did not find any significant effect of gender on flow velocity across the implanted valve, tricuspid regurgitation velocity, and pulmonary regurgitation throughout the five years follow-up despite the study being well-powered to do so. There are possibly gender-specific differences on pathophysiology of valvular stenosis. The two main factors leading to restenosis are calcification and fibrosis. Studies have shown that for similar severity of aortic stenosis, women have less valvular calcification, but more fibrosis compared to men with similar aortic valve disease.[16] Animal studies have shown gender to have a significant effect on the gene expression pattern of porcine valve interstitial cells.[17] Female patients are underrepresented in research which leads to lack of gender-specific disease criteria and limited use of body surface area indexed values. This results in under-recognition of severe valvar disease, delayed referral for intervention, and worse outcomes in women.[18] This is even more important for women in childbearing ages. The significance of gender differences in patients with repaired Tetralogy of Fallot was demonstrated in a recent study, which depicted higher biventricular MRI-derived volumes and masses, indexed for body surface area, in males compared to females and highlighted the importance of gender-specific thresholds or Z-scores for decision planning of pulmonary valve replacement.[19]

The present study adds to existing evidence that percutaneous pulmonary valve implantation is an established alternative to surgical pulmonary valve replacement[2] and based on our medium-term follow-up data both valves seem equally effective in treating right ventricular outflow tract disease in both paediatric and adult patients with CHD. All patients in the pulmonary stenosis and mixed pulmonary valve disease group improved their haemodynamic profile after percutaneous pulmonary valve implantation and throughout the follow-up with a significant decrease in estimated right ventricular pressure and right ventricular outflow tract pressure gradient. This finding is consistent with previous reports.[3] Moreover, the implanted valve remains competent during mid-term follow-up with no clinically significant regurgitation. Patients with pulmonary regurgitation as indication for percutaneous pulmonary valve implantation did not have statistically significant restenosis during the five years of follow-up. This is important as replacing pulmonary regurgitation with iatrogenic pulmonary stenosis would not be ideal for the long-term health of right ventricle as previous study demonstrated both pulmonary stenosis and regurgitation to be independent predictors of right ventricular fibrosis.[20]

Restenosis independent from valve type was observed in the paediatric population three years after percutaneous pulmonary valve implantation, but not in the adult population. This can be explained as paediatric patients have smaller conduits before percutaneous pulmonary valve implantation and body growth renders the implanted valve relatively small as patients become older. The median age of our paediatric population was 13 years, which means that a large number of patients received percutaneous pulmonary valve implantation well before their growth spurt. Percutaneous pulmonary valve implantation is mainly used in the paediatric population with the overall aim to delay conduit change and spare an additional thoracotomy ideally until growth spurt finishes. Children received more often a Melody valve compared to adults as Melody valve implantation is the preferred option in our practice for smaller right ventricular outflow tract size conduits and predominantly right ventricular outflow tract stenosis, whereas Edwards valves are more often implanted in larger right

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ventricular outflow tracts with pulmonary regurgitation as an indication.[6] However, we did not find a significant difference on follow-up right ventricular outflow tract pressure gradient or tricuspid regurgitation velocity when the two valve types were compared. This is consistent with previous reports.[5,6]

We found a significant negative correlation between post implant right ventricular outflow tract and tricuspid regurgitation velocity and the implanted valve Z-score, which demonstrates that the ratio of valve size to body surface area is an important factor that should be carefully considered in percutaneous pulmonary valve implantation candidates even in adult population. Patients with right ventricular outflow tract size already small for their body size may benefit from a surgical intervention to enlarge right ventricular outflow tract to accommodate an appropriate size pulmonary valve in the following years. This approach can result in improved clinical outcomes and future percutaneous pulmonary valve implantation lasting for longer time as a post-implantation residual right ventricular outflow tract gradient > 15 mmHg is a risk factor for death and valve failure.[21]

We found a reduction in MRI measured right ventricular volumes following percutaneous pulmonary valve implantation, but this was not statistically significant possibly due to the small number of patients undergoing MRI during follow-up in our centre. However, existing evidence suggests percutaneous pulmonary valve implantation leads to right ventricular remodelling and regression of right ventricular volumes.[3,22] The improvement on reported NYHA following percutaneous pulmonary valve implantation in our population is consistent with these results. The incidence of endocarditis following percutaneous pulmonary valve implantation in our centre was similar to existing literature despite having much longer follow-up compared to most of the current reports.[2,23]

All patients had antiplatelet treatment for at least six months until when endothelisation is expected to occur.[24] However, 14% of the patients stopped antiplatelet treatment following percutaneous pulmonary valve implantation, but this did not result in any significant difference on right ventricular outflow tract flow velocity, when these patients were compared to those who continued treatment for longer than six months. There is uncertainty whether antiplatelet treatment is possibly a major contributor in post implantation valve dysfunction as current data suggest the main problem following percutaneous pulmonary valve implantation is restenosis and not regurgitation. There are no guidelines for antiplatelet treatment post percutaneous pulmonary valve implantation. A recent survey demonstrated substantial variation on clinical practice.[25] Clot formation on the surface of non-endothelialised valve leaflets is implicated on subsequent pulmonary valve dysfunction with pannus formation[26] and calcification leading to restenosis. This issue is more prominent in younger patients.[27] There is evidence that post surgical pulmonary valve replacement antiplatelet treatment is associated with lower risk of subsequent valve dysfunction.[28] Antiplatelet treatment can be more rigorous in percutaneous pulmonary valve implantation patients in comparison to surgical pulmonary valve replacement as the risk of bleeding post procedure is minimal once it is established by the final angiography an uncomplicated interventional outcome. A recent study demonstrated that oral anticoagulation was associated with significantly lower rates of subclinical leaflet thrombosis (hypoattenuated leaflet thickening, reduced leaflet motion, or hypoattenuation affecting motion) at 30 days following transcatheter aortic valve implantation compared to single or dual antiplatelet therapy, and there was no apparent benefit of dual over single antiplatelet therapy.[29] Randomised controlled trials are needed to find the best anticoagulation or antiplatelet regime in both adult and paediatric population following transcatheter valve implantation.

Limitations

This was a single centre retrospective clinical study. There was a continuous attrition of patients contributing data in the follow-up period resulting in variable number of patients contributing data in each time point and wider confidence intervals towards the end of follow-up. Another significant limitation was the small number of paediatric patients which did not allow in depth subgroup analysis. P-values were not adjusted for multiple comparisons as this was an exploratory study. Finally, the study group was anatomically and physiologically heterogeneous with mixed criteria for intervention, but all fulfilled the clinical indications for percutaneous pulmonary valve implantation.

Conclusions

In the present study, gender seems not to be a significant clinical parameter affecting valve function following percutaneous pulmonary valve implantation. However, we found a significant negative correlation between the implanted valve Z-score and subsequent right ventricular outflow tract and tricuspid regurgitation velocity during follow-up, which emphasises the importance of considering patients' age and body surface area in relation to existing right ventricular outflow tract size in the planning decisions for percutaneous pulmonary valve implantation.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951123004328.

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Competing interests. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees (Study registration number: UHL audit registration number 10,615).

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