Pure Aortic Regurgitation in Pediatric Patients

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Aortic regurgitation (AR) continues to be an important cause of morbidity and mortality in pediatric patients. Although echocardiographic parameters are well established for the adults, there are no clear cut-off values for AR severity in children. Cardiac magnetic resonance (CMR) imaging is considered a "gold standard" for a quantitative evaluation of the AR, but it is not widely available. This study assesses which echo parameter can accurately define AR severity as assessed by CMR in pediatric patients. A total of 27 pediatric patients (12 ± 3 years, range 6 to 18 years) with different degree of AR underwent echo assessment within an average of 35 days from CMR. CMR included phase-contrast velocity-encoded imaging for the measurement of regurgitant fraction (RF). Severe AR was defined as RF >33%. Echo evaluation included vena contracta, pressure half time, the ratio between the AR jet and the left ventricular outflow tract diameter (jet/left ventricular outflow tract), presence of holodiastolic reversal flow in abdominal aorta, the ratio between the velocity-time integral of the reversal flow over the forward flow in descending aorta (echoRF). Among the studied parameters, the strongest predictor of severe AR, as assessed by CMR, was echoRF. Receiver-operating characteristic curve showed, for a cut-off >0.38, an area under the curve of 0.886 ($p < 0.0001$), a sensitivity of 71%, and a specificity of 100%. Correlation coefficient between echoRF and RF was $R = 0.929$ ($p < 0.0001$). In conclusion, echoRF is a strong echo-Doppler marker of severe AR in the pediatric population. This parameter should be routinely added in the standard echo evaluation of pediatric patients with AR.

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Aortic regurgitation (AR) continues to be an important cause of morbidity and mortality,[1] also in pediatric age.[2−4] Echocardiography has a primary role in the AR evaluation[5,6]: it can describe valve anatomy, estimate the severity of the regurgitation through different semiquantitative parameters, evaluate the mechanisms of AR, determine the feasibility of valve repair. Unfortunately, for children with AR there are no well-established echocardiographic cut-off values. Cardiac magnetic resonance (CMR) imaging is the gold standard technique for evaluation of ventricular volumes and ejection fraction,[7] and it can accurately quantify AR volume and the regurgitant fraction (RF). The latter one has proved high reproducibility[8] and prognostic value; a RF >33% at CMR has been correlated with a poor outcome, identifying patients who would progress to surgery.[9,10] The aim of our study is to assess which echo parameter can accurately define AR severity as assessed by CMR in pediatric patients.

Methods

The study population was recruited from the out patients of the Royal Brompton Hospital, London (UK), from October 2016 to October 2018. We included all the patients who had CMR for either congenital or acquired aortic valve regurgitation (the reason to perform CMR was the assessment of valve regurgitation, ventricular volumes, and ventricular function or a concomitant cardiovascular disease). Exclusion criteria were age >18 years, aortic valve stenosis, poor image quality echo studies for either extremely uncooperative patient or bad acoustic window. Parental and patient informed consent was obtained.

CMR was performed using a 1.5T CMR scanner (Avanto; Siemens Medical Systems, Erlangen, Germany). Phase-contrast velocity-encoded sequence was acquired perpendicular to the ascending aorta at the sinotubular junction. The CMR protocol included sequences to determine the configuration of the aortic valve, quantification of biventricular volumes, ejection fraction, and myocardial mass. Aortic RF was calculated by dividing reverse flow volume by forward flow volume at the sinotubular junction. Breath hold sequences were used for both phase-contrast velocity-encoded and cine sequences. All CMR analyses were performed offline, using validated software (cmr42, Circle Cardiovascular Imaging Inc., Canada). In the present study, a RF >33% was considered the cutoff for severe AR.[9,10]

Echocardiographic examinations were performed using E9 and E95 (GE Vingmed Ultrasound AS, Horten, Norway) and Epiq 7 (Philips Electronics Nederland B.V.) machines. Offline analysis was performed using McKesson Cardiology 13.0 software (McKesson Europe AG). An experienced pediatric echocardiographer performed the analysis, blind to the CMR results.

AR was assessed by multiple echo-Doppler parameters. The diameter of the regurgitant jet in relation to the left ventricular outflow tract diameter (jet/LVOT) and the smallest

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width of the regurgitant jet at the valvular level, the vena contracta (VC), were measured in the parasternal long-axis view. Pressure half time (PHT) was measured by continuous wave Doppler in apical 5-chamber view. The blood flow in the descending aorta was assessed from suprasternal view by pulsed wave Doppler: the velocity-time integral (VTI) of the anterograde flow and the VTI of the reversal flow were measured at the isthmus level, and then the ratio between them calculated (echoRF: VTI descending aorta reversal flow/VTI descending aorta anterograde flow, Figure 1). The presence of holodiastolic reversal flow in descending aorta and in abdominal aorta was assessed. Left ventricular (LV) size, LV end-diastolic and end-systolic diameters, end-diastolic and end-systolic volumes indexed to body surface area, and biplane ejection fraction, were measured.

All analyses were performed using MedCalc for Windows release 11.3.3.0 (MedCalc Software, Mariakerke, Belgium). The distributions of continuous parameters were determined using the D'Agostino-Pearson test. Parameters with normal distributions are expressed as mean ± standard deviation, and those with non-normal distributions are expressed as median (interquartile range). The correlation coefficient was calculated to measure the strength of the linear relation between continues variables. Receiver-operating characteristic curve analyses were performed to determine the area under the curve (AUC) for independent risk factors detected by ascendant stepwise logistic regression, and optimal cutoffs were selected by optimizing sensitivity plus specificity.

For reproducibility analysis, Bland-Altman plot and intraclass correlation coefficient was performed in 10 randomly selected patients, and the mean difference between observers and 2-sided 95% limits of agreement were calculated. The null hypothesis was rejected for a p value <0.05.

Results

Twenty-seven patients, age range 6 to 18 years, 21 male children, with AR formed our study cohort. General characteristics of the studied population and CMR's data are presented in Table 1. Echocardiography was performed within an average of 35 days from CMR. There was no change of therapy between echo and CMR study, and heart rate and arterial blood pressure were comparable between the studies. Of the studied patients, 22 had a bicuspid aortic valve, 13 had a dilated ascending aorta. There was no statistical difference between left ventricle ejection fraction as assessed by echocardiography versus CMR (respectively 65 ± 5% and 66 ± 5%, p = 0.390). Comparing the LV ejection fraction of patients with RF >33% and <33%, no difference was found neither by echocardiography (respectively 63 ± 7% and 66 ± 4%, p = 0.115) nor by CMR (respectively 65 ± 8% and 67 ± 4%, p = 0.359). There was a strong correlation between the ventricular volumes assessed by echocardiography and by CMR (end diastolic volume: R = 0.868, p <0.0001; end-systolic volume: R = 0.827, p <0.0001), although on average the echo values were significantly lower than the CMR values (end-diastolic volume: echo = 81 ± 31 ml vs CMR = 143 ± 50 ml, p <0.0001; end-systolic volume: echo = 28 ± 12 ml vs

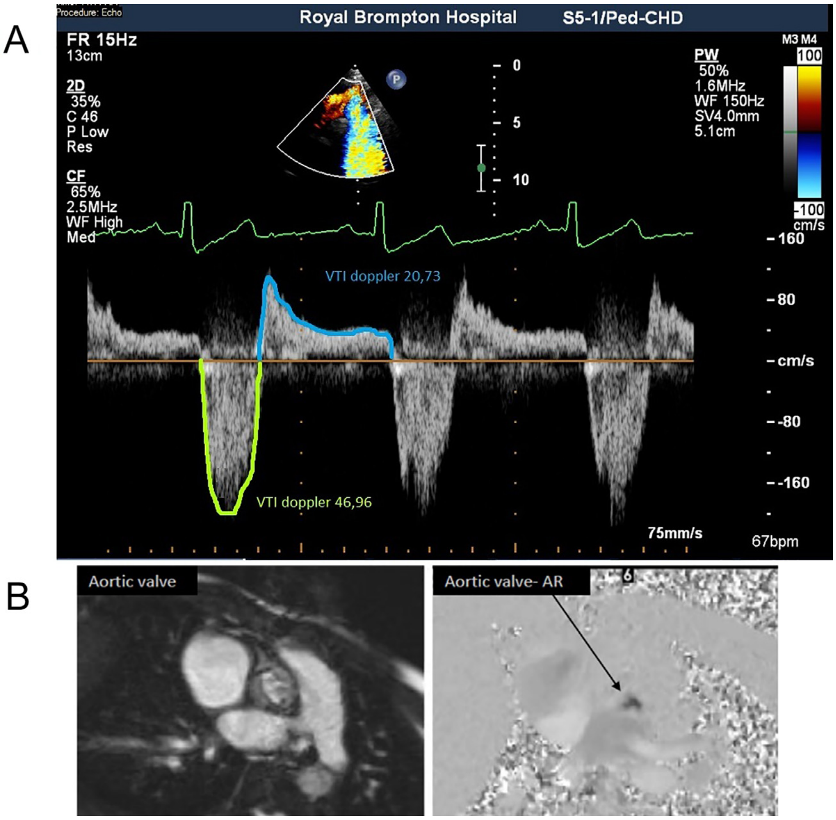

Figure 1. (*A*) echoRF is calculated as the fraction between the VTI of the reversal and the anterograde flow in descending aorta. (*B*). CMR images of the aortic valve and AR in the same patient. AR = aortic regurgitation; CMR = cardiac magnetic resonance; VTI = velocity-time integral.

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Table 1
General characteristics of the studied population and cardiac magnetic resonance's data

Patient	Age (years)	Sex	Height (m)	Weight (kg)	Body surface area (m^2)	Body mass index (kg/m^2)	End diastolic volume (ml)	End-systolic volume (ml)	Ejection fraction (%)	Stroke volume (ml)	Mass (g)	Regurgitant fraction (%)
1	6	M	1.20	19	0.81	13	73	15	80	58	55	30
2	7	M	1.30	28	1.01	17	92	29	69	63	88	33
3	7	M	1.25	25	0.93	16	71	23	68	48	50	1
4	8	M	1.21	34	1.04	23	95	27	72	68	61	2
5	8	M	1.29	26	0.97	16	57	21	62	35	55	6
6	9	M	1.42	34	1.17	17	110	36	67	74	75	17
7	9	M	1.35	29	1.05	16	81	26	68	55	53	24
8	10	M	1.50	40	1.30	18	133	33	75	100	117	44
9	10	F	1.55	40	1.33	17	139	43	69	96	109	21
10	10	M	1.30	20	0.87	12	108	32	71	77	95	33
11	11	F	1.39	40	1.23	21	109	33	70	76	65	5
12	12	M	1.51	53	1.48	23	172	71	59	101	103	22
13	12	M	1.65	38	1.37	14	190	88	54	102	81	37
14	12	M	1.48	38	1.26	17	132	42	68	90	92	23
15	12	F	1.65	53	1.57	19	152	44	72	110	97	37
16	13	M	1.70	90	2.01	31	147	34	77	113	91	25
17	13	M	1.69	60	1.69	21	209	44	79	165	160	20
18	13	M	1.74	58	1.70	19	215	81	62	73	88	45
19	14	M	1.72	56	1.66	19	170	60	65	110	174	30
20	14	M	1.78	78	1.96	25	161	47	71	114	142	2
21	15	M	1.64	52	1.55	19	185	73	60	112	126	9
22	15	M	1.90	65	1.90	18	136	52	62	84	132	2
23	15	F	1.65	61	1.67	22	188	61	68	127	119	22
24	16	M	1.75	67	1.81	22	252	90	64	162	156	29
25	16	F	1.65	52	1.56	19	114	35	69	79	100	5
26	16	M	1.78	68	1.85	21	166	53	68	113	117	5
27	18	F	1.63	64	1.69	24	199	89	55	110	62	33

F = female; M = male.

CMR = 48 ± 22 ml, $p < 0.0001$). In the studied cohort, the average RF was 21 ± 14% (range 1% to 45%). A RF value >33% was found in 7 patients (26%).

The presence of holodiastolic reversal flow in descending aorta was identified in 13 patients (48%). The average RF for these patients was 32 ± 8%, compared with an average RF of 9 ± 8% in the patients without holodiastolic reversal flow in descending aorta (p value <0.0001). Among the patients with holodiastolic reversal flow in descending aorta, 6 (46%) had a RF >33% at CMR assessment (sensitivity of 86% and a specificity of 65%). The holodiastolic reversal flow in abdominal aorta was present in 6 patients (22%). The average RF for these patients was 35 ± 8%, compared with an average RF of 17 ± 12% in the patients without holodiastolic reversal flow in abdominal aorta (p value <0.0001). Between patients with holodiastolic reversal flow in abdominal aorta, 4 (67%) had a RF >33% at CMR assessment (sensitivity of 57% and a specificity of 90%).

Among all the studied quantitative echo-Doppler parameters, the best correlation with RF at CMR was found by echoRF ($R = 0.929$, $p < 0.0001$). The other echo parameters showed a good correlation with RF measured by CMR [PHT ($R = -0.832$, $p < 0.0001$); VC diameter ($R = 0.822$, $p < 0.0001$); jet/LVOT ($R = 0.823$, $p < 0.0001$)]. To identify the best cut-off value for echoRF, a receiver-operating characteristic curve analysis was performed. For a cut-off value >0.38 an AUC 0.886, $p < 0.0001$, with a sensitivity of 71% and a specificity of 100%, was found (Figure 2). The other studied quantitative echo-Doppler parameters showed a smaller AUC (PHT cutoff <407 ms, AUC 0.857, $p < 0.0001$, sensitivity 86%, specificity 70%; VC cutoff >4 mm: AUC 0.793, $p = 0.0005$, sensitivity 71%, specificity 75%; a jet/LVOT cutoff >0.35: AUC 0.793, $p = 0.002$, sensitivity 71%, specificity 85%).

For reproducibility analysis, Bland-Altman plot was performed: the mean difference for echoRF between observers was −0.02 (95% confidence interval [CI] −0.11 to 0.06), for VC was −0.1 (95% CI −2.2 to 2.1), for jet/LVOT was −0.06 (95% CI −0.16 to 0.05), for PHT was −29 (95% CI −229 to 171). The intraclass correlation coefficient for interobserver reproducibility for echoRF was 0.966 (95% CI 0.863 to 0.992), for VC was 0.769 (95% CI −0.737 to 0.893), for jet/LVOT was 0.905 (95% CI 0.618 to 0.976), for PHT was 0.533 (95% CI −1.282 to 0.859). The intraclass correlation coefficient for intraobserver reproducibility for echoRF was 0.971 (95% CI 0.882 to 0.993), for VC was 0.719 (95% CI −0.938 to 0.880), for jet/LVOT was 0.936 (95% CI 0.741 to 0.984), for PHT was 0.568 (95% CI −1.142 to 0.868).

Discussion

Management of AR in pediatric age is still a challenge and recommendations are much less evidence based than in adults, without any pediatric-specific cut-off value for AR severity by echocardiography.[11,12] Although echocardiography has demonstrated to be the key technique to diagnose AR, semiquantitatively assessing its severity and providing prognostic information,[6] the use of CMR to evaluate pediatric patients with AR is becoming more and more frequent,

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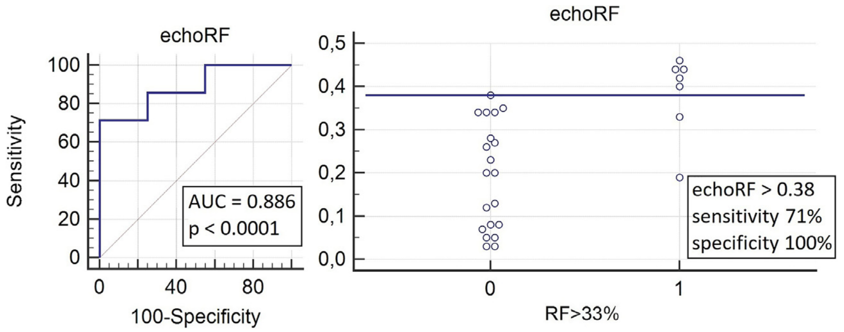

Figure 2. echoRF: ROC curve analysis identifies, for a cut-off value >0.38, an AUC of 0.886, with a sensitivity of 71% and a specificity of 100%. AUC = area under the curve; RF = regurgitant fraction; ROC = receiver-operating characteristic.

for its ability to give quantitative and reproducible parameters, such as AR RF[8] and LV volumes and ejection fraction. However, the systematic use of CMR is limited by the cost, growing but still limited availability, long acquisition and postprocessing time, the need of general anesthesia (in patients younger than 8 years), and frequent poor cooperation even in older children.

Previous studies in young patients have investigated the power of CMR's parameters to correlate with the severity of AR as assessed by echo with rather conflicting results. Kutty et al[13] showed in a population of 43 patients, including children and young adults (mean age 13 ± 5 years, age range not stated) how the subjective estimation of AR by echo often does not correlate well with CMR's RF. Ley et al[14] demonstrated on 30 young patients (mean age 14 ± 6 years, range 3 to 28 years) a good correlation (R = 0.7) between aortic valve RF calculated by echo versus that measured by CMR, although the absolute values were different between the 2 modalities. To the best of our knowledge, this is the first study to investigate, in a pediatric population (≤18 years), how objective echo-Doppler parameters for the assessment of AR correlates with the RF calculated by CMR.

The comparison between echo-Doppler parameters used to assess AR and CMR's AR RF showed an acceptable correlation, only echoRF demonstrated a strong correlation with CMR RF (R = 0.929, p <0.0001). For the studied AR parameters, we also provided a cut-off value specific for the pediatric population. This is of interest, because the cut-off values generally reported in the literature refer only to the adult population.

The presence of holodiastolic reversal flow in descending or in abdominal aorta showed a discrete ability to predict an AR RF >33% at CMR assessment, with the first showing a good sensitivity (86%) and the second one demonstrating a high specificity (90%), in agreement with previous studies.[8,15] This is not surprising since the presence of reversal flow in descending aorta, per se, being closer to the aortic valve, is more sensitive but less specific for severe AR than reversal flow in abdominal aorta. Our findings confirm that only when the amount of reversal flow in descending aorta reach a certain value (>0.38 compared with the forward flow) it becomes a marker of severe AR.

The reproducibility analysis showed the lowest interobserver variabilities for echoRF, with better results compared with VC, PHT, and jet/LVOT. These results suggest that echoRF can be a reliable parameter in the clinical practice.

In addition, our study confirms that also in pediatric population LV volumes obtained by echocardiography are strongly correlated by those obtained by CMR. However, they cannot be used interchangeably because echocardiography systematically underestimates volumes compared with CMR.

Our study carries several limitations. First, our findings need to be confirmed in larger sample studies. However, considering previous studies on the same topic,[13,14] our study includes the largest pediatric sample. The average interval between the echocardiography and CMR assessments was 35 days in our study. However, there was no significant difference in terms of blood pressure, heart rate, medications and clinical status between the 2 exams. We did not include proximal isovelocity surface area-derived parameters in our echo evaluation because, in our clinical practice, proximal isovelocity surface area parameters are not routinely assessed because of high interobserver variability.

Our findings demonstrated that echoRF >0.38 at echo Doppler assessment strongly correlated with a RF >33% as assessed by CMR in a pediatric cohort. This simple parameter demonstrated a very good reproducibility and should be added in the routine standard echo-Doppler evaluation of pediatric patients with AR. Based on our findings we suggest to perform CMR in AR patients when echoRF is >0.38, when the amount of LV dilatation does not match the degree of AR as assessed by echo, or when there is any discrepancy between clinical and echo findings suggesting a more severe disease than that showed by echo.

Disclosures

The authors have no conflicts of interest to disclose.

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