Cardiology in the Young

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Echocardiographic examination of mitral valve abnormalities in the paediatric population: current practices

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Review Article

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Abstract

We reviewed the recent literature for echocardiographic assessment of mitral valve abnormalities in children. A literature search was performed within the National Library of Medicine using the keywords "mitral regurgitation and/or stenosis, children." The search was refined by adding the keywords "echocardiographic definition, classification, and evaluation." Thirty-one studies were finally included. Significant advances in echocardiographic imaging of mitral valve defects, mainly due to the implementation of three-dimensional technology, contribute to a better understanding of the underlying anatomy. However, heterogeneity between classification systems of mitral valve disease severity is a serious problem. For regurgitant lesions, there is only very limited evidence from small studies that support the adoption of quantitative/semi-quantitative indexes commonly employed in adults. Despite the lack of evidence base, qualitative evaluation of regurgitation severity is often employed. For stenotic lesions, no clear categorisation based on trans-valvular echocardiography-derived "gradients" has been consistently applied to define mild, moderate, or severe obstruction across different paediatric age ranges. Quantitative parameters such as valve area have also been poorly validated in children. Adult recommendations are frequently applied without validation for the paediatric age. In conclusion, significant advances in the anatomical evaluation of mitral valve diseases have been made, thanks to three-dimensional echocardiography; however, limitations remain in the quantitative/semi-quantitative estimation of disease severity, both with respect to valvular regurgitation and stenosis. Because adult echocardiographic recommendations should not be simply translated to the paediatric age, more specific paediatric guidelines and standards for the assessment of mitral valve diseases are needed.

Mitral valve diseases are common at all ages,[1–3] including children.[4–42] In the paediatric age group, mitral valve diseases may be congenital or acquired and may present either in isolation or within the context of other congenital heart lesions. Significant anomalies of the mitral valve account for 0.4% of CHDs; however, minor anomalies of the mitral valve may be detected in up to 4% of school-aged children.[8–19,43–50] Echocardiographic evaluation of mitral valve diseases in the paediatric age group requires a careful sequential analysis of multiple valvular elements (annulus, leaflets, chordae, inter-chordal space, and papillary muscles) and knowledge of anatomical variants and of associated CHD. Beside the anatomical analysis, a quantitative and semi-quantitative evaluation of disease severity (i.e. the grade of stenosis and/or regurgitation) is also required. Guidelines for the management of valvular heart disease in adults have recently been revised,[1–3] but their utility in children (from 0 to 18 years of age) has been poorly evaluated. Currently, in children, there is no standardised approach for the echocardiographic quantitative and or semi-quantitative echocardiographic assessment of mitral valve disease and no validated classification of their severity of stenosis or regurgitation in children exists. Parameters and cut-off values used in adults have been applied to children[4–6] without any validation. There are many factors in the child with CHD which complicate reliable quantitative assessment of atrio-ventricular valve stenosis or regurgitation. These include (1) the massive range of body size negating the use of "cut off values" with respect to, for example, valve area or effective regurgitant orifice area; (2) the diversity of morphology even within a single valve

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category which may impact the shape and location or regurgitant zones; (3) changes in myocardial function with age which may impact on Doppler – derived gradients across valves; (4) the impact of changes of heart rate with age/growth which may lead, for example, to fusion and summation of inflow velocities; (5) indexation of any values such as valve area or effective regurgitant orifice area for body size (e.g. how to do?); (6) impact of intra-cardiac shunts on volume flow or flow redistribution within/outside the heart.

Over the past decade, the introduction and refinement of three-dimensional echocardiographic techniques means that real-time techniques can be applied to great en face views of the mitral valve to measure parameters such as annulus size and shape, valvar area, and the size and shape of regurgitant jets.[46]

The aim of the present work is to review the current literature on paediatric mitral valve disease, focusing on the heterogeneity, limitations of current echocardiographic classification systems, and the lack of robust quantitative or semi-quantitative criteria for mitral stenosis and regurgitation quantification. The potential for new three-dimensional techniques will be also addressed.

Methods

Search strategy

Potential publications were identified from a systematic search in the National Library of Medicine (PubMed access to MEDLINE citations, http://www.ncbi.nlm.nih.gov/PubMed/) conducted in April 2018. The search strategy included a mix of MeSH and free text terms for the key concepts starting from *mitral, stenosis, and regurgitation in children*. The search was further refined by adding the keywords *echocardiographic definition, classification, or evaluation*. In addition, we identified other potentially relevant publications using a manual search of references from all eligible studies and review articles as well as from Science Citation Index Expanded on Web of Science. Titles and abstracts of all articles identified by this search strategy were evaluated, and manuscripts were excluded if (a) the study population involved mixed adult and paediatric populations; (b) used definitions or classification systems that were not based on echocardiographic parameters; (c) written in a language different from English; (d) involved neonatal critical diseases, as these lesions represent a different category of valvular heart disease; and (e) the study involved mitral valve (left atrioventricular valve) in the univentricular heart. Finally, analysis of rheumatic mitral valve disease was excluded as it was beyond the scope of this search. The review focuses on articles reporting quantitative and semi-quantitative methods for mitral valve stenosis and regurgitation quantification. All articles were assessed independently by two reviewers and included into the study after consensus was reached.

Results

Search results

Out of 75 publications identified for potential inclusion into the study, 44 (58.6%) studies were excluded based on the criteria listed above, while 31 (41.4%) were finally selected for analysis and the following systematic review.

Methodological limitations

Limitations in methodology were seen in most of the studies. Several reports presented data on only a limited number of healthy control subjects, and some described findings in children from infants to teenagers with total sample sizes less than 50 subjects.[28,29,31] This makes it impossible to create size or age specific normal ranges. Because of the absence of a standardised methodology based on expert consensus to measure valvular gradients and severity of regurgitation in the paediatric population, all studies used different approaches. Systems to classify mitral stenosis severity have been rarely reported, and when employed[10,12] different cut-off values have been used to define mild, moderate, and severe stenosis. For regurgitant lesions, variable echocardiographic views (four-chamber and/or parasternal views)[29–31] and parameters to evaluate disease severity (i.e. proximal isovelocity surface area or vena contracta) have been used. In addition, few studies addressed technical issues[2,3,43,44] related to settings on the echocardiographic systems (such as image and colour gain as well as the Nyquist limit for Doppler interrogation).

General principles

For stenotic lesions, the "ideal" echocardiographic evaluation should provide the following information: (1) valvular anatomy; (2) quantitative parameters such as trans-valvular pressure gradient, orifice area, and annular diameter; (3) semi-quantitative assessment of the left ventricle, right ventricle, left atrium, and right atrium (i.e. diameters, volumes, left ventricle wall thickness and/or mass, and systolic and diastolic function; and (4) associated CHDs. Similarly, evaluation of regurgitant lesions should include both qualitative and quantitative assessment of the regurgitant jet.

The diagnosis of mitral valve defects is generally made by transthoracic two-dimensional echocardiography.[1–4] Other modalities including three-dimensional[43–47] and trans-oesophageal echocardiography may provide additional information to guide management.[8,9]

Anatomical evaluation. A detailed anatomical description of the stenotic and/or insufficient mitral valve anatomy and its apparatus is required through a segmental approach of the supra-valvular region, annulus, leaflets, commissures, chords, and papillary muscles.[8,9,43–48] In mitral valve defects in fact usually all the components of the mitral valve apparatus (e.g. supra-valvular, annular, and sub-valvular region) may take part in the lesion.[8,9,43–48] The supra-valvular region should be explored in order to detect the presence of a mitral ring, an anomaly that usually present in association with left-sided obstructive lesions.[8,9,43–46] The size of the annulus (that may be hypoplasic or dilated) needs to be carefully evaluated and compared with range of normality according to paediatric nomograms.[8,9,15] Leaflets may present various anomalies including thickness, dysplasia, deficiency, underdevelopment, cleft, motion abnormalities (restriction or prolapse regarding one or more scallops or the entire area), and presence of accessory tissue.[8,9,43–48] The commissures furthermore may be underdeveloped or absent.[8,9,43–48] Attachment and anatomical detail of tendinous chordae (thickening, shortening versus elongation, intracordal spaces obliteration/fusion) also need to be evaluated.[8,9,43–48] Finally, the detailed papillary muscles anatomy should be assessed for their number, size, and location, regarding hypertrophy/hypoplasia, agenesis, fusion, elongation, and position/symmetry (e.g. location higher in the left ventricle) (Tables 1 and 2).[8,9,43–48]

Specific lesions

Congenital mitral valve defects

Various anatomical and functional classification systems have been used to describe congenital mitral valve defects[8,9,11–14] according

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Table 1. Congenital MV disease: major classification systems proposed in literature

Author	Sample size	Study design	Classification proposed
MR and MS			
Seguela[9]	29 (<2 years)	Surgical plus autopsy series	Group 1: Leaflets anomalies: supra-valvular ring, mitral cleft, accessory orifice MV, accessory mitral valvular tissue, Ebstein's malformation of inverted tricuspid valve
			Group 2: Anomalies involving the commissures
			Group 3: Anomalies involving the chordae tendineae (short chordae, long chordae)
			Group 4: Anomalies involving the papillary muscle (mitral arcade, parachute MV), abnormal position of papillary muscles, obstruction by abnormal papillary muscle
			Group 5: Anomalies involving more than one apparatus
			Group 6: Acquired anomalies (infarction of papillary muscle)
Carpentier 1976[11]	47 (0–12 years)	Surgical series	Group 1: MR due to valvular lesion (annular dilatation, cleft leaflet, leaflet agenesis)
			Group 2: MR with sub-valvular lesion (chordae agenesis or retraction, chordae elongation, papillary muscle agenesis or hypoplasia, prolapsed papillary muscle due to elongation/abnormal insertion)
			Group 3: MR and MS: commissural fusion, Hammock valve, parachute valve, hypertrophic papillary muscle
			Group 4: MS (commissure fusion, Hammock, Parachute valve, funnel-shaped)
Mitruka[13]	–	Congenital heart surgery and database project	(1) Haemodynamic: MR, MS, or mixed
			(2)Segmental
			Supra-valvular (mitral ring)
			Valvular (A: annular; B: leaflet)
			Sub-valvular (A: chordal; B: papillary muscle)
			Mixed
Oppido[14]	71 (0–20 years)	Surgical series	(1) Haemodynamic: predominant MR or MS
			(2) Functional (like Carpentier): (i) normal leaflet motion, (ii) leaflet prolapse; (iii) restricted leaflet motion
			(3) Leaflet: (i) dysplastic (usually lack of valvular tissue), (ii) non-dysplastic (with annular dilation, with or without elongation of the chordae or the papillary muscle)
			(4) Fusion of papillary muscles commissure, arcade (Hammock) MV, and parachute MV
Baird et al.[48]	Review		Anatomic/morphologic classification
			Shortened chordae tendineae
			Reduction in inter-chordal space and intra-papillary muscle distance
			Hypoplastic complex malformation syndrome (e.g. HLHS)
			Supra-mitral ring
			Parachute MV
			Functional classification
			Type A (normal papillary muscle)
			Supra-valvular ring
			Leaflet fusion
			Type B (abnormal papillary muscles)
			Parachute deformity
			Primary papillary muscle abnormality

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Table 1. (*Continued*)

Author	Sample size	Study design	Classification proposed
MS			
Seguela[9] Severe congenital MS in infants	85 (0–2 years)	Echo/surgery	Group 1: Typical hypoplastic MV (defined as hypoplastic MV and apparatus with short chordal attachments to small, symmetric, closely spaced papillary muscles)
			Group2: Atypical hypoplastic MV (defined as hypoplastic MV with short, unbalanced chordal attachments to either a predominant antero-lateral or posterior-medial papillary muscle)
			Group 3: Parachute MV
			Group 4: Supra-mitral ring
			Group 5: Double orifice
Collins-Nakai[12]	38 (0–12.5 years)	Echo/surgery/autopsy series	Group 1: Isolated MV disease
			Group 2: Supra-valvular mitral ring ± other CHDs
			Group 3: MS + left to right shunt and/or another left-sided lesion, 4) MS + tetralogy of Fallot
Seguela[9]	49 (0–28 years)	Autopsy series	Group 1: Typical congenital MS with short chordae tendineae, obliteration of inter-chordal spaces, and reduction of inter-papillary distance
			Group 2: Hypoplastic congenital MS (almost always associated with HLHS)
			Group 3: Parachute MV
			Group 4: Supra-mitral ring
MR			
Carpentier 1998[11]	145 (0–12 years)	Surgical series	See above

HLHS = hypoplastic left heart syndrome; MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve.

to the predominant lesion,[11] associated lesions,[12] segmental approach,[13,14] hemodynamic evaluation (predominant mitral regurgitation or stenosis),[13,14] functional analysis (leaflet prolapse/restricted leaflet motion),[14] and presence/absence of leaflet dysplasia.[14] The presence of "non-classic" forms of mitral valve disease that are frequently encountered and the overlapping of some lesions that classically have been considered as distinct entity may at least in part explain these discrepancies in the classification systems.[8,9,43–48] In Table 1, an overview of major classification systems published so far for congenital mitral stenosis has been reported, while in Table 2 a summary of the definitions and anatomical substrates of various congenital mitral defects has been provided (Table 2).

Mitral stenosis

Mitral valve stenosis rarely occurs as an isolated congenital defect. It presents more commonly as an acquired lesion, or in association with multi-level left heart hypoplasia or other CHDs.[8,9,43–47] Most complex congenital mitral defects including double orifice mitral valve,[8,9,44–46] supra-mitral ring,[48] mitral arcade,[9,44] and parachute mitral valve[9,44] are typically associated with mitral valve stenosis.

Quantitative evaluation. In adults, cut-off values for various parameters are used to define mild, moderate, and severe mitral stenosis including the mean trans-valvular gradient (<5, 5–10, >10 mmHg), pulmonary artery systolic pressure (<30, 30–50, >50 mmHg), and valve area (>1.5, 1.0–1.5, <1.0 cm^2).[2] No parameters for the echocardiographic quantification of mitral stenosis severity have been fully validated for a paediatric population,[6] and only a few paediatric works proposed mitral valve stenosis classifications according to gradients derived either by pulsed Doppler[10] or cardiac catheterisation.[12] The range of gradients proposed to define mild, moderate, and severe mitral stenosis, however, is very discordant by publication[10,12] and differs from adult recommendations (Table 3).[6] In children, quantitative estimation of mitral valve stenosis includes at least the evaluation of trans-valvular pressure gradient, orifice area, and annular diameter.[6] All these parameters, however, are affected by significant physiologic variations with growth, and thus cut-off values to estimate disease severity (if applicable) should be modulated according to age and body size. The impact of other co-existent shunts (e.g. ventricular septal defects which may increase trans-mitral flow, or atrial septal defects which may reduce mitral valve flow by permitting shunting to the right atrium) also needs to be considered. The Doppler velocity time integral of the inflow tracing from mitral valve inflow velocity waves is commonly employed to estimate the mean gradient. However, studies comparing the accuracy of gradient estimated at echo with those derived from invasive assessment are limited.[6,10] Banerjee and colleagues,[10] in 14 children (0–18 years) with congenital mitral valve stenosis of various nature, demonstrated fair correlation (r = 0.75) between mean mitral valve pressure gradient obtained by Doppler and cardiac catheterisation. In contrast,[10] the correlation between the mitral valve areas calculated by the Doppler pressure half-time method and by the Gorlin formula was poor (r = 0.57).

Theoretically, velocity time integral should be evaluated with reference to normative data, considering that mitral valve velocity waves profiles change with age.[51] The peak blood flow early diastolic velocity (E wave) increases up to 5 years of age and stabilises thereafter (with little age variations),[51] while the peak blood flow in late diastolic velocity (A wave) increases within the first 12 months

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Table 2. Congenital mitral valve disease: definition, anatomical and echocardiographic detail, and associated anomalies. Authors' summary

	Definition	Anatomical/echocardiographic characteristics/differential analysis	Associated anomalies
	Predominant MS		
Mitral ring	Supra-mitral ring is a fibrous membrane originating just above the MV annulus usually not adherent to the leaflet and associated with normal sub-valvular apparatus The intramural ring thin membrane located within the two leaflets of the MV, adherent to the leaflets and usually present in association with abnormal sub-valvular apparatus	Can be differentiated by cor triatriatum, since in the latter the membrane is between the level of the LA appendage and the pulmonary veins, while in supra-mitral ring the membrane is beneath the LA appendage The ring may be complete or partial and usually create a stenosis to the flow at various degrees that tend to be progressive	Often plus parachute MV Shone complex, ventricular septal defect, obstructive left-sided lesions
Double orifice mitral valve	An accessory bridge or limbs of tissue partially or completely divide the MV orifice into two orifices that usually are of different sizes Type 1: the incomplete bridge type (characterised by a small stand of tissue that connects the anterior and posterior leaflets) Type 2: the complete bridge type (a fibrous bridge tissue completely divides the mitral orifice from the leaflet edge to the annulus) Type 3: the hole type (a secondary orifice with sub-valvular apparatus is present in the lateral commissure of the MV)	Can be differentiated from duplicate MV (two distinct MV annuli and valvular apparatus) Two echo signs are characteristic: The presence of two circles opening in diastole (SA view) The visualisation of two jets of antegrade flow through the MV	Obstructive left-sided lesions and cyanotic CHD
	Both MR and MS		
Mitral arcade or Hammock valve	Anomalous connection of the LV papillary muscles to the MV leaflet, either directly or through the interposition of unusually short tendinous chords	Thickening of the leaflets and shortening and thickening of tendinous chordae PM resembles two pillars with a bridging fibrous tissue in between the papillary muscles (when the space between the abnormal chordae is completely obliterated) Echo short chordae, restricted leaflet movement with limited coaptation and multiple jet through reduced intracordal spaces	Obstructive left-sided CHD
Parachute MV	Insertion of usually shortened, thickened, and often fused chordae into a single papillary muscle	Intracordal spaces are partially or completely obliterated, commissures are often underdeveloped, and the leaflets may be dysplastic or deficient Single papillary muscle Echo: Single papillary muscle may be seen in SA view, while in four-chamber view a pear shape of the MV may be seen (with LA forming the base and the leaflets the apex)	Supra-mitral ring, sub-aortic obstruction, and coarctation of the aorta (often in Shone's complex)
Parachute-like form	See above	One PM is dominant and receives the majority of tendinous chords (classical posterior-medial) and the other muscle is hypoplastic, elongated, located higher in the LV with its tip reaching to the annulus, and is attached at both its base and lateral side to the LV wall	See above
	MR predominant		

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Table 2. (*Continued*)

	Definition	Anatomical/echocardiographic characteristics/differential analysis	Associated anomalies
Isolated cleft	Cleft usually located at the level of the anterior leaflet (more rarely in the posterior leaflet at P2 scallop)	Isolated MV cleft versus AVSD	
		In isolated MV cleft, the cleft is typically directed towards the insufficiency jet appear to point the left ventricular outflow tract. In contrast, the zone of apposition between the bridging leaflets is directed towards to those of AVSD that point at the interventricular septum; the position of papillary muscle furthermore is rotated counterclockwise in AVSD while in isolated cleft is generally normal	
		In AVSD, there is no posterior MV leaflet but a mural leaflet which is usually triangular-shaped, unlike cleft MV where the posterior MV leaflet generally retains its crescentic shape	
		Furthermore, in AVSD, the "cleft" extends right to/across the ventricular septum via bridging leaflets, and in a true "cleft" MV, the cleft typically does not extend through the entire leaflet	
Mitral Ebstein's like anomaly	Downward displacement of the posterior valve leaflet (and MV orifice) into the LV	Unlike tricuspid valve Ebstein's malformation, the atrialised portion is not thinned	
Mitral valve prolapse	Systolic billowing of 1 or both mitral leaflets into the LA ± mitral insufficiency Can be familial or non-familial	There is intracordal hooding due to leaflets redundancy, leaflets fibrosis, thinning e/or elongation of chordae tendinea and friction rub	Tricuspid regurgitation, atrial septal defect, supra-ventricular arrhythmias (due to the left-sided atrio-ventricular bypass); fibrin deposit at the MV–LA angle

AVSD = atrio-ventricular septal defect; MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve; LA = left atrium; LV = left ventricle; SA = short axis.

Table 3. Cut-off employed to define mitral stenosis severity in different studies.

	Method	Population	Mild	Moderate	Severe
Banerjee et al.[10]	Pulsed Doppler	Nr 65 Age 0–18 years	Peak gradient 8–10 mmHg	Peak gradient 11–15 mmHg	Peak gradient >15 mmHg
Collins et al.[12]	Cath gradient	Nr 38 pts	Peak gradient	Peak gradient	Peak gradient
		Age:0–15 years	7–15 mmHg	16–25 mmHg	>25 mmHg
Adult recommendations[6]					
Valve area (cm^2)			>1.5	1.5–1.0	>1.0
Mean gradient (mmHg)			<5	5–10	>10
Pulmonary pressure (mmHg)			<30	30–50	>50

but decreases thereafter. Paediatric nomograms for mitral valve velocity time integral, however, are absent. Furthermore, mitral valve inflow flow velocities are dependent on the diastolic filling period and can be augmented by faster heart rates in infants and children (particularly in the neonatal age)[44] that remain a major issue.[6,10] Recently, z scores for prosthetic mitral valve have been proposed[52] for various indexes including peak E velocity (m/s), mean pressure gradient, velocity time integral ratio of prosthetic mitral valve inflow to left ventricular out flow body surface area-indexed effective orifice area (cm^2/m^2), and pressure half time. However, these z scores have been built by using a very small sample size (e.g. 24 examinations performed at various times in 12 children (age 6.6–18.1 years)).[52]

Measurements of the annulus are quite reproducible by two-dimensional echocardiography and robust nomograms are available.[53] In contrast, mitral valve area can be assessed by two-dimensional echocardiography; however, validation with invasive catheterisation measurements has shown contrasting results[10,24] and nomograms are limited.[4] Furthermore, congenital mitral stenosis often includes multi-level obstruction and thus the narrowest point may be above the annulus (e.g. supra-mitral l ring) or at a lower level (funnel-shaped mitral valve). In this context,

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Table 4. Adult recommendations to quantify mitral regurgitation severity

	MR mild	MR moderate	MR severe
Qualitative			
Valve morphology	Normal/abnormal	Normal/abnormal	Flail leaflet/ruptured PM/large coaptation defect
Colour flow regurgitant jet	Small, central	Intermediate	Very large central jet or eccentric jet adhering, swirling and reaching the left atrial posterior wall
CW signal of regurgitant jet	Faint/parabolic	Dense/parabolic	Dense/triangular
Other	No or small flow CZ		Large flow CZ
Semi-quantitative			
Vena contracta width (mm)	<3	3–7	≥7 (>8 for biplane)
Upstream vein flow	Systolic dominance	Systolic blunting	Systolic pulmonary vein flow reversal
Inflow	A wave dominant	Variable	E-wave dominant ≥ 1.5 m/s^2
Other	TVI MV/TVI Ao<1	Intermediate	TVI MV/TVI Ao > 1.4
Quantitative			
Effective regurgitant orifice area (mm^2)	Primary	Primary	Primary ≥ 40
	<20	Mild to moderate	Secondary ≥ 20
		20–29	
		Moderate to severe	
		30–39	
Regurgitant volume (ml/beat)	Primary	Primary	Primary ≥ 60
	<30	Mild to moderate	Secondary ≥ 30
		30–44	
		Moderate to severe	
		45–59	
Enlargement of cardiac chamber/vessels	LA, LV	LA, LV	LA, LV

Ao = aorta; CZ = convergence zone; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; MV = mitral valve; TVI = time velocity integral.

the use of 3D echo may help for a better visualisation of the whole mitral valve anatomy and a more accurate estimation of the real orifice at the narrowest point.[46,50] However, nomograms for mitral valve evaluated by 3D echocardiography are limited.[53]

Evaluation of left heart parameters and indirect estimation of pulmonary pressure. Evaluation of left atrium and left ventricle dimensions and function is an essential part of estimation of mitral stenosis severity.[2,3] In moderate-to-severe mitral valve disease, the left atrium wall bulges to the right, and the left atrium is usually dilated.[2,3] The left ventricle may be dilated when there is both mitral valve stenosis and regurgitation or may be hypoplastic in patients with Shone's complex.[43–48] When evaluating left atrium dilatation, it is important to index measurements. z scores for the paediatric population have been recently become available.[4] The presence of tricuspid insufficiency should be monitored for indirect quantification of pulmonary pressure and response to exercise may be important.[6] In the neonatal period, the presence of a patent foramen ovale needs to be carefully evaluated for quantification of differences among atrial pressure and to estimate the degree of left to right shunt that may an indirect indicator of inflow obstruction and left ventricle non-compliance.[54] The potential to shunt at atrial level also confounds measurements of trans-mitral flow.

Mitral valve regurgitation

Acute mitral regurgitation is extremely rare in children and may be due to trauma,[1,8,9] idiopathic (due to acute chordal rupture),[55] or more often iatrogenic following surgical or catheter intervention.[1,8,9] Chronic mitral regurgitation instead is common and may present in isolation[8,9] or more commonly in the context of other cardiac/systemic disease. Secondary causes of mitral regurgitation include connective tissue diseases (i.e. Marfan syndrome), rheumatic disease (especially in developing countries), and various CHDs (before and after correction/palliation).[6,23–33] Mitral regurgitation may be found in association with stenosis in all complex congenital mitral defects, as detailed in Tables 1 and 2. Rare anatomical defects of mitral valve apparatus that may cause mitral regurgitation include isolated cleft of the mitral valve,[9,34,44,45] mitral arcade or hammock valve,[8,9,32,44,45] and Ebstein's like anomaly (Tables 1 and 2).[35]

Quantitative and semi-quantitative assessment. A quantitative assessment is often important to guide management of children with mitral regurgitation.[23–33] At the present time, there are no clear criteria to grade mitral regurgitation in children. New echocardiographic indices and classification systems for semi-quantitative and quantitative evaluation have been proposed in adults; however, their validity and reproducibility in children are unknown.[5] The use of vena contracta that is strongly advised in adults[1–3] was validated in a single paediatric study[25] (Table 4).

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Table 5. A few studies evaluating diagnostic accuracy of some echocardiographic parameters to grade mitral regurgitation in children

Authors	Population	Diseases	Methods to asses MR	Majors results
Gabriel Lactu[30] Monaco (France)	54 pts 1 week 19 years	(29 without and 25 with MR) 6 MVP, 1 rheumatic, 2 Marfan, 1 myxoid MV, 6 MV cleft, 2 MV restriction, 2 ischemia, 3 MV dilatation	RF by MRI (PISA) RF by 3D echo	RV by PISA and 3D well correlated ($r = 0.83$; $p < 0.001$) RF also well correlated ($r = 0.79$, $p = 0.006$)
Ziani[31] Tolouse France	31 pts aged 1 month to 20 years, median 69months)	17 had MR and 14 had ventricular shunt MR 4 cleft, 5 restriction, 5 prolapse, 1 MV annulus dilatation	2D PISA (four-chamber view) EROA and RV 3D PISA EROA and RV***	EROA and RV by 2DE and 3DE were different, $p = 0.019$). The PISA rarely hemispherical, more often prolate or oblate hemispheroid
Başpinar[29] Gaziantep, Turkey	31 pts (mean age 12.3 ± 3.1 years)	Chronic rheumatic MR Inclusion criteria: (1) more than trace MR at colour Doppler (2) presence of a recognisable proximal flow convergence region (3) absence of concomitant lesions	2D PISA method EROA and RV Semi-quantitative Doppler and other measures >The MR jet graded as first, second, third, and fourth degree by colour Doppler. The RJA within the left atrium **The jet length	No differences in the EROA and RV by the PISA method and the quantitative Doppler ($p > 0.05$) but different from 2Decho Excellent correlations between the EROA, R vol, and the radius of the proximal flow convergence hemisphere ($r = 0.882$, $r = 0.925$, $r = 0.880$; $p < 0.05$). Very good correlation between the regurgitant orifice area obtained by the PISA and left ventricular end diastolic diameters, the ratio of the jet/left atrial area, grading with colour Doppler imaging ($r = 0.763$, $r = 0.745$, $r = 0.618$; $p < 0.05$)
Prakash[25] United States of America	149 children <17.5 years	AVSD (complete, partial or transitional) after biventricular repair.	1*: Qualitative MR grade* (none/trace, mild, moderate, severe) 2: *VC width* lateral and anterior posterior from 4Ch and parasternal long axis, index by BSA* 3: *VC area* 4: *RF and RV*	Vena contracta width lateral indexed by BSA, iWCWap, and indexed vena contracta cross-sectional area best associated with LVEDV ($r^2 = 0.54$, $r^2 = 0.24$, $r^2 = 0.46$) and highest infra-observer agreement (ICC = 0.62,0.73 and 0.68) Qualitative MR, RV/BSA, and RF associated with LVEDV ($r^2 = 0.31$; $r^2 = 0.45$; $r^2 = 0.45$) but poor infra-observer agreement (kappa 0.56, ICC = 0.28, and 0.17)
Aotsuka[28] Japan	20 children 7 months to 12 years (average 4.7 years)	Inclusion criteria: MR but without interventricular shunt or aortic stenosis was selected for this study. 9 AVSD after repair, 4 ventricular septal defect post repair, 3 rheumatic, 2 MVP, 1 TGA after arterial switch operation, 1 PDA	Regurgitant stroke volume Pisa by colour M-mode RSVD RF2D	Maximal regurgitant flow ratio, RV, and RF can be accurately predicted in children using the PISA method by colour M-mode

Ao = aortic; 2D = two dimensional; AVSD = atrio-ventricular septal defect; BSA = body surface area; EROA = effective regurgitant orifice area; ICC = intraclass correlation coefficient; i-VCW ap = vena contracta width anterior-posterior indexed by BSA; LVEDV = left ventricular end diastolic volume; MR = mitral regurgitation; MV = mitral valve, MVP = mitral valve prolapse, PISA = proximal isovelocity surface area, r = PISA radius; RF = regurgitant fraction; RJA = regurgitant jet area (measured by planimetry from the frame with the maximal systolic regurgitant jet area); RV = regurgitant volume, r is radius of proximal flow convergence and Vr is aliasing velocity; V = aliasing velocity; VC = vena contracta.

*Subjects with >1 jet of regurgitation were excluded. BSA formula was not specified.

**The jet length was defined as the maximal distance of the regurgitant signals from the MV orifice.

***EROA = $(2r^2) \times$ (the velocity at which the aliasing surface occurred/peak velocity of the MR and VS jet).

This study evaluated mitral regurgitation in 149 infants after biventricular correction for atrio-ventricular septal defect. The lateral, antero-posterior, and cross-sectional vena contracta area indexed for body surface area correlated moderately with z scores of left ventricular end diastolic volumes and showed high inter-observer agreement.[25] The use of flow convergence method is now the most recommended approach for a quantitative evaluation of mitral regurgitation in adults, but this has been tested only in a few paediatric studies.[28,29] These studies were all numerical limited included (less than 35 patients) and evaluated a wide range of patient ages from the neonatal period to adult life.[28,29] Technical issues including application of adult Nyquist limits (15–40 cm/s) at the high heart rates encountered in the paediatric age have not been addressed. The use of three-dimensional echocardiography may provide additional information in the evaluation of mitral regurgitation by the proximal isovelocity surface area method.[30] A small study by Ziani and colleagues (31 patients 1 month–20 years) showed the benefit of three-dimensional echocardiography to describe the true proximal isovolumetric surface area shape in children with mitral regurgitation. They showed that the proximal isovelocity surface area shape was more often prolate or oblate hemispheroid[31] than hemispherical (Tables 4 and 5). Significant differences were observed among regurgitant volume calculated by two-dimensional and three-dimensional methods. In contrast, in a study of 54 children from 1 to 19 years with mitral regurgitation,[30] proximal isovelocity surface area by 3D echocardiography was well correlated with regurgitant volume ($r = 0.83$) and regurgitant fractions ($r = 0.79$). Another small paediatric study[29] showed good correlation of effective regurgitant area and regurgitant volume by the proximal isovelocity surface area method with those obtained by Doppler. The presence of multiple regurgitant jets in the setting of repaired atrio-ventricular septal defect is another issue to be considered (Figs 1–3 and Supplementary videos 1 and 2).[56,57] A multimodal approach combining echocardiography and MRI may enable improved evaluation of ventricular volumes and flows and quantification of multiple regurgitant jets after atrio-ventricular septal defect repair.[56] A study of 32 cases (age 26 ± 12 years) with mitral regurgitation after atrio-ventricular septal defect correction reported poor correlations between qualitative echocardiographic grading and MRI methods ($r = 0.51$).[56] Studies comparing quantitative echocardiographic assessment of mitral regurgitation with MRI are lacking.

Evaluation of left heart parameters and indirect estimation of pulmonary pressure. Analogous consideration made for mitral stenosis is also valid for mitral regurgitation, where the volumes and function of the left heart and evaluation of pulmonary pressures play an essential role in the estimation of disease severity.[2,3] Pulmonary vein systolic reversal is another important indicator of severe mitral regurgitation.[2,3]

Newer techniques: three-dimensional echocardiography

Multiple case reports[43,45–48] and review papers[44] show that the use of 3D echocardiography[43–48] may help to better appreciate the anatomy of complex mitral stenosis including double orifice mitral valve,[45–49] mitral ring,[48] mitral archade,[44] and parachute mitral valve[9,44] (Fig 2 and Supplementary video 1). Trans-thoracic three-dimensional echocardiographic evaluation of the mitral valve is made by using multiple views including parasternal long-axis, parasternal short-axis view, and apical four chamber.[43–48]

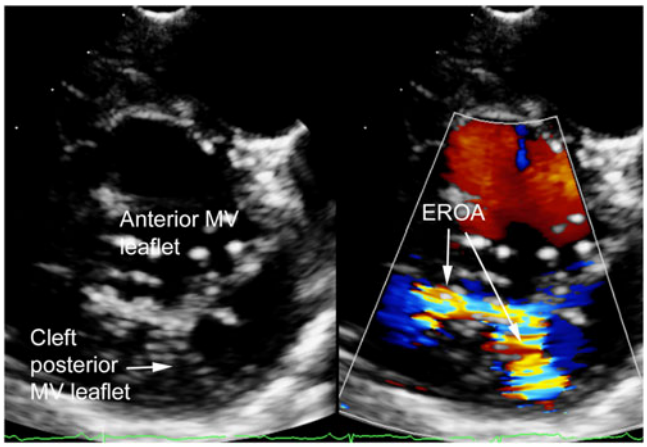

Figure 1. 2D short-axis MV view showing regurgitation with isolated posterior MV cleft. EROA = effective regurgitant orifice area; MV = mitral valve. See Table 3 for definition of isolated MV cleft.

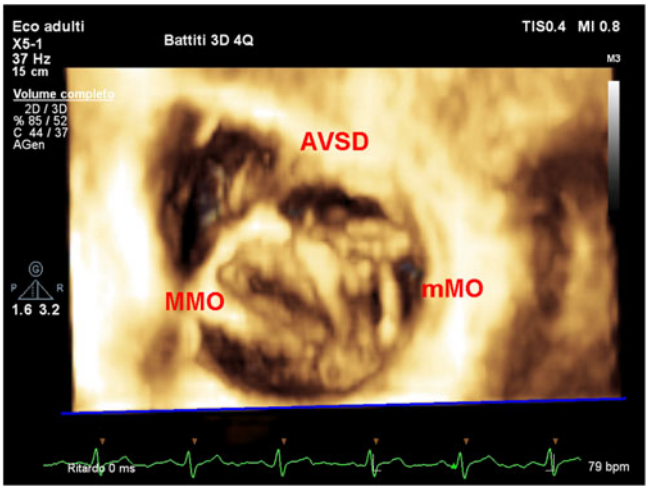

Figure 2. 3D en face view showing a double orifice mitral valve in AVSD. AVSD = atrio-ventricular septal defect; MMO = major mitral orifice; mMO = minor mitral orifice.

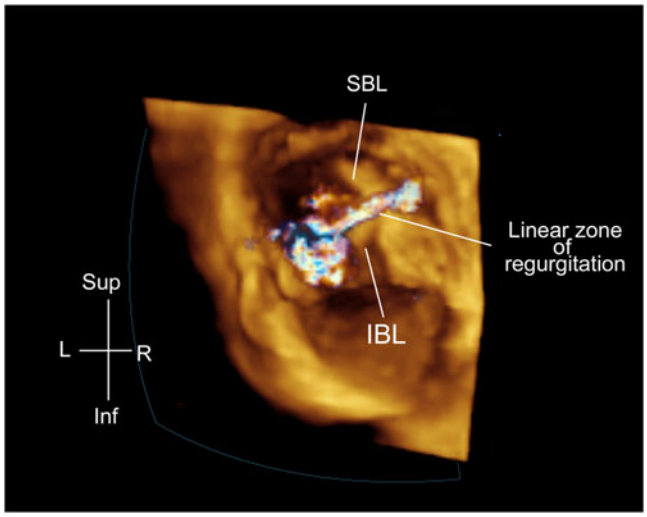

Figure 3. 3D en face view showing a linear left atrial valve regurgitation post-AVSD repair. AVSD = atrio-ventricular septal defect; SBL = superior bridging leaflet; IBL = inferior bridging leaflet.

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Trans-oesophageal projections include four-chamber view at a mid-oesophageal level at 0–30°, a mid-oesophageal level at 120–130°, or a trans-gastric view at 0–30° (i.e. short-axis view).[43–48] In mitral stenosis, the use of 3D echocardiography may help to plan the surgical strategy, by en face view of valve anatomy and the identification of the principal site of stenosis (valvular, supravalvular, or sub-valvular).[46] In addition, the anatomy of chordal support apparatus can be defined in a manner that is not possible by two-dimensional echocardiography. Similarly for interventional purpose in regurgitant lesions, 3D echocardiography may allow to better identify the presence of cleft, leaflets prolapse (Fig 3 and Supplementary video 2), and the degree size, shape, number, and location of multiple regurgitant jets in repaired atrio-ventricular septal defect lesions such as atrio-ventricular septal defect.[56,57] Furthermore, three-dimensional echo may allow for a more precise measurement of the mitral valve annulus estimation of the real mitral annulus (that can be misinterpreted with single plane views),[45–47,50] mitral valve area, effective regurgitant area, and proximal isovelocity surface area calculation[30,31] (Supplementary video 3).

Concluding remarks

There are multiple and heterogeneous approaches to the evaluation and management of paediatric atrio-ventricular valves disease. Adult guidelines cannot be simply translated to children. Consensus documents, based on current studies and expert consensus (when evidences are lacking), are needed to identify the limitations in the current classification systems and to establish practice standards in terms of treatment and follow-up. Recommendations should be based on anatomic and functional findings. In addition, paediatric recommendations must account for the effects of age, particularly in terms of the faster heart rates, and poor patient cooperation in neonates and infants.[52] These issues will have technical implications, including the settings used during the echocardiographic examination. Any evaluation must also address the presence of associated defects as they may influence management approaches. The role of an integrated multi-imaging approach with MRI or cardiac CT[56] should also be discussed.

A consensus document[57] could highlight the gaps of evidence and propose new approaches to overcome them. New studies should be based on wider population[58] and evaluate multiple indices including pressure gradients, vena contracta, proximal isovelocity surface area, effective regurgitant area, regurgitant fraction, and chamber dimensions. They should also integrate newer indices derived from three-dimensional echocardiography and strain analysis and provide comparisons with MRI and invasive data in specific clinical situations.

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