

Supplementary Material.

Supplementary Table 1. World Heart Federation Echocardiographic Criteria.

World Heart Federation's Criteria for Echocardiographic Diagnosis of Rheumatic Heart Disease		
<p>Congenital, acquired and degenerative heart disease should always be excluded as the aetiology of mitral and aortic valve abnormalities. Echocardiographic features should be interpreted in conjunction with demographics, regional differences and clinical findings.</p>		
<p>Echo criteria for children ≤ 20 years of age</p>		
<p>Definite RHD (either A, B, C or D):</p> <p>A) Pathological MR and at least two morphological features of RHD of the MV B) MS mean gradient ≥ to 4 mmHg (NB – exclude congenital MV anomalies) C) Pathological AR and at least two morphological features of RHD of the AV (NB – exclude bicuspid aortic valve and dilated aortic root) D) Borderline disease of both the aortic and mitral valves*</p>		
<p>Borderline RHD (either A, B or C):</p> <p>A) At least two morphological features of RHD of the MV without pathological MR or MS B) Pathological MR C) Pathological AR</p>		
<p>Normal Echocardiographic findings (all A, B and C);</p> <p>A) MR that does not meet all four Doppler criteria (Physiological MR) B) AR that does not meet all four Doppler criteria (Physiological AR) C) An isolated morphological feature of RHD of the MV or the AV (e.g. valvar thickening) without any associated pathological stenosis or regurgitation</p>		
<p>Pathological Regurgitation</p>		
<p>Mitral Regurgitation (all four Doppler criteria must be met)</p>		<p>Aortic Regurgitation (all four Doppler criteria must be met)</p>
<ol style="list-style-type: none"> 1. Seen in 2 views 2. In at least one view jet length ≥ 2 cm† 3. Peak velocity ≥ 3m/sec 4. Pansystolic jet for at least one envelope 		<ol style="list-style-type: none"> 1. Seen in 2 views 2. In at least one view jet length ≥ 1 cm† 3. Peak velocity ≥ 3m/sec 4. Pandiastolic jet for at least one envelope
<p>Morphological features of RHD</p>		
<p>Mitral Valve</p>		<p>Aortic Valve</p>
<ol style="list-style-type: none"> 1. AMVL thickening ≥ 3mm (age-specific)‡ 2. Chordal thickening 3. Restricted leaflet motion § 4. Excessive leaflet tip motion during systole ** 		<ol style="list-style-type: none"> 1. Irregular or focal thickening# 2. Coaptation defect 3. Restricted leaflet motion 4. Prolapse
<p>RHD – Rheumatic Heart Disease, MS – Mitral Stenosis, AMVL – Anterior Mitral Valve Leaflet</p>		<p>MR – Mitral Regurgitation, AR – Aortic Regurgitation, MV – Mitral Valve, AV – Aortic Valve,</p>

Footnotes:

* **Combined pathological AR and MR** in the absence of morphological features is not specific for RHD. It meets the criteria for definite RHD in those aged under-20 as, in the absence of congenital heart disease, it is the most likely aetiology.

† A **regurgitant jet length** should be measured from the vena contracta to the last pixel of regurgitant colour (blue or red) on non-magnified (non-zoomed) images.

‡ **AMVL thickness** should be measured during diastole at full excursion. Measurement should be taken at the thickest portion of the leaflet including focal thickening, beading and nodularity. Measurement should be performed on a frame with maximal separation of chordae from the leaflet tissue. Valve thickness can only be assessed if the images were acquired at optimal gain settings without harmonics and with a frequency ≥ 2.0 MHz. Note, that many adults may not have adequate images for valve thickness assessment. Abnormal thickening of the AMVL is age specific and defined as follows:
 ≥ 20 years of age ≥ 3 mm; 21- 40 years of age ≥ 4 mm; >40 years of age ≥ 5 mm;

§ **Restricted leaflet motion** of either the anterior or the posterior MV leaflet is usually the result of chordal shortening or fusion, commissural fusion or leaflet thickening.

The morphological feature of **excessive leaflet motion applies only to those who are under 35 years of age. Beyond the third decade RHD is rarely characterised by excessive leaflet motion and almost never without associated restriction of other leaflet scallops and chordal or valvar thickening. The entity **mitral valve prolapse or Barlow's disease** is well defined echocardiographically as billowing of the body of the leaflet in systole ≥ 2 mm beyond the annulus. In RHD, it is the leaflet edges (the rough zone) that become hypermobile as a result of elongation of the primary chords. This leads to displacement of an involved leaflet's edge towards the left atrium resulting in abnormal coaptation and regurgitation without necessarily meeting the standard echocardiographic definition of prolapse or Barlow's disease but meeting the surgical criteria of prolapse. To avoid the confusion between Barlow's disease and what is commonly seen in RHD (prolapse of the free-edges or the leaflet tips), the descriptive term "excessive leaflet tip motion" will be used. In the presence of a **flail mitral valve leaflet** in the young (under 20 years of age) this single morphological feature is sufficient to meet the morphological criteria for RHD (i.e. where the criteria state "at least two morphological features of RHD of the MV" a flail leaflet in a person under 20 years of age is sufficient) providing there is no better explanation and that severe forms of connective tissue disease, endocarditis and trauma have been excluded by clinical context.

In the parasternal short axis view the right and non-coronary **aortic cusp** closure line often appears echogenic (thickened) in healthy individuals and this should be considered as normal.

General comments:

1. "**Dog-leg deformity**" (also know as "elbow deformity" or "hockey stick deformity"), is the result of valvar thickening as well as restrictive leaflet motion secondary to chordal shortening and / or commissural fusion. Hence it meets two of the morphological criteria.
2. **Aortic stenosis** and **tricuspid regurgitation** are not included in the definitions as rarely, if ever, are isolated manifestations of RHD.
3. In tropical and subtropical Africa where **endomyocardial fibrosis** is prevalent, the above diagnostic criteria may not be specific enough to differentiate RHD from endomyocardial fibrosis. In these geographic locations more detailed assessment for specific features of endomyocardial fibrosis is required.

Echo machine settings:

1. Nyquist limits for colour-Doppler should be set on maximum to avoid overestimation of jet length.
2. Images for assessment of valvar and chordal thickness should be acquired with harmonics turned off and probes with variable frequency set on 2.0 MHz or higher. Low frequency settings and harmonics exaggerate valve and chordal thickness.
3. Ambient room lighting should be optimal for echocardiography as it impacts on gain settings. Gain settings should be adjusted to achieve optimal resolution. Images acquired with an over-gained setting will not be suitable for objective valve thickness measurements.
4. All other settings (including depth, sector size and focus) should also be optimised to achieve maximal frame rate and resolution.

Supplementary Table 2. Characteristics at diagnosis according to ARF status

in 290 patients admitted with no major cardiovascular event. ARF, acute rheumatic fever. RHD, rheumatic heart disease. MR, mitral regurgitation. MS, mitral stenosis. AR, aortic regurgitation. AS, aortic stenosis. TR, tricuspid regurgitation. LVEF, left ventricular ejection fraction. PASP, pulmonary artery systolic pressure. *Missing data in 9 cases. **Up to 2nd degree relatives; missing data in 153 cases. ***Defined as paroxysmal or persistent atrial fibrillation, flutter or atrial tachycardia, Fischer exact test. §Defined as mild RHD if single or multiple left sided valve disease graded as mild; moderate RHD defined as at least mitral or aortic moderate valve disease (regurgitation or stenosis); severe RHD defined as at least mitral or aortic severe valve disease (regurgitation or stenosis). §§Missing data in 13 cases.

Characteristics at diagnosis	NO ARF N=105	ARF at presentation N=185	All N=290	P
Age, median (IQR)	31 (15-47)	11 (9-15)	13 (10-31)	<0.001
Male, n (%)	43 (40.9)	88 (47.6)	131 (45.2)	0.3
Ethnicity*, n (%)				
-Indigenous Melanesians	73 (70.9)	127 (71.7)	200 (69.0)	0.12
-Polynesians	20 (19.4)	43 (24.3)	63 (21.7)	
-Other	10 (9.7)	8 (4.5)	18 (6.2)	
Family history of RHD or ARF**, n (%)	39 (56.5)	52 (76.5)	91 (66.4)	0.01
Supra ventricular arrhythmias***	7 (6.7)	0 (0.0)	7 (2.4)	<0.001
Initial left-sided valve disease on echocardiogram				
Mitral regurgitation, n (%)				0.06
Nil	21 (20.0)	17 (9.2)	38 (13.1)	
Grade 1/4	44 (41.9)	91 (49.2)	135 (46.6)	
Grade 2/4	28 (26.7)	58 (31.3)	86 (29.7)	
Grade ≥ 3/4	12 (11.4)	19 (10.3)	31 (10.7)	
-Mitral stenosis, n (%)				<0.001
Nil	16 (15.2)	161 (87.0)	177 (61.0)	
Mild	14 (13.3)	15 (8.1)	29 (10.0)	
Moderate	59 (56.2)	6 (3.2)	65 (22.4)	
Severe	16 (15.2)	3 (1.6)	19 (6.6)	
Aortic regurgitation, n (%)				<0.001
Nil	51 (48.6)	102 (55.1)	153 (52.8)	
Grade 1/4	23 (21.9)	69 (37.3)	92 (31.7)	
Grade 2/4	23 (21.9)	8 (4.3)	31 (10.7)	
Grade ≥3/4	8 (7.6)	6 (3.2)	14 (4.8)	
Aortic stenosis, n (%)				0.004†
Nil	94 (89.5)	182 (98.4)	276 (95.2)	
Mild	5 (4.7)	1 (0.5)	6 (2.0)	
Moderate	4 (3.8)	2 (1.1)	6 (2.0)	
Severe	2 (1.9)	0 (0.0)	2 (0.7)	
Multiple left-sided valve disease, n (%)	70 (66.7)	81 (43.8)	151 (52.0)	<0.001
Overall severity of RHD§				
-Mild	27 (25.7)	97 (52.4)	124 (42.8)	<0.001
-Moderate	44 (41.9)	61 (33.0)	105 (36.2)	
-Severe	34 (32.4)	27 (14.6)	61 (21.0)	
Moderate or severe TR§§, n (%)	2 (2.0)	2 (1.1)	4 (1.4)	0.35
LVEF<60%, n (%)	7 (6.7)	2 (1.1)	9 (3.1)	0.01
PASP>35 mmHg, n (%)	13 (12.4)	8 (4.3)	21 (7.2)	0.01

Supplementary Table 3. Incidence rates for major cardiovascular events per 1000 persons year in the 290 patients with no MACE at presentation.

Events	Incidence per 1 000 persons year (95% CI)
MACE	59.05 (44.35-73.75)
MACE excluding heart valve interventions	36.71 (25.61-47.82)
Death	4.74 (0.95-8.54)
Cardiovascular death	3.16 (0.06-6.26)
Heart Failure	29.06 (19.29-38.82)
Stroke	7.26 (2.52-12.01)
Non-neurologic embolism	1.59 (0-3.78)
Heart valve interventions	36.47 (25.17-47.77)