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Screening for rheumatic heart disease: evaluation of a simplified echocardiography-based approach

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Aims Portable echocardiography has emerged as a potential tool to detect rheumatic heart disease (RHD) early. Complex echocardiographic criteria used in recent epidemiological studies may be difficult to translate into daily practice in areas where the burden of RHD is greatest and skilled practitioners are lacking. The aim of this study was to evaluate a simplified echo approach for RHD screening among children in low-income countries.

Methods and results Retrospective analysis of data from a cross-sectional echocardiography-based study carried out in 2005 through the examination of 2170 school children in Maputo, Mozambique. We aimed to evaluate the value of a reference set of criteria (defined as a combination of Doppler and morphological rheumatic features of the aortic and/or mitral valves) compared with an easy-to-use single mitral regurgitation jet-length criterion (simplified set of criteria). All suspected lesions (according to reference or simplified criteria) detected in the field by a portable echo machine were reassessed by non-portable echocardiography and then read by three independent experts. Definite RHD cases in both groups were finally ascertained according to the reference criteria. Portable echocardiography detected valve regurgitation in 208 children. According to the reference criteria, 18 children were detected with suspected RHD on site. Of these, 15 children (83%) were considered to have definite RHD, giving a prevalence of 6.9 per 1000 (95% CI: 3.9–11.4). The simplified mitral regurgitation jet-length criteria detected 12 children at school, 11 of whom were subsequently confirmed to have definite RHD, giving an estimated prevalence of 5.1 per 1000 (95% CI: 2.5–9.1) ($P = 0.12$, exact McNemar test). When compared with the reference criteria, the simplified approach yields a maximum sensitivity of 73% for case detection, with a positive predictive value of 92%.

Conclusion Simplified echocardiography-based screening for RHD appears feasible, allowing rapid and appropriate detection of a significant number of RHD cases on site.

Keywords Rheumatic heart disease • Ultrasounds • Valve • Prevention • Developing countries

Introduction

Rheumatic heart disease (RHD) results from an abnormal inflammatory response to Group A streptococcus exposure in a genetically susceptible host.[1,2] Combined strategies including improved living conditions, and primary and secondary prophylaxis have led to near eradication of the disease in Western countries (outbreaks have, however, been described recently).[3] The situation in developing countries, however, has barely changed over the past two decades in spite of existing cost-effective preventive measures.[4] Indeed, RHD remains a major health problem accounting for most cases of heart disease in children and young adults in developing countries, and is responsible for ~250 000 deaths per year.[5]

The presentation of RHD includes a spectrum varying from subclinical to severe valve disease that may develop insidiously, even in the absence of acute rheumatic fever. Unfortunately, RHD presents at an advanced stage in many cases, when invasive treatments such as surgery are needed.[6] This has prompted the World Health

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Organization (WHO) to recommend active surveillance in endemic regions.[7,8] Early detection is therefore paramount to efficient secondary prevention. In this context, echocardiography has emerged as a valuable tool to detect mild lesions, inaudible on clinical examination, thereby leading to the concept of subclinical RHD.[9]

Seminal studies for detecting subclinical RHD by ultrasound have used very elaborate echocardiographic criteria, requiring expertise, sophisticated equipment, and specialized reviews in hospital.[9,10] Difficulties with this approach are mainly due to the fact that relatively minimal changes in echocardiographic criteria may result in strikingly different case-detection rates.[11] A consensus seems to have emerged where the diagnosis of subclinical RHD requires a combination of significant Doppler measurements associated with a number of morphological changes of the left-sided valves.[12] Although a complex methodology is suitable for research and epidemiological studies, more simplified criteria are required for widespread use, notably in remote locations and in emerging nations where specialist expertise is scarce. We aimed to assess the accuracy of a very simple echocardiographic approach for RHD screening among school children.

Methods

Design, setting, and participants

The study population, sample size calculation and design have been previously described.[9] Briefly, 2370 children aged 6–17 years, attending 42 classrooms in 6 schools located in Maputo City or in its suburban area (Mozambique) were randomly selected. Of these, 2170 children provided informed consent via their parents or guardians and were then enrolled in the study.

All children underwent careful cardiac auscultation and systematic echocardiography with a portable machine (Sonosite, 4.2 MHz probe) at school. All suspected cases detected at school had a second evaluation at the Maputo Heart Institute to determine whether they had or did not have definite RHD. This second echocardiographic examination used non-portable equipment (Philips Sonos 4500 4.7 MHz probe), and was recorded (super-VHS videotape) for further review by three independent experts.

Definition of echocardiographic criteria and final definite RHD diagnosis

Only left-sided valves were considered, as isolated pulmonary or tricuspid regurgitation is seldom due to RHD. Special attention was paid to detect congenital heart abnormalities, and mitral valve prolapse due to Barlow's disease, which were excluded from the analysis. All individual echo criteria were collected prospectively, but the proposed combination of reference criteria in the present analysis was undertaken retrospectively.

The reference criteria were defined as a combination of (i) 2001's WHO Doppler criteria and (ii) morphological rheumatic features of the mitral valve (*Table 1* and *Figure 1A*). The WHO Doppler criteria have been established by expert consensus, and include (i) a regurgitant jet >1 cm in length; (ii) a regurgitant jet seen in at least two planes; (iii) a mosaic colour Doppler jet with a peak velocity >2.5 m/s; and (iv) a persisting jet throughout systole (mitral valve) or diastole (aortic valve).[13] Morphological changes were defined by the presence of at least two out of the three following features: (i) abnormal leaflet morphology (typically marked thickening of the margins); (ii) abnormal leaflet mobility (abnormal motion due to posterior leaflet restriction); and (iii) abnormal subvalvular apparatus morphology (prominent thickening, most often just below the valve, and shortening of chordal structures).

Table 1 Definition of echocardiography criteria used in the field (on-site echocardiogram)

Simplified criterion	Reference criteria
Mitral regurgitation jet length ≥2 cm	WHO Doppler criteria Jet length ≥1 cm Seen in at least two planes Mosaic colour jet with peak velocity >2.5 m/s Persisting through systole (mitral valve) or diastole (aortic valve) *Associated with:* At least two valvular morphological criteria Leaflet thickening Leaflet mobility (restriction) Subvalvular apparatus morphology (thickening, shortened chordae)

As the proposed alternative, the set of simplified criteria were constituted from a single measurement defined by a mitral regurgitation (MR) jet length of 2 cm or more seen in any plane, independent of its velocity or duration during the heart cycle, and regardless of any morphological valve changes (*Table 1* and *Figure 1B*). The MR jet length was measured from the vena contracta to the last pixel of the regurgitant colour map.

Definite RHD cases of both groups were finally ascertained according to the reference criteria on review of the hospital-based scan, only in the case of agreement of all three reviewers.[9]

Main outcome measures

The main outcome measures were to determine for both sets of criteria (i) the respective estimate of RHD prevalence defined by the number of definite RHD cases among the 2170 participants (maximum sensitivity, assuming that all RHD cases were detected on site) and (ii) the proportion of definite RHD cases attested after the hospital-based scan when compared with the total of cases detected on site (specificity).

Statistical analysis

All patients' characteristics were described as the mean (SD) or proportions, as appropriate. RHD prevalence with exact 95% confidence intervals (CIs) was computed for the whole sample. The exact McNemar test for paired data was used for comparison of prevalence rates. Regarding the degree of consistency of echocardiographic interpretation of rheumatic valve changes between the three echocardiographic experts, we used the mean percentage of concordant cases observed for each pair of observers, the kappa test being of limited value due to the low number of subjects. Prevalence rates of RHD (according to simplified and reference criteria) were compared between age and sex with the use of the exact χ^2 test. Odds ratios with exact CIs for positive diagnosis were calculated. A two-sided *P*-value <0.05 was considered statistically significant. All data were analysed at the Paris Cardiovascular Research Centre, INSERM 970,

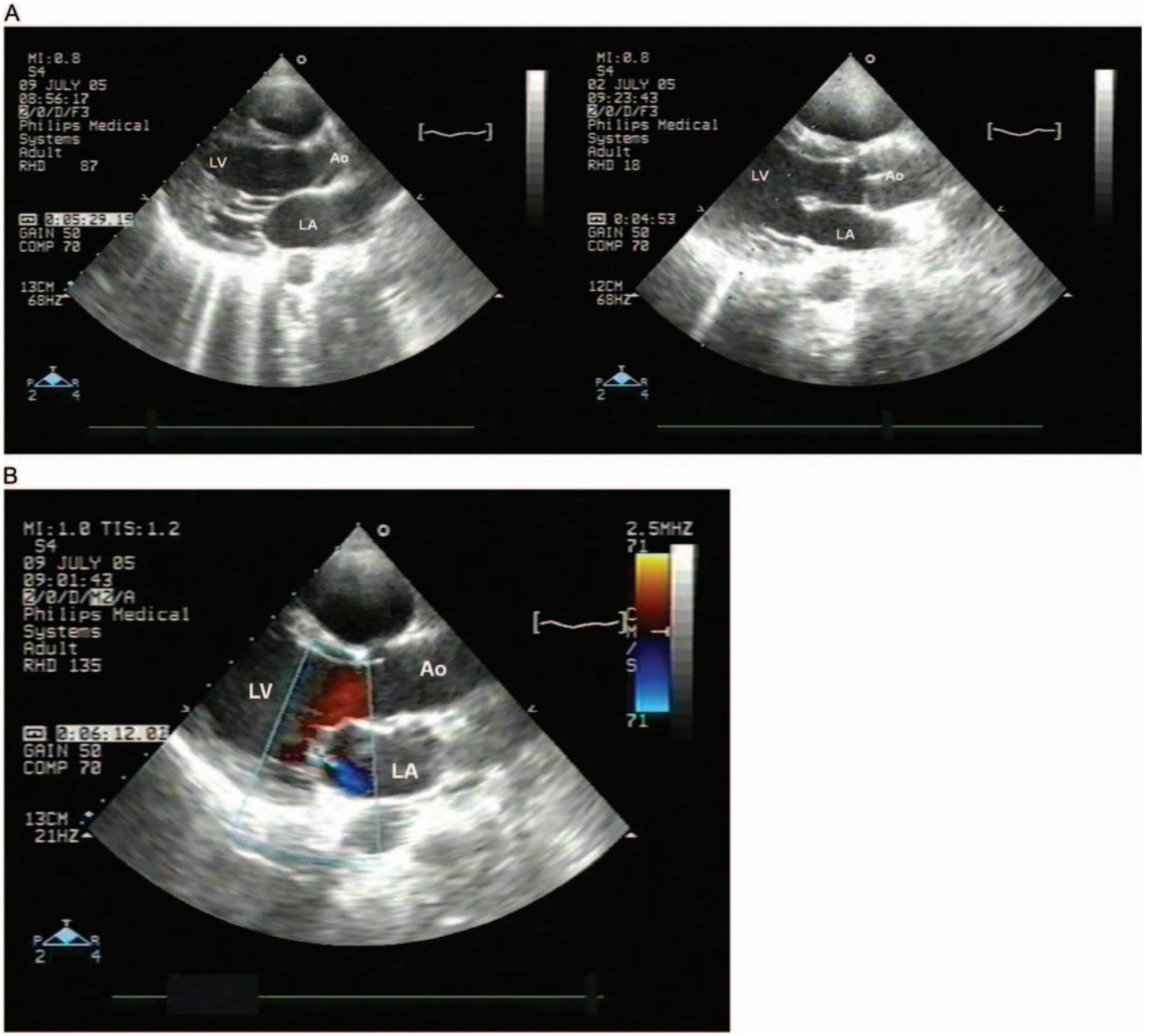

Figure 1 (*A*) Trans-thoracic echocardiography: parasternal long-axis view in a case meeting the reference criteria. Morphological features were in the presented case: (i) prominent thickening, and shortening of chordal structures (left panel), and (ii) marked thickening of the margins (right panel). Ao, aorta; LA, left atrium; LV, left ventricle. (*B*) Trans-thoracic echocardiography: parasternal long-axis view in a case meeting the 'simplified' criterion (i.e. MR jet length $\geq$2 cm). Ao, aorta; LA, left atrium; LV, left ventricle.

Paris, France, with the use of Statistical Analysis System software (version 9.1).

Results

In the whole screened population, the mean age was 10.6 (2.5) years and 47.5% were males. Among 456 children with a cardiac murmur, 91 were suspected to have organic lesions on auscultation. Clinical evidence of RHD confirmed by echocardiography (e.g. pathological murmur related to RHD) was found in five children, corresponding to a clinical prevalence of 2.3 cases per 1000 (95% CI: 0.7–5.4).

During school screening, 208 children (9.6%) had some degree of valve regurgitation on echocardiography. The results regarding the detection ability on site as well as the proportion of cases confirmed after the formal review process are summarized in *Figure 2*. Among these 208 cases, 18 children were suspected to fulfil the reference criteria on site, of whom 15 (83%) were confirmed on the hospital-based scan, corresponding to a final estimated RHD prevalence of 6.9 cases per 1000 (95% CI: 3.9–11.4). All 15 cases had isolated mitral valve disease. On the other hand, 12 children were diagnosed with suspected RHD at school according to simplified criteria, of whom 11 (92%) were considered to have definite RHD after review, giving an estimated final RHD prevalence by the simplified criteria of 5.1 per 1000 (95% CI: 2.5–9.1) (*Figure 3*). Demographic characteristics of the children screened positive by echocardiography are depicted in *Table 2*.

Using the simplified criteria on site, we detected 73% of the cases identified by the reference criteria, with a positive predictive value of 92%. There was no significant difference in terms of prevalence rates between the two sets of criteria (exact McNemar test, $P = 0.12$). Reproducibility observed during the review by the three experts was higher for the simplified criteria, (94.4% of cases being confirmed) than for the reference criteria (88.8%).

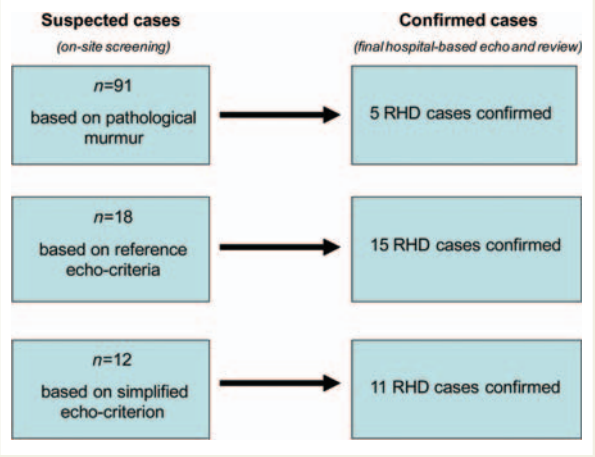

Figure 2 Comparison between suspected cases during on-site screening, and finally confirmed cases according to the two defined sets of criteria after a formal review of hospital-based scans.

A higher prevalence of subclinical RHD in older children was observed, mainly by the use of the reference criteria ($P = 0.06$). There was also a trend towards female predominance by the simplified criteria (6.1 vs. 3.9 per 1000, $P = 0.55$) (*Table 2*).

Discussion

RHD remains a major health issue in developing countries. The use of echocardiography has shed new light on this disease, for which no other significant medical progress has been achieved in the past 30 years.[2,9,10,14–16] Detection of valve lesions on echocardiography may become a surrogate marker for RHD in the near future.[17] However, translating research advances into clinical practice remains challenging. The lack of qualified personnel is one of the major hurdles to the widespread implementation of echo-based screening. The choice of diagnostic criteria is critical in this regard. In the search for more widely applicable criteria, our data suggest that a simple single criterion yields acceptable maximum sensitivity, and is specific and reproducible. Thus, a single measurement—MR jet length—could be an attractive option for screening campaigns.

We have previously shown how the prevalence of estimated RHD cases vary according to the echocardiography criteria used.[11] Studies give rise to different prevalence estimates that may truly reflect the epidemiology of RHD across countries, or may be confounded by over- or under-diagnosis. In this context, the definition of subclinical RHD diagnosed by echocardiography has been recently revisited.[12] Led by New Zealand and Australian teams, and supported by the World Heart Federation, a combination of semi-quantitative Doppler and morphological features is the likely consensus choice. The reference criteria used in our study appears relatively similar to that established by the recent expert consensus, combining both semi-quantitative Doppler measurements and morphological changes of the left-sided valves.[12] As others, the echocardiographic

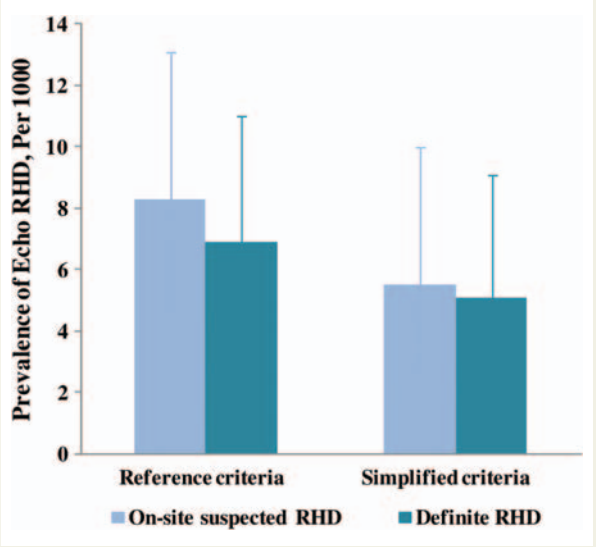

Figure 3 Prevalence rates of RHD according to the set of criteria used.

Table 2 Characteristics of participants according to the two sets of echocardiographic findings on the final hospital-based scan

	Simplified criterion	Reference criteria
Number	11	15
Baseline characteristics		
Age mean (SD), years	10.9 (2.1)	11.5 (2.1)
Males, *n* (%)	4 (36.4)	7 (46.7)
Prevalence of RHD, per 1000 (exact 95% CI)	5.1 (2.5–9.1)	6.9 (3.9–11.4)
Prevalence by sex		
Girls	6.1 (2.5–12.6)	7.0 (3.0–13.8)
Boys	3.9 (1.1–9.9)	8.7 (4.0–16.5)
Prevalence by age tertiles		
6–9 years	2.7 (0.3–9.7)	2.7 (0.3–9.7)
10–11 years	5.9 (1.6–15.0)	5.9 (1.6–15.0)
12–17 years	6.7 (2.2–15.5)	12.0 (5.5–22.7)
Estimated cases in Maputo City, *n* (95% CI)	5814 (2850–10 374)	7866 (4446–12 996)

criteria we used in our first publication were less stringent than what have been recently agreed upon by the international group of experts.[9,10,15,16,18] It is likely that the majority of the cases detected in many studies would be considered as 'Borderline' lesions in the World Heart Federation (WHF) guidelines.

Although the standardization of echo criteria was timely, it involved teams experienced in imaging rheumatic valves. This may have led to complex algorithms that could end up being inapplicable in remote, less experienced centres. One example of the complexity of very elaborate criteria involves the measurement of mitral valve thickness. The detection of these subtle changes requires highly skilled operators and readers, and may be time consuming. However, the implementation of remote echo-screening has to be appropriate to realities 'in the field', with regard to machine quality, timing, and expertise. Echo-screening should involve basic trained technicians able to scan large numbers of children with no need for further review. A detailed scan may last between 4 and 10 min per child, without taking into account the additional time allocated to the review, and could be significantly shortened when targeting a simple and single on-site measurement.[10,19] If the reproducibility of the simplified criteria is proved among less skilled users, this strategy would significantly lessen the workload. Hand-held echo machines may be an option in this setting.

Beyond technical issues, the meaning of minimal valve lesions detected on echocardiography may be questionable by some authors. Recent and unique data from New Zealand are of particular interest, emphasizing that the presence of significant MR is likely due to RHD in endemic regions. Indeed, the authors showed a higher prevalence rate of MR in children whose ethnic and socio-economic backgrounds made subclinical RHD likely.[20] In addition, these valve lesions remain unchanged in a significant proportion of cases under secondary prophylaxis, and present similar short-term outcomes as in subclinical acute carditis, thereby suggesting their pathogenicity.[14,21–23] In our study, most children with a $\geq$2 cm MR jet length (92%) clearly presented with concomitant morphological changes, highly suggestive of the rheumatic origin of the lesions in endemic regions. Likewise the majority of cases with significant morphological changes had also $\geq$2 cm MR jet length ($\sim$75%). These findings are consistent with those of other groups.[24]

Over-simplification may potentially impact on the ability to detect rheumatic and other pathologies. We discarded the analysis of morphological lesions in the simplified criteria. We do acknowledge the importance of morphological changes in the left-sided valves, since some children have lesions that suggest previous rheumatic carditis without significant regurgitation, although it may represent a small proportion of cases. Likewise, we decided not to consider the aortic valve in our new simplified criteria due to the extremely low prevalence of isolated aortic valve abnormalities in children with RHD.[9,10] We acknowledge that some rare cases of isolated aortic regurgitation may be missed by using a simplified set of criteria. Nevertheless, our findings suggest that there is no major impact on prevalence estimate rates by simplifying the diagnostic criteria. Some may argue that the simplified criteria would not diagnose congenital defects.[15] We outline here a strategy to be implemented in low-income countries where public health strategies should focus on cost-efficient policies such as prevention (i.e. the use of penicillin), cardiac surgery usually being unaffordable in these settings.

We acknowledge that our study has a number of potential limitations. The lack of a diagnostic gold standard for RHD makes difficult any research in this field. We did not undertake a confirmation scan in all participants for organization issues and assumed all cases were detected on-site, the reason why we mention maximum sensitivity. Further studies are warranted to assess both the clinical significance during the follow-up, and the applicability of these simple criteria, such as their potential use by health technicians after basic training. Finally, a prospective

study that would compare the recent WHF criteria to simplified criterion as the MR jet length would validate our findings.

Conclusion

Early detection of RHD using a simplified echo-based cardiac screening in the field appears specific and relatively sensitive in an endemic region, and may be of potential interest, particularly for widespread use in remote and low-income settings.

Conflict of interest: None declared.

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