

# Echocardiographic Screening for Rheumatic Heart Disease

## Issues for the Cardiology Community

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### ABSTRACT

The advent of portable echocardiography has led to screening for rheumatic heart disease (RHD) with high disease prevalence found in many countries. Data are presented from studies from India, Africa, and New Zealand. The natural history of subclinical echocardiographically detected RHD is the most important research question to be answered before more widespread screening is endorsed. The 2012 World Heart Federation (WHF) criteria for the echocardiographic diagnosis of RHD provide standardization of RHD diagnosis, increasing the specificity for definite RHD and raising the threshold for borderline RHD. Use of the criteria should reduce the false positive rate for minor echocardiographic changes due to physiological valvular regurgitation. This review highlights issues of screening for RHD that are of relevance to the cardiology community.

In developing countries, rheumatic heart disease (RHD) remains a significant cause of cardiovascular morbidity and mortality [1,2]. Epidemiological studies from India in the last decade, using clinical screening followed by echocardiography have shown a consistent decrease in the prevalence of RHD [3–5]. However, several studies in other parts of the world have shown a very high prevalence of RHD when asymptomatic children are screened by echocardiography [6–9]. It is suggested that echocardiographic screening with institution of secondary prophylaxis for positive cases may lessen the burden of RHD, and in 2004, the WHO recommended echocardiographic screening for RHD in high-prevalence regions [1]. However, the natural history of subclinical RHD, identified using an echocardiographic screening protocol is not known. Some of the data on echocardiographic screening from India, Africa, and New Zealand are described herein. The purpose of this review is to highlight issues of screening for RHD that are of relevance to cardiologists and cardiac surgeons.

### ECHOCARDIOGRAPHIC SCREENING DATA FROM INDIA

This cross-sectional epidemiological survey, the RHEUMATIC (Rheumatic Heart Echo Utilization and Monitoring Actuarial Trends in Indian Children) study [10], was conducted in the rural primary and secondary schools, in the Ballabgarh Block of Haryana, North India. After obtaining institutional ethical approval, consent was taken from principals of schools and parents of children studying in these schools. The aim of the study was to diagnose RHD in asymptomatic children ages 5 to 15 years, living in rural areas, using portable echocardiography. After cluster sampling, 6,270 children, ages 5 to 15 years were recruited

from various government and private schools. After a focused history and examination, echo-Doppler was performed using a bedside portable echocardiography machine.

The modified World Health Organization (WHO) criteria [11] define RHD using echocardiography including fulfilling Doppler criteria (a regurgitant jet of >1 cm in length, regurgitant jet in at least 2 planes, a mosaic color jet with a peak velocity of >2.5 m/s, and jet persisting throughout systole or diastole) associated with at least 2 morphologic signs including leaflet restriction, subvalvular thickening, and valve leaflet thickening. Other criteria for diagnosing “definite” RHD by echocardiography included mitral stenosis, mitral valve involvement with aortic regurgitation (AR) in the absence of alternative cause for AR, and isolated mitral regurgitation with documented history of rheumatic fever (RF). Two investigators with experience in interpreting echocardiography separately analyzed the images. In case of disparity, an opinion of a third cardiologist was taken. The parents were counseled if any abnormality was detected either during clinical examination or by echocardiography. Patients with clinical RHD and those with moderate regurgitation on echocardiogram were advised to commence secondary prophylaxis. Patients with subclinical RHD were advised to report sore throat, fever, or joint pain to the local health center.

### Results

Of the 6,270 children included, 52.65% were male with a mean age of  $10.78 \pm 2.63$  years (range 5 to 15 years). Nearly one-third (1,908) of these children were studying in government-funded schools. Clinical examination detected mitral regurgitation that was confirmed on echocardiography in 5 patients and the estimated prevalence of clinical

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RHD was 0.8 per 1,000 schoolchildren. Echocardiography diagnosed RHD in 128 cases, a prevalence of 20.4 per 1,000 schoolchildren (95% confidence interval [CI]: -16.9 to 23.9 per 1,000 children). On multivariate analysis, older age (odds ratio [OR]: 1.93, 95% CI: -1.29 to 2.88;  $p = 0.001$ ), female sex (OR: 1.84, 95% CI: -1.25 to 2.72;  $p = 0.002$ ), and studying in a government-funded school (OR: 1.55, 95% CI: -1.02 to 2.34;  $p = 0.039$ ) were found to be independent predictors of subclinical RHD. Thus, the prevalence of RHD is several fold higher using echocardiographic screening. Prevalence is higher in children who are economically less privileged.

### ECHOCARDIOGRAPHIC SCREENING DATA FROM DIFFERENT REGIONS OF AFRICA

The first echocardiographic screening study was performed in Kenya in 1999, demonstrating the feasibility of echo-based screening in asymptomatic populations [12]. Since this first report, several studies have been conducted in various parts of Africa [13].

#### Data from Mozambique

Data from Mozambique has been published [7] and has proven to be a sentinel study in raising awareness of the prevalence of previously undetected RHD. In brief, 2,170 children mean age 10.6 years (range 6 to 17) were recruited randomly from 6 primary schools in the capital, Maputo. Two-thirds of those children were from suburban schools and one-third from urban schools. Criteria for echocardiographic diagnosis of RHD were defined as presence of any definite evidence of mitral or aortic valve regurgitation seen in 2 planes by Doppler echocardiography, accompanied by at least 2 of the 3 morphologic abnormalities of the regurgitant valve (restricted leaflet mobility, focal or generalized valvular thickening, and abnormal subvalvular thickening).

**Results** The prevalence of echocardiographic RHD was 30.4 per 1,000 children compared with 2.3 per 1,000 diagnosed clinically. The prevalence was higher in girls than in boys and in suburban than in urban children. Retrospective reanalyses of the same cohort using different criteria highlighted the need for standardized definitions for diagnosis of subclinical disease [14] as the initial high prevalence rates were not confirmed by subsequent criteria. Their recently proposed “simplified” criteria [15] may have merit but should be tested prospectively against the World Heart Federation (WHF) criteria before recommending that other groups adopt their use.

#### Data from Mali

A total of 3,092 children were selected randomly living in an urban quarter in Bamako [16]. The age range was 5 to 16 years. After physical examination, screening echocardiograms were performed using parasternal long- and short-axis views and apical 4-chamber view. Those

children for whom the screening echocardiogram was considered abnormal had a complete study performed and reviewed by 2 cardiologists. Diagnostic criteria were as per WHO guidelines [11]. Follow-up echocardiograms were performed every 6 to 12 months.

**Results** Twenty-one children had definite RHD, 46 probable RHD, and 233 possible RHD. Overall, approximately 20 per 1,000 children have probable or definite evidence of RHD by screening echocardiography [16].

#### Data from Uganda

A recent study conducted in Uganda reported a 2-min screening echocardiogram of the left-sided valves by a single operator [17]. This was followed by detailed echocardiograms at a tertiary center by experienced operators. This screening method was able to screen >200 participants per day.

**Results** A total of 4,869 children were screened with 25 cases detected. The overall prevalence was 5.1 per 1,000 (95% CI: 3.49 to 7.6), significantly lower prevalence rate compared with the Mozambique study. The concept of abbreviated echocardiograms has potential, especially in rural areas where follow-up is problematic. An immediate assessment would aid immediate counseling of participants and family.

#### Data from Senegal

A school-based screening program [18] conducted in 2010 in Dakar, Senegal, included 2 groups of schoolchildren: group 1 ( $n = 1,116$ ) were 5 to 15 years old; group 2 ( $n = 888$ ) were 16 to 18 years old.

**Results** The prevalence rates in group 1 were almost one-half those for group 2: 5.4 per 1,000 (95% CI: 2.0 to 11.7) and 10.1 per 1,000 (95% CI: 4.6 to 19.2) concordant with previous clinical screening programs showing higher case detection rates in older children [19]. This study indicates that screening age is an important consideration in planning a screening program.

#### Data from Eritrea

The majority of screening programs in Africa have focused on schoolchildren [20]. The concern regarding the high risk of morbidity and mortality due to RHD in pregnant women led to a screening study of pregnant women in Keren, Eritrea, using echocardiography [21]. The study was conducted by 2 specially trained medical students under the supervision of an experienced cardiologist.

**Results** Eight of the 348 screened women had definite RHD. This corresponds to a prevalence of 23 per 1,000 (95% CI: 7 to 39). Further studies designed to evaluate the clinical significance of screening for RHD in early pregnancy are needed.

## ECHOCARDIOGRAPHIC SCREENING IN NEW ZEALAND

The results of the initial screening study of 1,274 children ages 10 to 13 years in urban schools in a high RF prevalence region are reported [9]. The study used modified WHO criteria [11] but a mitral regurgitant jet of length >2 cm was considered pathological. There was a 26 per 1,000 prevalence of definite or probable RHD and 30 per 1,000 prevalence of possible RHD using those definitions. Since then, another 2,494 children have been screened in 3 separate rural populations and 1 urban region. Implementation of the 2012 WHF criteria [22] in the 2 most recent regions found a 10 per 1,000 definite RHD prevalence and a 24 per 1,000 borderline RHD prevalence, significantly lower rates than those using the modified WHO criteria. Following the initial program [9], only those with a positive test proceed to a specialist clinical consultation with auscultation [23]. The study found that a considerable health personnel and logistical load was required for the screening program, the clinical evaluation, and counseling those with a positive test [23].

Another study of a control population of 400 children in a high socioeconomic region in New Zealand did not find any cases of definite RHD, but 2 children with mild mitral regurgitation met borderline RHD criteria [24]. This study provided data about the very low, but not zero prevalence of subclinical mild mitral regurgitation in low RF prevalence regions.

## ISSUES FOR THE GLOBAL DEVELOPMENT OF RHD SCREENING

### The need to standardize RHD echocardiographic criteria

As illustrated in this paper, the different criteria used to define echocardiographic RHD accounts for some of the differences of RHD prevalence [3,6–9,23] and essentially make epidemiological comparisons invalid. In 2009, an international RHD echocardiographic standardization study was started with 21 investigators from 11 countries who had by this time practical experience of screening many thousands of cases. All available echocardiographic, pathological, and surgical descriptions of RHD were analyzed. The aim was to define the minimal diagnostic criteria for a diagnosis of RHD that could be used in clinical cardiology practice as well as for screening programs. The results were published as the 2012 WHF criteria for echocardiographic diagnosis of RHD [22]. The 2012 WHF criteria for definite RHD are more specific than previous definitions were and the threshold has been raised for possible RHD (renamed “borderline RHD”). It was judged that increasing the threshold for borderline RHD will reduce the false positive rate of RHD by excluding those with physiological mitral and aortic regurgitation. The WHF criteria have quickly been adopted as the current gold standard for echocardiographic screening [25,26].

The investigators are also undertaking a detailed interobserver and intraobserver study of the criteria. The WHF criteria should facilitate further echocardiographic RHD research, such as epidemiological studies, long-term evaluation of the natural history of subclinical RHD, the evaluation of secondary prophylaxis for echocardiographically detected RHD, and cardiology evaluation of group A streptococcal vaccine trials.

### Does echocardiography meet the requirements for a population-screening test?

At first sight, echocardiographic screening for RHD meets the 3 main requirements for disease screening. First, there is a suitable condition (RHD); second, the condition is detectable (by echocardiography); and third, it is treatable (by long-acting benzathine penicillin [25]). A more detailed list of requirements for screening suggested by the New Zealand National Health Committee [27] and the Council of Europe [28] are found on their respective websites.

The first requirement is met as most subjects positive for RHD by echocardiography have subclinical disease, which is latent and pre-clinical. They have the most to gain from such a program by prevention of progressive RHD. However, currently, we do not know the natural history of subclinical RHD. It is known that those with an episode of acute RF are at high risk of RHD recurrences and progression of RHD severity [1,2], but it is not known whether an individual with RHD identified by echocardiography is at the same risk of RHD progression and or clinical acute RF recurrences. Roberts et al. [25] discussed this and other aspects of echocardiography screening and concluded that this is the most important question hindering the recommendation of wider use of echocardiography screening for RHD. It is important to be aware that in the short term, RHD screening will increase the prevalence of RHD within the region and additional resources will need to be allocated to effectively deliver secondary prophylaxis. It follows that it is unethical to begin a screening program if secondary penicillin delivery is not available in the region being screened [29].

Each region should decide before screening who should receive secondary prophylaxis. As already outlined, in the northern region of India and in New Zealand, those with borderline RHD by the WHF criteria [22] or possible RHD by the WHO criteria [11], have *not* commenced on penicillin. The lack of disease progression of these categories over 2 to 4 years as reported recently in 3 reports [8,10,30] gives support to continue the policy of *not* recommending penicillin for borderline RHD until the natural history of this category is known. It is still appropriate to provide “active surveillance,” which is used for cancers that may not progress [31,32]. Active surveillance involves prospectively following the case through time and rescreening at intervals to monitor that the disease has not progressed. No other active intervention is offered, unless disease progression is found. When considered as an

alternative to antibiotic prophylaxis, an active surveillance approach is appealing as patients are saved the 4-weekly intramuscular penicillin injections and the RF secondary prophylaxis register is not inundated with cases that may never need penicillin.

No single country to date has had the statistical power by numbers screened and length of follow-up to answer the question of efficacy of treatment for definite RHD even though it seems logical to treat this category. It has been judged that a treatment RCT for definite RHD is not feasible currently for 3 broad reasons. First, few regions have sufficiently reliable secondary prophylaxis programs that randomization to penicillin or not would be problematic. Second, intramuscular penicillin is not universally administered due to the issues of needles/acquired immunodeficiency syndrome/safe penicillin availability; and third, many judge it unethical not to treat definite RHD. In addition, many programs would not receive funding unless those detected with RHD were treated. A case-control study of definite RHD faces the same logistical problems as outlined herein, especially as many groups will not enroll if they cannot intend to treat by penicillin. A logical next level of evidence is the use of registry data as used by many international groups such as, International Society of Heart and Lung Transplantation, and interventional cardiology registries.

A prospective, international, multicenter registry of definite and borderline RHD (known as the DefineRHD registry) is being implemented. Follow-up of secondary prophylaxis status with frequent reporting (3-monthly) and echocardiography changes (2-yearly) should answer the question whether those with definite RHD receiving good secondary prophylaxis will show less disease progression and more disease regression than will those with no or poor secondary prophylaxis. Powering allows for a 25% difference in proportions deteriorating between the treatment arms over 4 years. The significance of the study is that it provides a realistic chance of defining the natural history of subclinical echocardiographically detected definite RHD in the shortest possible time. If the study does not prove that those with definite RHD are at increased risk of progression of RHD, then borderline RHD will also not be a risk factor for RHD progression.

Observational data about RHD disease control may also come from small well-defined geographical regions such as the Pacific Islands of Tonga, Samoa, and Fiji. Screening has continued on a regular basis in Tonga, population 90,000, following the original study [6]. Another 11,000 children have been screened, which represents a large proportion of the country's youth at risk of RF (T. Fakakovikaetau, personal communication, June 2010). Due to considerations, such as the high prevalence of RHD, the restricted access to surgery, and geographic isolation, a decision was made to provide secondary prophylaxis for those with definite and borderline changes as well as definite RHD changes. This policy may well result in reduced RHD disease burden in defined small regions.

**TABLE 1.** Differential diagnosis of mitral regurgitation in school-aged children in regions with high prevalence of rheumatic fever

1. RHD
2. Upper limit of physiological mitral valve regurgitation
3. Congenital mitral valve prolapse or floppy mitral valve syndrome*
4. Infective endocarditis
5. Congenital malformation of the mitral valve, for example, double orifice MV, parachute MV, hammock MV, funnel-shaped MV, or cleft MV
6. Congenital heart disease with mitral regurgitation, for example, primum or secundum atrial septal defect

MV, mitral valve; RHD, rheumatic heart disease.  
\*May be associated with abnormal body habitus, Marfan syndrome or other connective tissue disorders; endomyocardial fibrosis is common in some countries.

On the other hand, in light of recent follow-up studies [8,10,30], it is likely that minor echocardiographic changes may have been overtreated.

Those planning RHD screening should be aware of a wider discussion of optimal active and passive surveillance for RHD [11] and the current controversies of screening [25,26]. Echocardiography screening has increased the advocacy for RF and RHD, but it has not yet proven to be cost-effective for disease control. It may be logical for resource-limited countries to pre-select patients with pathological murmurs for echocardiography, allowing a much larger population to be screened for the same dollar value [33,34]. Sadiq et al. [33] were able to screen an impressive 24,980 Pakistani children using this model.

### Issues for cardiologists

Cardiologists may be asked to review echocardiograms from screening programs. The cardiologist should be familiar with the differential diagnoses of rheumatic mitral regurgitation as listed in Table 1. A mid-systolic click associated with mitral regurgitation strongly suggests congenital mitral valve prolapse not RHD, and congenital mitral variants appear in about 1% of the population [9]. Physiological mitral regurgitation needs to be excluded [8,9] to prevent overdiagnosis. Aortic regurgitation is less of a diagnostic problem as the same echocardiogram excludes bicuspid aortic valve and a dilated aortic root as

**TABLE 2.** Differential diagnosis of aortic regurgitation in school-aged children in regions with high prevalence of rheumatic fever

1. RHD
2. Bicuspid aortic valve with aortic regurgitation
3. Dilated aortic sinus or root
4. Infective endocarditis

RHD, rheumatic heart disease.

**TABLE 3.** Logistical considerations for RHD echocardiographic screening

1. RF register with secondary prophylaxis delivery structure
2. Public health, pediatric, cardiology, and community nursing partnership
3. Cardiologists to read the abnormal echocardiograms (ideally with second opinion capability)
4. Clinicians to counsel those with abnormalities
5. Financial cost of staff, echocardiography, secondary prophylaxis, clinical follow-up

RF, rheumatic fever; RHD, rheumatic heart disease.

causes of aortic regurgitation (Table 2). The WHF criteria [22] are also available on the WHF website.

The acceptability of long-term secondary prophylaxis for those with echocardiographically detected RHD has not been established or researched. In most regions, children with an episode of acute RF are admitted to the hospital with the acute illness, often with painful arthritis. This allows families to understand well and accept, usually, the importance of secondary prophylaxis. In contrast, the logic for secondary prophylaxis may not be understood by the family of an otherwise healthy child who is found to have echocardiographic RHD.

Logistical issues for echocardiographic screening are summarized in Table 3. The program will also detect cases of congenital heart disease, which require clinical management [9].

### Issues for cardiac surgeons

The majority of children with RHD detected by screening have mild disease. However, some individuals will have severe disease and cardiac surgery may be indicated. This must be taken into account from the outset before screening is planned. Many regions with high prevalence of RHD do not have access to cardiac surgery. The cardiology community must continue to advocate for improving secondary prophylaxis, ideally through registry-based programs [11], as they remain the proven method to prevent RHD progression [35,36].

### SUMMARY

Portable echocardiography is a relatively new screening tool for RHD, which has raised awareness of the high prevalence of RHD in many countries. Many requirements of a screening test are met, but the natural history of subclinical RHD needs further clarification. Use of the 2012 WHF criteria for the echocardiographic diagnosis of RHD is strongly recommended. Cardiologists and cardiac surgeons should help provide advocacy for improving secondary prophylaxis programs, as this remains pivotal for RHD control.

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