Echocardiographic Screening for Rheumatic Heart Disease

Running title: Tani; Echo screening for RHD

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Rheumatic Fever (RF) continues to be a major health challenge in developing countries, where it is the most common cause of acquired cardiac disease in children and young adults. Worldwide, it is estimated that at least 470,000 cases of RF occur annually, with the majority occurring in children 5-14 years of age. The majority of cases occur in developing countries and in indigenous populations, where the reported incidence is as high as 200-300 per 100,000. Because of the difficulty in obtaining data in these regions and populations, it is possible that the true incidence in some areas is even higher; community-based surveillance suggests that the true incidence in some settings may be as high as 500/100,000. In sharp contrast, there has been a significant decline in the incidence of RF over the last 50 years in most developed countries of the world. The initial decline began at least partly due to improved socioeconomic conditions, with further acceleration in the rate of decline of RF seen after the initiation of penicillin. The prevalence of rheumatic heart disease (RHD) parallels the reported incidences of RF. Both RF and RHD continue essentially unabated in many developing countries and in indigenous populations (such as that which occurs in Australia); in these settings, RHD remains an important and significant cause of morbidity and mortality. Worldwide, it is estimated that 15-20 million people have RHD. Given the current estimates of RF incidence and the proportion of patients who develop RHD, it is estimated that at least 282,000 people develop RHD each year. Compared to cases occurring in industrialized countries, the initial episode of RF in these high risk populations often occurs at a younger age, and often goes unnoticed. In these settings, it has been estimated that as many as 50% or more of patients are unaware of their RHD and as many as 70% do not receive secondary prophylaxis.

Efforts to decrease the incidence of RF and the prevalence and severity of RHD have focused on a combination of primordial prophylaxis, primary prevention, and secondary
prophylaxis. The most effective way to decrease the burden of RF and RHD in developing countries may be by reducing exposure to GAS, termed by some as *primordial prophylaxis*. Such primordial prevention can occur in at least two ways. Since improvement in socioeconomic conditions in industrialized countries has led to a significant decrease in the incidence of RF and the prevalence of RHD, it is not unreasonable to think that similar improvements in developing countries may result in similar benefit. There are also ongoing efforts to develop an effective group A streptococcal vaccine that could prevent the infection leading to RF and RHD. These efforts have been challenged by the potential for developing vaccine-related RF and RHD and the multiple group A streptococcal serotypes.\(^8\)\(^9\) Beyond this primordial prophylaxis, it is well established that *primary prevention* through appropriate treatment of streptococcal pharyngitis with antibiotics markedly decreases the risk of developing RF.\(^10\)\(^-\)\(^12\) Unfortunately, for as many as one-third to two-thirds of patients, the strep pharyngitis is subclinical\(^13\), precluding effective primary prevention. In the absence of specific and effective treatment for RF, preventing RF recurrences (*secondary prophylaxis*) is the most effective means of decreasing the likelihood and severity of long-term chronic RHD.\(^7\)\(^,\)\(^8\)\(^,\)\(^14\) All patients who have had RF, especially those with cardiac involvement, are at risk for recurrences. Some studies report this risk to be as high as 40 to 60% for patients with cardiac involvement.\(^15\)

Unfortunately, there are at least 2 reasons why many patients with RHD do not receive secondary prophylaxis. First, in order for secondary prophylaxis to be effective in reducing the RF recurrences and thus the prevalence and evolution of chronic RHD, patients who would benefit from such a prophylaxis program must be identified. Many patients with RHD do not recall having had prior RF and are unaware of their heart disease until they either develop symptoms are have their valvular abnormality detected incidentally. Second, once patients who
would benefit from secondary prophylaxis have been identified, compliance must be optimized. The World Health Organization and World Heart Federation (WHF) recommend register-based control programs that include school-based screening to identify such patients along with promoting education, training, recognition of RF and RHD, and optimization of and coordination of care, including providing secondary prophylaxis.⁷,¹⁶

With this background, a number of studies have been performed using various screening methods, including auscultation and/or echocardiography.⁷,¹⁶ Studies performed in Mozambique, Cambodia, and Tonga report the prevalence of RHD detected using echocardiography to be 10-13 times greater than using clinical auscultation alone (90% of RHD cases were only detected by echocardiography).¹⁷,¹⁸

So, if screening for RHD is best done using echocardiography, what constitutes echocardiographic RHD? In the absence of a diagnostic test (gold standard), the diagnosis of subclinical RHD will remain imperfect, based on criteria that balance sensitivity and specificity. The ‘bar’ or criteria set for what is considered pathologic is important. If the bar is set too low, one risks over-diagnosis, with false positives, resulting in labelling unaffected individuals as having chronic disease, unnecessarily utilizing the already limited resources, and subjecting these individuals to the regular injections of penicillin (along with the potential consequences of antibiotic overuse on development of antibiotic resistance). If the bar is set too high, one risks under-diagnosis and not preventing recurrences of RF and progression of RHD in some individuals. The World Heart Federation recently published echocardiographic criteria for definite and borderline RHD.¹⁶

In this issue of Circulation, Roberts and colleagues used these echocardiographic diagnostic criteria for RHD to establish the prevalence of RHD in the high risk indigenous
population of Australia, comparing the findings to Australian children at low risk. These WHF criteria were designed for children without a history of RF, aiming to differentiate mild RHD from normal findings by using specific definitions of left-sided valvular morphologic and Doppler abnormalities. The findings of their study are relatively straightforward. How the results should be interpreted is less clear. The authors found that none of the low-risk children and 34 high-risk children met WHF criteria for Definite RHD, concluding that the echocardiographic findings meeting the WHF definitions of Definite RHD likely represent true pathology. In addition, 5 low-risk children and 66 high risk children met WHF criteria for Borderline RHD. The authors state that all 5 low-risk children with Borderline RHD were thought not to have RHD, but rather showed upper-range normal findings, interpreting this data as supporting the WHF assertion that a diagnosis of Borderline RHD may not represent true disease. While there is little doubt that the numbers of low-risk children with subclinical RHD would be expected to be low, it is not reasonable to expect that the rate of subclinical RHD be zero. In fact, Parnaby and Carapetis (reference 15 of the Roberts paper), report that “92% of people with RHD are Indigenous” (in Australia), which implies that 8% are not, and that RF does occur, albeit at much lower rates, in this low risk group 20. So although the 5 low-risk children with Borderline RHD may represent false positives as the authors propose, an equally if not more plausible explanation is that many of those with Borderline RHD do in fact have mild RHD. Unless one believes the high-risk and low-risk groups are different in their underlying cardiac structure and function at baseline, what other explanation would there be for the significantly greater numbers of high risk children meeting these criteria? Further, one might speculate that one of the reasons the cardiologists reviewing the echocardiograms identified over twice as many cases of RHD as were identified using the WHF criteria is that the WHF criteria are too stringent
and not sensitive enough.

What is clear is that the natural history of RHD in children with subclinical abnormalities detected by echocardiography remains unknown. As Roberts and colleagues emphasize, further study, especially of the group with ‘Borderline RHD’, will be critical to our understanding of both the natural history of these subclinical findings along with refinement of the screening process and criteria. Their study adds an important ‘piece to the puzzle’, establishing the prevalence of RHD using the WHF diagnostic criteria. As with all good studies, questions are raised that will hopefully form the basis for future study. Given the continuing challenge of RF and RHD in many parts of the world, studies aimed at decreasing the burden of RHD should be given priority.

Conflict of Interest Disclosures: None.

References:


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