Prevalence of rheumatic heart disease in young adults from New Caledonia

Prévalence de la valvulopathie rhumatismale chez l’adulte jeune en Nouvelle-Calédonie

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Summary
Background. — Rheumatic heart disease (RHD) is an important public health issue, particularly in the Pacific region, but its true burden is unknown.
Objectives. — To evaluate the prevalence of rheumatic heart disease (RHD) in young adults from New Caledonia, based on echocardiography, and to evaluate the accuracy of dynamic criteria, focusing on mitral valve (MV) leaflet motion.
Methods. — Blind analysis of echocardiography by three cardiologists; diagnosis of RHD required at least one dynamic criterion (exaggerated or restricted MV leaflet motion); subjects with morphological criteria (MV leaflet thickening), but without dynamic criteria, were considered as borderline.
Results. — There were 834 subjects from three socioeconomic groups, aged 18–22 years: 699 had normal echocardiography; 93 (11.5\%) had physiological regurgitation; nine (0.9\%) had borderline RHD; and five (0.59\%) had RHD. The prevalence of RHD in New Caledonia was thus estimated at 5.9 per 1000 (95\% confidence interval 2.6–12.2). The RHD cases were of Pacific

KEYWORDS
Rheumatic heart disease; Echocardiography; Public health; Screening; Adult

Abbreviations: AR, aortic regurgitation; CI, confidence interval; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; RHD, rheumatic heart disease.
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Background

Rheumatic heart disease (RHD) is an important public health issue worldwide [1—4] and particularly in the Pacific region [5—9]. In many countries, school-based echocardiographic screening for RHD is being conducted [5,7—10]. These and other studies suggest that the prevalence of RHD increases steadily during the teenage years, peaking in young adults [11]. However, by not including older adolescents and young adults, school-based RHD screening programmes may underestimate the true burden of RHD in the population. Unfortunately, screening of adults is notoriously difficult, mainly because of low participation rates, but at least one study (in Nicaragua) has managed to screen for RHD in an adult population [10].

Echocardiography is a very sensitive tool for the screening of RHD, compared with cardiac auscultation [5,7,8]. The echocardiographical criteria required for the diagnosis of RHD have been debated [12,13], although the recent publication of the World Heart Federation criteria for echocardiographical diagnosis of RHD provides an evidence-based foundation for future research and practice [14]. The diagnosis of RHD requires the presence of Doppler criteria confirming pathological valvular regurgitation, and a range of morphological criteria.

Morphological criteria can be separated into static criteria, analysed on frozen two-dimensional images (thickening and/or retraction of the valve leaflets and/or subvalvular apparatus), and dynamic criteria, assessed by frame-by-frame analysis (excessive or restricted mobility of valve leaflets). We hypothesized that any significant chordal and/or subvalvular mitral valve (MV) apparatus shortening or retraction should translate into a limitation of MV leaflet tip motion, which could be accurately and highly reproducibly assessed with a dynamic analysis of two-dimensional echocardiography images, focusing on the position of the MV leaflet tips with regard to the MV annulus plane throughout the cardiac cycle.

Since 2007, echocardiography has been used as a screening tool for RHD in 10-year-old school children in New Caledonia [15]. Although a list of criteria and recommendations for RHD diagnosis were established by the coordinator of the programme (Agence Sanitaire de New Caledonia), the final diagnosis of RHD is confirmed by the cardiologists...
Table 1 Echocardiographical criteria used for the diagnosis of rheumatic heart disease [14].

<table>
<thead>
<tr>
<th>RHD diagnosis categories</th>
<th>Doppler criteria (the diagnosis of pathological valvular regurgitation [e.g. non-physiological] required all four criteria)</th>
<th>Morphological criteria Static criteria: MV</th>
<th>Morphological criteria Static criteria: AV</th>
<th>Morphological criteria Dynamic criteria: MV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal echocardiography</td>
<td>No valvular regurgitation and no MS</td>
<td>Retraction or thickening of chordal/subvalvular apparatus</td>
<td>AMVL thickening ≥ 3 mm</td>
<td>Coaptation defect Decreased mobility of PMVL, with normal mobility of AMVL: false prolapse of AMVL (leading to a posterior direction of MR jet) Decreased mobility of AMVL tip (dog-leg or MS aspect) Excessive mobility of AMVL or PMVL: valve prolapse due to chordal elongation or chordal rupture</td>
</tr>
<tr>
<td>Physiological regurgitation</td>
<td>Valvular regurgitation, without all four Doppler criteria and without morphological criteria Pathological valvular regurgitation, with at least one morphological static criterion, but without dynamic criteria No valvular regurgitation, with morphological criteria, but without dynamic criteria Pathological regurgitation and at least one dynamic criterion or MS</td>
<td>Holosystolic (MR) or holodiastolic (AR) jets (with homogeneous spectral envelope on at least three consecutive cardiac cycles)</td>
<td>Peak velocity ≥ 3.5 m/s Seen in two views Regurgitation jet length ≥ 2 cm (in at least one view)</td>
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<tr>
<td>Borderline RHD</td>
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<tr>
<td>Definite RHD</td>
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Table 1 (Continued)

<table>
<thead>
<tr>
<th>RHD diagnosis diagnosis of rheumatic heart disease categories</th>
<th>Dynamic criteria: AV</th>
<th>Restricted motion in opening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral stenosis (mean gradient ≥ 4 mmHg)</td>
<td>AMVL: anterior mitral valve leaflet; AR: aortic regurgitation; AV: aortic valve; MR: mitral regurgitation; MS: mitral stenosis; MV: mitral valve; PMVL: posterior mitral valve leaflet; RHD: rheumatic heart disease.</td>
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</table>

* According to Doppler and morphological criteria.

participating in the programme, on the basis of their own expertise. Using this method, the prevalence of RHD in 10-year-old children has been found to be approximately 13 per 1000 (unpublished data from Agence Sanitaire de New Caledonia).

Because the prevalence of RHD in adults in New Caledonia is unknown, we conducted a prospective echocardiographical screening study to evaluate the prevalence of RHD among young adults (aged 18–22 years) from New Caledonia. Our secondary aims were to identify high-risk subgroups as screening targets for future prevention programmes and to evaluate the accuracy and reproducibility of the echocardiographical criteria we used for the diagnosis of RHD, putting special emphasis on the dynamic analysis of MV leaflet motion.

Methods

Study design and participants

New Caledonia is administratively divided into three provinces: North, South and Islands. The population is 246,000, with two-thirds living in Nouméa and its suburbs in the South Province [16]. The population of New Caledonia includes people of Pacific ethnicity (Melanesians, 44%; Polynesians, 14% [composed of Wallisians, Futunians and French Polynesians]) and non-Pacific ethnicity (Caucasians, 34%; Asians, 8%).

The population of people aged 18–22 years is estimated as being 13,500 in the South Province [16], and they can be divided into three distinct groups: 6480 (48%) are students; 3645 (27%) are workers or apprentices; and 3375 (25%) are non-schooled and unemployed (this is the lowest socioeconomic group, who frequently live in tribal villages or shanty towns) [16].

Sampling

Based on an anticipated RHD prevalence of 30 per 1000, the minimum sample size required was 1250 for a 95% confidence interval (CI) of ± 10 per 1000.

We aimed to sample the three groups roughly according to their distribution in the population, as reported in the 2009 census supplied by Institut de la Statistique et des Études Économiques (ITSEE) [16]. The group of students (group 1, n = 596) was composed of subjects randomly
selected from an enrolment list obtained from universities; the group of workers (group 2, \( n = 335 \)) was composed of subjects randomly selected from a list of apprentices in the Chamber of Commerce of Nouméa or from the Department of Occupational Medicine of New Caledonia; the group of out-of-school and unemployed subjects (group 3, \( n = 339 \) subjects) was planned to be composed of subjects recruited using purposive sampling by our local social workers’ network.

Ethics approval was obtained from the Public Health Authorities of the South Province. Information about the study and RHD was provided to the institutions involved and to sampled subjects. Written informed consent was obtained from all participants before screening was performed.

Vital status on 31st December 2012 was checked in the national register; no patient with RHD died during the follow-up period (median 2.3 years).

**Screening procedure**

Personal or familial past history of acute rheumatic fever or RHD was recorded by asking the participants. The subject’s ethnic group was defined by the subject. Cardiac auscultation was not performed.

All echocardiographical examinations were performed by a single operator (investigator 1), between May and December 2010, in either an infirmary or a dedicated classroom, using a Vivid i™ (GE Healthcare, Freiburg, Germany) portable cardiac ultrasound machine and a multifrequency 3S adult probe (1.9–3.8 MHz).

A standard protocol was used for the acquisition, recording and storage of echocardiographical data. Imaging was performed in standard parasternal long and short axis, and apical four-chamber views. Depth, sector size and gain were optimized to achieve maximal frame rate and resolution; a second harmonic frequency was used if needed. Colour Doppler was used with the highest aliasing velocity allowed by the machine; pulsed and continuous Doppler were used to assess velocity and the spectral envelope of transvalvular flow and regurgitations.

**Reading of echocardiograms**

A blind and separate analysis was performed by the three investigators, reviewing stored images directly on the echocardiography machine; in case of disagreement, the final diagnosis was established by consensus between the investigators. Each reader was asked to categorize each echocardiogram as normal, physiological regurgitation, borderline RHD or definite RHD, according to predefined criteria established by our group in 2009, before the World Heart Federation RHD criteria were published and became the gold standard for RHD screening in 2012 (Table 1).

In contrast to the World Heart Federation criteria, we required the presence of at least one dynamic criterion to accept the diagnosis of definite RHD; in the absence of abnormal MV leaflet motion, or even in the presence of one or several static morphological criteria (leaflet thickening and/or subvalvular apparatus retraction), the case was labelled as ‘borderline RHD’.

In case of an abnormal echocardiogram, the patient was referred to their primary care doctor for further management.

**Statistical methods**

Data were entered and analysed using Microsoft Office Excel 2007 software. Prevalence rates and confidence intervals were computed using binomial probability tables. Fisher’s exact test was used to compare prevalence rates between groups. Cohen’s Kappa coefficient was calculated according to the referenced method [17].

**Results**

**Sampling of the population**

The total number of subjects sampled was 1161; the number of subjects sampled for group 1 (\( n = 717 \)) and group 2 (\( n = 390 \)) were in agreement with the number of subjects determined with respect to our stratification plan (596 and 335 subjects, respectively, for groups 1 and 2). However, we had difficulty recruiting for group 3, and managed to enrol only 54 of the 339 subjects planned (15% [or 7% of the total study population]); all of these subjects were sampled from a list of 104 prisoners obtained from the prison in Nouméa (Table 2).

Of the 1161 subjects sampled and invited to participate to our study, 834 finally had an echocardiographical examination: 280 subjects were absent on the day of screening and 47 subjects refused to participate for personal reasons (four of these subjects reported that they already had RHD). Participation rates as a proportion of those invited to participate were 70% for group 1, 72% for group 2 and 100% for group 3.

Of the 834 subjects included, there were 451 (55%) men and the mean age (± standard deviation) was 20.0 ± 1.5 years; 517 (62%) subjects were from the Pacific...
in our population was therefore estimated at 5.9 per 1000 (95% CI 2.6—12.2).

Twenty-eight participants (3.4%) had non-rheumatic cardiac abnormalities, many of which were minor (Table 4).

The rate of physiological regurgitation was significantly higher in subjects of Pacific ethnicity (71/517, 13.7%) than in those of non-Pacific ethnicity (22/317, 6.9%) (odds ratio 2.39, 95% CI 1.41—4.10; P = 0.0001).

**Characteristics of subjects with rheumatic heart disease**

Of the five subjects with definite RHD (three of whom were men), one had been diagnosed previously as having RHD at the age of 11 years; none of the other four reported any previous history of acute rheumatic fever or RHD.

One subject had pure severe mitral stenosis (MS) with a mean gradient of 10 mm and mild AR; two subjects had mixed MV disease (mild MS and MR) associated with mild AR; and two subjects had mild MR and AR. In all subjects, MR was due to a restricted systolic motion of the posterior MV leaflet, with normal systolic motion of the anterior MV leaflet (false prolapse of anterior MV leaflet), with a posteriorly directed MR jet.

All five definite RHD cases were of Pacific ethnicity (Melanesian, n = 4; Polynesian, n = 1), giving a prevalence of definite RHD in Pacific subjects of 9.7 per 1000 (95% CI 4.3—19.7). The difference in prevalence between Pacific and non-Pacific participants did not reach statistical significance for definite, borderline or all RHD.

The prevalence of RHD was higher in group 3 (18.6 per 1000, 95% CI 4.5—66) than in group 1 (6 per 1000, 95% CI 2.6—12) or group 2 (3.6 per 1000, 95% CI 0.9—13), although the difference was not statistically significant when groups 1 and 2 were pooled and compared with group 3. However, all borderline cases were found in groups 1 and 2.

**Interobserver reproducibility**

The global Kappa coefficient between the three observers was 0.62 (Z = 17.9; P < 0.0001), indicating good interobserver reliability.

All five cases of RHD were correctly identified by the three reviewers during separate analyses; thus, there was no disagreement between reviewers concerning dynamic criteria. In contrast, in six out of nine borderline subjects, the separate analysis was discordant between the investigators. In all six cases, the discordance related to the presence of morphological criteria rather than regurgitation: (observer A, two cases; observer B, one case; observer C, three cases); all these cases were finally classified as borderline during consensual review.

**Discussion**

Based on a systematic echocardiographical screening of 834 young adults, aged 18—22 years, we estimated the prevalence rate of definite RHD in New Caledonia to be 5.9 per 1000. However, all RHD cases, and most borderline RHD cases, were in people of Pacific ethnicity, resulting in a prevalence of almost 1% (9.7 per 1000) for definite RHD in
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We found a slightly lower prevalence of RHD among adults than school-age children [10], although among Aboriginal Australians, the prevalence in adults aged 15–34 years is much higher than the prevalence in those aged 5–14 years [11]. Other potential explanations for the difference include sampling issues (we undersampled people in the lowest socioeconomic groups), our highly specific echocardiographical criteria and the rigorous methodology using independent readings by three cardiologists. We note that the new World Heart Federation criteria [14] are also highly specific and are quite similar to the criteria we used, so we suspect that future prevalence studies using those criteria will find slightly lower rates than have been reported in the last few years in many developing countries.

In our study, we decided to systematically increase the specificity of the diagnosis of RHD, starting with strict optimization of the settings of the machine during image acquisition. The colour Doppler velocity was set at the highest level to avoid overestimation of the colour Doppler jet extension. In contrast to the combined criteria proposed by Marijon et al. [12], our algorithm required the presence of pathological regurgitation (unless MS was present) for the diagnosis of RHD. Moreover, all pathological regurgitation are not rheumatic [13]: using strict criteria, we identified a significant subgroup of patients (14 subjects, 16.8 per 1000) with non-rheumatic pathological MR or AR due to valve dysplasia or minor congenital abnormalities. The rate of non-rheumatic pathological valvular abnormalities should be reported clearly in every study to ensure that this kind of overestimation of RHD is avoided.

It is generally accepted that some degree of MV chordal shortening (and hence valvular motion restriction) is almost always present in established RHD [14]. Hence, in most studies, ‘chordal shortening’, and ‘mitral subvalvar apparatus thickening’ are accepted as major morphological criteria for the diagnosis of RHD [7,8,10,11]. However, chordal shortening or thickening are obviously subjective criteria. Therefore, we proposed to analyse the direct consequence of chordal retraction, represented by the limitation of the motion of MV leaflets, helped (if needed) by its surrogate marker, MR jet direction. In all our RHD cases, we observed a previously described typical pattern, combining restriction of the mobility of the posterior MV leaflet with preserved mobility of the anterior MV leaflet, leading to a posteriorly directed MR jet (‘false prolapse of anterior MV leaflet’) [14–18]. In our view, the diagnosis of RHD must be seriously questioned if any degree of mitral false prolapse cannot be demonstrated.

The analysis of dynamic criteria proved to be highly concordant between the three reviewers. Indeed, there was no disagreement between our three reviewers concerning the analysis of the dynamic criteria. In contrast, all six disagreements between the reviewers concerned the presence or absence of one morphological static criterion; those six cases were finally considered to be borderline cases after consensual review. Further refinements of the diagnostic criteria should perhaps emphasize the importance of the dynamic criteria, given that these appear to be the most reproducible between different reviewers.

The prevalence of physiological MR and/or AR was 11.5%, within the range of what has been reported in previous studies [19]. However, the prevalence of physiological
regurgitation was significantly higher in the Pacific community (13.7%) than in the non-Pacific community (6.9%; \(P < 0.0001\)); to the best of our knowledge, such a trend has not been reported before. As the Pacific community is also most affected by RHD, the existence of some link or continuum between RHD and physiological regurgitation, as suggested by Marijon et al. [12], is possible. Determining the risk of these cases of mild physiological regurgitation later degenerating to significant RHD will require longitudinal follow-up in highly endemic countries.

A major challenge facing the New Caledonia health care system is ensuring that RHD patients, such as those detected in this study, receive appropriate care – indeed this is a prerequisite for embarking on a screening programme. In New Caledonia, it has been estimated that only 40% of subjects prescribed monthly injections of benzathine penicillin for secondary prophylaxis actually receive all the 12 planned injections each year [15]. Clearly, there is work to do in New Caledonia to strengthen this critical element of RHD control.

Study limitations

We were not able to enrol the expected 1250 participants. Echocardiographical screening for subclinical RHD among young adults is not easy because some groups (non-schooled, not job seekers) are difficult to reach; this is an important obstacle to overcome, because the rate of RHD is very high (18.6%), and it probably explains why borderline RHD was not found in group 3.

Conclusions

We conclude that RHD in New Caledonia causes a significant burden in adults, particularly in those of Pacific ethnicity and low socioeconomic circumstances. This high-risk group should be the preferred target for further interventions aimed at controlling the RHD disease burden, potentially including systematic screening in New Caledonia. Our study suggests that the prevalence of RHD may be lower in New Caledonia than in other neighbouring Pacific Islands, although this requires confirmation in further studies. Our results also suggest that the analysis of dynamic criteria, focusing on the analysis of MV leaflet tip mobility, is more accurate, reproducible and specific than the standard morphological criteria.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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