Novel cardiac imaging technologies : implications in clinical decision making

Delgado, V.

Chapter 22

No increased risk on valvular heart disease in adult post-streptococcal reactive arthritis

J.M. van Bemmel, V. Delgado, E.R. Holman, C.F. Allaart, T.W.J. Huizinga,
J.J. Bax, A.H.M. van der Helm-van Mil.

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ABSTRACT

Background: Poststreptococcal Reactive Arthritis (PSRA) is a (poly)arthritis presenting after a *Streptococcus* group A infection. Acute Rheumatic Fever (ARF), albeit caused by the same pathogen, has different risk characteristics and is considered as a separate entity. Whereas ARF is notorious to cause carditis, the risk on carditis in adult PSRA is unknown. Consequently, the prevailing recommendations on long-term antibiotic prophylaxis in PSRA are imprecise and derived from the data on ARF. This study investigates the development of valvular heart disease in an unselected cohort of adult PRSA-patients that had not received antibiotic prophylaxis and is followed prospectively.

Methods: This study evaluated all patients presenting with early arthritis to a Caucasian inception cohort consisting of >2,000 patients. The patients presenting with PSRA were selected (n=75). After a mean follow-up of 7.7 years the occurrence of valvular heart disease was evaluated by transthoracic echocardiography in 60 patients. Controls were matched for age, gender, body surface area and left ventricular function (patient:control ratio 1:2).

Results: No differences were seen in left ventricular dimensions. Morphologic abnormalities on mitral or aortic valve were not more prevalent in patients compared to controls. Mild mitral regurgitation was present in 23% and 21% (patients and controls respectively), mild aortic regurgitation in 10% and 11% and mild tricuspid regurgitation in 43% and 39% respectively, revealing no significant differences.

Conclusion: The current prospective study observed no increased risk on valvular heart disease in adult PSRA. Based on these data routine long-term antibiotic prophylaxis is not recommended in adult PSRA.

INTRODUCTION

Poststreptococcal Reactive Arthritis (PSRA) is a (poly)arthritis presenting after a *Streptococcus* group A pharyngitis. The same holds for Acute Rheumatic Fever (ARF), which is a common public health problem particularly in developing countries. Although the incidence has decreased in developed countries, ARF is still a serious disease with carditis as potentially lethal manifestation. Other manifestations of ARF are chorea, subcutaneous nodules and erythema marginatum. ARF has the highest incidence before adolescence and a first attack is rare in adults older than 35 years.[1] The Jones criteria are used to establish the diagnosis ARF.[2] Arthritis that follows a group A β-hemolytic Streptococcus infection in patients whose illness does not meet the Jones criteria were first described in 1959.[3] In 1982 Goldsmith and Long described this syndrome as Post Streptococcal Reactive Arthritis (PSRA).[4] Although these first reports concerned children, the occurrence of PSRA is not restricted to childhood as the age distribution is bimodal with a second peak in adulthood.[5] The arthritis in PSRA is typically nonmigratory, more severe and prolonged and usually has a poor response to salicylates, compared to the arthritis in ARF which is characterised by an exquisite sensitivity to aspirin and which has a migratory self-limiting disease course.[6-9] Subsequent to the dissimilarities in clinical features between PSRA and ARF, differences in genetic and immunological characteristics are identified,[6,10,11] providing further support for the notion that PSRA and ARF are distinct disease entities. Paradoxically, although accumulating data suggests that PSRA and ARF are different in nature, the recommendation to initiate long-term penicillin prophylaxis is similar for both diseases as the recommendations for PSRA are derived from the recommendations in ARF (a monthly injection of 1.2 million units benzylpenicillin for 5 years or till adulthood).[6,7,10] In ARF the need for antibiotic prophylaxis is well recognized; carditis occurs in 33% of the adults and mitral regurgitation is the most frequent valvular abnormality. In contrast, data on the risk to develop valvular heart disease in adult PSRA are lacking. Sensitive screening on valvular heart disease in adults with PSRA requires echocardiography. Thus far, echocardiography in adult PSRA has been performed in two case series containing 3 and 6 patients, in whom no valvular abnormalities were observed.[12,13] Since no prospective studies in an unselected cohort of PSRA patients are performed, the question whether PSRA is predisposing adults to valvular heart disease is still unresolved.

We hypothesized that, considering the different clinical and genetic characteristics of PSRA and ARF, the risk on valvular heart disease is different as well. The present study is the first that performed echocardiography in an unselected cohort of adult PSRA patients. All patients that presented with PSRA to the Leiden Early Arthritis Clinic, an inception cohort consisting of >2,000 patients with early arthritis, were followed prospectively. After a mean follow-up of 7.7 years transthoracic echocardiography was performed to evaluate the occurrence of valvular heart disease.

METHODS

Study population

The present study comprised all patients that presented with PSRA to the Leiden Early Arthritis Clinic. The Leiden EAC is a phenotypically well characterized inception cohort that started in 1993 at the Department of Rheumatology of the Leiden University Medical Center for patients with recent onset arthritis. It is the only referral center for rheumatology in a health care region of ~ 400,000 inhabitants in the Netherlands.[14] General practitioners were encouraged to refer patients directly when arthritis was suspected and patients were included if physical examination revealed arthritis. The Leiden EAC is approved by the local Ethical Committee and patients gave informed consent. At first visit various variables were collected by anamnesis, physical, and laboratory examination. Joint examinations were performed and acute phase reactants as well as anti-streptolysin O titer (ASO) and anti-deoxyribonuclease B titer against streptococcal antigen (Anti-Dnase B) were measured.
The present study included all patients that presented with PSRA; PSRA was diagnosed in patients with recent arthritis fulfilling all of the following conditions: a) recent fever, cough or angina preexisting before development of arthritis, and b) increased titers of ASO (> 320units/mL), an increased anti-Dnase B (>400IE/ml), or a 4-fold ASO rise within 2-3 weeks after first laboratory ASO test. The cutoff levels for ASO and antiDnaseB were chosen more stringent than the reference value in our population (>200IE/ml for both) to avoid false positive misclassification. In our clinic, long-term antibiotic prophylaxis was not prescribed for PSRA. Patients with ARF received antiobiotic prophylaxis and were excluded from this study. Patients who at first presentation were known with pre-existing valvular heart disease were excluded from echocardiography.

Control Population

The controls were selected from an echocardiographic database; these controls were referred for either atypical chest pain, palpitations or syncope without murmur. Subjects who were referred for echocardiographic evaluation of known valvular disease, murmur, or heart failure were excluded. Subjects whose echocardiography revealed any structural heart disease, left ventricular dilatation or known valvulopathy were carefully excluded.[15] All controls were selected in a patient:control ratio of 1:2 and were matched for age, gender, body surface area (BSA) and left ventricular (LV) systolic function. We controlled for systolic LV function to avoid inclusion of patients with mitral regurgitation due to LV enlargement, with subsequent incomplete mitral leaflet closure. The echocardiographic data of the controls retrieved from the database were measured and analyzed by the same readers using the same method as in the patients.

Echocardiography

Patients and control subjects were imaged in the left lateral decubitus position using a commercially available system (Vivid 7, General Electric Vingmed, Milwaukee, Wisconsin, USA) equipped with a 3.5-MHz transducer. Standard gray-scale two-dimensional images were obtained in the parasternal (standard long and short axis) and apical views (2- and 4-chamber and long-apical axis views). M-

mode images were obtained from the parasternal long-axis views for quantitative assessment of LV dimensions: LV end-diastolic diameter and end-systolic diameter (ESD), interventricular septum thickness (IVST) and posterior wall thickness (PWT). LV end-diastolic (EDV) and end-systolic volumes (ESV) were derived and LV ejection fraction (EF) was calculated from apical 2- and 4-chamber views by Simpson's rule.[16] LV mass (LVM) was calculated by the cube formula and using the correction formula proposed by Devereux et al.[17]: $0.8 \times (1.04[(LVEDD + PWT + IVST)^3 - (LVEDD)^3]) + 0.6$, and was corrected for BSA to obtain LV mass index (LVMi).

The morphology and function of the mitral, aortic and tricuspid valves were studied with special attention. Color Doppler echocardiography was performed in all views after optimizing gain and Nyquist limit. Standard continuous-wave and pulsed-wave Doppler examinations were performed. When tricuspid regurgitation was present, pulmonary artery pressure was estimated using the modified Bernoulli equation. The evaluation of regurgitant valve disease was performed by two independent expert readers using the semiquantitative and quantitative methods recommended by the American Society of Echocardiography.[18] The severity of valvular regurgitation was determined on a qualitative scale according to the ACC/AHA guidelines for the management of patients with valvular heart disease:[19,20] mild (grade 1), moderate (grade 2) and severe (grades 3-4). Significant valvular disease was determined using the U.S. Food and Drug Administration case definition:[21] mild or greater aortic regurgitation or mitral regurgitation equal to or more than moderate severity. In addition, leaflet or cusp abnormalities were evaluated and comprised the presence of local or widespread thickening more than 5 mm, the presence of calcifications and leaflet or cusp motion abnormalities (restrictive or excessive). Valves were deemed as restrictive if leaflets were stiffer than normal and if retraction of leaflets or subvalvular apparatus towards the apex existed (in mitral and tricuspid valves). Aortic valve was regarded as restrictive when the valve showed evident doming of the cusps. In addition, valves were regarded as having excessive motion when leaflet or cusps prolapse was observed (according to the ACC/AHA guidelines).[19]

After echocardiography the length and weight were measured. In the patients also the blood pressure was taken.

Statistical analysis

The statistical Package for Social Sciences (SPSS) version 14.0 was used to analyze the data. The non-paired t-test was used to compare the LV dimensions data and the chi-square test to compare the prevalence of valvular regurgitation between the patient group and the control group. For all tests, p-values of <0.05 were considered as statistically significant.

RESULTS

Study population

Of all patients included in the Leiden Early Arthritis Clinic at the moment of analysis (n=2090), 286 early arthritis patients had serological evidence of a recent streptococcal group A infection. Of

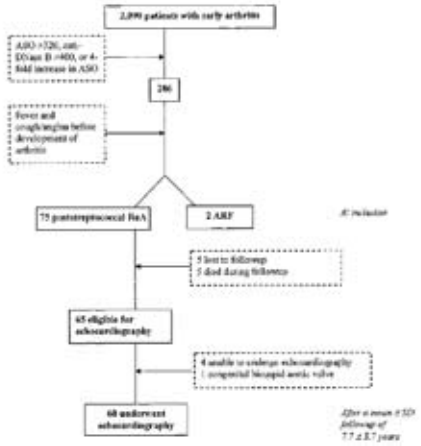

Figure 1. Study population at inclusion and during follow-up.

these, 77 patients had experienced fever, cough or angina before the development of arthritis (Figure 1). Two of these patients were diagnosed with ARF according to the Jones criteria (presence of 2 major criteria) and were prescribed long term antibiotic prophylaxis. Seventy-five patients were diagnosed with PSRA at inclusion and did not receive antibiotic prophylaxis.

During follow-up, five patients moved house and were lost to follow-up and five patients died due to pulmonary embolism (1), disseminated melanoma, (2) lung cancer (2) and "old age"(1). Importantly, none of these patients were reported to suffer from cardiac disease during life. Therefore, 65 patients were eligible for echocardiography. One patient was excluded because of the presence of a congenital bicuspid aortic valve and four patients were incapable to undergo echocardiography because of dementia and practical considerations. These four patients were questioned on the presence of symptoms that may be related to cardiac disease; none of them reported to have such complaints. In conclusion, 60 of the 75 patients that were diagnosed with PSRA at baseline underwent echocardiography.

Clinical characteristics

The characteristics of the PSRA-patients at inclusion are presented in Table 1. Inherent to the design of an inception cohort, the duration of follow-up is variable. The mean (±SD) duration of follow-up was 7.7 (3.9) years (minimal follow-up 1.1 year, median follow-up 8.9 years, maximal follow-up 13.1 years). The controls were matched to the patients for gender, age, BSA and LV systolic function at the time of echocardiography.

Left ventricular dimensions

The LV function and dimensions were not statistically different between the PSRA patients and controls (Table 2).

Mitral Valve

The results of the valvular studies are presented in Table 3. Echocardiographic examination on the morphology of the mitral valve revealed no differences in calcification, restrictive motion and excessive motion between patients and controls. Leaflet thickening was more frequent in controls than in patients (21% vs 8%, p=0.04). Mitral stenosis was absent in patients as well as in controls. The frequency of mild mitral regurgitation was found to be similar in patients and controls (23% and 21% respectively).

Table 1. Characteristics at inclusion of Post-Streptococcal Reactive Arthritis patients

	PSRA (n=60)
Baseline characteristics	
Female gender, No (%)	34 (57)
Age at inclusion (years), mean (SD)	37.9 (13.3)
Race, Caucasian, No (%)	51 (85)
Symptoms of arthritis	
Duration of joint symptoms (weeks), mean (SD)	9.7 (13.9)
Number of swollen joints, mean (SD)	3.7 (3.5)
Distribution of involved joints, No (%)	
Small joints of hand/foot	14 (23)
Large joints	35 (58)
Both small and large joints	11(18)
Distribution of involved joints, No (%)	
Upper extremity	11 (18)
Lower extremity	30 (50)
Both upper and lower extremities	19 (32)
Symmetrical distribution, No (%)	36 (60)
Laboratory findings	
ASO, mean, (SD)	695.3 (713.9)
Anti-Dnase B, mean, (SD)	529.3 (469.0)
4 -fold raise ASO, No (%)*	4 (14)
ESR, mean (SD)	45.2 (32.2)
C-reactive protein, mean (SD), (reference <10 mg/L)	48.9 (59.3)

** In 29 out of 60 patients a repeated ASO test was performed*

Aortic Valve

Morphologic characteristics were not significantly different between patients and controls. Aortic stenosis was detected in 2% of the patients and 2% of the controls. Mild aortic regurgitation was observed in 10% of the patients and 11% of controls, also revealing no statistically significant differences (Table 3).

Tricuspid Valve

No morphologic abnormalities of the tricuspid valve were observed in the controls (Table 3). Five percent of PSRA patients had tricuspid calcifications (p=0.04), all of these were spot calcifications that did neither affect the annulus nor the motion of the valve. Stenosis of the tricuspid valve was absent. Mild regurgitation of the tricuspid valve occurred in 43% of the patients and in 39% of the controls; one patient (2%) had a moderate regurgitation; these frequencies were not significantly different.

Table 2. Characteristics during echocardiography and left ventricular measurements

	PSRA-patients (N = 60)	Controls (N= 120)	p-value
Age (yrs)	45 ± 13	47 ± 7	0.2
Gender (M/F)	26 / 34	52 / 68	0.2
BSA (m^2)	2 ± 0.2	1.9 ± 0.2	0.2
RR systolic (mmHG)	137 ± 17.2	N.A.	
RR diastolic (mmHG)	82.7 ± 11.4	N.A.	
LV EDD (mm)	51 ± 5	50 ± 6	0.8
LV ESD (mm)	29 ± 5	31 ± 5	0.05
IVST (mm)	11 ± 3	10 ± 2	0.1
PWT (mm)	10 ± 1	10 ± 2	0.1
LVMi (gr/m^2)	101 ± 22	96 ± 26	0.2
LV EDV (ml)	100 ± 23	98 ± 27	0.6
LV ESV (ml)	43 ± 12	40 ± 13	0.2
LV EF (%)	57 ± 7	59 ± 6	0.2

Data presented as mean ± SD.

Abbreviations: BSA = body surface area, RR=blood pressure, LV=left ventricular, EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; ESD = end-systolic diameter; ESV = end-systolic volume; IVST = inter-ventricular septum thickness; LV = left ventricular; LVMi = left ventricular mass index; PWT = posterior wall thickness; N.A. = not applicable

Pulmonary Valve

None of the patients and controls had stenosis of the pulmonary valve. Among the PSRA-patients mild regurgitation of the pulmonary valve was more frequent compared to controls (47% vs 26%, p=0.01). Although the difference is statistically significant, mild regurgitations of the pulmonary valve are considered physiological and are not of clinical importance.

DISCUSSION

The present study is the first that examined the risk on valvular heart disease in an unselected cohort of adult patients with PSRA in a prospective study. No increased frequency of valvular abnormalities was observed. The value of a sensitive tool for the detection of valvular disease is underlined by recent studies in ARF showing that echocardiographic screening resulted in a considerable higher prevalence (almost ten times as high) of rheumatic heart disease compared to clinical screening.[22,23] Thus far echocardiography was only used in small case series of PSRA patients with a limited duration of follow-up.[12,13] We aimed to determine the risk on developing carditis in adult PSRA and therefore performed a comprehensive echocardiographic evaluation of an entire, unselected cohort of Caucasian adult PSRA patients. The current sample size allows, with 80% power and 95% confidence the detection of a OR of 2.6. Since the risk on any valvular disease in the aged-matched general

Table 3. Valve morphology and function

	PSRA-patients (N=60)	Controls (N=120)
Mitral valve		
Morphologic abnormalities - Calcifications	10 (17)	12 (10)
- Leaflet thickening	5 (8)	25 (21) *
- Restrictive motion	0	1 (1)
- Excessive motion	0	2 (2)
Stenosis	0	0
Regurgitation Grade: - Mild	14 (23)	25 (21)
- Moderate	0	0
- Severe	0	0
Aortic valve		
Morphologic abnormalities - Calcifications	13 (22)	23 (19)
- Leaflet thickening	7 (12)	6 (5)
- Restrictive motion	1 (2)	2 (2)
- Excessive motion	0	0
Stenosis	1 (2)	2 (2)
Regurgitation Grade: - Mild	6 (10)	13 (11)
- Moderate	0	0
- Severe	0	0
Tricuspid valve		
Morphologic abnormalities - Calcifications	3 (5)	0 *
- Leaflet thickening	0	0
- Restrictive motion	0	0
- Excessive motion	0	0
Stenosis	0	0
Regurgitation Grade: - Mild	26 (43)	47 (39)
- Moderate	1 (2)	0
- Severe	0	0
Pulmonary valve		
Stenosis	0	0
Regurgitation Grade: - Mild	28 (47)	31 (26)**
- Moderate	0	0
- Severe	0	0

** P= 0.04, ** P=0.01. Data presented in number of patients and percentage*

population is 0.4% REF) and the risk on valvular heart disease in ARF is >30%, the present study provides adequate power to identify a significantly increased risk on carditis.

Our data, revealing no increased frequency of valvular heart disease in PSRA patients compared to matched controls, may have important consequences for the recommendation to prescribe long-term antibiotics. In the current literature a monthly injection of benzylpenicillin is recommended for adult patients with PSRA, herewith referring to the guidelines in ARF.[6,7,10] Guidelines by authorative entities are missing; the American Heart Association refers only to pediatric literature on PSRA but gives no definite advice for adult patients with PSRA.[24] The present study may overcome this deficit.

Based on the present observations, routine long-term antibiotic prophylaxis in adult Caucasian patients with PSRA is not advocated.

The valvular abnormalities that were more frequent in patients than in controls are calcifications of the tricuspid valve and mild regurgitation of the pulmonary valve. However, the latter is considered physiological and is of no clinical significance. Likewise, spot calcifications of the tricuspid valve have no clinical impact and do not hamper the function of the valve. Moreover, the valvular abnormalities that are known to associate with ARF are mitral regurgitation, in frequency followed by aortic regurgitation. In our study these valve regurgitations were not more prevalent amongst patients compared to controls. Additionally, the prevalence of these regurgitations in our control group are in line with reported age-matched prevalence of regurgitations in patients with structurally normal hearts.[25]

The discrimination between the diagnoses ARF and PSRA is ambiguous by the lack of generally accepted definition or set of criteria for PSRA. In the present study we defined PSRA by having a) recent arthritis, b) recent fever, cough or angina preceding before the development of arthritis, and c) serological evidence of an antecedental streptococcal infection. Two patients were excluded because of the diagnosis ARF based on fulfilling the Jones criteria with having two major criteria. Thirty patients had arthritis combined with fever and an increased ESR or CRP and can be argued to fulfill the Jones criteria (one major and two minor criteria). Since the arthritis in these patients was not a polyarthritis, was atypical in its time course and/or did not responded dramatically to anti-inflammatory agents, these patients were classified as PSRA and not as ARF, which is in line with recommendations in the updated guidelines for the diagnosis ARF.[2] Importantly, the updated Jones criteria represent recommendations to supplement practitioners in the exercise of their clinical diagnosis and are not a substitute for clinical judgment. It is also essential to note that the Jones criteria implicate a risk for overdiagnosis of ARF, particularly in developed countries that have a declining incidence of ARF (jama ref). To assess whether these thirty patients affected the results, analyses with and without these patients were performed, giving comparable results (data not shown).

Intriguingly, the risk on valvular heart disease is not only different per diagnosis (ARF vs PSRA), but may also be different between children and adults. In ARF, carditis occurs in 50% of the children compared to 33% in adults.[12,13,28-30] In the pediatric literature on PSRA three studies performed echocardiographic screening on valvular heart disease in respectively 12, 24 and 40 children.[29-31] In the combined number of 76 patients valvular disease was detected in 6 cases (7.8%). Although these studies did not include a control group, these data indicate a possible difference in the occurrence of valvular heart disease between pediatric and adult PSRA.

The differences in frequency of valvular heart disease per disease entity lead to the questions what pathogenetic mechanisms are involved in the development of rheumatic heart disease. Again, most research is done on ARF. Molecular mimicry between streptococcal and human proteins is considered as the triggering factor for arthritis as well as for rheumatic heart disease. Antibodies to elements of the cell wall of Group A streptococci are observed to cross-react with glycoproteins present in heart valves and also with cardiac myosin and laminin, the latter also being present in cardiac valves. Cross reacting antibodies are able to bind to the endothelial surface, induce inflam-

mation and cellular infiltration and subsequently the valve is scarred.[30] Individuals carrying certain HLA-Clas II molecules or polymorphisms in the innate immune system (TNF-308, Mannose Binding Lectin) are predisposed to rheumatic heart disease.[30-33] Additionally, characteristics of the Streptococci determine the disease outcome. Traditionally this 'rheumatogenecity' has been considered as a feature of strains belonging to certain M serotypes (the serotypes M3 and M18 have been related to ARF). Recent genome wide analyses of group A Streptococci revealed that the heterogeneity in disease severity caused by Group A Streptococci is mediated by genetic variation in a signal transduction system, that affects the expression of virulence factors.[34,35] The combination of a susceptible host and a virulent Group A *Streptococcus* may induce an exaggerated immune response, inducing valvular heart disease. Although the HLA-Class II alleles that predispose to PSRA or ARF differ,[10] it is yet not elucidated which combinations of characteristics of the host and the microorganism determine whether a group A Streptococcal throat infection is followed by ARF or PSRA. Similarly, it is unknown which risk profiles explain the differences in risk on valvular heart disease.

CONCLUSIONS

The present study evaluated the risk on valvular heart disease in a prospective cohort of Caucasian adult PSRA-patients and observed no increase risk compared to matched controls. Based on these data, routine long-term antibiotic prophylaxis is not recommended in adult PSRA.

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