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Original Article

# Role of inflammation in nonrheumatic, regurgitant heart valve disease. A comparative, descriptive study regarding apolipoproteins and inflammatory cells in nonrheumatic heart valve disease

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**Abstract**

**Background:** Nonrheumatic aortic stenosis is the predominant cause of heart valve surgery in the Western world. Aortic and mitral regurgitation account for a lesser amount of the heart valve surgery. During the 1990s, inflammatory cell infiltrates have been demonstrated in nonrheumatic stenotic aortic valves. These findings suggest an inflammatory component in the pathogenesis of nonrheumatic aortic valve stenosis. However, nonrheumatic regurgitant aortic and mitral valves have not been investigated in this respect. The aim of this study was to compare nonrheumatic regurgitant aortic and mitral valves with stenotic aortic valves regarding the presence of T lymphocytes, macrophages, apolipoprotein B, and apolipoprotein A-I. **Methods:** Valve specimens were obtained from 42 patients referred to hospital for surgery because of significant heart valve disease. From these patients, 29 aortic stenotic valves, 9 aortic regurgitant, and 6 mitral regurgitant valves, all nonrheumatic, were obtained for the study. Fourteen valves collected from subjects undergoing clinical/medicolegal autopsy were used as control. In order to identify mononuclear inflammatory cells and apolipoproteins, sections were investigated with immunohistochemical analyses and then categorized semiquantitatively. **Results:** Regurgitant and control valves showed a significantly lower degree of inflammatory cell infiltrate and a lower degree of apolipoprotein deposition as compared to stenotic aortic valves. **Conclusions:** The signs of inflammation seen in nonrheumatic aortic stenosis are not prominent features in the nonrheumatic, regurgitant valves. This is consistent with the multi-factorial pathogenesis of these conditions. 

*Keywords:* Aortic valve regurgitation; Mitral valve regurgitation; T Lymphocytes; Apolipoproteins

## 1. Introduction

During the 1990s and the beginning of the 21st century, the opinion about the pathogenesis of calcific aortic stenosis has changed. The previous "wear-and-tear" concept has been questioned in favor of a more diversified pathogenesis, where the view of aortic stenosis is the result of a possible valve anomaly, valve stress, and/or inflammatory mechanisms [1–4]. Furthermore, the infiltration of the valve tissue by T lymphocytes and macrophages, and the presence of neutral lipid, lipoproteins, and lipid oxidation resemble the inflammatory process of the atherosclerotic disease [5–11]. In a previous publication from our study, we reported our findings of similar signs of inflammation in aortic stenosis regardless of whether the valve was tricuspid or bicuspid [12]. In the present paper, we compare nonrheumatic, regurgitant aortic, and mitral valves with the stenotic aortic valves regarding presence of T lymphocytes, macrophages, apolipoprotein B, and apolipoprotein A-I.

## 2. Methods

Seventy-six patients (19 mitral valves, 62 aortic valves), consecutively accepted for heart valve surgery, were

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Table 1
Clinical characteristics of patients undergoing valve replacement due to nonrheumatic aortic stenosis, aortic, and/or mitral regurgitation

| | AS ($n$=29) | AR ($n$=9) | MR ($n$=6) |
|---|---|---|---|
| Mean age, years (range) | 69 (60–77) | 48 (22–50) | 60 (50–72) |
| Sex, male/female | 14/15 | 8/1 | 6/0 |
| Hypertension | 7 | 3 | 0 |
| Smokers | 9 | 5 | 4 |
| Diabetes mellitus | 2 | 0 | 1 |
| Cerebrovascular disease | 1 | 0 | 0 |
| Peripheral vascular disease | 2 | 1 | 1 |
| Myocardial infarction | 1 | 1 | 1 |
| Coronary angiography/CAD | 29/10 | 5/3 | 6/1 |

AS indicates aortic stenosis; AR, aortic regurgitation; MR, mitral regurgitation; CAD, coronary artery disease.

enrolled in the study. Diagnosis was made on preoperative Doppler echocardiography. Patients with Marfan's syndrome, congenital heart disease, or valvular disease due to myocardial infarction were excluded by study design.

For technical and logistical reasons, valve specimens from 19 patients (6 mitral valves, 14 aortic valves) were not submitted for histological analysis. According to established macroscopic and microscopic criteria for rheumatic heart valve disease [13,14], 15 patients (7 mitral valves, 10 aortic valves) were excluded from the study. Thus, 42 patients, 16 women and 26 men [mean age, 64 years (range, 22–81 years)], yielded 44 nonrheumatic valves for histopathological and immunohistochemical studies; 9 aortic regurgitant valves (4 bicuspid and 5 tricuspid), 6 mitral regurgitant valves. and 29 aortic stenotic valves. The clinical characteristics of the three groups are shown in Table 1. Gross pathology as judged by echocardiographic characteristics and perioperative surgical comments is shown in Tables 2 and 3. Fourteen control valves, from a representative range of age of the study subjects, free from macroscopic evidence of heart valve disease, were collected from subjects undergoing clinical/medicolegal autopsy (12/2). These valves consisted of 6 mitral valves (women, 3; men, 3) and 8 tricuspid aortic valves (women, 3; men, 5).

### 2.1. Biochemistry

Blood samples for routine biochemistry and serum electrophoresis were obtained at the time of the preoperative investigation.

### 2.2. Histopathological analyses

After fixation in 10% formalin, the valves were measured and examined macroscopically as described by Schoen [14].

Table 2
Characteristics of regurgitant aortic valves

| Patient sex, age | Valve | Echo characteristics | Perioperative comments | Other clinically important disease |
|---|---|---|---|---|
| F, 72 | Tricuspid | Normal aortic root, valves with slightly increased echodensity, opening amplitudes seen | . . .aorta slightly wide, the valves moderately calcified, curled up | Hypertension |
| M, 69 | Tricuspid | Moderately widened aortic root, severely dilated ascendant aorta, valves with normal echodensity, and opening amplitudes | Thin, partly prolapsing cusps | Pernicious anemia, giant-cell arteritis, hypertension, on steroid medication |
| M, 55 | Tricuspid | Normal aortic root. Valves with increased echodensity, opening amplitudes are seen | The valves curled up, distended without calcification | Hypertension |
| M, 53 | Tricuspid | The aortic root is normal, valves slightly thickened and with normal opening amplitudes | The heart and great vessels are covered with a thin, tough coating as after pericarditis. The aortic valves have slightly thickened and shriveled cusps | – |
| M, 50 | Bicuspid | Slightly dilated aortic root with slightly changed valves | Bicuspid, fused cusps partly prolapsing, slight calcification in cusp margins | – |
| M, 48 | Tricuspid | Normal aortic root, the noncoronary cusp does not seem to fit | The valves are thickened with shrunken cusps | Severe RA |
| M, 42 | Bicuspid | The aortic root is slightly dilated with slightly changed valves | Markedly thickened valves without any calcification | – |
| M, 24 | Bicuspid | Moderately widened aortic root, slender valves with normal opening amplitudes | Valves without calcification | – |
| M, 22 | Bicuspid | Normal aortic root with slightly changed valves | The valves slightly shrunken | – |

M indicates male; F, female.