# Inflammatory biomarker kinetics after mechanical and bioprosthetic valve replacement

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## Summary

**Introduction:** valve disease is an important cause of heart failure. There is a direct relationship between valve deterioration and the patient's inflammatory status and cytokines: interleukin-6, interleukin-1, tumor necrosis factor, and C-reactive protein, involved in this major state of inflammation.
**Objective:** to report a series of cases of valve replacement, using a bioprosthetic or mechanical valve, and the inflammatory profile of them.
**Methods:** patients older than 18 years and with bioprosthetic or mechanical valve placed for a minimum of 6 months and maximum of 2 years were included. In addition to the demographic characteristics of each patient, inflammatory markers were measured and a comparison was made of echocardiographic results before (based on medical records) and after surgery. A total of 46 patients were enrolled, 23 with mechanical valve and 23 with bioprosthetic valve.
**Results:** of the 46 patients, 20 presented complete data were included, 12 with bioprosthetic and 8 with mechanical valve. There was no difference between types of prosthesis or implant site for the values of inflammatory markers although they were all above reference range.
**Discussion:** patients undergoing aortic mechanical valve implant benefited more than those undergoing bioprosthetic implant and both with much better results than those of valve replacements performed on mitral valve. In short, there was no difference in relation to inflammatory biomarkers.

**Keywords:** interleukin-6, heart failure, aortic valve stenosis, heart valve prosthesis.

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**Conflict of interest:** none

## Introduction

Heart diseases that affect valve leaflets are the main cause of heart failure.[1]

Recent data indicate that the number of deaths caused by heart valve diseases in the United States reaches a rate of 20,000 individuals per year, i.e., 7/100,000 people in the general population.[2] Aortic and mitral valves are most often affected, although dysfunctional pulmonary and tricuspid valves are indicators of adverse evolution. The durability of biological valves is limited to 10-15 years,[3] and around 50% of the patients develop complications within 10 years.[4]

A recent meta-analysis revealed that in male patients a biological valve lasts 15.1 years when implantation occurs at the age of 55, 16.8 years at the age of 65, and 18.8 years when individuals are 75 years of age. Structural valve degeneration was not observed in mechanical valve models.[3]

One of the causes for this diversity of events is more strictly connected to the inflammatory cascade mediated by interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF-α) and ultra-sensitive C-reactive protein (usCRP) than to the similarity to the evolution process of rheumatic or degenerative valve disease.

We reported the relation of a series of cases of aortic and mitral valve replacements (mechanical and biological) with the inflammatory markers IL-1, IL-6, usCRP and TNF-α in a hospital environment. The aim of this study, however, was to report not only the cases, but also the inflammatory profile of these patients.

## Methods

This is a report of a series of cases of patients with valve diseases who underwent surgery between January 2008 and March 2010.

Inclusion criteria were: adult individuals, aged 18 or over, with bioprosthetic or mechanical valve replacement over a period of no less than 6 months and no more than 2 years. Exclusion criteria were: body mass index (BMI) ≥25, diabetes, the presence of chronic kidney disease in patients with glomerular filtration rate below 60 mL/min/1.73m$^2$, the presence of hepatic disease, Aids, patients undergoing immunosuppressant therapy, patients who routinely made use of non-steroidal anti-inflammatory drugs, patients who were hospitalized within a period of 6 months prior to the screening interview for problems unrelated to valve replacement, loss to follow-up and death.

Within this period there were 46 patients who underwent valve replacement: 23 with St. Jude Epic heart valve bioprostheses (St. Jude Medical Inc., Minneapolis, MN, USA) and 23 with mechanical valves.

During a second phase of the study the measurement of usCRP, IL-1, IL-6 and TNF-α was performed using chemiluminescent immunoenzymatic assay with an Immulite 2000® analyzer (Siemens®, Frankfurt, Germany).

The echocardiographic parameters established for the sake of comparison of pre- and postoperative values were: Troy equation for the calculation of left ventricular mass; Bernoulli equation for the calculation of transvalvular flow velocity (mean transvalvular gradient); ejection fraction and left atrial diameter for patients with mitral prosthesis.

All individuals who were included in this study, previously approved by the Ethics and Research Committee of the ABC Medical School under number 012/2011, signed an informed consent form.

The results of the continuous variables were presented as their mean value and respective standard deviation.

## Results

The analysis of 46 medical records (23 patients in the bioprosthetic valve group and 23 in the mechanical valve group) was carried out in the period between August-September 2011.

Of these, 26 patients were excluded due to loss to follow-up, mortality or incomplete data supplied. A total of 20 patients were left, 12 with bioprosthetic valve and 8 with mechanical prosthesis valve (Table 1).

Table 1 shows a higher prevalence of male patients. The mean age was of 42.66 years for the bioprosthetic mitral valve replacement group and 61 years for the mechanical aortic valve replacement group.

An increased differential in the ejection fraction could be observed only in patients submitted to aortic valve replacement with a value of 10% in the biological group and of 4.85% in the mechanical valve group. Regarding the group submitted to mitral valve replacement, there was a subtle decrease in the postoperative ejection fraction value (Table 2).

As to the inflammatory markers, no differences between the types of prosthesis and implant sites could be observed in regard to the measured values of IL-1, IL-6, usCRP and TNF-α. However, their overall values were increased.

## Discussion

A case-by-case approach suggests that, in this series, patients who underwent aortic mechanical valve replacement benefited more than those who were submitted to biological implant, and both procedures showed much

**TABLE 1** Comparison between inflammatory biomarkers and type of valve used

| Variables | Bioprosthetic aortic (n = 7) | Metallic aortic (n = 7) | Bioprosthetic mitral (n = 5) | Metallic mitral (n = 1) |
|---|---|---|---|---|
| Age (years) | 62.12 ± 10,84 | 61 ± 1 | 42.66 ± 13.86 | 52 |
| Male (%) | 75 | 42,8 | 66.6 | 0 |
| Δ Ejection fraction (%) | 10.00 ± 9.38 | 4.85 ± 9.02 | -0.80 ± 8.46 | -8.0 |
| CRPus (mg/L) | 7.27 ± 4.56 | 6.10 ± 6.19 | 4.72 ± 4.08 | 5.2 |
| TNF-α (pg/mL) | 10.40 ± 2.19 | 10.64 ± 3.20 | 11.17 ± 3.52 | 9.8 |
| IL-1 (pg/mL) | 5.40 ± 1.19 | 5.00 ± 0.12 | 5.84 ± 2.10 | 6.6 |
| IL-6 (pg/mL) | 3.55 ± 0.84 | 2.75 ± 0.87 | 2.88 ± 1.16 | 4.8 |

**TABLE 2** Difference in echocardiographic parameters compared to pre-operative measures

| Valve | Delta ejection fraction | Delta left ventricle mass |
|---|---|---|
| Bioprosthetic aortic | 24.04 | - 43.55 |
| Bioprosthetic mitral | 6.78 | -37.61 |
| Metallic aortic | 7.78 | -24.7 |
| Metallic mitral | -13.11 | -36.54 |

better results than the ones found in the performance of mitral valve replacements.

As time passes by, after the implantation of biological and mechanical valves, the onset of a deposit of extracellular matrix and calcification of the leaflets can be observed.[5,6] Many reports point to the existence of alterations in the *serum* levels of cytokines, namely IL-1, IL-6, usCRP and TNF-α. These variations are not exclusive to valve replacement procedures. Nevertheless, they are present, and are likely to cause valve degeneration.[7-9]

The individual analysis of each patient revealed that the levels of *serum* inflammatory markers had no direct relation with their clinical and echocardiographic data, since high *serum* concentrations of cytokines could be observed in hemodynamically and clinically stable patients and, on the other hand, lower *serum* values were found in those with higher functional class and lower ejection fraction.

In their study, Kastellanos et al.[4] showed a decrease in usCRP and TNF-α *serum* levels in the medium term (6 months). However, the decrease in TNF-α values proved to be a more reliable marker of inflammation recovery than usCRP. Although no significant differences in cytokine values could be observed regarding sex, there was a stronger tendency for women to present higher levels of usCRP when they were submitted to aortic valve replacement.[4]

Taking into consideration the differences in the ejection fraction before and after the replacement procedure, the conclusion is that there was a better response in patients who had the aortic rather than the mitral valve replaced. Moreover, no differences in the values of IL-1, IL-6, TNF-α and usCRP could be observed regardless of the type of valve used or the implant site.

## Resumo

Cinética dos marcadores inflamatórios após troca valvar protética mecânica e bioprótese: série de casos.

**Introdução:** doença valvar é importante causa de insuficiência cardíaca. Existe relação direta entre a deterioração valvar e o estado inflamatório do paciente, sendo as citocinas interleucina-6, interleucina-1, fator de necrose tumoral e a proteína C reativa as principais envolvidas nesse estado de estimulação.
**Objetivo**: relatar uma série de casos de troca valvar, bioprótese ou mecânica e seu perfil inflamatório.
**Métodos:** pacientes maiores de 18 anos e portadores de bioprótese ou protética mecânica, com período mínimo de 6 meses e máximo de 2 anos, foram incluídos. Além das características demográficas de cada paciente, colheram-se os marcadores inflamatórios e comparou-se o ecocardiograma conforme registro de prontuário antes e depois da cirurgia. Um total de 46 pacientes foi incluído, tendo sido 23 com valva mecânica e 23 de bioprótese.
**Resultados:** dos 46 pacientes, chegamos ao total de 20 pacientes com dados completos, sendo 12 com bioprótese e 8 com protética mecânica. Não houve diferença entre tipo de prótese ou local de implante para os valores dos marcadores inflamatórios, contudo, na média, seus valores estavam aumentados.
**Discussão:** pacientes submetidos ao implante de valva protética mecânica aórtica beneficiaram-se mais do que os submetidos ao implante de bioprótese e ambos com resultado bem superior às trocas realizadas na valva mitral. Não houve diferença em relação aos biomarcadores inflamatórios.

**Palavras-chave:** insuficiência cardíaca, estenose da valva aórtica, interleucina-6, bioprótese.

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