Original Research

Time Course of C-Reactive Protein, Tumour Necrosis Factor-Alpha and Monocyte Chemoattractant Protein-1 Following the Surgical Treatment of Patients with Aortic Valve Stenosis

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Introduction: Patients with aortic valve stenosis show elevated levels of inflammatory markers in peripheral blood. The aim of this study was to investigate the time course of changes in these markers and to look for sex-related changes in their biological behaviour following aortic valve replacement.

Methods: We studied 52 patients (32 men, 20 women) who underwent aortic valve replacement and had no concomitant coronary artery disease. Men and women did not differ significantly with respect to age, body surface area, or body mass index. Levels of high sensitivity C-reactive protein (hsCRP), tumour necrosis factor-alpha (TNF-α) and monocyte chemoattractant protein-1 (MCP-1) were measured from venous blood samples taken before, and 10 days, 3 months and 6 months after aortic valve replacement.

Results: Baseline hsCRP levels were 5.34 ± 5.71 mg/dl and 7.64 ± 7.46 mg/dl for men and women, respectively. Levels increased significantly at 10 d (49.11 ± 32.15 and 51.63 ± 34.3 mg/dl, $p < 0.001$), then reduced at 3 m (5.85 ± 5.04 and 8.49 ± 7.69 mg/dl, $p < 0.001$) and 6 m (3.41 ± 0.83 and 7.84 ± 7.32 mg/dl, $p < 0.001$). Women had higher levels than men at 6 m ($p = 0.027$). Levels of TNF-α reduced progressively, from 212.4 ± 119.5 and 255.7 ± 171.3 pg/ml at baseline, to 121.6 ± 47.7 and 150.0 ± 33.5 pg/ml at 10 d, 134.7 ± 25.3 and 138.6 ± 30.9 at 3 m, and 48.7 ± 8.8 and 44.9 ± 10.5 pg/ml at 6 m ($p < 0.001$). MCP-1 levels also reduced progressively, from 157 ± 64.8 and 145.6 ± 13.4 pg/ml at baseline, to 128.6 ± 18.8 and 122.7 ± 10.3 pg/ml at 10 d, 49.0 ± 12.4 and 56.6 ± 11.5 pg/ml at 3 m, and 29.1 ± 6.4 and 30.6 ± 7.3 pg/ml at 6 m ($p < 0.001$). The time course of the changes in these indexes was identical for men and women, except that 6 m hsCRP levels were significantly higher in women.

Conclusions: After aortic valve replacement, hsCRP levels show an early increase followed by a decrease, whereas both TNF-α and MCP-1 are reduced progressively. The time course curve is identical in men and women, except that hsCRP levels are higher in women than in men 6 months after aortic valve replacement.

I n contrast to the older "wear and tear" hypothesis, the prevailing view today is that aortic valve stenosis is due to a chronic inflammatory process that leads to fibrosis, calcification of the leaflets, and progressive narrowing of the aortic valve orifice.[1-7] This view has been confirmed by many histopathological studies[8-12] that show-

ed inflammatory infiltration of the leaflets, as well as by clinical observations demonstrating an increase in the levels of biological markers of inflammation, such as high sensitivity C-reactive protein (hsCRP),[13,14] tumour necrosis factor-alpha (TNF-α),[15] and monocyte chemoattractant protein-1 (MCP-1).[16,19] In addition, Gerber et al[20]

showed that hsCRP levels are reduced 6 months after aortic valve replacement, indirectly suggesting the inflammatory pathogenesis of aortic valve stenosis. However, that study did not report the intermediate time course of hsCRP changes following replacement of the valve. Furthermore, it is not known how the levels of other inflammatory markers, TNF-α and MCP-1, change during long-term follow up after aortic valve replacement.

The aim of the present study was to investigate the time course of changes in hsCRP, TNF-α and MCP-1 and to look for sex-related differences in the biological behaviour of these inflammatory markers following aortic valve replacement in patients with severe aortic valve stenosis.

Material and methods

The study population included 52 patients, mean age 67 ± 10 years, with severe aortic stenosis, who underwent surgical replacement of the aortic valve. Thirty-two (61.5%) of the patients were men and 20 (38.4%) were women.

Patients with concomitant coronary artery disease, recent infection, atrial fibrillation, a history of rheumatic fever, or other rheumatic or non-rheumatic disease that could cause an inflammatory reaction, were excluded from the study.

Blood samples were taken with the patient in a supine position. Samples were taken a few days before, and 10 days, 3 months and 6 months after aortic valve replacement. Samples were immediately centrifuged and serum was stored at -70° C. Measurements of hsCRP, TNF-α and MCP-1 were made after completion of the study protocol.

hsCRP

Measurements were made by nephelometry using a Date Behring reagent. The method is based on the principle that polystyrene molecules coated with monoclonal antibodies specific for human CRP cluster together when they are mixed with blood samples containing CRP. These clusters will diffract a light beam passing through a blood sample that is placed in the nephelometer. The intensity of the light that is scattered through a particular angle is in proportion to the CRP concentration in the sample.[21]

TNF-α and MCP-1

Levels were measured by the ELISA method using a Biomedica reagent. The method is based on the double antibody (sandwich) principle.[22]

Statistical analysis

Measurements are given as mean ± standard deviation, while discrete variables are given as percentages. Changes over time were analysed using one-way ANOVA and pairs of values from two time points were compared using Tukey's honestly significant difference test. The linear correlation between inflammatory markers was examined using the Pearson correlation test. A p-value <0.05 was the criterion of significance. All statistical analyses were performed using the SPSS 11.0 software package (SPSS Inc., Chicago, Ill).

Results

Table 1 shows that age, height, weight, body surface area and body mass index did not differ significantly between men and women.

hsCRP

The variations in levels of hsCRP are shown in table 2. Before aortic valve replacement, the mean hsCRP

Table 1. Patient characteristics comparing men and women.

	All patients (n=52)	Men (n=32)	Women (n=20)	p
Age (years)	67.1 ± 10.4	66.0 ± 11.0	68.9 ± 9.3	0.335
Height (m)	1.66 ± 0.08	1.66 ± 0.09	1.67 ± 0.08	0.711
Weight (kg)	74.3 ± 12.2	73.5 ± 9.6	75.5 ± 15.7	0.575
BMI (kg/m^2)	26.9 ± 3.9	26.9 ± 3.6	27.0 ± 4.4	0.870
BSA (m^2)	1.82 ± 0.17	1.81 ± 0.15	1.84 ± 0.20	0.616

BMI – body mass index; BSA – body surface area.

level for the patients considered as a single group was 6.36 ± 6.56 mg/dl. Ten days after surgery hsCRP had increased significantly to 50.33 ± 32.72 mg/dl. Some degree of increase in hsCRP levels was seen in every patient at 10 days. By 3 and 6 months after operation hsCRP levels had fallen to 7.39 ± 6.72 mg/dl and 5.70 ± 5.67 mg/dl, respectively. Although each change in hsCRP during the follow-up period was statistically significant (p<0.001), the 6-month level did not differ significantly from the baseline value (p=0.461, Figure 1).

The changes in hsCRP followed an identical time course in men and women, except that 6-month levels were significantly higher in women than in men (p=0.027, Figure 1). At the other time points there was no significant difference between men and women (p=0.258 at 10 d, p=0.353 at 3 m).

High initial hsCRP levels (normal level ≤3.5 mg/dl, according to the control sample in the manufacturer's kit) were found in 20 (38%) of the 52 patients. The clin-

ical and morphometric characteristics did not differ between patients with high initial hsCRP and those with normal hsCRP levels prior to operation.

Although the initial difference between these two subgroups was highly significant (p<0.001), at the other time points the difference was not significant (p=0.141 at 10 d, p=0.120 at 3 m, p=0.213 at 6m). In addition, the 6-month hsCRP level did not differ significantly from baseline in either subgroup (p=0.056 for high hsCRP, p=0.137 for normal hsCRP, Figure 2).

TNF-α

Table 3 shows the changes in TNF-α during the study period. The mean level of TNF-α before aortic valve replacement was 231.5 ± 144.4 pg/ml. TNF-α reduced progressively to 135.4 ± 43.3 pg/ml at 10 days, 137.0 ± 28.2 pg/ml at 3 months and 46.8 ± 9.7 pg/ml at 6 months. The initial values of TNF-α were extremely
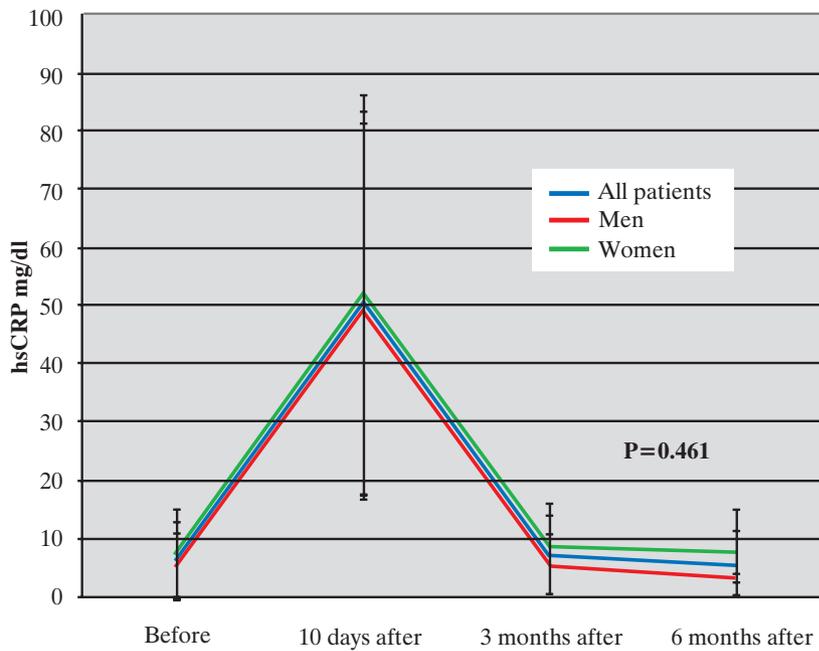

Figure 1. Graphical representation of the time course of mean hsCRP levels in all patients, and in men and women separately, before and after aortic valve replacement. The levels six months after surgery were not significantly different from those before.

Table 2. Time course of changes in hsCRP (mg/dl) before and after aortic valve replacement.

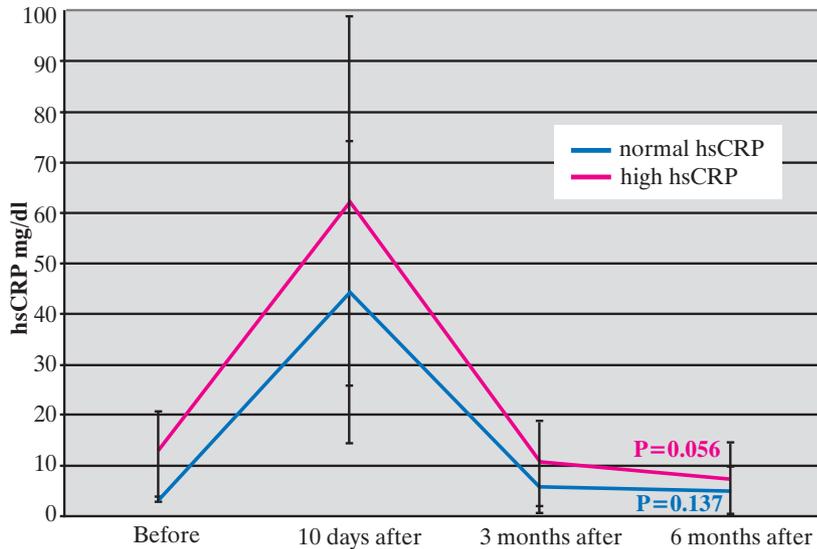|	Before	10 days after	3 months after	6 months after	p
All patients	6.36 ± 6.56	50.33 ± 32.72	7.39 ± 6.72	5.70 ± 5.67	<0.001
Men	5.34 ± 5.71	49.11 ± 32.15	5.85 ± 5.04	3.41 ± 0.83	<0.001
Women	7.64 ± 7.46	51.63 ± 34.33	8.49 ± 7.69	7.84 ± 7.32	<0.001
p men vs. women	NS	NS	NS	0.027	

Figure 2. Graphical representation of the time course of mean hsCRP levels in patients with normal and elevated hsCRP levels prior to surgery. The levels six months after surgery were not significantly different from those before.

elevated, but a more detailed analysis revealed that 9 patients had normal initial levels (normal value ≤51 pg/ml, according to the control sample in the manufacturer's kit). Six of these 9 patients were in the upper normal range (51 pg/ml).

At 6 months post procedure all patients had TNF-α levels within the normal range. TNF-α levels were similar in men and women (p:NS) and followed the same time course during follow up in both sexes (Figure 3).

MCP-1

Changes in MCP-1 levels are given in Table 4. The mean level of MCP-1 was 151.7 ± 48.2 pg/ml before aortic valve replacement, and reduced progressively to 125.5 ± 15.0 pg/ml at 10 days, 53.3 ± 12.2 pg/ml at 3 months, and 29.9 ± 6.8 pg/ml at 6 months after operation. Only 1 patient had a normal MCP-1 level before surgery. At 6 months post procedure 11 patients had MCP-1 levels above the normal range (15-26 pg/ml, according to the control sample in the manufacturer's kit). MCP-1 levels were similar and followed the same time course during follow up in men and women (Figure 4).

Correlations between markers

Statistical analysis revealed a significant correlation between levels of hsCRP and MCP-1 (Figure 5), and a highly significant correlation between MCP-1 and TNF-α (Figure 6).

Table 3. Time course of changes in TNF-α (pg/ml) before and after aortic valve replacement.

	Before	10 days after	3 months after	6 months after	p
All patients	231.5 ± 144.4	135.4 ± 43.3	137.0 ± 28.2	46.8 ± 9.7	<0.001
Men	212.4 ± 119.5	121.6 ± 47.7	134.7 ± 25.3	48.7 ± 8.8	<0.001
Women	255.7 ± 171.3	150.0 ± 33.5	138.6 ± 30.9	44.9 ± 10.5	<0.001

Table 4. Time course of changes in MCP-1 (pg/ml) before and after aortic valve replacement.

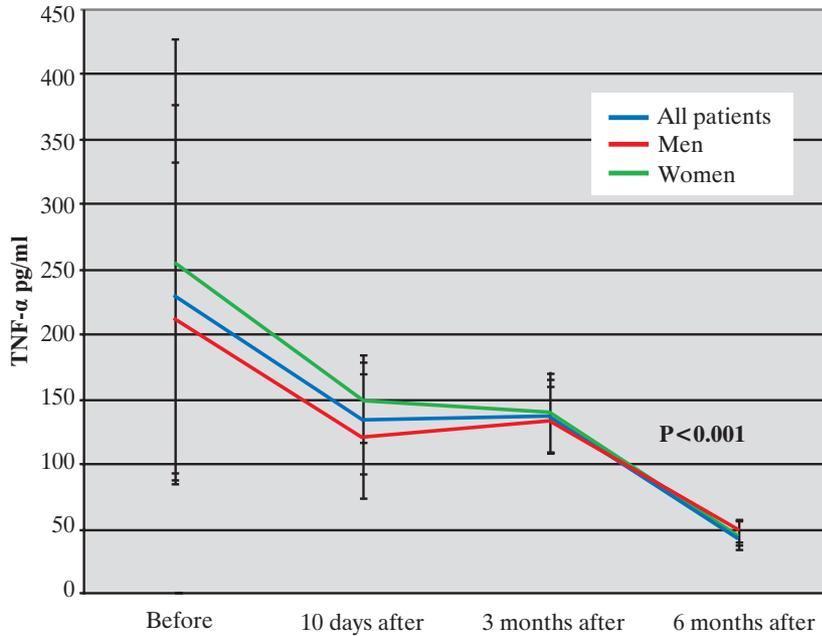|	Before	10 days after	3 months after	6 months after	p
All patients	151.7 ± 48.2	125.5 ± 15.0	53.3 ± 12.2	29.9 ± 6.8	<0.001
Men	157.0 ± 64.8	128.6 ± 18.8	49.0 ± 12.4	29.1 ± 6.4	<0.001
Women	145.6 ± 13.4	122.7 ± 10.3	56.6 ± 11.5	30.6 ± 7.3	<0.001

Figure 3. Graphical representation of the time course of mean TNF-α values in all patients, and in men and women separately, before and after aortic valve replacement.
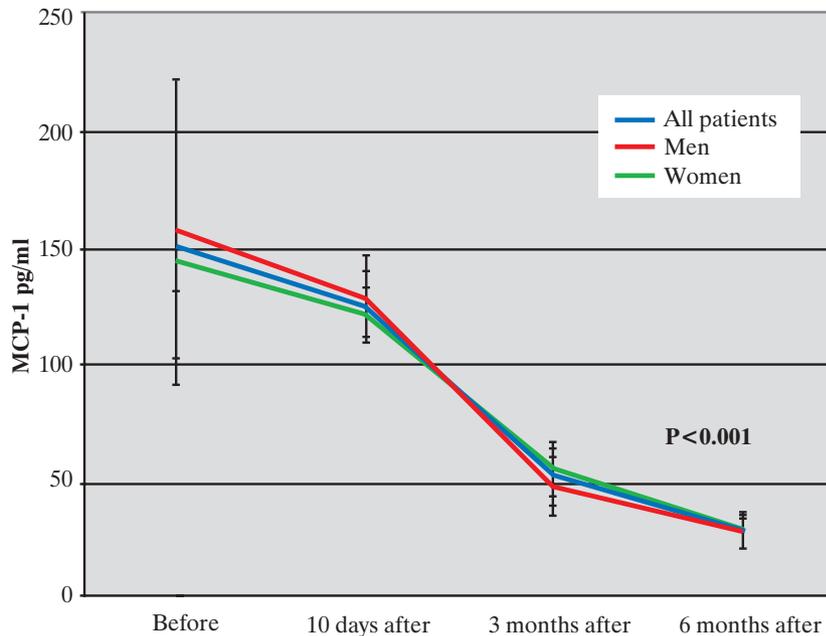

Figure 4. Graphical representation of the time course of mean MCP-1 values in all patients, and in men and women separately, before and after aortic valve replacement.

Discussion

The most important findings of this study are as follows:

- Levels of hsCRP are significantly increased 10 days after surgery in patients with aortic valve stenosis. Although mean hsCRP levels are restored to baseline levels at 3 months and slightly lower at 6 months post procedure, in 13.4% of patients they nevertheless remain high.

- TNF-α levels reduce progressively, returning to normal 6 months after operation.
- A similar reduction is seen in MCP-1. However, 21% of patients still show high levels of MCP-1 6 months postoperatively.
- The time course of hsCRP, TNF-α and MCP-1 is identical in men and women, except that women have higher levels of hsCRP 6 months after surgery.
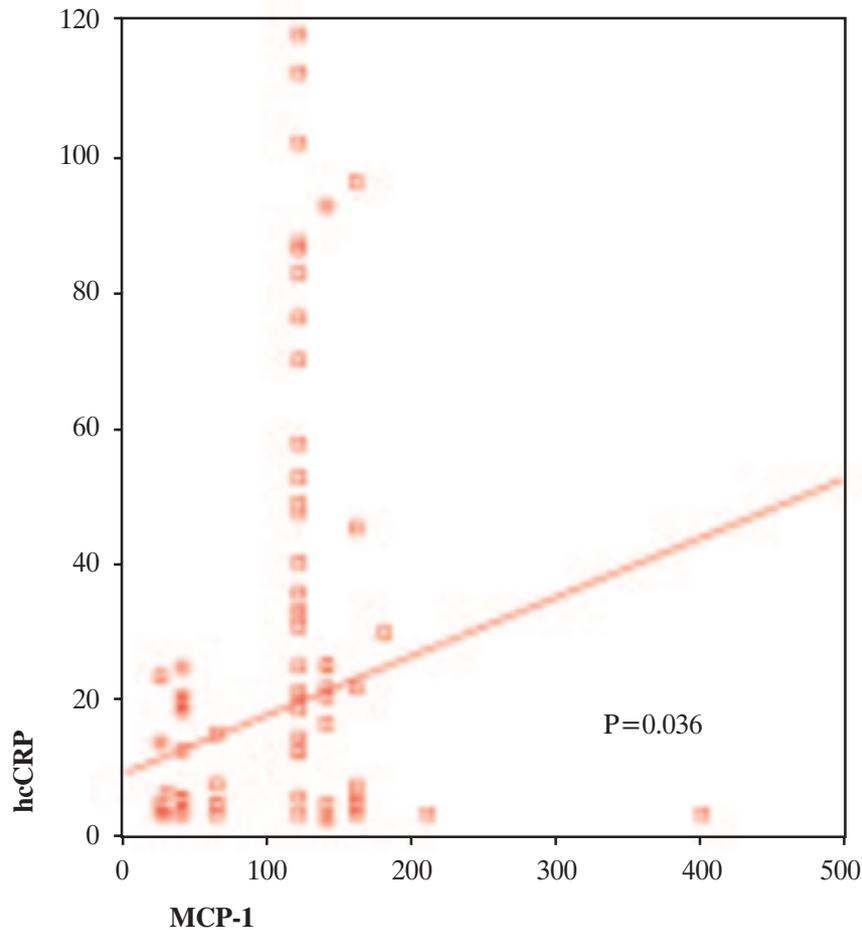
Figure 5. Correlation between levels of hsCRP and TNF-α in all patients.

hsCRP

hsCRP is one of the acute phase proteins and is considered to be a non-specific but sensitive marker of local, acute, or chronic inflammation.[23-25] hsCRP is produced in the liver, probably also in other cells, and has a multifaceted action on the cardiovascular system.[23-27] Galante et al,[13] followed by other investigators, found that hsCRP levels are elevated in patients with degenerative aortic valve stenosis. Gerber et al[20] observed that hsCRP levels after aortic valve surgery are decreased in comparison with those before, indirectly supporting the view that active local inflammation plays a role in the pathogenesis of degenerative aortic valve stenosis.

The findings of Gerber et al indicated that although hsCRP levels 6 months after operation were lower than before, they were not significantly so (p=0.06). Our own findings agree with this observation, since we also found a small but not significant reduction in 6-month hsCRP levels compared to baseline (Figure 1). This could be attributed to the fact that 7 of our patients (13.4%) continued to have high hsCRP levels at 6 months (>3.5 mg/dl). Furthermore, before operation 62% of our patients had normal hsCRP levels and only 38% showed elevated hsCRP. The clinical and morphometric characteristics were similar in patients with normal and those with elevated hsCRP levels. The only statistically significant difference in the 20 patients (38%) with abnormal hsCRP prior to surgery was the elevated hsCRP level itself.

At 10 days post surgery hsCRP levels had increased significantly in all patients (Figure 1, Table 2) and at 6 months hsCRP levels were higher in women than in men (p=0.027).

From the international literature it is clear that the role of hsCRP in the inflammatory pathogenesis of aortic valve stenosis is beyond doubt.[20-26] Indeed, this pro-
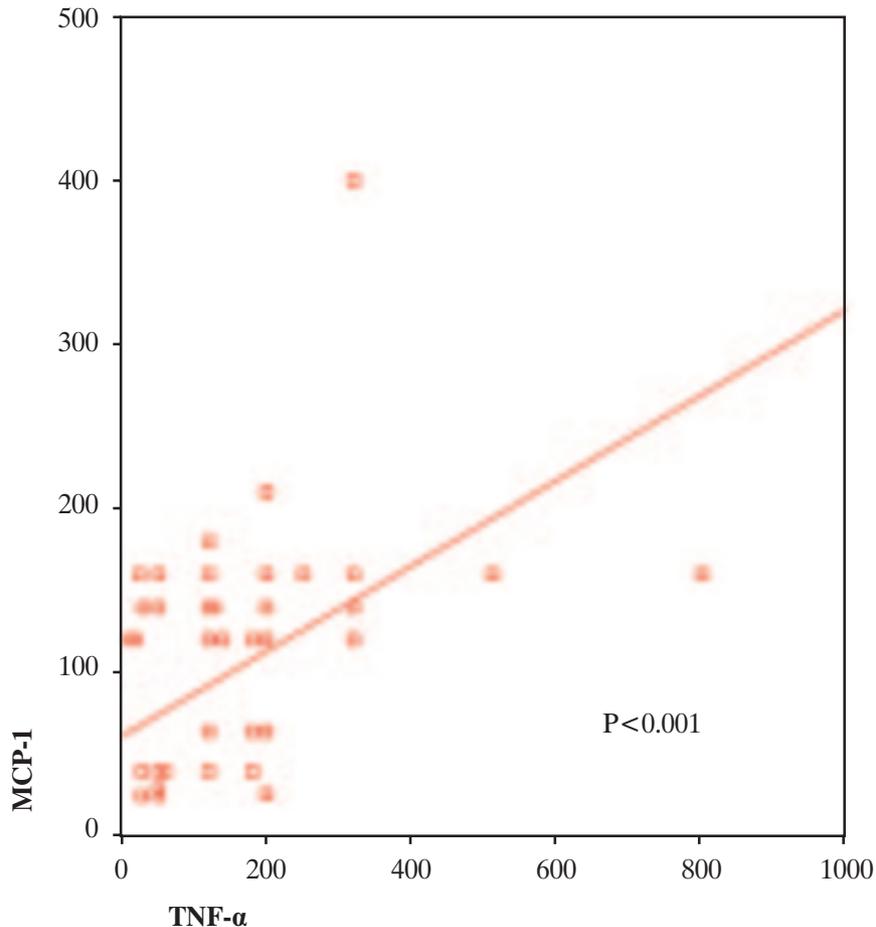
Figure 6. Correlation between levels of TNF-α and MCP-1 in all patients.

tein has been found in the leaflets of patients with aortic valve stenosis, suggesting that high hsCRP levels in the peripheral blood reflect the inflammatory process within the valve leaflets themselves.[27,28] The absence of elevated hsCRP levels in the majority of the patients with severe aortic valve stenosis in our study could be explained by a milder local inflammatory reaction in the leaflets because of the advanced degeneration and severe calcification of the aortic valve. This observation is in agreement with the findings of Fox[26] and Sanchez,[25] who found an inverse correlation between hsCRP levels and the degree of calcification of the aortic valve. This probably means that the most intense local inflammatory process in the aortic valve leaflets occurs in the earliest stage of development of valvular disease, as was suggested by the findings of Otto et al.[8]

The increase in hsCRP levels early (10 days) after operation could be attributed to a local inflam-matory reaction to the median sternotomy, or to infection. A possible interpretation of the failure of hsCRP levels to return to normal in all our patients 6 months after operation could be the persistence of latent infection. However, in none of our patients was there clinical suspicion of latent microbial or other infection. This obliges us to accept another mechanism for the existence of elevated hsCRP levels in a small number of patients at 6 months. Such a mechanism could be the presence of a low level inflammatory reaction in the myocardium, which was described in a recent study of patients with left ventricular systolic overload and cardiac hypertrophy,[29] or another extracardiac cause. The higher levels of hsCRP in women than in men we observed at 6 months are understandable, given that elderly women suffer more frequently from extracardiac diseases and exhibit more serious postoperative complications than men of similar age.

TNF-α

The cachectin TNF-α is a proinflammatory polypeptide cytokine that is produced by stimulated macrophages and other types of cell and activates the expression of many genes that contribute to inflammation, as do hsCRP, MCP-1, and other peptides.[30-34] TNF-α is not found in the hearts of healthy individuals.[15] However, in patients with aortic valve stenosis it appears to be involved in the mechanisms of dystrophic calcification, heterotopic ossification of the valve, and structural remodelling of the left ventricular myocardium.[34] Kapadia et al,[15] in a clinical study, found much higher levels of TNF-α in patients with severe aortic valve stenosis than in those with severe mitral regurgitation. In addition, Vanderheyden et al[35] reported that the genetic expression of cytokines in the myocardium is higher in aortic valve stenosis than in idiopathic dilated cardiomyopathy.

Although our own findings tend to confirm the observation of Kapadia et al, our results show that 9 patients (17%) had TNF-α levels within the normal range prior to operation. An important finding of our study, which to our knowledge has not been reported before in the international literature, is that in contrast to hsCRP the time course of TNF-α in our patients showed a steady decrease, returning almost to normal values 6 months after surgery (Table 3, Figure 3). The unexpected biological behaviour of TNF-α early after operation could be due to the more rapid reduction in levels (within 10 days, according to the study protocol) in comparison to levels of hsCRP. This is also supported by the fact that, in contrast to hsCRP levels, which remained high in some cases, levels of TNF-α were restored to normal in all our patients 6 months after operation. Whatever the reason for the increase in hsCRP in the first 10 days after surgery, this biochemical marker cannot be used for the early estimation of a reduction in local inflammation. In contrast, TNF-α appears to be a more reliable index of the early or late regression of local inflammation following removal of the diseased aortic valve leaflets.

Another important finding of our study is that levels of TNF-α had an excellent correlation with levels of MCP-1. This relationship demonstrates that mild inflammation of the aortic valve leaflets is the common triggering mechanism for the production and elevation of these biochemical markers of inflammation in the peripheral blood.[30,35]

MCP-1

MCP-1 belongs to the chemokines; it induces chemotaxis and the migration of monocytes, and plays an important role in the development of atherosclerosis.[36] Many studies have shown that, although atherosclerosis does not have precisely the same pathogenetic mechanism as aortic valve stenosis, the two processes have the element of inflammation in common and share the same risk factors.[37-40] It is thus to be expected that patients with aortic valve stenosis, like those with atherosclerosis, would have elevated levels of MCP-1 in the peripheral blood.

The findings of the present study confirm that MCP-1 levels before operation were indeed significantly elevated in almost all our patients with aortic valve stenosis. After surgery, levels of MCP-1, like those of TNF-α, showed a progressive decrease over time (Table 4, Figure 3). At 6 months post operation only 11 patients still had elevated MCP-1 levels. The time course of MCP-1 following surgical treatment makes it another reliable index of the early and late regression of inflammation after the removal of the aortic valve leaflets and the implantation of a prosthetic valve.

Men versus women

The international literature does not contain any reference to whether the behaviour of biological markers of inflammation after the surgical treatment of aortic valve stenosis differs between men and women. Our study found that the time course of levels of hsCRP, TNF-α and MCP-1 is identical for men and women (Tables 2, 3, 4, Figures 1, 3, 4), with the sole exception that women have higher hsCRP levels 6 months after operation.

Limitations of the study

The determination of hsCRP levels was made using the reagent employed in everyday clinical practice. However, for TNF-α and MCP-1 measurements we used reagents that are not in wide clinical use and were supplied by the manufacturer only for research purposes.

The study did not include a control group. The normal values used for the biological markers were those supplied by the manufacturer in the control sample included in the kit.

Conclusions

Levels of hsCRP and TNF-α are not elevated in all

patients undergoing surgical treatment of aortic valve stenosis.

Ten days after aortic valve replacement, hsCRP levels are significantly increased, then decrease progressively by 3 and 6 months after operation. This substance is therefore not a reliable marker for the early prognosis of regression of inflammation. In contrast, the progressive reduction in levels of TNF-α and MCP-1 following surgery shows that these substances have greater reliability as markers of early and late regression of inflammation.

Six months after operation, levels of hsCRP and MCP-1 remain elevated in 13.4% and 21% of patients, respectively.

The time course of all three biochemical markers is identical in men and women, except that women have higher hsCRP levels than men 6 months after aortic valve replacement.

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