



Egyptian Society of Cardiology
The Egyptian Heart Journal

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ORIGINAL ARTICLE

Inflammatory status in patients with rheumatic mitral stenosis: Guilty before and after balloon mitral valvuloplasty



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Received 14 July 2015; accepted 8 February 2016

Available online 8 March 2016

KEYWORDS

Rheumatic mitral stenosis;
High sensitivity C-reactive protein;
Balloon mitral valvuloplasty

Abstract *Aim:* We studied the inflammatory status, suggested by high sensitivity C-reactive protein (hsCRP) in patients with rheumatic mitral stenosis (MS) before, immediately after, and 1-month after balloon mitral valvuloplasty (BMV).

Methods and results: We studied 31 BMV candidates [35.6 ± 12.8 years, 20 (65%) females, and 9 (29%) had atrial fibrillation rhythm]. Mitral valve area (MVA) and hsCRP were measured before, immediately after BMV, and 1 month after BMV in 13 patients. In addition, hsCRP was measured in 15 controls. hsCRP was significantly higher in MS patients than control, significantly increased after BMV, and dropped 1 month after BMV to values comparable to basal but still higher than normal. hsCRP showed a trend for correlation with MVA after BMV ($r = 0.384$, $p = 0.07$), and the absolute increase in MVA (d-MVA) correlated significantly with the absolute increase in hsCRP (d-CRP) ($r = 0.523$, $p = 0.01$).

21 patients had successful BMV and 10 patients had unsuccessful BMV. The increase in hsCRP post compared to pre-BMV was attenuated in patients with unsuccessful BMV, and receiver operator characteristic curve suggested that hsCRP > 3.6 before BMV and d-CRP < 2.25 mg/dL can detect patients with unsuccessful BMV with good sensitivities and specificities.

Conclusion: Inflammatory pathogenesis of rheumatic fever, suggested by hsCRP, seems fixed both before, and after BMV. A basal increase in hsCRP before BMV is related to BMV success and an acute increase immediately after BMV seems related to trauma of balloon dilatations.

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1. Introduction

The principal cause of mitral stenosis (MS) is rheumatic fever, which remains endemic, therefore a major public health problem, in developing countries. Despite the striking decrease in

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Peer review under responsibility of Egyptian Society of Cardiology.

<http://dx.doi.org/10.1016/j.ehj.2016.02.005>

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the prevalence of rheumatic fever, MS is still a major problem for older patients in Western countries.¹

Inflammation is a very important part of the mechanism of development of MS as a sequel of rheumatic fever, and many studies have shown that inflammatory markers, such as high sensitivity C-reactive protein (hsCRP), are associated with the active phase, chronic status, and the progression of rheumatic valvular disease.²⁻⁴

Percutaneous balloon mitral valvuloplasty (BMV) has become the standard treatment option for symptomatic patients with mitral stenosis (MS) who have pliable morphology of the mitral valve. The increased clinical applications of this invasive procedure and cumulative clinical experience have been accompanied by significant improvements in its success rate and safety.^{5,6}

C-reactive protein (CRP) is increased in patients with acute rheumatic fever, and was said to increase during chronic rheumatic valvular disease.^{2,3} The exact natural history of relations of levels of hsCRP and rheumatic MS with considerations of treatment with BMV is not yet studied.

The aim of this study was twofold, first, to study the inflammatory status, suggested by hsCRP in patients with MS before, immediately after, and 1-month after BMV, and, second, to test the effect of inflammatory status of rheumatic fever on outcomes of BMV.

2. Methods

The study included 31 consecutive mitral stenosis (MS) patients who were candidates for balloon mitral valvuloplasty (BMV) in Ain Shams University hospital. Patients were excluded if they had any other local or systemic inflammatory process suspected to increase the basal inflammatory status of the patients. 13 patients were followed up 1 month after BMV. All patients studied had their hsCRP measured and echocardiography done before, after, and 1 month after BMV. In addition, 15 age and sex matched control subjects who had no risk factors and no apparent cause of inflammation had their hsCRP measured and compared with other study groups. The Institutional Review Board on Biomedical Research at Ain-Shams University Hospital, Cairo, Egypt, approved the study protocol, and all study subjects gave informed consent consistent with this protocol.

3. Measurement of hsCRP

Venous blood samples were drawn under aseptic conditions and centrifuged and 2 ml serum was collected and stored at minus 20 °C. All the serum samples were then analyzed for high sensitivity C-reactive protein (hsCRP) levels at our pathology department using ELISA technique. CRP was measured from all patients before and after BMV. hsCRP was also measured from 13 patients 1 month after BMV and from 15 controls and compared.

4. Echocardiographic studies

Echocardiographic studies were done before and immediately after BMV, and 1 month after BMV with a commercially available echocardiography system using a 2.5 MHz multi-frequency

phased array transducer (Vivid 5; GE Vingmed Ultrasound AS, Horten, Norway). Mitral valve area was assessed using 2-D planimetry. The smallest orifice of the mitral valve was identified by scanning from the left atrium in the direction of the LV apex using basal-LV short-axis view. The gain settings were adjusted until the lowest level was determined, at which the circumference of the mitral orifice was still visible. Mitral valve area was calculated by planimetry of the mitral valve contour after identification of the frame with the orifice at its maximal opening in early diastole.

Mitral valve flow envelope was acquired using continuous wave Doppler from the mitral position, while keeping the interrogation line parallel to the color Doppler signal on the mitral position. The mean transvalvular pressure gradient was calculated with the modified Bernoulli equation. Two experienced echocardiographers working separately reviewed all echocardiographic data, and all measurements were made in ≥ 3 consecutive cardiac cycles and in ≥ 5 cycles if the patient's rhythm was atrial fibrillation. The average values were used for the final analyses.

5. Definition of success of BMV

Patients were considered to have successful BMV if they had a final mitral valve area $> 1.5 \text{ cm}^2$ and a 50% increase in mitral valve area. Accordingly, patients were classified into patients with successful BMV and patients with unsuccessful BMV.

6. Statistical analysis

Categorical data were expressed as number (%) and were compared using chi-square test. Continuous data were expressed as mean \pm SD and were compared using student *t*-test if they were normally distributed and Mann Whitney *U*-test if they were not normally distributed. Normal distribution of the continuous data was checked using Kolmogorov–Smirnov test. Correlations were checked for inflammatory markers using Pearson correlation coefficient. The ability of pre-BMV hsCRP to predict unsuccessful BMV was checked using receiver operator characteristic curve (ROC-curve), by which the best cutoff value for prediction that shows best sensitivity and specificity was checked. One-way ANOVA test was used to compare different continuous variable before, directly after and one month after BMV. *P*-value < 0.05 was considered statistically significant. All the analyses were performed with commercially available software (SPSS version 21.0, SPSS, Inc., Chicago, IL, USA).

7. Results

Table 1 summarizes the demographic and clinical data. The mean age was 35.6 ± 12.8 years, 20 patients (65%) were females and 9 patients (29%) had atrial fibrillation rhythm (Af). 15 patients (48%) had moderate MS and 16 (52%) had severe MS. 25 patients (81%) had mild mitral regurgitation (MR), and 6 patients (19%) had moderate MR. After BMV, MR remained mild in 22 patients (71%), 6 patients had moderate MR (19%) and 3 patients had severe MR (10%).

The mean age of the control subjects was 41 ± 7 and 10 (66.7%) were females. There was no significant difference

Table 1 Demographics and basic data.

Variable	(n = 31)
Age (years)	35.6 ± 12.8
Male/female n(%)	11(35)/20(65)
Sinus/atrial fibrillation n(%)	22(71)/9(29)
MS severity before n(%)	
Moderate/severe	15(48)/16(52)
MR before n(%)	
Mild/moderate	25(81)/6(19)
MR after n(%)	
Mild/moderate/severe	22(71)/6(19)/3(10)
Success/unsuccessful n(%)	21(66)/10(33)

Continuous variables are expressed as mean ± SD and categorical variables are expressed as n(%). MS, mitral stenosis and MR, mitral regurgitation.

between patients and controls regarding age ($p = 0.125$) or sex ($p = 0.886$).

8. MVA and hsCRP after BMV and at 1-month follow-up

Table 2 summarizes the pressures, echocardiographic data and inflammatory markers before and after BMV. In addition, Wilkin's echocardiographic score for all patients before BMV was 6.3 ± 0.9 .

As expected, MVA and PG increased significantly after compared to before BMV (Table 2). One month after BMV, it was found that MVA and PG did not significantly change compared to those after BMV while MVA remained significantly higher and PG remained significantly lower than their corresponding values before BMV (Table 3). Interestingly, hsCRP significantly increased after compared to before BMV (Table 2, Fig. 1), and it was found that hsCRP values at one month dropped significantly compared to after BMV, however was not different than their values before BMV (Table 3, Fig. 1). Compared to controls, the basal hsCRP before BMV was significantly higher. After 1 month from BMV, hsCRP continued to be higher than controls (Table 3, Fig. 1).

While MVA significantly increased After BMV, significant decrease was noticed for LAP, RVSP, and PG. There was no significant difference in case of RAP, LAV or RAV.

9. Comparisons according to success of BMV

21 (66%) patients were shown to have had sufficient dilatation of their mitral valve and were considered successful, and 10 (33%) patients were considered to have had unsuccessful procedures due to insufficient dilatation. Table 4 summarizes comparisons between patients with and without successful BMV.

Before BMV, there was no significant difference between patients with successful versus non-successful BMV regarding LAP, MVA, or CRP. After BMV, there was no significant difference between patients with successful versus non-successful BMV regarding LAP, or CRP, while d-CRP was significantly lower in patient with unsuccessful BMV (3.5 ± 2.3 vs. 1.4 ± 1.6 mg/dL, $p = 0.041$).

It is important to note that, as expected from the classification, patients with successful BMV had significantly higher

Table 2 Comparisons before and after BMV.

	Before	After	p-value
LAP (mmHg)	27.8 ± 6.3	15.4 ± 5.9	< 0.001
RVSP (mmHg)	52.6 ± 17	38.2 ± 11	0.007
RAP (mmHg)	10 ± 4	9 ± 4.1	0.46
PG (mmHg)	12.2 ± 6.7	5.7 ± 2.6	< 0.001
LAV (ml)	125.3 ± 40	112 ± 35	0.26
RAV (ml)	55.6 ± 32	50 ± 31.7	0.57
MVA (cm ²)	0.98 ± 0.27	2.03 ± 0.55	< 0.001
hsCRP (mg/dL)	3.98 ± 1.9	6.5 ± 2.3	< 0.001

LAP, left atrial pressure, RVSP, right ventricular systolic pressure, RAP, right atrial pressure, PG, mean pressure gradient across mitral valve, LAV, left atrial volume, RAV, right atrial volume, MVA, mitral valve area and hsCRP, high sensitivity C-reactive protein.

MVA after BMV and higher d-MVA (1.25 ± 0.4 vs. 0.34 ± 0.22 cm², $p = < 0.001$).

It is also worth noting that, both patients with successful and unsuccessful BMV, had their LAP significantly decreased, and MVA significantly increased. As for hsCRP, values significantly increased after compared to before BMV only in patients with successful BMV, while this increase was attenuated in unsuccessful cases.

10. Correlations with inflammatory markers and prediction of success of BMV

A trend of correlation for hsCRP with MVA after BMV was noticed ($r = 0.384$, $p = 0.07$), while there was no correlation before BMV ($r = 0.022$, $p = 0.912$). Interestingly, d-CRP showed a significant correlation with d-MVA ($r = 0.523$, $p = 0.01$).

Receiver operator characteristic curves (ROC-curves) for values that best detect unsuccessful BMV were initiated for pre-BMV hsCRP and for d-CRP. ROC-curves suggested that CRP before BMV > 3.6 and d-CRP < 2.25 mg/dL, could predict unsuccessful BMV with sensitivities of 78% and 86% and specificities of 72% and 63% (Fig. 2).

11. Discussion

Our study demonstrated that:

1. hsCRP is increased in patients with rheumatic MS. Further increase occurs immediately after BMV, which decreases back again after 1 month to values comparable to their corresponding before BMV, however was still considered higher than normal.
2. Higher levels of hsCRP before BMV and less increase in hsCRP after BMV are predictive of unsuccessful procedures.

12. Inflammation in the course of natural history of MS

The most accepted hypothesis to explain the valvular damage in acute rheumatic fever is based upon an antigenic similarity

Table 3 Comparisons for inflammatory markers after 1 month follow-up.

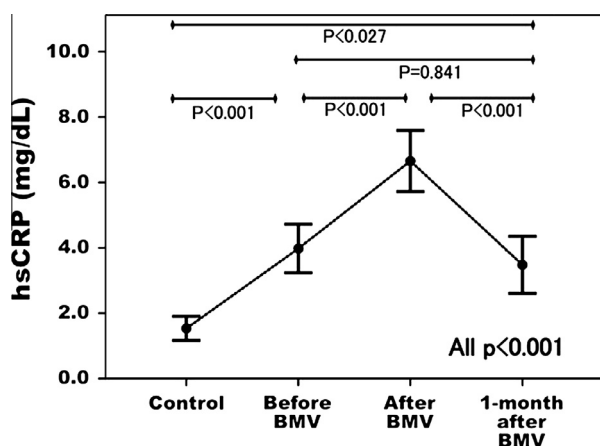
	Control	Before	After	1 month	<i>p</i> -value
MVA	–	0.98 ± 0.27	2.03 ± 0.55	2.02 ± 0.65	<0.001*
PG	–	12.2 ± 6.7	5.7 ± 2.6	5.2 ± 2.8	<0.001**
hsCRP (mg/dL)	1.5 ± 0.7	3.98 ± 1.9	6.5 ± 2.3	3.5 ± 1.5	<0.001***

Continuous variables are expressed as mean ± SD and categorical variables are expressed as n(%). MVA, mitral valve area, PG, mean Doppler derived pressure gradient and hsCRP, high sensitivity C-reactive protein.

* $p = 0.962$ between 1 month and after BMV, $p < 0.001$ between 1 month and before BMV.

** $p = 0.992$ between 1 month and after BMV, $p = 0.005$ between 1 month and before BMV.

*** $p < 0.001$ between 1 month and after BMV, $p = 0.841$ between 1 month and before BMV, <0.001 between controls and before BMV, <0.001 between controls and after BMV, 0.027 between controls and 1 month after BMV.

**Figure 1** Comparisons of hsCRP between controls and patients before, after and 1 month after BMV.

between human heart valves and group A beta hemolytic streptococci that causes abnormal antibody response leading to an autoimmune process, which causes damage to the heart valves, most commonly a stenotic mitral valve.⁷⁻⁹

Our study showed that, compared to controls, patients with chronic MS had significantly high levels of hsCRP, which supports the previous claim of an ongoing inflammatory process as a part of the pathogenesis of MS.^{6,10,11} It was not surprising, however, to have the levels of hsCRP significantly elevated immediately after BMV, because the nature of the procedure itself is traumatic and should cause an increased level of acute phase reactants, especially when more trauma, and thus more dilatation, is exerted. This procedural trauma–inflammation relationship was proven in our study by the direct correlation between the d-CRP and d-MVA, which means that, the more

the trauma exerted by balloon dilatations, the larger MVA in comparison with its value before BMV, but also the higher the circulating levels of hsCRP because of trauma.

Interestingly, levels of hsCRP after 1 month fell back to values comparable to their correspondents before BMV, which are still higher than normal.

It is reasonable to suspect that, this continuing increase in hsCRP during follow-up is an indicator of the chronic status of inflammation of rheumatic heart disease. Thus, despite that stenosis itself might be alleviated, the valve might be still subject to the same pathophysiological mechanism that originally caused the stenosis. The expected consequence of that later in life would be occurrence of mitral valve restenosis. We have previously reported the relation between the status of ongoing inflammation and the development of mitral valve restenosis for patients studied in the long follow-up after BMV.¹² In this study, despite patients were not followed up to check for development of restenosis, a possible evidence of the ongoing inflammation that might lay the foundation for the development of restenosis is found. According to the conclusion of our previous report, only those patients who show a further increase in inflammatory markers would develop restenosis, and thus patients of our current study should be followed up before suspicion of restenosis is made.

13. Role of hsCRP in prediction of success after BMV

In our study, two variables related to hsCRP were found to predict the occurrence of unsuccessful procedure. The first one was high hsCRP before BMV, and the second one was the less increase in hsCRP after BMV. According to the definition used in our study, unsuccessful procedure was the one with outcomes suggestive of failure to sufficiently dilate the mitral valve. In our point of view, the two variables explain

Table 4 Comparisons before and after BMV according to success of procedure.

	Successful BMV (<i>n</i> = 21)			Unsuccessful BMV		
	Before	After	<i>p</i>	Before	After	<i>p</i>
LAP (mmHg)	27.4 ± 7	14.6 ± 6	<0.001	29.8 ± 6	18.8 ± 4	0.003
MVA (cm ²)	0.96 ± 0.29	2.2 ± 0.4	<0.001	0.98 ± 0.3	1.3 ± 0.22	0.04
CRP (mg/dL)	3.7 ± 1.9	6.9 ± 2.3	<0.001	4.6 ± 1.8	5.9 ± 2.4	0.351

Abbreviations as in Table 3.

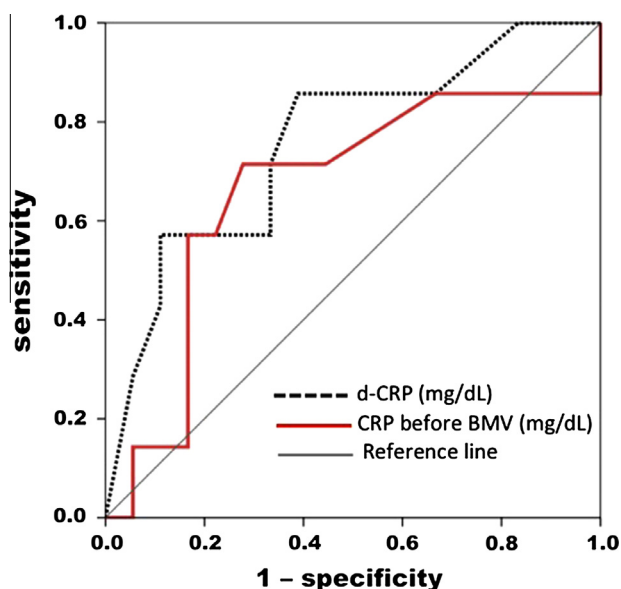


Figure 2 Receiver operator characteristic curve for d-CRP (dashed black line) and hsCRP before BMV (solid red line) for detection of successful BMV.

the same mechanism of occurrence of unsuccessful BMV from different perspectives. Higher basal hsCRP might suggest a severer basal inflammatory process. If so, valves subjected to such state of inflammation might have developed more fibrosis and thus became more difficult to sufficiently increase in size in response to balloon dilatation. A supporting evidence for that was the reported correlation with Wilkin's echo score and hsCRP before BMV. Moreover, less increase in hsCRP after BMV, might signify, less effort exerted during balloon dilatation, thus suggesting, again, the relation of traumatic effect of BMV to dilatation of the mitral valve and release of inflammatory markers.

It is important to note that, the predictive role of pre-BMV levels of hsCRP is a confirmation of a previous report that showed similar result.¹³

14. Limitations

The study suffered some important limitations. First, the study included a small number of patients, a lot of whom were lost during follow-up. Thus further studies should confirm the current study findings using a larger number of patients. Second, it seems more appropriate to study patients before BMV, and to follow them up for development of restenosis after BMV. Because this would be extremely time consuming, future prospective long-term follow-up studies should test the effects of the found ongoing inflammatory process on development of mitral valve restenosis. Third, the study was only concerned with the anatomical status of the mitral valve post BMV and 1 month after BMV; thus, further studies should also focus on the effects of ongoing inflammation on the clinical picture immediately after BMV and at follow-up.

15. Conclusion

Inflammatory process linked to pathogenesis of rheumatic fever, suggested by hsCRP, seems fixed both before, and after BMV. A basal increase in hsCRP before BMV is related to BMV procedural success and an acute increase immediately after BMV seems related to trauma exerted by balloon dilatations, which, at short term, falls back to values that are still higher than normal thus suggesting ongoing pathogenic effects of rheumatic fever on the mitral valve even after BMV.

Conflict of interest

Author states that there is no conflict of interest.

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