Central Asian Journal of Medicine

TACTICAL ASPECTS IN MANAGING OF RHEUMATIC MITRAL VALVE STENOSIS WITH ATRIAL FIBRILLATION

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ABSTRACT

Despite the sufficient level of understanding in the treatment of mitral stenosis, a number of unresolved issues persist. The review article discusses the fundamental strategies in managing patients with rheumatic mitral stenosis complicated by atrial fibrillation. In patients with mitral stenosis, the prevalence of atrial fibrillation ranges from 17% to 60%, depending on age, leading to a fivefold increase in the risk of stroke and a twofold increase in the risk of mortality.

Key words: mitral valve stenosis, rheumatism, atrial fibrillation, balloon mitral valvuloplasty.

INTRODUCTION

Atrial fibrillation (AF) is a common complication in patients with mitral valve stenosis (MVS). Over time, increased pressure in the left atrium leads to structural and electrophysiological changes, which heighten the likelihood of AF development, particularly in elderly patients. AF significantly impairs cardiac function, reduces physical endurance, and increases the risk of thromboembolic events [22]. This type of arrhythmia markedly worsens the prognosis of the disease and often persists even after surgical or endovascular interventions. Managing heart rhythm or rate control is crucial in these patients, considering hemodynamic alterations and the deterioration of cardiac pump function.

In patients with AF associated with MVS, the use of warfarin is always recommended, regardless of the stroke risk assessment using the CHA2DS2-VASc score. The effectiveness and safety of novel oral anticoagulants require further investigation in this patient population [10]. Balloon mitral valvuloplasty (BMV) is the primary treatment for patients with critical MVS, but its impact on AF prevention and the maintenance of sinus rhythm (SR) needs further study (Fig. 1) [22]. Electrical cardioversion and radiofrequency catheter ablation (RFCA) may be considered for AF management; however, the outcomes of RFCA in patients with MVS require additional research. The efficacy of AF ablation may vary depending on factors such as age, comorbidities, and the extent of cardiac remodeling [10].

AF occurs in approximately one-third of patients with MVS and significantly worsens the disease prognosis [32]. Preventing AF and properly managing this patient population are crucial in determining treatment strategies, including the selection of optimal medical therapy and surgical and endovascular treatment options (such as BMV).

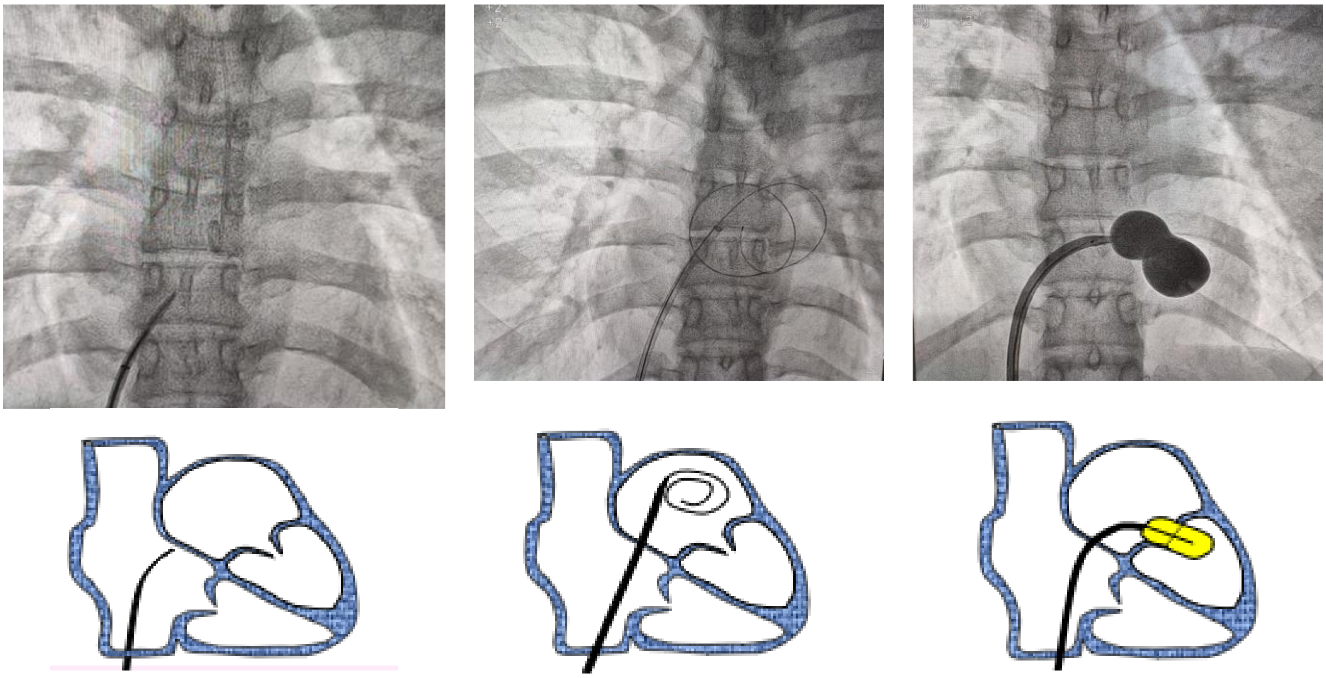

Figure 1. Key stages of balloon mitral valvuloplasty as seen on radiographic images (top row) and schematic representations (bottom row).

Epidemiology of Mitral Valve Stenosis

Rheumatic fever is the primary cause of MVS in young and middle-aged patients. In rheumatic MVS, autoimmune inflammation leads to commissural fusion of the mitral valve, thickening of the leaflets, and calcium deposition. Unlike rheumatic MVS, degenerative processes in the valve are characterized by predominant calcification of the mitral annulus, which may extend to the mitral leaflets without commissural fusion [10].

The severity of MVS is influenced by the frequency of acute rheumatic fever episodes and the effectiveness of prevention and treatment. The prevalence of rheumatic heart disease varies significantly by geographic location. For example, in the United States, the incidence of rheumatic heart disease is low at 0.1%, while in European countries it reaches up to 9%, with 85% of cases being of rheumatic etiology. In low- and middle-income countries, the incidence of rheumatism is 20-30 per 1000 population [32].

Cardiac Hemodynamics in Mitral Valve Stenosis

The increased pressure gradient from the left atrium to the left ventricle through the narrowed mitral orifice leads to overstretching and dilation of the left atrium (LA). The geometric pattern of this LA dilation is isometric, making it necessary to measure the volume, rather than the diameter, of the LA using M-mode or planimetric methods to accurately assess its remodeling [25].

There is a direct correlation between the degree of mitral stenosis, associated hemodynamic changes, and the likelihood of developing AF. Additionally, the patient's age influences both the frequency and severity of AF. For example, in individuals under 35 years of age, the prevalence of persistent AF is 15-20%, while in patients over 45 years, this figure can rise to 35-60% (Table 1) [1, 3, 5, 7, 11, 21, 27, 29, 30].

A study by Shaw et al. (2003) demonstrated that after BMV, the prevalence of sinus rhythm (SR) decreases with age. For instance, approximately 80% of patients under 40 years old maintained sinus rhythm, whereas in patients over 70 years old, this rate dropped to 15%. This indicates an increased incidence of AF with age, which is associated not only with mitral valve pathology but also with age-related changes in cardiac rhythm [28].

Table 1.

The prevalence of permanent atrial fibrillation following balloon mitral valvuloplasty (Iung B. et al., 2018г.). [10]

Trials	Number of patients	Age	Mitral orifice area (cm^2)	Atrial fibrillation (%)
Arora et al.[5]	4850	27	0,7	15
Fawzy et al.[6]	547	32	0,9	13
Ben Farhat et al.[7]	654	33	1,0	29
Stefanadis et al.[8]	441	44	1,0	46
Lung et al.[9]	2773	47	1,0	31
Hernandez et al.[10]	561	53	1,0	57
Meneveau et al.[11]	532	54	1,0	45
Palacios et al.[12]	879	55	0,9	49
Tomai et al.[13]	527	55	1,0	45

The data from the table allow for the assessment of the relationship between mitral orifice area and the likelihood of developing atrial fibrillation in patients of different ages.

Structural Remodeling of the Left Atrium

Rheumatic fever induces specific inflammation characterized by the formation of Aschoff bodies; however, recent histological studies have not found a statistically significant association between these bodies and the development of AF. Predictors of AF include cardiomyocyte cytolysis, while hypertrophy of left atrial cardiomyocytes and glycogen deposition in them are associated with the maintenance of SR. Approximately 90% of patients who develop AF have interstitial fibrosis. In addition to morphological changes, structural alterations in the heart, including left atrial dilation, contribute to the development of AF [10].

Myocardial fibrosis is a crucial component of structural cardiac remodeling and is directly correlated with the incidence of AF. In patients who have undergone mitral valve replacement, the onset of persistent AF has been associated with increased left atrial size, more pronounced fibrosis, and older age (over 50 years), as compared to those with SR [32].

Electrical Remodeling of the Left Atrium

Arrhythmogenic foci in the pulmonary veins play a crucial role in the development of AF, and RFCA of these veins is a key treatment method, especially for patients with paroxysmal AF and MVS. However, RFCA is not the method of choice for patients with persistent AF and MVS, as this form of AF is less amenable to ablation, and the arrhythmia is not always associated with arrhythmogenic foci in the pulmonary veins. A more sustained effect can be expected in patients with paroxysmal AF and MVS [8, 15, 20].

Electrical remodeling of the myocardium, characterized by changes in the electrical properties of cardiomyocytes, plays an important role in both maintaining and exacerbating AF. AF can induce electrical remodeling, and vice versa, leading to a self-perpetuating arrhythmia. There is a correlation between electrical remodeling and structural remodeling of the myocardium, which is accompanied by increased frequency of AF occurrence and maintenance: "AF begets AF."

Studies assessing the electrophysiological properties of the heart are relatively few. One such study included patients with MVS prior to mitral commissurotomy, compared with patients undergoing RFCA of the left accessory pathway in Wolff-Parkinson-White (WPW) syndrome. In patients with MVS, both atria showed delayed electrical impulse conduction and increased effective refractory period, as well as low atrial potential voltages and a higher frequency of electrically silent areas ("scar tissue"), compared to the group without MVS. However, the study did not determine whether electrical remodeling preceded or followed structural myocardial remodeling [15].

Thus, research indicates that patients with MVS experience delayed electrical impulse conduction and increased refractory period in both atria, which may be associated with electrical remodeling. However, it is not clear whether electrical remodeling precedes structural remodeling or vice versa. Undoubtedly, the coexistence of electrical and structural remodeling is associated with a higher frequency of AF occurrence and maintenance.

These data suggest that electrical remodeling may at least partially be caused by the overload and stretching of the left atrium. Therefore, timely correction of structural changes, such as MVS, may help prevent the progression of electrical remodeling.

Diagnosis of Mitral Valve Stenosis

The diagnosis of MVS is often confirmed through physical examination, which may reveal a loud first heart sound, a mitral valve opening snap, and a diastolic murmur during ventricular diastole. However, the primary diagnostic method is echocardiography (EchoCG). The normal mitral orifice area is 4-6 cm^2. The severity of stenosis is classified based on the mitral orifice area: mild (area > 2 cm^2), moderate (area 1.0-2.0 cm^2), and severe (critical, area < 1 cm^2), with significant stenosis considered when the mitral orifice area is < 1.5 cm^2.

Literature indicates significantly worse survival rates for patients with AF compared to those with SR. Ten-year and twenty-year survival rates for patients with AF were 25% and 0%, respectively, while those with SR had survival rates of 47% and 30%, respectively. Mortality rates are associated with age and the presence of heart failure. However, the role of AF and other comorbid conditions in increasing mortality remains unclear [10].

Multivariate analysis showed that patients with AF had worse outcomes following intervention compared to patients with SR. AF following BMV or closed mitral commissurotomy (CMC) was associated with reduced survival over a 20-year follow-up period (Fig. 2) [30].

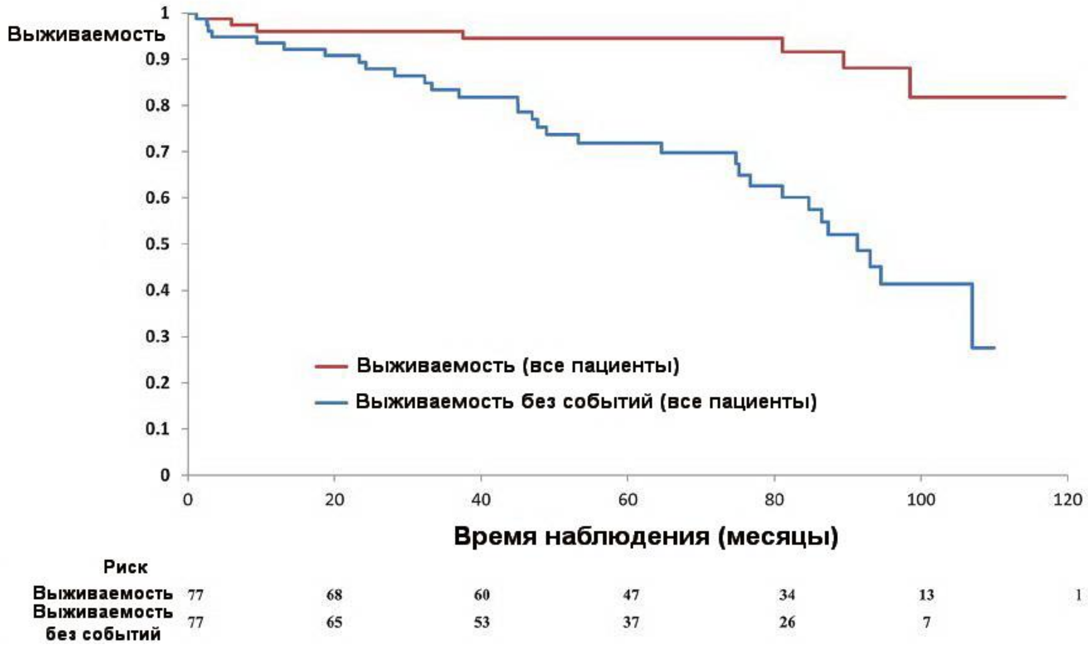

Figure 2. Survival and event-free survival curves following successful balloon mitral valvuloplasty (BMV) for a patient group (n=77) are presented.

Clinical events were defined as death from any cause, hospitalization for heart failure, repeat BMV, mitral valve replacement, and stroke. The data are based on the study by Miura S. et al. (2016) [22].

Management of Atrial Fibrillation with Antiarrhythmic Drugs

Rhythm control is a treatment strategy aimed at maintaining SR after the termination of AF. Rate control involves maintaining an optimal ventricular rate while AF persists. Rate control is generally easier to achieve compared to rhythm control.

Both rhythm and rate control play significant roles in the management of AF, especially in patients with MVS. Preference for rate control is usually due to its simpler implementation compared to rhythm control.

For most patients with persistent AF and MVS, restoring SR before performing BMV often presents a challenging task and requires a careful approach to therapy. However, even with successful restoration of SR, AF frequently recurs. It is believed that a combination of BMV and antiarrhythmic therapy is most favorable for ensuring long-term maintenance of SR [14, 16, 18].

The duration of AF, left atrial size, and patient age are key factors affecting the success of cardioversion and maintenance of SR. It is also important to note that the efficacy of early antiarrhythmic drug use in paroxysmal AF requires further study.

Most medical publications indicate that amiodarone is one of the most effective drugs for treating AF, both before and after electrical cardioversion

(ECV). However, it is important to note that most available data is based on observational studies. The rate of SR restoration with amiodarone ranges from approximately 20% to 40% [12].

Results from studies examining SR restoration after ECV combined with amiodarone in patients with heart failure and AF indicate that SR is maintained in 48-80% of cases over 18-30 months of follow-up [19]. RFCA of AF in this patient group has helped to solidify these results [23]. ECV is recommended to be performed after achieving amiodarone saturation, typically about one month after the initiation of therapy.

In 2006, Hu et al. conducted the first randomized study evaluating the efficacy of rhythm control versus rate control in patients following BMV. This study demonstrated that amiodarone combined with ECV successfully maintains SR in 96% of patients over the course of one year, which is associated with improved symptoms, quality of life, and exercise tolerance [9].

Another study also confirmed the significant efficacy of amiodarone in maintaining SR in patients with AF compared to placebo. According to these data, SR was maintained in 78% of patients in the amiodarone group three months after ECV and in 55% after 12 months, whereas in the placebo group, the respective figures were 35% and 17% [32].

Amiodarone is more effective than sotalol and Class IC antiarrhythmics, including in patients with rheumatic mitral valve disease after surgical correction or BMV [16, 19]. However, there are randomized studies that do not confirm the expected clinical benefit of maintaining SR in patients with AF. Participants in these studies were younger than those with MVS, which may lead to misleading conclusions [32].

Further research is needed to evaluate the long-term safety of amiodarone use. Additional studies are also required to explore other antiarrhythmics, such as dronedarone, and their potential impact on maintaining SR in patients with AF. Dronedarone, a Class III antiarrhythmic, does not contain iodine and thus does not cause the side effects associated with amiodarone. Additionally, Class IC antiarrhythmics may be used to maintain SR in selected patients with young age, normal myocardial contractility, and absence of coronary artery disease.

Rate control strategy may also be applied to patients with MVS and recurrent AF after attempts to restore SR with amiodarone, or when amiodarone is contraindicated or undesirable. According to the 2020 American Heart Association (AHA) and American College of Cardiology (ACC) Guidelines for the Management of Patients with Valvular Heart Disease [24, 26, 31], rate control is classified as a Class IIa recommendation, with no specific tactical algorithms provided. There is also no clarity in the 2021 ESC Guidelines for the Management of Atrial Fibrillation [8].

Anticoagulants and Atrial Fibrillation

The effectiveness of anticoagulant therapy for AF has been predominantly assessed retrospectively in various studies. However, early use of anticoagulants, such as heparin, is justified in patients at high risk of thromboembolic complications, particularly those with AF associated with heart failure. It is also important to strive for prompt restoration of sinus rhythm.

According to the guidelines of the AHA /ACC and the European Society of Cardiology (ESC), the use of vitamin K antagonists, such as warfarin, is mandatory for patients with persistent AF and mitral valve insufficiency, regardless of the CHA_2DS_2-VASc score and the degree of mitral stenosis (Class I recommendation). The target range for the international normalized ratio (INR) should be between 2.0 and 3.0. Aspirin is not considered effective in this situation.

For newer oral anticoagulants (NOACs), such as rivaroxaban and apixaban, they may be used in patients with AF who have aortic valve disease or mitral insufficiency. However, there is currently insufficient data on the efficacy of NOACs in patients with mitral stenosis, so their use in this patient population is not recommended [24, 31].

Interventional Treatment Methods

Modern randomized trials do not provide data on the relationship between the outcomes of BMV and the course of AF. However, according to Krasuski et al., approximately 20% of patients with sustained SR after BMV experienced AF during a three-year follow-up. Multivariate analysis revealed that the development of AF was associated with age and left atrial size but not with the results of the BMV procedure itself. In other words, it is suggested that successful BMV does not influence the likelihood of developing AF in patients with MVS [17].

RFCA of the PV ostia is an effective rhythm control method for patients with AF. However, there are currently no clear recommendations for determining indications for interventional treatment of AF in patients with combined AF and MVS (Figure 3) [28]. Nevertheless, small non-randomized studies have shown that SR can be maintained in 55-80% of patients for several years after RFCA. However, there are no precise data on the criteria for patient selection for the intervention (e.g., left atrial size, characteristics and duration of AF, age, comorbid conditions) and which factors may predict the success of the procedure. RFCA performed several years after BMV or mitral valve replacement has improved the clinical condition of patients, but recurrence of AF occurred at varying times after

RFCA. As a result of the lack of systematic data, the question of interventional treatment for AF in patients with MVS remains relevant [10].

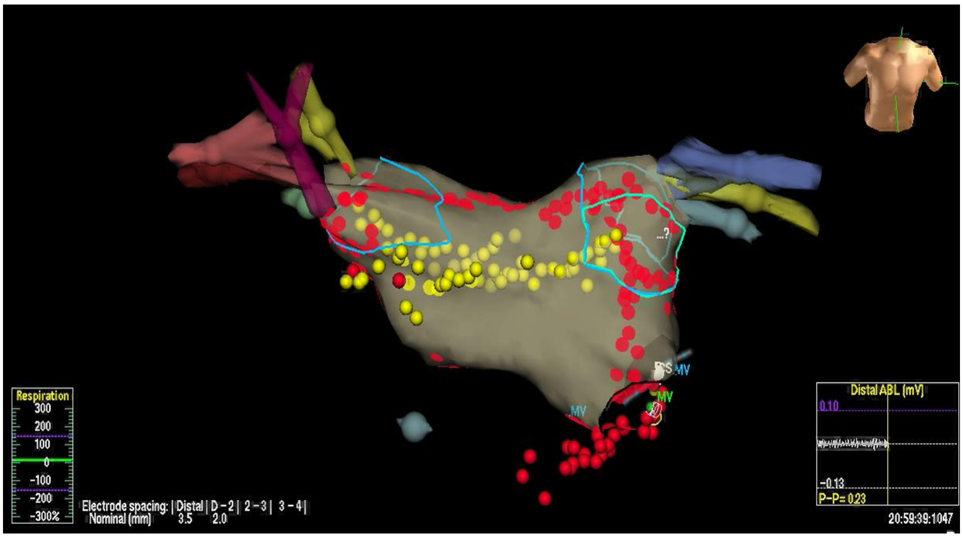

Figure 3. 3D Mapping of the left atrium during radiofrequency catheter ablation of atrial fibrillation using a navigation system.

In Gillinov et al. trial investigating the outcomes of AF ablation during surgical mitral valve disease treatment, data from 260 patients with varying durations of AF were analyzed. These patients underwent mitral valve replacement with intraoperative AF ablation or mitral valve replacement alone. The results demonstrated that SR was maintained in 63% of patients who underwent surgical AF ablation for 12 months, compared to 29% in those who had only mitral valve replacement ($p<0.001$). Additionally, there was a trend toward reduced mortality in the AF ablation group [6].

According to the Society of Thoracic Surgeons (STS) Guidelines 2023, surgical AF ablation does not increase the risk of operative complications or mortality and is recommended during mitral valve surgery to maintain SR. However, some studies suggest that AF ablation may be associated with reduced left atrial contractility and a decline in quality of life [33].

Several studies have indicated that AF ablation may be associated with reduced left atrial contractility, which correlates with a decrease in quality of life [2].

In cases where adequate rate control or maintenance of SR cannot be achieved with AF, radiofrequency ablation of the atrioventricular node followed by permanent pacemaker implantation may be considered [8]. This decision may be made for patients with mitral valve disease, taking into account the risks associated with pacemaker implantation.

It is important to note that one study involving patients after mitral valve replacement indicated that reducing left atrial size plays a role in maintaining SR [34].

CONCLUSION

The issue of AF and its impact on clinical outcomes in patients with MS remains pertinent and requires further investigation. The occurrence of AF in patients with MS necessitates the use of vitamin K antagonists to prevent thromboembolic complications. The efficacy and safety of new oral anticoagulants in this patient population have yet to be established.

Indications for the use of antiarrhythmic drugs or interventional treatment for AF in patients with MS are still not fully understood. Further research is needed to identify optimal treatment methods for this patient group. It is possible that radiofrequency ablation of AF may prove to be a more effective method compared to pharmacological therapy for maintaining sinus rhythm in patients with MS. Initial steps should involve interventional or surgical correction of MS. However, individual patient characteristics must be considered, and treatment decisions should be based on a comprehensive analysis of clinical data.

Overall, the aforementioned highlights the importance of continued research in the field of interventional treatment for AF and MS. Only through further investigation can optimal treatment strategies be developed and therapeutic outcomes for this patient population improved.

Author contributions. Mirjamol Zufarov and Vadim Im were the initiators of the proposed concept and made significant contributions to the final manuscript. Sanjar Khamdamov was responsible for the development of the theoretical framework and provided support in data collection.

Conflict of interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Declaration of interests: No declare.

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