AF is a common arrhythmia associated with large burden of morbidity and mortality. In areas with a high prevalence of rheumatic heart disease, valve disease is the most common substrate for the occurrence of AF and this problem assumes greater importance because the resulting escalation in morbidity and mortality involves relatively younger population. As is true of the general population, the prevalence of AF in patients with rheumatic mitral valve disease (RMVD) increases with advancing age. When compared to patients with mitral valve disease without AF, those with AF are at a higher NYHA class, have more severe left ventricular dysfunction and show greater left atrial enlargement. Mitral valve is the most commonly involved valve among patients with AF with valvular heart disease. Mitral stenosis, Mitral regurgitation and Tricuspid regurgitation comprise 70% of valvular heart disease related to AF. Diker et al in an Echo Doppler study had found AF in 29% of patients with isolated mitral stenosis, in 16% with isolated mitral regurgitation, in 52% in combined mitral stenosis and regurgitation but in only 1% of patients with aortic valvular disease.

Pathophysiology And Electrophysiology

While the mechanisms of non-valvular AF have been extensively studied, the literature is sparse concerning pathophysiological mechanisms leading to AF in patients with underlying valvular diseases. There are apparent differences in the patho-logical findings in these two subsets of patients. Occurrence of AF is known to correlate with LA size; the incidence of AF rises from 3% when the left atrial diameter is < 40mm to 54% if the left atrial diameter is > 40 mm. Mitral valve disease is associated with large left atria, and the elevated left atrial pressure causes myocardial stretch, which in turn results in slow conduction velocities, increased dispersion of refractoriness and increased automaticity, all of which create the milieu for initiating and perpetuating sustained AF.

A large postmortem study on patients with AF and associated organic heart disease showed a spectrum of histologic abnormalities that diffusely involved both the right and left atria. It was postulated that fibrosis and degeneration of the atrial myocardium in valvular heart disease, especially those of rheumatic etiology, disturb impulse propagation in the atria and lead to AF. Atrial fibrosis probably contributes to persistent AF after balloon valvuloplasty or surgical valve replacement and repair. AF also occurs more frequently when mitral valve is calcified or is prolapsing.

An insight into the role of substrate in perpetuation of AF in patients with mitral stenosis was provided in an elegant study by Fan et al. The regional ERPs in the atria increased after mitral valvuloplasty in patients with sinus rhythm and in AF; but in those with AF the increase was heterogenous, while in those with sinus rhythm it was homogenous. A study of a small group of patients with rheumatic AF, who had undergone balloon...
mitral valvuloplasty, had revealed that there was an organized atrial activity most often at the Os of the Coronary Venous Sinus preceding initiation of AF, with no evidence of focal firing from the pulmonary veins. In our small series, the electroanatomic maps showed extensive left atrial scarring of diverse patterns [Fig 1]. The significance of this finding remains speculative at this point and merits further investigation.

While the exact mechanism of development AF is yet to be fully elucidated the impact of it on the patient, especially patients with mitral stenosis has been studied. The impact almost entirely depends on the ventricular rate. As the ventricular rate increases the diastole decreases, therefore mitral flow increases. In MS increased mitral flow causes increased left atrial and pulmonary venous pressure. The loss of atrial contraction per se has minimal impact on the patient with significant MS. Unlike the situation in normal patients, atrial contraction does not cause an increase in flow across an obstructed mitral valve. This reflected as a loss of the A wave in the M-mode in echocardiogram of MS patients who are in sinus rhythm.

**Thrombo- Embolism and Anticoagulation**

AF is a major cause of systemic thrombo-embolism and in patients over the age of 65 years, it is responsible for more than one-third of all strokes. Advancing age, history of previous thromboembolic event, presence of mitral valve disease, congestive heart failure, enlarged left atrium, previous MI, hypertension and left atrial thrombus on transesophageal echocardiography predict occurrence of embolic strokes in patients with AF. The presence of AF multiplies the risk of stroke 5 times in a patient with structurally normal heart, and increases by a factor of 17 in those with mitral valvular disease. The lifetime recurrence rates for strokes in these patients may be as high as 30%–75%. The risk of recurrent strokes appears to be similar with chronic and paroxysmal AF. Transesophageal echocardiographic studies have shown that the presence of significant mitral regurgitation is associated with a lower incidence of spontaneous echo contrast in the left atrium and thus with a lower

Figure 1: Schematic diagram showing the varied scar pattern in the 5 rheumatic AF patients who underwent ablation. The overlap in numbers is due to patients having scar in more than one area. scars are coloured in red.
risk of thrombi and embolization as compared to Rheumatic mitral stenosis. A particular study has demonstrated that 20% of patients with mitral stenosis and none with mitral regurgitation show left atrial thrombi. More importantly, 28 of the 30 patients (93%) with atrial thrombi showed AF, demonstrating the role of rhythm disturbance in the generation of left atrial thrombus. In patients with mitral valve disease, thrombi are found not only in the left atrial appendage but also in the body of the left atrium. This is in contrast to nonvalvular AF in which thrombi form pre dominantly (90%) in the left atrial appendage.

In a surgical clinicopathologic study in patients with AF, the prevalence of left atrial clot with predominant mitral regurgitation was 8.3% in comparison with 54% in patients with predominant mitral stenosis (p < 0.0001). In sinus rhythm, the prevalence of left atrial clot was 0% in predominant mitral regurgitation and 14.3% in patients with mitral stenosis (p < 0.001). None of the patients with AF and severe mitral regurgitation had left atrial clot.

All patients with Rheumatic AF need to be anticoagulated in the absence of contraindications. The use and timing of anticoagulation for patients in sinus rhythm with mitral stenosis is still a moot point as the risk of thromboembolism is unrelated to the severity of the disease. However, successful balloon valvuoplasty results in resolution of echo contrast and decrease in thromboembolic risk. Correction of the valvular lesion thus should be undertaken whenever feasible. There are no dosing trials to guide anticoagulant therapy in patients with AF in valvular heart disease. Based on single-center studies in patients with valvular disease and on the results of large multicenter studies involving patients with AF of non-valvular etiology, however, similar recommendations can be made.

**Management**

The natural history of non-valvular AF is extremely variable. A good number of patients with non-valvular AF have paroxysmal episodes for long periods that become chronic or persistent in only a few. On the other hand, the initial attacks of AF in valvular heart disease are paroxysmal, but almost invariably progress to chronic AF. The symptoms are related to the irregular and rapid ventricular rate, development of heart failure and thromboembolic complications. These complications are related to the duration of AF and occur more often in AF associated with valvular heart disease. While the treatment of the underlying valvular disease is of primary importance, the management of the arrhythmia is aimed at either control of ventricular rate without attempting to restore sinus rhythm, or to restoration of sinus rhythm with followup aggressive therapy to maintain it. As embolic complications are the major cause of morbidity, chronic anticoagulant therapy is important in all patients with AF and valvular heart disease.

**Correction of underlying disorder**

Treatment of the underlying valvular abnormality should be considered, e.g. surgical repair or replacement of mitral or tricuspid valve in severe regurgitant lesions, or valvuloplasty in mitral stenosis. However, in patients with enlarged and dysfunctional atria, despite correction of the underlying valvular lesion, AF often persists. As a general rule in all these patients correction of reversible factors like thyrotoxicosis and alcohol intake must be addressed.

Delayed correction of underlying disorder would bring down the chance of maintaining these patients in sinus rhythm. This is partly reflected in the American Heart Association practice guidelines. It recommends mitral valve surgery in asymptomatic patients with severe MS as a Class IIb indication, if there is new onset AF. In patients with severe MR it is a Class IIa indication. However, this is based on consensus opinion and not on substantial data.

**Control of ventricular rate**

The control of ventricular rate is one of the main goals of the treatment of patients with all forms of AF when sinus rhythm cannot be restored immediately. This strategy remains the mainstay in patients with valvular heart disease as most of them have chronic AF not readily amenable to rhythm conversion. Of the several drugs used Digitalis, which was most often used earlier, is very often
ineffective during exercise because its electrophysiologic action is mediated largely through augmentation of vagal tone on the AV node. Beta-blockers such as propranolol, metoprolol and atenolol, as well as negative chronotropic calcium-channel blockers such as verapamil and diltiazem, are effective agents for control of ventricular rate with a low incidence of adverse effects. Studies have shown that combining digoxin and a beta-blocker that has intrinsic sympathomimetic activity keeps ventricular rates at peak exercise low while minimizing the effects of these drugs when heart rates are slowest, as is usually seen during the night. Catheter ablation of the AV junction and implantation of a rate-responsive ventricular permanent pacemaker should be considered in drug refractory patients or patients who cannot take beta-blockers and calcium-channel blockers.

Rhythm Control

The clinical advantage of maintaining patients in sinus rhythm following corrective procedures for mitral valvular disease has been demonstrated in a few studies. Vaturi et al showed worse functional class and increased transmitral gradients in patients with atrial fibrillation compared to those in sinus rhythm following Mitral Replacement Surgery.

In a study by Leon et al, patients with AF, BMV resulted in inferior immediate and long-term outcomes, as reflected in a smaller post-BMV mitral valve area (1.7 ± 0.7 vs. 2.6 ± 0.7 cm²; p < 0.0001) and a lower event free survival (freedom of death, redo-PMV and mitral valve surgery) at a mean follow-up time of 60 months (32% vs. 61%; p < 0.0001). AF by itself does not unfavorably influence the outcome, but is a marker for clinical and morphologic features associated with inferior results after PMV.

Maatouk et al compared outcomes at ten years in a fairly large group of patients with and without AF who underwent balloon mitral commissurotomy. They reported a lower ten year survival and a lower ten year event free survival in the AF group. The AF group also had higher rate of restenosis. However the cause of death were not reported and the events described were reinterventions and mitral valve replacements.

Rheumatic AF has also been shown to increase the incidence of prosthetic valve thrombosis in a study that was primarily looking at the results of thrombolytic therapy in patients with prosthetic valve thrombosis.

In patients with valvular AF, conversion and maintenance of sinus rhythm is difficult due to valvular abnormalities, large left atria and the presence of unhealthy substrate. Cardioversion to sinus rhythm may be achieved by chemical means or by electrical cardioversion. Chemical agents are less effective as in most cases the AF is of long duration. Antiarrhythmic agents of Vaughan Williams classes IA, IC or III are effective. Success rates in the range of 60% have been reported with flecainide, propafenone and amiodarone. Newer class III agents such as intravenous ibutilide and intravenous or oral dofetilide are most effective in atrial flutter and fibrillation of recent onset. Short-term amiodarone with or without electrical cardioversion has been shown to be effective in the restoration of sinus rhythm in chronic AF after mitral valve surgery. Prophylactic use of oral amiodarone and sotalol has been shown to prevent AF immediately following cardiac surgery.

The debate on preference of rate over rhythm control that was addressed by the AFFIRM, RACE, STAF trials predominantly involved non-valvular AF patients. These trials failed to demonstrate superiority of rhythm control strategy. However further analysis of the AFFIRM data showed that the presence of AF was associated with a 47% increased mortality compared with sinus rhythm and the use of an antiarrhythmic medication was associated with a 49% increased mortality, suggesting that any mortality benefit from the maintenance of sinus rhythm was offset by increased mortality from currently available antiarrhythmics. The more recently published randomized trial by Roy et al showed no benefit of rhythm control over rate control in patients with LV dysfunction. Non pharmacological methods, that have evolved from the surgical to radiofrequency catheter based pulmonary vein isolation with and without linear lesions have shown reasonable success in maintenance of sinus rhythm. Trials comparing these modalities against rate control need to be conducted for determining the guidelines for the best modality of management.
Suggested Management Algorithm

**RHEUMATIC AF**

**SIGNIFICANT VALVULAR HEART DISEASE**

See next page

**MILD & MOD VALVULAR DISEASE**

**AF BURDEN**

**Recurrent AF**

**SYMPTOMS/VENTRICULAR RATE DURING RECURRENCES**

Fast ventricular rate Symptomatic

RF ABLATION

Controlled ventricular rate No disabling symptoms

RATE CONTROL

**Infrequent AF**

RATE CONTROL

**SIGNIFICANT VALVULAR HEART DISEASE**

**CATHETER INTERVENTION (PBMV)**

**DCCV**

Successful

No recurrences Frequent recurrences Unsuccessful

**AF BURDEN, LA SIZE**

Persistent AF LA diameter > 50 mm

RATE CONTROL

Intermittent AF LA diameter ≤ 50 mm

RF ABLATION

**SURGICAL INTERVENTION**

**INTRA OPERATIVE RFA**
Both pharmacological and non-pharmacological methods of conversion and maintenance of sinus rhythm which have been studied in non-valvular AF have also been studied in valvular/rheumatic AF albeit in smaller and less well conducted studies. Similar to non-valvular AF there is no conclusive data to determine the best modality of management in rheumatic AF.

CRAAFT trial was a prospective study of 144 rheumatic valvular patients comparing rate control (using Diltiazem) and Rhythm control (Amiodarone versus placebo). Besides demonstrating a mortality benefit with rhythm control, the study showed a improvement in NYHA class, quality of life and exercise capacity on achievement of sinus rhythm. There was no difference in rates of hospitalization or thromboembolism or bleeds between the two groups. In contrast to the trials involving non-valvular AF, this study had individuals of young age (mean age 39 yrs), and only those who sustained sinus rhythm at one year (69%) were compared with the rate control group. The mortality observed in the rate control arm was due to prosthetic valve thrombosis. The other major limitation of the study was its small sample size, a dropout of 13% and a relatively short follow up. Another study that compared both modalities in patients undergoing balloon mitral valvuloplasty showed that the six minute walk test improved significantly in patients in whom sinus rhythm was maintained.

Maze surgery and its modifications have been successfully attempted by many investigators to restore sinus rhythm in RVHD and atrial fibrillation patients.

It may be recommended that all patients with a history of AF undergo concomitant AF surgery/ablation at the time of their valve procedure, if it can be performed without adding significant morbidity to the procedure.

Multiple approaches for catheter ablation of AF are under clinical investigation, and although preliminary results are encouraging, indications, safety and long-term success are still not well defined; it is particularly less well studied in rheumatic AF.

A small study among patients with AF and rheumatic heart disease has shown that in a good number the arrhythmia is a relatively organized rhythm with earliest atrial activity near the os of the coronary sinus. Catheter ablation in this area was successful in restoring sinus rhythm in most of these patients. All these patients were on amiodarone but details of long term follow up of these patients are not available.

Furthermore a recent study showed efficacy of Hybrid Therapy of Radiofrequency Catheter Ablation and BMV in Patients with Atrial Fibrillation and Mitral Stenosis. Twenty consecutive patients with drug-resistant AF and rheumatic MS underwent RFA combined with a BMV or transthoracic direct cardioversion (DC) following a BMV. During a mean follow-up period of 4.0 +/- 2.7 years, 8 patients (80%) in the RFA group were maintained in SR, as compared to 1 (10%) in the DC group. However if this efficacy translated into better clin-
Conclusions

In geographical regions where rheumatic heart disease is prevalent AF is an important health care issue affecting younger population. It significantly contributes to mortality and morbidity and constitutes a burden on healthcare resources of the society.

The benefit of long term anticoagulation is well established. Whether the rate control or rhythm control constitutes a better strategy is not clearly determined in non-valvular AF. Compared to patients with non-valvular AF maintenance of sinus rhythm in rheumatic AF patients appears to be more beneficial, particularly among those undergoing mitral valve surgery.

However, the benefit of restoring sinus rhythm are not clear in rheumatic heart disease patients who are haemodynamically stable and do not require valvular surgery. Although small studies have shown benefit in terms of functional class it remains to be seen if it will significantly alter important clinical endpoints.

Pharmacological methods of rhythm control have drawbacks and it appears prudent to compare nonpharmacological methods of rhythm control against rate control, considering the advances of these modalities and their success rates in maintenance of sinus rhythm.

Despite lack of large supportive evidence it seems reasonable to attempt conversion to sinus rhythm in rheumatic heart disease in patients undergoing corrective valve surgery. However the best strategy of achieving it is not well established.

References


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