SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA

PROJECT REPORT

Submitted during the course of

DM Cardiology

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DM Trainee

DEPARTMENT OF CARDIOLOGY

Jan 2010 – Dec 2012
DECLARATION

I, Dr. Raghuram A Krishnan, hereby declare that the projects in this book were undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram Dr. RAGHURAM A KRISHNAN
Date: DM Trainee

Forwarded

The candidate, Dr. Raghuram A Krishnan, has carried out the minimum required projects.

Thiruvananthapuram PROF. Dr. JAGAN MOHAN THARAKAN
Date: Head of the Department of Cardiology
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GENERAL CONTENTS

**Project I:** Optimal Strategy for Restoration and Maintenance of Sinus Rhythm in Patients with Rheumatic Mitral Stenosis and Atrial Fibrillation. A Prospective Randomized Study.

**Project II:** Evaluation of the index of microcirculatory resistance in coronary artery lesions of intermediate severity.
Optimal Strategy for Restoration and Maintenance of Sinus Rhythm in Patients with Rheumatic Mitral Stenosis and Atrial Fibrillation.

A Prospective Randomized Study.
INTRODUCTION

In patients with rheumatic mitral stenosis (MS), development of Atrial fibrillation (AF) is known to worsen functional status and increase the risk of thromboembolism.

Some of the earliest studies mention the overall incidence of AF in this condition to be about 40%\(^1\). Its frequency is only partly related to the severity of stenosis\(^2\). As in the general population, the frequency of atrial fibrillation is also strongly dependent on patient age\(^3\). AF often develops first in a paroxysmal form; later, it may progress to persistent form, but responds to antiarrhythmic therapy. Eventually, AF establishes itself permanently in a therapy-resistant form.

Pathophysiology of AF in mitral stenosis

AF is related to left atrial enlargement and left atrial hypertension. Initially appearing as a functional disturbance in the electrophysiologic mechanism, as a response to stretching of the atrial musculature, it eventually is perpetuated by structural changes, such as disintegration of the architecture of the atrial muscle\(^4\). Patients with very large left atria and those who have had AF for longer than 5 years are likely to have extensive disruption of their atrial musculature (i.e., atrial fibrosis and muscle atrophy) and therefore are unlikely to respond to cardioversion or antiarrhythmic therapy, even after a satisfactory surgical correction of the MS.

Hemodynamic effects of Atrial fibrillation

AF has a profound effect upon the natural history of MS. Hemodynamically, it causes lower resting cardiac output at comparable ventricular rates. The onset of AF is the most common factor bringing a previously asymptomatic patient into a stage of disability. The
rapid ventricular rate of acute onset AF episode is frequently responsible for many hospital admissions in patients with MS. Furthermore, even after the ventricular rate is brought under control, patients often find themselves in a lower effort capacity than prior to the onset of the arrhythmia due to loss of the atrial "kick" mechanism. Systemic emboli occur primarily in the presence of AF. It is not known whether AF is a sine qua non for this complication, with those reported as having embolism while in sinus rhythm (SR) possibly suffering from an unrecognized paroxysm of fibrillation, or whether mural thrombi may actually develop in the contracting atrium.

Annual linearized risk of thromboembolism in AF without anticoagulant therapy has been estimated to be 3.6% for moderate MS and 5.7% for severe MS. The corresponding figures for patients in SR were 0.25% for moderate MS and 0.85% for severe MS. In patients with atrial fibrillation, most embolic complications originate from left atrial thrombosis, which is located in the left atrial appendage. Embolic events are cerebral in location in 60% to 70% of patients, leave sequelae in 30% to 45% of patients, and are prone to recurrence.

**Treatment of AF- Rate versus rhythm control**

Initial therapy for AF is often directed toward the maintenance of SR by means of cardioversion and the use of antiarrhythmic drugs. The rationale for this “rhythm-control” approach includes the possibility of fewer symptoms, better exercise tolerance, a lower risk of stroke, better quality of life, and better survival, if SR can be maintained. However, AF is often poorly responsive to antiarrhythmic drugs, which may also have serious adverse effects.
An accepted, though often secondary, alternative to antiarrhythmic drug therapy is a strategy simply to control the ventricular response rate of AF with the use of atrioventricular nodal blocking agents or ablation of the atrioventricular junction and pacemaker implantation\textsuperscript{13}, in conjunction with continuing anticoagulation. This “rate-control” approach may simplify therapy and permit the use of drugs that are less toxic than antiarrhythmic drugs.

**Relevance of rate versus rhythm control in AF due to mitral stenosis.**

In patients with MS and AF, restoration of SR is superior to rate control to improve indices of functional capacity and quality of life.\textsuperscript{14} In patients with severe to critical MS, AF may not have a significant impact on the cardiac output as there is a continuous gradient between the Left atrium and left ventricle, however once an intervention has reduced the severity of MS, it is likely that the restoration of atrial contraction would be of benefit to the patient. Hence it is all the more necessary to attempt to convert the patient to SR rather than control ventricular rate alone.

**Combining DC version with anti-arrhythmic drugs**

With electrical cardioversion alone, SR can be re-established in many patients, although maintenance of SR is not assured thereafter. In fact, SR can be maintained at 1 year in only about 30\% of patients who receive placebo\textsuperscript{15}. Accordingly, preventive antiarrhythmic therapy is often mandatory.

**Ideal time for attempting rhythm control measures**

Due to various reasons, immediate post balloon mitral valvotomy (BMV) period may be an ideal time to attempt restoration of rhythm in these patients. During this time, the
patient has achieved the least left atrial mean pressures that is possible post BMV (except in patients who have developed significant mitral regurgitation). It is a well-recognized fact that patients who have undergone BMV are prone to develop restenosis at various time intervals after the initial procedure, hence waiting for a later time for cardioversion may not be without increasing the risk of failure of cardioversion. Aggressive rhythm maintenance with short-term antiarrhythmic treatment to facilitate remodeling of left atrium may also help in long-term maintenance of SR.

Despite the possible benefits in restoring and maintaining SR in patients with MS and AF, the optimal strategy for the same is yet to be defined. Most of the studies done from the subcontinent have not addressed the role of arrhythmia intervention in the immediate post-BMV period, arguably the optimal period for a strategy aimed at maintenance of SR. As the left atrium may witness significant structural remodelling during this phase, the role of facilitating ‘electrical remodelling’ by a combined approach of early restoration of SR by DC version and concomitant short-course of amiodarone is yet to be studied.
AIMS OF THE STUDY

We aimed to assess the optimal strategy for restoration and maintenance of sinus rhythm in patients with severe mitral stenosis undergoing Balloon mitral valvotomy (BMV). We hypothesized that preloading with 1g of amiodarone would improve the chances of restoration of sinus rhythm. We also aimed at assessing whether a three 3-month course of amiodarone had a superior affect on the maintenance of SR over a one year follow up.
MATERIALS & METHODS

Patients undergoing BMV during the study period (between November 2010 and March 2012) were screened in the study.

Inclusion criteria:

All patients with rheumatic mitral stenosis who underwent balloon mitral valvotomy and were having persistent /permanent AF were included in the study.

Exclusion criteria:

1. Patients with moderate to severe Mitral regurgitation post BMV
2. Pregnant women, patients with renal, hepatic dysfunction.
3. Patients with any significant comorbid illness
4. Patients who were already on amiodarone and those with h/o amiodarone toxicity
5. Periprocedural AF
6. Abnormal Thyroid function

We screened 270 patients who underwent BMV during the period, and of them we identified 42 patients with non-paroxysmal (persistent /permanent) AF. These patients were prospectively randomized into 2 groups (Group A and B) based on the strategies for restoration and maintenance of SR. 2 patients were left out - 1 patient developed severe Mitral regurgitation needing urgent surgery, other developed moderate pericardial effusion needing close follow up. Patients in Group A underwent DC Cardioversion alone within 24
hours of BMV, and in Group B, patients were given intravenous infusion of Amiodarone 1000mg over 24 hours. If they did not convert to SR after the infusion of amiodarone, they underwent DC cardioversion. The patients in this group were continued on oral amiodarone 200mg/day for 3 months. Cardioversion was performed with anteroposterior paddle position which is believed to be more effective for external cardioversion in AF.\(^\text{16}\)

**Follow up**

The patients were followed up at 1 month, 3 months, 6 months and at the end of 1 year. At each follow visits, 12-lead electrocardiogram and echocardiogram were performed. They were assessed for NYHA functional class status, and any recent heart failure episodes, thromboembolic episodes, bleeding phenomenon and any need for hospitalizations in the intervening period was documented. The patient’s thyroid profile, liver function tests and periodic PT/INR was also tested. The patient’s anticoagulant dosage was adjusted as per PT/INR reports. An INR value between 2.0 to 3.0 was maintained. In view of known drug interactions between amiodarone and warfarin and with the knowledge of consequent reduced dosage requirements of warfarin (by inhibition of metabolism of warfarin by CYP 2C9), the patients were advised weekly PT/INR monitoring and close follow up.

We have defined successful/failed cardioversions and recurrence of AF based on the current guidelines.\(^\text{17}\)

**Failed Electrical Cardioversion**

Failed electrical cardioversion is defined as the inability to restore SR for 30 seconds or longer following electrical cardioversion.

**Successful Electrical Cardioversion**
Successful electrical cardioversion is defined as the ability to restore SR for at least 30 seconds following cardioversion.

**Immediate AF Recurrence Post Cardioversion**

Immediate AF recurrence post cardioversion is defined as a recurrence of AF within 24 hours following cardioversion. The most common time for an immediate recurrence is within 30–60 minutes post cardioversion.

**Early AF Recurrence Post Cardioversion**

Early AF recurrence post cardioversion is defined as a recurrence of AF within 30 days of a successful cardioversion.

**Late AF Recurrence Post Cardioversion**

Late AF recurrence post cardioversion is defined as recurrence of AF more than 30 days following a successful cardioversion.

**Statistical Analysis**

All data were transferred to SPSS (version 20.0) software (SPSS Inc., Chicago, IL) for further analysis. Data are presented as mean +/- standard deviation. A comparison of means was performed using unpaired T test.
Figure 1 Study Design
REVIEW OF LITERATURE

There has been considerable debate regarding the best strategy for management of AF. Though there is no doubt regarding the continued need for oral anticoagulation, it is with regard to the whether rate control of these episodes or whether a strategy at attaining SR and its maintenance should be employed which has led to many studies coming to different conclusions.

The AFFIRM (The AF Follow Up Investigation Of Rhythm Management Trial)\textsuperscript{18} attempted to address this concern. A total of 4060 patients (mean age, 69.7 years) were enrolled in the study. Patients with significant valvular heart were not part of the study. There were two strategies employed, one was cardioversion and treatment with antiarrhythmic drugs to maintain SR, and the other is the use of rate-controlling drugs, allowing AF to persist. There were 356 deaths among the patients assigned to rhythm-control therapy and 310 deaths among those assigned to rate-control therapy (mortality at five years, 23.8 percent and 21.3 percent, respectively; hazard ratio, 1.15 [CI, 0.99 to 1.34]; P=0.08). More patients in the rhythm-control group than in the rate-control group were hospitalized, and there were more adverse drug effects in the rhythm-control group as well. This study concluded that management of AF with the rhythm-control strategy offers no survival advantage over the rate-control strategy, and there are potential advantages, such as a lower risk of adverse drug effects, with the rate-control strategy.

The Pharmacological Intervention in AF (PIAF)\textsuperscript{19} trial was a randomised trial in 252 patients with AF of between 7 days and 360 days duration, which compared rate (group A, 125 patients) with rhythm control (group B, 127 patients). In group A, diltiazem was used as first-line therapy and amiodarone was used in group B. The primary study endpoint was
improvement in symptoms related to AF. Over the entire observation period of 1 year, a similar proportion of patients reported improvement in symptoms in both groups (76 responders at 12 months in group A vs 70 responders in group B, p=0.317). Amiodarone administration resulted in pharmacological restoration of SR in 23% of patients. Walking distance in a 6 min walk test was better in group B compared with group A, but assessment of quality of life showed no differences between groups. The incidence of hospital admission was higher in group B (87 [69%] out of 127 vs30 [24%] out of 125 in group A, p=0.001). Adverse drug effects more frequently led to a change in therapy in group B (31 [25%] patients compared with 17 [14%] in group A, p=0.036).

The study concluded that with respect to symptomatic improvement in patients with AF, the therapeutic strategies of rate versus rhythm control yielded similar clinical results overall. However, exercise tolerance is better with rhythm control, although hospital admission is more frequent.

Vora et al\textsuperscript{20} undertook a study to compare the strategy of ventricular rate control versus maintenance of SR in rheumatic AF, and to evaluate the role of amiodarone in this patient population. They prospectively studied 144 patients with chronic rheumatic AF in a double-blind protocol-rhythm control (group I: 48 patients each with amiodarone -group Ia; and placebo -group Ib) and compared the effects with the ventricular rate control (group II) by diltiazem (n=48). Direct current cardioversion was attempted in group I. The mean age of the study population was 38.6+/−10.3 years, left atrial size was 4.7+/−0.6 cm, AF duration was 6.1+/−5.4 years, and 72.9% patients had undergone valvular interventions. At 1 year, 45 patients with SR in group I compared to 48 patients in group II demonstrated significant increase in exercise to SR time, had improvement in functional class and quality of life score. There was no difference in hospitalization rates, systemic bleeds or incidence of
thromboembolism. Five patients died in group II but none in group I (p=0.02). In group I, 73/87 (83.9%) patients converted, and 45/86 (52.3%) patients maintained SR at 1 year. Conversion rates were 38/43 (88.4%) with amiodarone versus 34/44 (77.3%) with placebo (p=0.49): corresponding rate for maintaining SR was 29/42 (69.1%) versus 16/44 (36.4%), p=0.008 respectively. They concluded that maintenance of SR appeared to be superior to ventricular rate control in patients with rheumatic AF in terms of an effect on mortality and morbidity. SR could be restored in the majority and amiodarone was superior to placebo in this regard.

Rhythm intervention after BMV/commisurotomy

Langerweld et al21 studied the long-term course of the supraventricular rhythm in 137 consecutive patients with severe MS, who underwent BMV. The rhythm before BMV was SR (SR) in 55% and chronic AF in 45% of patients. The mean follow-up time was 3.7±2.5 years (n=126). In patients with SR before BMV, SR persisted in 91% of patients at the end of follow-up. In patients with chronic AF before BMV, 84% of these patients were still in chronic AF at the end of follow-up, spontaneous conversion to SR did not occur. In 12 of 14 patients (85%), selected for cardioversion, SR was achieved, by DC cardioversion (n=11) or by drugs alone (n=1). After 2 years this outcome persisted, but after 4 years only 38% remained in SR.

The level of success rate of DC cardioversion mentioned in the Langerveld study is high compared with the success rate mentioned in surgical studies. Upton et al22 found in patients with mitral valve stenosis treated by closed mitral valvotomy DC cardioversion before discharge to be successful in 34% of patients and Flugelman et al23 in 60% of patients within 6 months after mitral valve surgery. Duration of AF before surgery, age, left atrial
dimension and functional class were believed to be factors influencing the immediate results
of DC cardioversion.

Sato et al\textsuperscript{24} had concluded that long duration of AF should probably not dissuade one
from attempting electrical cardioversion in patients after open commissurotomy. In their
study 35\% of patients who reverted to and maintained SR late post-operatively, had suffered
from AF for more than one pre-operative year.

In patients with chronic AF spontaneous recurrence of SR occurred neither
immediately following BMV nor during follow-up. Studies show that electrical cardioversion
is the most important factor in conversion to SR in these patients\textsuperscript{25}. Also it should be noted
that in the patients who were in SR after BMV, only around 2 \% tend to develop AF\textsuperscript{7},
probably related to the haemodynamic improvement after BMV.

Kavthale et al\textsuperscript{26} studied the efficacy of achieving and maintaining SR in patients with
chronic AF who underwent a successful balloon mitral valvotomy. Fifty-four patients (26
men, 28 women; age 36+/−8 years) received amiodarone 200 mg thrice daily in the first week,
and thereafter a maintenance dose of 200 mg once daily. Electrical cardioversion was
attempted at 1 and 3 months and patients were followed up at 6, 12 and 18 months. At the
end of 1, 3, 6, 12 and 18 months 81 percent, 72 percent, 60 percent, 54 percent and 49 percent
of patients, respectively, were in SR. Only one patient had a severe adverse effect
(hypothyroidism). Univariate analysis revealed that lower age, shorter duration of AF and
smaller left atrial size was associated with successful restoration to SR. On multivariate
analysis, the duration of AF was the only significant predictor of long-term maintenance of
SR. They also concluded that Amiodarone seemed safe and reasonably effective in
restoration and maintenance of SR in patients of AF with rheumatic heart disease.
Kapoor et al\textsuperscript{27} studied the safety and efficacy of low dose amiodarone among patients with persistent AF after BMV. Eighty-five patients with persistent AF following BMV received amiodarone (600 mg once daily for two weeks, 200 mg daily thereafter). Electrical cardioversion was performed in those with persistent AF (at six and 12 weeks of drug therapy).

Among patients, 33 (39\%) converted with amiodarone alone. Of 52 patients who underwent cardioversion at six weeks, 41 (79\%) converted to SR. Overall, 87\% of patients converted to SR. None of the 11 patients with persistent AF could be converted to SR, despite a second attempt with direct current (DC) cardioversion at 12 weeks. Those who converted to SR had significantly shorter AF duration (2.7+/-1.1 versus 3.2+/-0.7 years) and smaller left atrial (LA) size (50.0+/-7.7 versus 57.9+/-4.7 mm). Successful maintenance of SR was possible in 61/74 (82\%) patients at a mean follow up of 30.6+/-7.1 months (range: 16-43 months). Again, mean AFD was shorter (1.8+/-0.6 versus 3.0+/-0.7 years) and LA size smaller (48.9+/-7.5 versus 54.7+/-6.9 mm) among those who maintained SR. However, even in patients with AFD \(\geq\) 2 years, successful conversion and maintenance of SR was possible in 74\% and 62\% of patients, respectively. Among patients with LA size \(\geq\) 60 mm (n = 16), the corresponding value were 84\% and 77\%, respectively. On multivariate analysis, only AFD was a predictor of acute and long-term success. The probability of SR remaining in those with AFD <2 years at 21, 30 and 43 months was 96\%, 95\% and 94.6\%, respectively, while for those with AFD > or =2 years these values were 62\%, 48\% and 40\%.

Hu et al\textsuperscript{14} compared compare rate control and rhythm control strategies in patients with AF after percutaneous mitral balloon valvotomy. They studied 183 patients with AF after successful BMV, with AF duration \(\leq\) 12 months and post-PMV left atrial (LA) size \(\leq\) 45 mm, in a prospective, randomised trial. The primary end point was improvement in AF-
related symptoms. Secondary study end points were 6 min walk tests, quality of life (QOL), normalisation of LA size, number of hospital admissions and duration of hospital stay. They found that over one year, 2% patients in the rate control group had SR, as compared with 96% of patients in the rhythm control group (p <0.001). A greater proportion of patients reported improvement in symptoms in the rhythm control group than in the rate control group (p, 0.0001 at every visit time). Walking distance in a 6 min walk test, QOL and LA size normalisation were better in the rhythm control group than in the rate control group. The strategy of rhythm control was associated with similar numbers of hospital admissions but with longer duration of hospital admissions. Drug-related side effect did not differ between the rate control and rhythm control groups. During the follow-up period, no patients in either group had embolic or transitory ischemic neurological events. Hence they concluded that in patients with AF after BMV, AF duration ≤ 12 months and post-PMV LA size ≤ 45 mm, SR was easy and safe to achieve and maintain. Moreover, patients benefited from restoration and maintenance of SR in terms of improved AF-related symptoms, 6 min walk tests and QOL, and of LA size normalisation. Rhythm control should therefore be considered as the preferred initial therapy for this group of patients. It must be noted however that they excluded patients with LA size greater than 45 mm. They decided for this as they believed that larger the LA size higher is the risk of AF recurrence. They felt that in patients with recurrent AF, rhythm control is not necessary before rate control in these patients.
RESULTS

The study participant’s characteristics are listed in Table 1. There was no significant difference between group A and group B when baseline characteristics such as age, left atrial (LA) diameter, left ventricular ejection fraction (LVEF), pre BMV 2D mitral valve area (MVA), post BMV 2DMVA, risk factors such as diabetes, hypertension were compared. Males formed a larger part of the patients in group B. LA mean pressures in group B was significantly higher than in group A. None of the patients who were given amiodarone developed evidence of toxicity.

**Table 1 Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (n=20)</th>
<th>Group B(n=20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>48.6(33-61)</td>
<td>46.5(34 -66)</td>
<td>0.38</td>
</tr>
<tr>
<td>Males (n)</td>
<td>6(30%)</td>
<td>10(50%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Duration of AF(months)</td>
<td>51.15</td>
<td>50.75</td>
<td>0.49</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>47.8</td>
<td>49.95</td>
<td>0.14</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58.4 +/-9.0</td>
<td>62.8+-/8.2</td>
<td>0.13</td>
</tr>
<tr>
<td>2DMVA(cm2)</td>
<td>0.91+/- 0.1</td>
<td>0.91+/-0.11</td>
<td>0.47</td>
</tr>
<tr>
<td>Post procedure 2DMVA(cm2)</td>
<td>1.49+/- 0.3</td>
<td>1.53+/-0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Condition</td>
<td>Pre-BMV Count</td>
<td>Post-BMV Count</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Diabetes (n)</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (n)</td>
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<td>1</td>
<td>NS</td>
</tr>
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<td>Digoxin</td>
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<td>Betablockers</td>
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<td>Calcium channel blockers</td>
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<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td>20</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>LA size &lt; 45 (mm)</td>
<td>25%</td>
<td>30%</td>
<td>NS</td>
</tr>
<tr>
<td>LA 45-54 (mm)</td>
<td>60%</td>
<td>40%</td>
<td>NS</td>
</tr>
<tr>
<td>LA ≥ 55 (mm)</td>
<td>15%</td>
<td>30%</td>
<td>NS</td>
</tr>
<tr>
<td>Post BMV LA mean pressure</td>
<td>15.68 mmHg</td>
<td>10.81 mmHg</td>
<td>&lt;0.05</td>
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</tbody>
</table>
Figure 2 Group Allocation
Successful Cardioversion and immediate recurrence

In Group A, of the 20 patients, 17 patients were successfully cardioverted (85%) whereas in Group B, out of 20 patients, 16 attained SR (80%). The immediate recurrence rate of AF (i.e., within 24 hours) was 17% (3 out of 17) in Group A, whereas there was no immediate recurrence of AF in group B.

Maintenance of SR

There was a progressive attrition in the number of patients maintaining SR over the course of follow up in both groups. At 1 month, only 9 patients in group A had maintained SR (45%). Over a 6 month follow up, 2 more patients had a recurrence of AF. Of the 15 patients who have completed follow up of 12 months, 4 (26.6%) were in SR.

The recurrence rate was slower in group B. At 1 month 12/20 (60%) had maintained SR, and 50% at 3 months. After discontinuing amiodarone at the end of 3 months as per protocol, there was an increase in recurrence rate with only 4/13 (30.1%) maintaining SR at 1 year.

Failed Cardioversion group

Four out of the seven patients who had failed DC version were given oral amiodarone for 1 month and repeat DC version was performed. Out of them one patient had reverted to SR with oral amiodarone. The remaining three patients were taken up for DC cardioversion and all three successfully reverted to sinus. There was no immediate recurrence in any of them.
Left atrial size and Cardioversion success and recurrence rate

Based on the left atrial size, we made three subgroups, Subgroup 1 - LA size <45mm, Subgroup 2- LA size 45-54mm, Subgroup 3- LA > 54mm. In Group A, all patients with LA size <45mm converted, whereas among those with LA size between 45 -54mm, 83% converted and those with LA size >54mm, 2/3 (67%) converted. In group B, there was a similar rate of conversion across the three subgroups. However there appeared to be a slightly higher chance of restoration of SR among patients with LA size >54mm in group B (figure 4). On follow up, at 3 months and six months, the patients with LA size >54mm had a better chance of maintaining SR if they were on oral amiodarone (figure 5, 6)

Post BMV LA mean pressure

The LA mean pressures achieved post BMV did not show any effect on the success of cardioversion in both groups. (Table 2). LA mean pressure also did not have a bearing on the maintenance of SR at 6 months both in group A (p=0.39) and group B (p=0.29).
### Table 2 Comparison of Left Atrial pressures within both groups

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rhythm after DC version</strong></td>
<td>Mean Post BMV</td>
<td>Mean Post BMV</td>
</tr>
<tr>
<td></td>
<td><strong>LA pressure</strong></td>
<td><strong>LA pressure</strong></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>15.23 mmHg</td>
<td>10.3 mmHg</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16.66 mmHg</td>
<td>11.8 mmHg</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.6</td>
<td>0.44</td>
</tr>
</tbody>
</table>
Figure 3 A comparison of the strategies in maintainence of sinus rhythm.
Figure 4 Overall rate of sinus rhythm restoration
Figure 5 Maintenance of sinus rhythm at 3 months
Figure 6 Maintenance of Sinus rhythm at 6 months
DISCUSSION

This prospective randomized study showed that DC cardioversion has a high degree of success in converting patients with persistent AF after BMV to SR. Preloading the patient with 1g of intravenous amiodarone infusion did not improve the success rate of cardioversion. However there was a lesser degree of immediate recurrence (<24hours) of AF in this group. Further there was a reduced rate of recurrence of AF during the period amiodarone is continued.

Our data regarding the success of cardioversion was similar to the success rate in the study by Langerveld et al(85%). We were successful in cardioverting 82.5%(33/40) of our study population. Only 14 patients out of the 137 MS patients in the aforementioned study were selected for cardioversion, and of them- SR was achieved in 12 patients. This is an important finding, as in our study we attempted cardioversion in all the study subjects regardless of the duration of AF or left atrial size and we were still able to achieve a very high percentage of success at cardioversion.

Once amiodarone was stopped as per protocol at three months, there was a slightly higher attrition rate in that group, such that at 6 months and at 1 year there were a similar number of patients maintaining SR in both groups.

It was noted that the successful restoration and maintenance of SR had a relationship with the Left atrial size. Patients with a larger left atrium were more likely to convert to SR after preloading with amiodarone rather than DC version alone. Also it was more likely that a patient with a larger left atrium would maintain SR if he had been on amiodarone.
There have been several studies on AF and its management strategies; however there are very few studies done among patients with rheumatic MS and AF. Studies such as AFFIRM and RACE have not found any superior results with rhythm control strategy over rate control in patients with AF. However these studies did not include patients with RHD. Hence it would not be fair to extrapolate those results to patients with significant RHD. Also many of these studies have a short follow up period, which is not enough to determine outcomes such as mortality rates.

Vora et al had shown that in patients with rheumatic MS, DC cardioversion successfully restored SR in 38/43 (88.4%) with amiodarone versus 34/44 (77.3%) with placebo (p=0.49). Also corresponding rate for maintaining SR at one year was 29/42 (69.1%) versus 16/44 (36.4%), respectively.

The higher percentage of maintenance of SR in their study (69.1% versus 30.1%) can be explained by the fact that we have given amiodarone only for three months.

We have ascertained that there is no prolonged effect of a three month dose of amiodarone. Our data regarding maintenance of SR is similar to the number of patients in the placebo group of Vora et al (36.4%).

We have also shown that the left atrial size is a determinant of restoration of SR and that in patients with larger left atrial size, addition of amiodarone therapy has a better chance of maintaining SR. This data has not been shown earlier in patients with rheumatic MS.
LIMITATIONS

The total size of the study population was small. Hence no statistically significant results could be obtained. Follow up of these patients have to be longer in order to observe the trends of the outcomes. The duration of amiodarone therapy as per protocol was only for 3 months; hence the response to prolonged therapy of amiodarone is unknown.
CONCLUSION

This study showed that adjuvant amiodarone therapy when added to DC cardioversion in rheumatic mitral stenosis patients after Balloon mitral valvotomy reduced the risk of immediate and early recurrence of AF. In patients with larger left atrial size, adjuvant amiodarone therapy is a better strategy for both restoration and maintenance of SR. A short-term (3 months) amiodarone therapy does not contribute to the maintenance of sinus rhythm at one year follow up.


INTRODUCTION

The coronary microvasculature controls total coronary resistance and is the key to regulating myocardial blood flow. Although coronary artery disease is only visible in the epicardial coronary arteries, the microvasculature of the myocardium is also often affected by atherosclerosis. While numerous invasive and noninvasive methods are available to investigate the epicardial coronary arteries, microvascular disease is difficult to quantify, and no reliable invasive methodology is available to assess the microcirculation.

Theoretically, combined measurement of distal coronary blood flow and distal coronary pressure enables calculation of microvascular resistance. At present, however, absolute blood flow in a distal coronary artery cannot be determined.

The feasibility of simultaneous measurements of distal coronary pressure and temperature using one single guidewire has been shown in studies. Thus, using indicator dilution technique, a bolus of a few cubic centimeters of saline at room temperature can be injected into the ostium of a coronary artery during catheterization and the temperature can be measured in the distal coronary artery to calculate the mean transit time (Tmn) of the injectate. Theoretically, flow equals the ratio of epicardial vascular volume (V) and mean transit time (Tmn), coronary flow reserve and fractional flow reserve can be determined in that way in one single procedure, as demonstrated in animals and humans.

The ASSUMPTIONS made:

\[ F = \frac{V}{Tmn} \]  
\[ TMR = \frac{Pd}{F} \]
The vascular volume V may be assumed to remain constant after pretreatment by nitroglycerine.

Now by combining equations (1) and (2), it can be derived that TMR is proportional to the product of distal pressure and Tmn: \[ TMR \sim P_d \times T_{mn} \]

This product of Pd and Tmn at maximum hyperemia to reflect microvascular resistance \( \rightarrow \) index of myocardial resistance.

In the assessment of coronary artery disease, severity of epicardial stenosis is determined by FFR and has been validated in a number of studies and has been accepted as the intervention of choice. However, there has not been any universally accepted test for the measurement of the microcirculatory resistance. The presence of microvascular dysfunction lends a worsened prognosis for the patient outcome irrespective of the degree of epicardial stenosis and hence it is necessary to have a method of determining the same. Coronary flow reserve (CFR) has so far been the investigation of choice in the cath lab, however it is not independent of the severity of the epicardial stenosis and hence it becomes difficult to attribute a low value of CFR to either epicardial stenosis or microvascular dysfunction. In this context, the availability of IMR becomes important and makes it a reliable measure of the microvascular function. However, it is a relatively new method and it has not been validated extensively among Indian population. The present study aims to look at the feasibility of using IMR in the catheterization lab and whether there are any additional advantages of doing the same.
AIMS

➢ To determine the value of index of microcirculatory resistance in the patients undergoing fractional flow reserve assessment of intermediate coronary lesion.
➢ To examine the association between an intermediate lesion in the coronary and presence of microvascular dysfunction in patients with various cardiac risk factors.
MATERIALS AND METHODS

The study was carried out between January 2012 and July 2012.

Inclusion Criteria:

- All patients undergoing functional assessment of coronary lesions of intermediate severity in stable coronary artery disease, in whom intravenous adenosine infusion was preferred as the hyperemic agent of choice.

Exclusion criteria

- Patients with recent acute coronary syndrome (within 14 days)
- Patients with bronchial asthma, high grade AV blocks.
- Patients with renal and hepatic dysfunction

Procedure

Patients with intermediate lesions who were planned for further evaluation by fractional flow reserve measurement were chosen for the study. The patients received intravenous adenosine infusion @140 microgm/kg/min as the hyperemic agent of choice.

Coronary physiology measurements

For assessment of the lesion, a 0.014” floppy pressure guidewire (Pressure wire 4, Radi medical systems, Uppsala Sweden) was used. This wire has a microsensor at 3 cm from the floppy tip, which enables simultaneous recording of high-fidelity coronary pressure measurement as well as temperature measurement at the location of that sensor, with an accuracy of 0.02°C. The shaft of this wire, acting as an additional electric resistance, can be used as a second thermistor, providing the input signal at the coronary ostium of any fluid injection with a temperature different from blood.
For the determination of IMR the thermodilution method is used. 3 ml of room-temperature saline was injected down the culprit vessel 3 times at rest, and the resting transit time, which is inversely proportional to flow, were recorded and averaged. Maximal hyperemia was then induced using 140 μg/kg/min of intravenous adenosine via a venous line. 3ml of room-temperature saline was again injected down the culprit vessel, and the hyperemic transit time recorded and averaged. The mean aortic and distal coronary pressures were recorded during peak hyperemia.

IMR was calculated by dividing the mean distal coronary pressure by the inverse of the hyperemic transit time

i.e., multiplying the mean distal coronary pressure by the hyperemic transit time

\[ \text{IMR} = \frac{P_d}{T_{mn}} \]

Fractional flow reserve (FFR) was calculated by dividing the mean distal coronary pressure by the mean aortic pressure during maximal hyperemia.

Based on data from various studies and after review of literature, a cut off value of 30 was determined for IMR; values above 30 would indicate presence of microvascular disease

Quantitative coronary angiography.

Quantitative coronary analysis was performed using a computer-assisted, automated computerized edge-detection algorithm (Phillips Medical System, Eindhoven, Netherlands). The external diameter of the contrast-filled catheter was used as a calibration standard. Minimal luminal diameter, vessel diameter of the reference segment, and the percent diameter stenosis at end diastole were measured from the worst-view trace.

Further analysis of the lesion was based on length of ≤10 mm or > 10 mm and MLD % of ≤ 50 and >50. The QCA was compared with the measured FFR.

Statistical Analysis
All data were transferred to SPSS (version 20.0) software (SPSS Inc., Chicago, IL) for further analysis. Data are presented as mean +/- standard deviation. A comparison of means was performed using T test.
REVIEW OF LITERATURE

Functional Anatomy of the coronary arterial system

The coronary arterial system is composed of three compartments with different functions, although the borders of each compartment cannot be clearly defined anatomically.\(^1\)

The proximal compartment is represented by the large epicardial coronary arteries, which have a capacitance function and offer little resistance to coronary blood flow. The diameter of the epicardial coronary arteries ranges from approximately 500 μm to 2 to 5 mm. The intermediate compartment is represented by prearterioles, which are characterized by a measurable pressure drop along their length. These vessels are not under direct vasomotor control by diffusible myocardial metabolites because of their extramyocardial position and wall thickness. Their diameter ranges from approximately 100 to 500 μm, and their specific function is to maintain pressure at the origin of arterioles within a narrow range when coronary perfusion pressure or flow changes. The more distal compartment is represented by intramural arterioles, which are characterized by a considerable drop in pressure along their path. They have diameters of less than 100 μm, and their function is the matching of myocardial blood supply and oxygen consumption.

When flow changes, epicardial coronary arteries and proximal arterioles have an intrinsic tendency to maintain a given level of shear stress by endothelial-dependent dilatation\(^2\). When aortic pressure increases, distal prearterioles undergo myogenic constriction in order to maintain a constant pressure at the origin of the arterioles. Arterioles have a fundamental role in the metabolic regulation of coronary blood flow\(^3\). They have a high resting tone and dilate in response to the release of metabolites by the myocardium as a result of an increase in oxygen consumption. Arteriolar dilatation decreases both resistance in
the overall network and pressure in distal prearterioles, which in turn induce the dilatation of myogenically sensitive vessels. Furthermore, the dilatation of distal prearterioles and arterioles results in an increase in shear stress, which triggers flow-dependent dilatation in larger prearterioles and conductance arteries.

Thus, as proposed by Chilian\textsuperscript{4}, the coronary circulation matches blood flow with oxygen requirements by coordinating the resistances within different microvascular domains, each governed by distinct regulatory mechanisms. Such integration appears advantageous because the system does not rely on a single mechanism of control.

**Microvascular Dysfunction with Obstructive CAD**

**Stable CAD**

Studies of patients with single-vessel CAD and normal left ventricular function have documented the presence of abnormal coronary flow reserve in regions subtended by angiographically normal coronary arteries\textsuperscript{5,6}. In patients with stable angina, coronary microvascular dysfunction distal to coronary stenosis has an important role in determining the ischemic threshold. This was first demonstrated by Pupita et al.,\textsuperscript{7} who observed marked variability of the ischemic threshold in patients with a single total coronary occlusion and no previous myocardial infarction. In the absence of dynamic epicardial coronary artery stenoses, such variability could only be explained by coronary microvascular dysfunction, including that in the collateral circulation.

Coronary microvascular dysfunction distal to a critical coronary stenosis may be caused by two mechanisms: inappropriate subepicardial prearteriolar dilatation in the presence of increased myocardial oxygen consumption and prearteriolar and arteriolar constriction.
Acute Coronary Syndromes without ST-Segment Elevation

In patients with acute coronary syndromes without ST-segment elevation, coronary microvascular dysfunction distal to the critical stenosis plays an important role in determining the severity of myocardial ischemia, not only through the mechanisms operating in stable CAD but also through other mechanisms operating specifically in patients with unstable disease. Marzilli et al.\(^8\) found that in patients with unstable angina, episodes of transient myocardial ischemia at rest are associated with a brisk increase in coronary microvascular resistance and that this increase is prevented by the administration of antiplatelet drugs. Furthermore, the degree of coronary microvascular dysfunction is proportional to systemic levels of C-reactive protein, a prototypical marker of inflammation independent of traditional coronary risk factors, thus suggesting that the impairment caused by inflammation is independent of that caused by risk factors.\(^9\)

Acute Myocardial Infarction with ST-Segment Elevation

In patients with acute myocardial infarction, a reduction of baseline flow severe enough to impair regional wall motion in remote, normally contracting myocardium subtended by angiographically normal coronary arteries has been observed very early after the infarction. Both coronary microvascular dysfunction and the impairment of regional wall motion are relieved by alpha-blockers, thus suggesting that enhanced sympathetic activation is likely to contribute to these abnormal findings.\(^10\) Myocardial ischemia reflexively increases cardiac sympathetic nerve activity by stimulating cardiac ventricular and coronary nerve–ending receptors.\(^11\)

In patients with acute coronary syndromes with ST-segment elevation, coronary microvascular dysfunction in the territory of a recanalized infarct-related artery is responsible for the inability of a previously ischemic region to be reperfused (“no-reflow” phenomenon).\(^12\) This phenomenon is characterized by the lack of microvascular integrity and
patency despite the successful reopening of the infarct-related artery. It appears to be the result of pathologic changes that begin during ischemia\textsuperscript{13} and are aggravated during reperfusion.\textsuperscript{14} Extensively studied in both the experimental and clinical settings, this concept recognizes a multifactorial pathogenesis. Galiuto\textsuperscript{15} has recently proposed that this phenomenon can be classified into structural and functional forms, on the basis of the observation that the two forms differ with respect to pathogenesis, time course, clinical implications, and possible therapeutic strategies. In the structural type of no-reflow phenomenon, the cellular components of the walls of microvessels well confined within necrotic myocardium exhibit irreversible damage, whereas in the functional form, the patency of anatomically intact microvessels is compromised by the loss of endothelium-mediated vasomotion, alteration of sympathetic innervation, and external compression owing to interstitial edema and the plugging of platelets and neutrophils. The clinical relevance of the no-reflow phenomenon has been demonstrated by several studies correlating the microvascular damage with cardiac remodeling and with clinical outcome.\textsuperscript{16,17}

**Measurement of coronary microcirculation**

Guidewire based measurement of coronary flow reserve (CFR), either by Doppler flow or thermodilution techniques, has become an increasingly important invasive method for assessing the physiological significance of coronary disease.\textsuperscript{18,19}

However, use of CFR to interrogate the microcirculation independently is limited because CFR interrogates the flow status of both the epicardial artery and the microcirculation but does not allow discrimination between these 2 components. Furthermore, CFR is limited by its dependence on heart rate and blood pressure, thereby calling into question its reproducibility.\textsuperscript{20} With recent technological advances, it is now possible to measure pressure and to estimate coronary artery flow simultaneously with a single pressure-temperature sensor-tipped coronary wire.\textsuperscript{21,22} By the thermodilution
technique, the mean transit time (Tmn) of room-temperature saline injected down a coronary artery can be determined and has been shown to correlate inversely with absolute flow. From this technique, a thermodilution-based CFR can be derived that has been shown to correlate well with Doppler velocity wire-derived CFR and with absolute flow as measured by a flow probe but that has the same conceptual disadvantages as Doppler-derived CFR. Using this thermodilution method, a novel index of microcirculatory resistance (IMR) for assessing the status of the microcirculation independent of the epicardial artery was proposed. IMR, defined as the distal coronary pressure divided by the inverse of the hyperemic mean transit time, correlated well with an accepted experimental method for measuring microvascular resistance. Unlike CFR, IMR is derived at peak hyperemia, thereby eliminating the variability of resting vascular tone and hemodynamics.

Role of IMR in catheterization laboratory

- Assessing microvascular damage in Acute coronary syndrome or peri-PCI
- For risk stratification in patients with STEMI: after treatment of the epicardial vessel, IMR may be used to identify high risk patients who will continue to have persistent LV dysfunction as opposed to lower risk who will recover their LV function with time.
- May have application for adjunctive treatment such as stem cell therapy, given only to the high risk group.
- In conjunction with FFR, to distinguish between epicardial and microvascular disease in stable, chest pain patients.
- For assessment of microvascular dysfunction in patients with chest pain, but normal epicardial vessels.
- Serial evaluations as part of research protocols.
IMR has been found to be an independent predictor of acute microvascular damage after acute myocardial infarction and of 3-month LV functional recovery. Lim et al\textsuperscript{24} after successful primary percutaneous coronary intervention in 40 patients with anterior AMI, measured IMR value in them. Myocardial viability was quantified by 18F-Fluorodeoxyglucose (FDG) positron emission tomography in 38 patients. Echocardiographic regional wall motion was analysed to calculate the anterior wall motion score (A-WMS) and percent change in A-WMS after revascularization and at 6-month follow-up. IMR correlated significantly with regional myocardial FDG uptake (r= -.738, P<0.001) and it demonstrated significant correlation with percent change in A-WMS (r= -.464, p =0.003). They concluded that IMR is a reliable early on-site determinant of myocardial viability and LV recovery after primary stenting for AMI.

Fearon\textsuperscript{25} et al evaluated the predictive value of the index of microcirculatory resistance (IMR) in patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction. The study was conducted in 29 patients. The IMR correlated significantly with the peak creatinine kinase (CK) (R = 0.61, p = 0.0005) while the other measures of microvascular dysfunction did not. In patients with an IMR greater than the median value of 32 U, the peak CK was significantly higher compared with those having values <or=32 U (3,128 +/- 1,634 ng/ml vs. 1,201 +/- 911 ng/ml, p = 0.002). The IMR correlated significantly with 3-month echocardiographic wall motion score (WMS) (R = 0.59, p = 0.002) while the other measures of microvascular function did not. The WMS at 3-month follow-up was significantly worse in the group with an IMR >32 U compared with <or=32 U (28 +/- 7 vs. 20 +/- 4, p = 0.001). On multivariate analysis, IMR was the strongest predictor of peak CK and 3-month WMS. The IMR was the only significant predictor of recovery of left ventricular function on the basis of the percent change in WMS (R = 0.50, p < 0.01).
Cuisset et al\textsuperscript{26} conducted a randomized study to compare the effect of direct stenting (DS) and conventional stenting (CS) on post-procedural index of microcirculatory resistance (IMR) values. Fifty patients admitted for elective percutaneous coronary intervention (PCI) were included. All patients had stable angina (CCS class <IV) related to a lesion suitable for DS and were randomized to DS (n = 25) or CS (n = 25). Patients treated with CS had significantly greater IMR (DS 13 +/- 3, CS 24 +/- 14; p < 0.01) and tended to have greater post-PCI troponin T values (DS 0.035 +/- 0.04, CS 0.17 +/- 0.02; p = 0.07). In the whole sample, 20\% of patients had post-PCI troponin release (troponin T >0.03 ng/ml). Patients with troponin elevation had significantly greater post-PCI IMR values than patients without troponin elevation: 24.7 +/- 13.2 versus 16.9 +/- 10.2; p = 0.04.
RESULTS

A total of 15 coronary arteries (14 patients) were evaluated in the study. The clinical characteristics of the patients are presented in Table 1. All except one were male patients. More than half of the patients (53.3%) were above the age of 50 years. 8 lesions were found to have an IMR value $\leq$30U and 7 had an IMR value $>30U$. Only about a quarter (26.7%) of the patients being evaluated had single vessel disease. Rest had two vessel (6.7%) or three vessel (66.7%) disease. Angina was present in 46.7 % of the patients. Of the other patients, all had symptoms of dyspnea, barring two who were asymptomatic and underwent coronary angiogram for further risk stratification after a positive treadmill test.

Table 1 Baseline Characteristics

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<tr>
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Mean IMR value in patients aged ≤ 50 years of age was 20.02 U (10.44 – 33.88) whereas in patients aged >50 mean IMR was 45.14 U (16.5 - 94). A statistically significant difference (p =0.019) was obtained between the groups. Among Diabetic patients, mean IMR value was 34.21U whereas in non diabetics mean IMR value was 31.24U. No significant difference was obtained. In hypertensives, mean IMR value was 31.33U and in non
hypertensives it was 36.54U. There was no positive correlation between higher IMR value and presence of hypertension while there was a non significant positive correlation among diabetics. Current smokers (n=3) had a mean IMR value of 16.42U, whereas non-active smokers (including ex smokers and those who have never smoked) had a mean IMR value of 37.67U and demonstrated a statistically significant difference (p= 0.007). When patients who have never smoked (mean IMR = 47.06U) were compared with patients who are current smokers or were exsmokers, (mean IMR = 26.6), no statistically significant difference was observed, however there was a definite trend towards a lower IMR value among those who have smoked.

On evaluating QCA of the lesion with regard to its % MLD and length, we found that among the group of patients with a % MLD ≤ 50% along with lesion length < 10 mm, none were having FFR values of <0.8. On the other hand, lesions with % MLD >50% were more likely to have a significant FFR value (<0.8) if the length of the lesion was >10mm (60% vs 20%).

When evaluating the FFR values with the presence of angina, we found that patients who suffered from angina had a lower FFR value (0.76+/-.07)) compared to those who had no symptoms of angina (0.82+/-.03). This showed a trend towards statistical significance (p=0.055).

On comparing the values of FFR and IMR using Pearson correlation coefficient, no significant correlation (r=0.32) was obtained.
To calculate IMR, “Pd” is multiplied with value of “Hyp”, (which indicates the transit time). In this example, distal pressure is 62, it is multiplied with 0.32, giving an IMR value of 19.84U
Figure 2 Percentage distribution of the sample according to selected variables
Table 2 Comparison of IMR with various clinical characteristics

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</tr>
<tr>
<td>No</td>
<td>2</td>
<td>28.6</td>
<td>4</td>
</tr>
<tr>
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<td>5</td>
<td>71.4</td>
<td>2</td>
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<tr>
<td>Prior UA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>60.0</td>
<td>3</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>40.0</td>
<td>2</td>
</tr>
<tr>
<td>Angina</td>
<td>No</td>
<td>5</td>
<td>62.5</td>
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<td>--------</td>
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</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3</td>
<td>37.5</td>
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<tr>
<td>CAG vessel involvement</td>
<td>3VD</td>
<td>6</td>
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<tr>
<td></td>
<td>2VD</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>SVD</td>
<td>1</td>
<td>12.5</td>
</tr>
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</table>
Table 3 Comparison of lesion diameter and length with FFR

<table>
<thead>
<tr>
<th>% MLD and Length of lesion</th>
<th>(&lt;0.8)</th>
<th>(&gt;0.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>Length (&lt;10, % MLD \leq 50)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Length (&lt;10, % MLD &gt;50)</td>
<td>1</td>
<td>20.0</td>
</tr>
<tr>
<td>Length &gt;10, % MLD \leq 50</td>
<td>1</td>
<td>20.0</td>
</tr>
<tr>
<td>Length &gt;10, % MLD &gt;50</td>
<td>3</td>
<td>60.0</td>
</tr>
</tbody>
</table>

Bar chart showing the distribution of percentages for different categories of lesion length and % MLD.
DISCUSSION

In many patients presenting to the cardiac catheterization laboratory, the status of the coronary microcirculation, not just the epicardial arteries, is of clinical and prognostic relevance\textsuperscript{27}. However, to date, there is no simple, specific, and reproducible invasive measure of the status of the coronary microcirculation.

The index of microcirculatory resistance is a novel method which can be used to determine the coronary microvascular dysfunction. It is relatively easy to perform and does not add much time to the procedure.

In the present study we have determined the IMR value and observed for any association with known cardiac risk factors and other baseline characteristics such as prior unstable angina, number of vessel involvement etc. We also concurrently measured the FFR value and demonstrated its relation with the apparent severity and length (based on QCA). We also determined that there was no correlation between IMR and FFR values demonstrating that they are independent of each other at least in non-severe epicardial coronary artery lesions.

In our study, coronary microvascular dysfunction was demonstrated to be significantly associated with patient population above the age of 50 years. We could not demonstrate any association with traditional risk factors like diabetes and hypertension. There are different causes and mechanisms of coronary microvascular dysfunction. However, coronary microvascular dysfunction due to aging must be always kept in mind. Age is a recognized risk factor for cardiovascular disease, and it is associated with morphologic and functional changes in the coronary microvasculature.\textsuperscript{28} Studies in animals have shown that coronary flow reserve and the endothelium-dependent dilatation of the resistance arteries
decrease with age. It has been suggested that endothelium-dependent dilatation of the resistance coronary arteries evoked by acetylcholine may decrease with age in humans. With advancing age, nitrous oxide–dependent mechanical and agonist-mediated endothelial vasodilatation is reduced in humans and animals. Hence coronary microvascular dysfunction due to aging should not be underestimated.

Also in this study we found that current smokers with coronary artery disease had a lower IMR value. This was a surprising finding as smoking is known to cause microvascular dysfunction. This may partly be attributable to the relative lower age among the smokers (50.33 years vs 55.5 years, p=0.17). Also the numbers being small may make this a purely incidental finding. However this could also lead to the argument that overall, smokers are more likely to present with acute forms of CAD such as unstable angina and myocardial infarction rather than a stable form of coronary artery disease and may have lesser involvement of the microvasculature. However in our study, patients with acute CAD were excluded and hence this explanation may not hold weight.

The study examined whether it was possible to predict significant FFR values based on the lesion severity and length of the lesion. It could be shown that discrete lesions (< 10mm) with a % MLD < 50 were more likely to have FFR value of >0.8.

We also found a relation between the presence of angina and the FFR values. Patients who have angina were more likely to have a significant FFR value. However in this study, 10 patients had double or triple vessel disease and hence it is difficult to attribute cause of angina to the vessel being studied.

Correlation analysis showed that FFR and IMR values did not have any strong positive or negative linear correlation hence signifying that with lesions of intermediate severity, the two values were independent of each other.
However in cases of severe epicardial stenosis, if collateral flow (wedge pressure) is not accounted for, IMR increases with increasing stenosis severity$^{31}$. By measuring wedge pressure and incorporating this in the calculation, IMR remains fairly constant even with increasing stenosis severity.

This study has thus demonstrated that simultaneous measurement of FFR and IMR with a single pressure-temperature sensor-tipped coronary wire provides a simple means for comprehensive and specific assessment of coronary physiology at both epicardial and microvascular levels, respectively.
LIMITATIONS

Firstly its invasive nature limits the ability to perform follow-up evaluations in the same patients. Secondly IMR in its simplified form (distal pressure multiplied by hyperemic mean transit time), was used in this study, which may overestimate true microvascular resistance if significant collaterals are present. This occurs because the hyperemic mean transit time, the method used to estimate flow, is a reflection of coronary flow and not myocardial flow. In the presence of significant collaterals, coronary flow underestimates myocardial flow, and resistance is overestimated. However our study patients included only those with intermediate coronary lesions, hence it is unlikely that there would be significant collateral flow to the myocardial bed. Thirdly the sample size was small and this may explain why other clinical risk markers were not associated with elevated IMR
CONCLUSIONS

The index of microcirculatory resistance is independent of the FFR value and may be used to determine the microvascular function in the distal myocardial bed. Age more than 50 years is a risk factor for microvascular dysfunction regardless of associated diabetes or hypertension. Smokers were found to have lower IMR values, hence further studies with larger study population will be required to assess the microcirculation using IMR.
BIBLIOGRAPHY


