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PROJECT REPORT

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DECLARATION

I, **Dr. Dinesh Choudhary**, 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.

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GENERAL CONTENTS

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Project I

Radial left ventricular dyssynchrony by speckle tracking in apical versus non apical right ventricular pacing- Evidence of dyssynchrony on medium term follow-up

Introduction

Cardiac pacing has been an effective treatment in the management of patients with bradyarrhythmias and in drug refractory heart failure in the form of CRT (cardiac resynchronization therapy) (1, 2). Traditional site of pacing is right ventricular (RV) apex. Right ventricular (RV) apical pacing causes deleterious effects on the left ventricular (LV) function due to adverse remodelling and ventricular dyssynchrony. The association between RV apical pacing and mechanical dyssynchrony as well as their effects on cardiac function has been studied in various trials (3-11). These trials have provided important pathophysiologic information, however there is currently insufficient data to recommend an optimal RV pacing site among the various alternate sites proposed .Exact location of lead insertion on RV septum is highly variable and not uniform in the studies .This retrospective-prospective study was planned to identify various lead positions with the help of fluoroscopy and to compare the lead, ECG and dyssynchrony parameters for the various pacing sites in RV (apical and non apical (mid septal and RVOT)) and to correlate with changes in ventricular function on medium term follow up.

Tissue Doppler imaging and derived strain and strain rate measurements for ventricular synchrony depend on Doppler angle and lack reproducibility, which limit their clinical application. More recently 2-dimensional (2D) strain, a new echocardiographic technique based on speckle tracking, enables simultaneous evaluation of the 3 components of myocardial deformation (i.e., circumferential strain [CS], longitudinal strain [LS], and radial strain [RS]) by automatic tracking of myocardial segments. This 2D speckle tracking technique for strain measurement has attractions with respect to signal noise, angle dependency, and the ability to monitor strain in two dimensions rather than one dimension. Hence this study was planned with

2D speckle tracking for radial strain as the main measure of LV dyssynchrony to observe the effects of various RV pacing leads location.

Aims of the study

To identify LV dyssynchrony as assessed by the novel measure of radial left ventricular strain by speckle tracking in patients with apical versus non apical RV (mid septal or low RVOT) pacing and correlate with changes in ventricular function on medium term follow up.

Review of literature

Cardiac pacing is used for bradyarrhythmias, tachyarrhythmias and nowadays in Drug - refractory heart failure in the form of CRT: Cardiac resynchronization therapy (1, 2). The traditional pacing site is right ventricular (RV) apex. RV apical pacing causes abnormal electrical and mechanical activation pattern of the ventricles (or ventricular dyssynchrony) and leads to detrimental effects on cardiac structure and left ventricular (LV) function (3). Many large randomized clinical trials have shown the effect of RV apical pacing on cardiac function leading to cardiac morbidity and mortality and provided important information for selection of the optimal pacing mode (4, 5, 6, 7, 8, 9, 10). It has also been shown that RV apical pacing induced mechanical dyssynchrony is associated with deterioration of LV function and clinical status (11).

MOST (Mode Selection Trial) (5) trial showed a strong association between percentage of RV pacing and the risk of heart failure hospitalization and atrial fibrillation in both "physiologic pacing" (dual-chamber pacing [DDDR]: n 707) and ventricular pacing (single-chamber ventricular pacing [VVIR]: n 632). 40% of ventricular pacing in the DDDR group was associated with an increased risk of heart failure hospitalization (hazard ratio [HR]: 2.60; 95% confidence interval [CI]: 1.05 to 6.47; p 0.05) and that 80% of ventricular pacing in the VVIR group was associated with an increased risk of heart failure hospitalization (HR: 2.50; 95% CI: 1.44 to 4.36; p 0.05).

In the DAVID (Dual Chamber and VVI Implantable Defibrillator) trial (6), patients with a standard indication for a defibrillator implantation, but without an indication for anti-bradycardia pacing, were randomized to either physiologic pacing (DDDR mode, lower rate of 70 beats/ min) or ventricular backup pacing (VVIR mode, lower rate of 40 beats/min). After a median follow-up

of 8.4 months, the primary outcome measure (freedom from death and absence of hospitalization for new or worsened heart failure) was lower in the VVIR-40 group than in the DDDR-70 group (relative hazard: 1.61; 95% CI: 1.06 to 2.44; p 0.03) and worse survival at 12 months .

These trials suggest that there is no clinical benefit of physiologic DDDR pacing over VVIR. The beneficial effect of maintaining AV synchrony by physiologic DDDR pacing may be reduced by the deleterious effects of RV apical pacing itself. Exact amount of RV apical pacing that causes adverse cardiac function remains unclear from these trials.

Maintaining physiologic AV synchrony by DDD pacing may be useful in patients with heart failure (12), however as amount of RV pacing increases it produces deleterious effects and it is also more detrimental if baseline LV function is depressed (3, 13). Still further studies are needed to understand the beneficial and deleterious effects of RV apical pacing.

Electrical and Mechanical Dyssynchrony with RV apical pacing:

Adverse effects of RV apical pacing have been attributed to the abnormal electrical and mechanical activation of the ventricles (9). During RV apical pacing, the conduction of the electrical wave front propagates through the myocardium more slowly and induces heterogeneity in electrical activation of the myocardium resulting a single breakthrough at the interventricular septum and the latest activation at the inferoposterior base of the LV (14, 15, 16). Onset and pattern of mechanical activation of the LV is also changed during RV apical pacing (9). Early activated regions near the pacing site exhibit rapid early systolic shortening, resulting in pre-stretch of the late-activated regions (10, 17). As a result, these regions exhibit an increase in (delayed) systolic shortening, imposing systolic stretch to the early activated regions exhibiting

premature relaxation. This abnormal contraction pattern of the various regions of the LV may result in a redistribution of myocardial strain and work and subsequent less effective contraction (10).Both the abnormal electrical and mechanical activation pattern of the ventricles can result in changes in cardiac metabolism and perfusion (18,19), remodeling (asymmetric hypertrophy, histopathological changes, ventricular dilation, functional mitral regurgitation) (20-24), hemodynamics (decreased cardiac output, increased LV filling pressures) (8), and mechanical function (changes in myocardial strain, interventricular mechanical dyssynchrony, intraventricular mechanical dyssynchrony).

Changes in myocardial strain and timing of regional strain may occur during RV apical pacing. Prinzen et al. (10) noted a decrease in strain in the regions close to the pacing site and increase in myocardial strain in remote regions with change in timing of peak strain which is often known as "mechanical dyssynchrony" (25).

Right ventricular apical pacing can induce both interventricular dyssynchrony (between the RV and the LV) and intraventricular dyssynchrony (within the LV) (11). Ventricular dyssynchrony is responsible for increased risk of cardiac morbidity and mortality (26, 27) in heart failure (HF) patients. Mechanical dyssynchrony causes reduced LV systolic function and deterioration in functional capacity (11). Restoration of normal conduction and "cardiac synchrony" by CRT results in normalization of LV systolic function (28, 29). Assessment of ventricular dyssynchrony by echocardiographic may provide important information in patients with permanent RV apical pacing. These echocardiographic techniques include conventional Doppler techniques, tissue Doppler imaging, strain analysis based on Doppler and speckle tracking by 2D, and novel 3 dimensional echocardiography.

The majority of the echocardiographic techniques have been used to quantify interventricular and intraventricular dyssynchrony in heart failure patients referred for CRT (30). These techniques can be used during acute and long-term RV apical pacing.

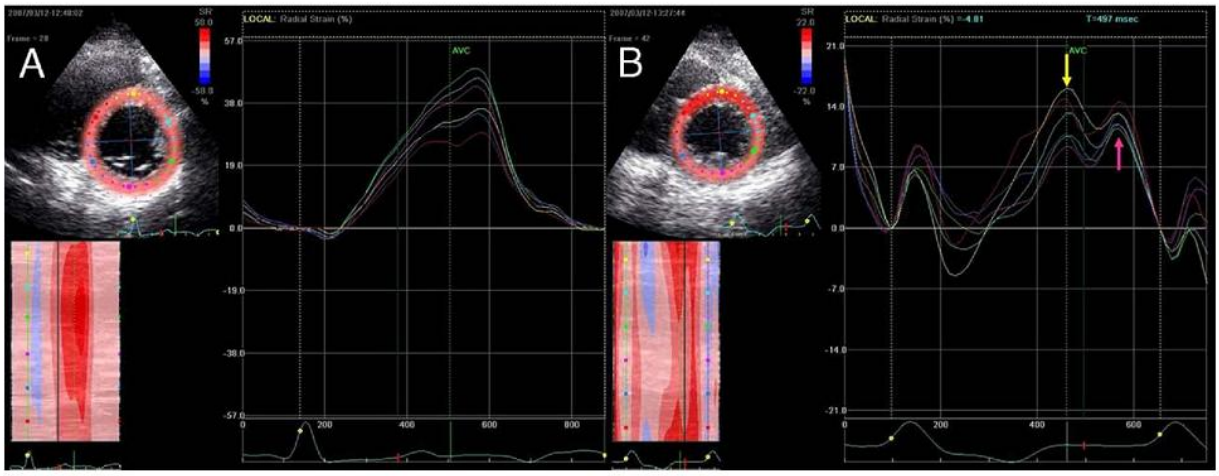
For interventricular dyssynchrony, conventional Doppler techniques are typically used. For both ventricles, the electromechanical delay is calculated as the time from onset of the QRS complex to the onset of pulmonary systolic flow (RV electromechanical delay: Q Po) or aortic systolic flow (LV electromechanical delay: Q Ao). The time difference between the RV and LV electromechanical delay represents interventricular dyssynchrony (Q Ao-Q Po) and an interventricular delay **≥40 ms** used as a cutoff value for interventricular dyssynchrony (31). RV apical pacing can induce significant interventricular dyssynchrony (11, 32).

For the assessment of intraventricular (or LV) dyssynchrony, tissue Doppler imaging, 2-dimensional speckle tracking strain analysis, and real-time 3-dimensional echocardiography are available (33). In general, LV dyssynchrony is defined as delay in mechanical activation between the interventricular septum and the posterior /lateral wall.

Gomes et al. (34) probably first demonstrated the effect of RV apical pacing on the mechanical delay between the septum and the posterior wall. Recent studies have shown that RV apical pacing can induce significant intraventricular mechanical dyssynchrony, which has been related to reduced LV function (35, 36, 37, 38).However, in daily clinical practice not all patients who receive RV apical pacing will experience these adverse events (13). Chen L et al showed (in a retrospective study including 286 patients) that left ventricular ejection fraction (LVEF) decreased significantly in only 9% of the patients during follow-up with permanent pacing after AV junction ablation (39). Zhang XH et al studied the clinical outcome after at least 1 year of

RV apical pacing in a retrospective study of 304 patients with pacemaker implantation for high degree AV block (40). 26% patients developed new-onset HF after a mean of 6.5 +/- 5.7 years of pacing. It appears that some patients are more susceptible to the detrimental effects of RV apical pacing than other patients are, possibly due to mechanical ventricular dyssynchrony. Ventricular dyssynchrony may be seen in up to 50% of the patients after long-term RV apical pacing (32, 35, 41) which may lead to LV dilation and a deterioration of LV systolic function and functional capacity (11).

Delgado V et al showed that significant LV dyssynchrony may be induced acutely in up to 36% of individuals in patients with structurally normal hearts undergoing electrophysiological testing (42). This is shown in the figure below: Echocardiographic analysis of LV dyssynchrony during intrinsic rhythm (A) and immediately after onset of RV apical pacing (B). Speckle-tracking strain analysis enables the evaluation of the timing of systolic strain. The color-coded curves represent the time-strain curves of 6 midventricular segments of the LV. During intrinsic rhythm (A), a synchronous contraction of all LV segments is present. In contrast, during RV apical pacing, significant LV dyssynchrony is present: there is a significant delay **(130 ms)** between the time-to-peak strain of the anteroseptum (yellow arrow) and the posterolateral segment (purple arrow)



Impairment in LV systolic function was also observed in the form of reduction of LVEF (from 56 +/- 8% to 48 +/- 9%, p 0.001) and LV longitudinal strain (from –18.3 +/- 3.5% to –11.8 +/- 3.6%, p 0.001).

Pastore et al. (43) assessed LV dyssynchrony using tissue Doppler echocardiography at baseline and after at least 24 h (mean 1.7 +/- 0.3 days) of continuous RV apical pacing. 66% patients exhibited significant LV dyssynchrony. Varma N showed that conduction abnormalities induced by RV apical pacing may be enhanced by accompanying conduction disease at baseline (44). Above mentioned studies (42, 43, 44) assessed LV dyssynchrony and LV function in the acute phase. Negative effects of the abnormal LV activation sequence may sustain even after termination of RV apical pacing (45). Acute dyssynchrony and its effect on long term LV dysfunction may be due to differences in pacing lead location within the RV apex and some echocardiographic techniques may not be sensitive enough to detect small changes in electromechanical activation (46). So more studies needed on this aspect.

Based on the present evidences percentage of ventricular pacing should be kept to a minimum due to detrimental effects of RV apical pacing (3). However, in a large proportion of patients, RV pacing is inevitable (1). For these patients, a number of alternative strategies have been proposed. These are: upgrade from RV pacing to CRT, "de novo" CRT, and alternative pacing sites.

Several studies have demonstrated beneficial effects of the upgrade from RV apical pacing to CRT (47- 52). Eldadah ZA et al (49) studied 12 consecutive patients with class III HF who had a previously implanted pacemaker or implantable Cardioverter defibrillator. Tissue Doppler and strain rate imaging (TDI and SRI, respectively) were performed immediately before each upgrade and 4-6 weeks afterward to quantify changes in regional wall motion and synchrony with CRT. CRT significantly reduced the mean QRS duration (205 ms to 156 ms; P<.0001), and increased the ejection fraction (30.7%+/-5.1% to 35.8%+/-5.1%; P<.01). Left ventricular end-systolic and end-diastolic dimensions were also significantly reduced. Clinically, patients improved by an average of one New York Heart Association (NYHA) functional class after upgrade (P = .006). The parameter exhibiting greatest improvement was the coefficient of variation (CoV: standard deviation/mean) of time to peak systolic strain rate, a marker of ventricular dyssynchrony, which decreased from 34.3%+/-13.0% to 19.0%+/-6.6% (P<.01). Reduction in CoV of time to peak systolic strain rate was maximally seen in the mid ventricle (38.2%+/-19.6% to 16.5%+/-9.7%; P<.01).Upgrading chronically RV-paced HF patients to CRT improves global and regional systolic function as biventricular pacing synchronizes mechanical activation in different myocardial regions in patients upgraded from RV pacing.

Some trials have demonstrated a clear long-term benefit of CRT over RV pacing with regard to peak VO2 or the distance walked during the 6-min walk test (53,54), others have demonstrated only modest (55,56) or no benefit at all (57).

The ongoing BioPace (Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization) trial will demonstrate if CRT actually provides benefit in morbidity and mortality over conventional RV apical pacing (58).

Alternatives for RV apical pacing may be important in patients who have a depressed LV function at baseline or patients who are expected to be paced frequently (complete AV block) or for a longer period of time (young patients, congenital AV block). Various pacing strategies have been suggested to minimize the amount of RV apical pacing.

Atrial-based pacing may be preferred over RV apical pacing in sick sinus syndrome patients, because it prevents cardiac desynchronization by maintaining normal ventricular electrical activation (59). But in a recent meta-analysis from 5 randomized clinical trials comparing atrial-based and ventricular pacing, no significant reduction in mortality with atrial-based pacing could be demonstrated (HR: 0.95; 95% CI: 0.87 to 1.03; p 0.19). In addition, no differences were found in the composite end point of stroke, cardiovascular death, and heart failure hospitalization between the different pacing modes. However, a significant reduction in atrial fibrillation was noted with atrial-based pacing (HR: 0.80; 95% CI: 0.72 to 0.89; p 0.001) (60). Nielsen JC et al found that the incidence of progression to symptomatic AV block in sick sinus syndrome patients was 1.9% per year (59).So there is still concern about atrial-based pacing in patients with sinus node disease, because of the development of AV block in these patients (61). So atrial-based

pacing for the maintenance of ventricular synchrony is only recommended in patients with sinus node disease without AV conduction abnormalities (1).

Specific pacing algorithms have been introduced to minimize unnecessary RV pacing. These algorithms promote normal AV conduction and target maintenance of intrinsic ventricular conduction (62, 63), thus avoiding the induction of LV dyssynchrony. In the INTRINSIC RV (Inhibition of Unnecessary RV Pacing With AVSH in ICDs) study (62), the effects of the use of an AV search hysteresis algorithm were studied. A total of 988 patients with an indication for an implantable cardioverter defibrillator were randomized between VVI-40 backup pacing and DDDR pacing with the AV search hysteresis algorithm. In the DDDR group, 32 patients (6.4%) met the composite primary end point of all-cause mortality and heart failure hospitalization, as compared with 46 patients (9.5%) in the VVI group (p 0.001). It was concluded that the use of the AV search hysteresis algorithm was associated with similar clinical outcomes compared with VVIR backup pacing (62). Similarly, in the SAVE Pace (Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction) trial, 1,065 patients with sinus node disease and intact AV conduction were randomized between conventional dual-chamber pacing and dual-chamber minimal ventricular pacing (63). With the use of the minimal RV pacing algorithm, the percentage of paced ventricular beats was significantly reduced, as compared with conventional dual-chamber ventricular pacing (9.1% vs. 99.0%, p 0.001). After a mean of 1.7 +/- 1.0 years, the development of persistent atrial fibrillation was significantly reduced with minimal ventricular pacing (7.9% in minimal RV pacing vs. 12.7% in conventional dual-chamber pacing, p 0.004). This is directly related to the decrease in RV apical pacing, but a better AV coupling may also be contributed. But no significant difference in mortality or heart failure hospitalizations between the 2 groups was observed (63). Thus these studies suggest a

favorable effect of minimizing ventricular pacing algorithms, still more studies are needed to fully appreciate the exact clinical benefits in daily practice (1).

Pacing at the RV outflow tract, septal pacing and direct His bundle pacing has been suggested as alternatives to the RV apex when pacing is inevitable (64). Because of the closer proximity to the normal conduction system, these sites may result in less electrical activation delay (represented by a shorter QRS duration) and less mechanical dyssynchrony.

From all alternative RV pacing sites, the RV outflow tract has been studied the most extensively. In a metaanalysis (65), using a Cochrane search strategy, 9 studies were selected to analyze the hemodynamic effects of right ventricular outflow-tract pacing. The results of these studies (n 217) were pooled and indicated a significantly better hemodynamic effect (odds ratio 0.34, confidence interval 0.15–0.53) compared with right ventricular apex pacing. Therefore, these data suggest that right ventricular outflow tract pacing may offer a modest but significant benefit over right ventricular apex pacing in patients selected for pacemaker implantation on the basis of symptomatic bradyarrhythmias. Unfortunately, the majority of the studies involved short-term follow-up only.

Another retrospective study by G Vanerio et al demonstrated a better survival in patients with RV outflow tract pacing as compared with RV apical pacing (66). They retrospectively analyzed 150 consecutive patients who underwent pacemaker implantation because of complete AV block (spontaneous or after AV node ablation), symptomatic second-degree AV block, and symptomatic atrial fibrillation with slow ventricular response between July 1999 and December 2004. All patients included were greater than 70% ventricular paced during pacemaker follow-up. Patients older than 85 years were excluded from the analysis. Age, pacemaker mode, sex,

ejection fraction, diabetes, and structural cardiac disease were analyzed. Mean age was 72 ± 7 years (median 74 years, range 27–85 years), 101 (67%) were male, 56 had implanted a VVI PM, and 94 patients a DDD PM. Patients were divided into two groups: outflow tract (55 patients) and apical pacing (95 patients). Mean follow-up was 1,231 ± 642 days (median 1,158 days, range 9 to 2,694 days), which ended on July 2007. During follow-up, 18 patients (32%) died in the outflow tract group and 49 (51%) in the apical group (log-rank p = 0.02). Cox regression multivariate analysis showed that outflow tract pacing and left ventricular ejection fraction (<40%) were the only independent variables with significant correlation with survival (p = 0.006 and 0.003, respectively).They concluded that outflow tract pacing appears to improve medium- and long-term survival. Prospective randomized trials with a greater amount of patients are necessary to confirm the findings of this study.

The favorable effect of RV outflow tract pacing may be related to the more physiologic activation pattern, resulting in less LV dyssynchrony. However, a small study with 14 patients could not demonstrate a benefit of RV outflow tract pacing over RV apical pacing with regard to LV dyssynchrony (Tim J.F. ten Cate et al) (67). 14 patients with a DDD-pacemaker (7 RVA, 7 RVOT) and normal LVF without other cardiac abnormalities were studied. Wall motion score (WMS), longitudinal LV strain, and tissue Doppler imaging for electromechanical delay were assessed with echocardiography during AAI pacing constituting baseline and during DDD pacing. The WMS was normal at baseline (AAI pacing) in all patients and LV dyssynchrony was absent. Acute RVA and RVOT pacing deteriorated WMS, electromechanical delay, and longitudinal LV strain, but no difference in deterioration between both pacing sites was present and dyssynchrony did not emerge. They concluded that acute RVA and RVOT pacing negatively affect WMS, longitudinal LV strain, and mechanical activation times, without clear differences

between both pacing sites. More studies with dyssynchrony analysis and long-term follow-up comparing RV outflow pacing and RV apical pacing are therefore needed.

One concern, however, is how long the clinical trials should be conducted? As stated earlier, most studies were either acute or lasted about six months. Tse et al (68) compared pacing from the RVOT with RV apex and differences were not significant until 18-months post implant. Lewicka-Nowak et al (69) conducted a small 7-year follow up of 27 patients randomized between RVOT pacing and RV apical pacing. Although once again the cases were not necessarily septal, there was a significant drop in left ventricular ejection fraction with RV apical pacing whilst no drop was noted with RVOT pacing. The NT-pro BNP levels were also significantly higher and there was more tricuspid regurgitation in the RV apical pacing group. These studies suggest that future studies should be conducted for a minimum of two years.

Septal pacing may be another good alternative for RV apical pacing. Short-term studies have suggested good results compared with RV apical pacing (70), with good pacing thresholds and lead stability (71). Victor F (70) et al did ablation of the atrioventricular junction for permanent AF, followed by implantation of a DDDR pacemaker connected to two ventricular leads in 28 patients. One lead screwed into the septum and another placed at the apex were connected to the atrial and ventricular port, respectively. Septum or apex was paced by programming AAIR or VVIR modes, respectively. Patients were randomly assigned, 4 months later, to pacing at one site for 3 months, and crossed over to the other for 3 months. New York Heart Association class, QRS width and axis, left ventricular ejection fraction (LVEF), exercise duration, and peak oxygen uptake were measured. Results in patients with LVEF >45% and ≤45% were compared. Septal pacing was associated with shorter QRS (145 ± 4 msec vs. 170 ± 4 msec, $P < 0.01$) and

normal axis (40°± 10° vs. −71 ± 4°, P < 0.01). At 3 months, among patients with baseline LVEF ≤45%, LVEF was 42 ± 5% after septal pacing versus 37 ± 4% after apical pacing (P < 0.001). They concluded that in contrast to RV apical pacing, chronic RV septal pacing preserved LVEF in patients with baseline LVEF ≤45%.

Burri H et al (71) reviewed data at implantation and follow-up of 362 consecutive recipients of the same model of active fixation lead (Medtronic 5076-58, Minneapolis, MN, USA) to avoid differences due to lead characteristics. Patients were divided into two groups according to whether the lead was positioned on the interventricular septum (n = 157) or at the right ventricular apex (n = 205). Thresholds, lead impedance, and requirement for lead repositioning were compared between groups at implantation and follow-up. There were no differences between the septal and apical groups in sensing and pacing thresholds or lead impedance, either at implantation or during a 24-month follow-up. In the septal group, the lead had to be repositioned in four patients (2.5%) due to lead dislodgement in two patients, acute threshold rise in one patient, and pericardial effusion in another patient (the lead had unintentionally been positioned on the anterior free wall in these last two patients). In the apical group, the lead had to be repositioned in eight patients (3.9%, P = 0.56) due to lead dislodgement in three patients and acute threshold rise in five patients. They found that acute and chronic thresholds associated with septal pacing are similar to those observed with apical pacing, and risk of lead dislodgement is low. However, multiple radioscopic views must be used to avoid inadvertent positioning of the lead on the anterior free wall.

In addition, less ventricular dyssynchrony may be present during septal pacing as compared with RV apical pacing (72). Yu CC (72) et al prospectively studied 42 patients without structural heart

diseases and with symptomatic bradycardia. There were 10 patients receiving atrial pacing (AAI) pacemakers, 18 patients having AV sequential pacing at RV apex (DDDapx) and 14 patients being AV sequentially paced at septum (DDDspt). Echocardiography was performed before and within 72 h after the pacemaker implantation. The ventricular mechanical performance and asynchrony was compared in conditions of programmed rates of 60, 80 and 100/min. Myocardial performance index was significantly better in DDDspt than in DDDapx patients (p=0.003). With faster programmed rate, the QRS/RR increased (p<0.05) in DDDapx patients with more inter- and intraventricular asynchrony, implicating the disadvantage of prolonged depolarization time. The DDDspt group demonstrated comparable parameters of diastolic function to AAI patients and preserved mechanical performance during accelerated pacing. RV septal pacing showed the advantages of shorter depolarization time, less ventricular contractile asynchrony, better mechanical performance and preserved chronotropic response on myocardial contractility in comparison with apical pacing.

However, at long-term follow-up, septal pacing may not be superior over RV apical pacing. In a randomized study including 98 patients with AV block (53 septal pacing vs. 45 apical pacing), no differences in LVEF and exercise capacity were found after 18 months of follow-up (73).

Direct His bundle pacing or para-Hisian pacing has also been suggested as an alternative to RV apical pacing. In one of the first clinical studies with permanent direct His bundle pacing, Deshmukh et al. (74) demonstrated the feasibility of this strategy. Implantation was successful in 12 of 14 patients (86%), with maintenance of His bundle capture at long-term follow-up in 11 patients (92%). After a mean of 23.4 +/- 8.3 months, LV end-diastolic diameter had decreased from 51 +/- 10 mm to 43 +/- 8 mm (p 0.01) and LVEF had increased from 18.2 +/- 9.8% to 28.6

+/-11.2% (p 0.05) (72). Importantly, it has been demonstrated that His bundle pacing may result in less inter- and intraventricular dyssynchrony (75, 76). In a randomized study comparing RV apical pacing and para-Hisian pacing in 16 patients, Occhetta et al. (76) noted a significant reduction in interventricular dyssynchrony during para-Hisian pacing as compared with RV apical pacing (34 +/- 18 ms vs. 47 +/- 19 ms, p 0.05). Although the various studies have demonstrated beneficial effects of the alternative pacing sites, at present, septal and direct His bundle pacing are still not recommended in patients requiring permanent cardiac pacing because of difficulties with lead positioning and concerns about lead stability and threshold (1). In addition, it should be remembered that any electrical stimulation outside the normal conduction system may ultimately result in electromechanical changes with deleterious effects on LV function. Furthermore, the majority of the studies on alternative pacing sites were nonrandomized studies with small study populations and short-term follow-up. Nonetheless, there is increasing evidence that these alternative sites may provide benefit over conventional RV apical pacing.

Materials and methods of the study

Type of study: Retrospective-prospective study

Patients

30 patients with single chamber (VVI) pacemaker, 15 each from RV apical (RV apex and apical septum) and non apical (mid septal and low RVOT), were included in the study.

Inclusion criteria

1. Age > 18,
2. ≥80% pacing at follow up by interrogation or in 2 ECGs taken at two different times,
3. normal pacemaker function,
4. No structural heart disease before implantation.
5. Follow up of at least 1 year
6. Ability to give informed consent for Fluoroscopy and Echocardiography

Exclusion criteria

Exclusion criteria included: patients with coronary artery disease, prominent valvular heart disease, cardiomyopathies, and a LV ejection fraction less than 60% before device implantation, patients with structural heart diseases and post cardiac surgery pacemaker implantation.

Implantation data

The date of implantation, indication for implantation, lead implant location, lead parameters and hardware used were noted from patients' records.

Fluoroscopy

After obtaining consent from patients fluoroscopy was performed. The lead location and orientation of the lead tip were noted and archived by fluoroscopy (AP view, RAO 40, LAO 40 and left lateral).

Electrocardiography (ECG)

A 12 lead ECG was archived with and without magnet. Maximum QRS duration, QTc (by using Bazett's formula (QT/√RR interval) and QRS axis were calculated for all patients.

Programming of pacemaker

Interrogation of pacemaker was done to see pacemaker function, percentage of pacing and to check various lead parameters (threshold and lead impedance).Then 100% ventricular pacing was programmed for evaluation by echo.

Echocardiography

Echo was done in 100% pacing state. Echo machine used was PHILIPS iE 33, CANADA. During Echocardiography a standard echocardiography was performed and an attempt made to localize the lead tip using standard views including sub costal views.

Radial strain and dyssynchrony: 2D echo images of the left ventricle in short axis at the mid papillary muscle level were archived with breath held in expiration. Frame rate was kept between 50 to 80 frames per second and 4 loops were archived. This technique has attractions with respect to signal noise, angle dependency, and the ability to monitor strain in two dimensions

rather than one dimension in respect to Doppler derived strain and strain rate and dyssynchrony indices. Speckles are ultrasound reflectors within tissue, are highly reproducible, and essentially behave like magnetic resonance tags. Shortening may be calculated by comparison of these speckles from frame to frame, although attention to technical detail is important, because comparisons at high frame rates are associated with high levels of noise, and comparisons at low frame rates risk loss of correlation because of excessive displacement of the speckles. Offline analysis for radial dyssynchrony was done using Q-lab software in PHILIPS iE 33 machine. Endocardium was traced manually at the end-systolic frame and divided into 6 segments. The strain curves for each segment were constructed. We measured the time to peak radial strain of each segment. The absolute time interval of peak strain between anteroseptum and posterior segment was calculated and radial dyssynchrony was calculated.

Other methods of dyssynchrony: Intraventricular dyssynchrony was further assessed by the septal to posterior wall delay (SPWD) by M-Mode, septal to lateral wall delay (SLWD) by tissue Doppler imaging (TDI).

Interventricular dyssynchrony was assessed by the difference in the electromechanical delay (Q-aortic ejection and Q-pulmonary artery ejection).

Statistical Analysis

Statistical analysis was done using SPSS 14 software (SPSS Inc, Chicago, Illinois). Categorical data were analyzed using chi square test .Continuous data were analyzed by student t test and presented as mean +/- SD. P value < 0.05 was considered as significant. Pearson correlation coefficient test was used to see correlation between various dyssynchrony indices.

Observations and Results

Table no 1 shows that in both apical and non apical groups 7 patients (46.6%) were males and 8 (53.3%) were females. Mean age of males in apical group was 63 +/- 21.9 years and in non apical group was 60.7 +/- 16.5 years (*p* 0.829) while age of females was 61.1 +/- 7.3 years vs. 63 +/- 18.7 years respectively (*p* 0.796).Overall it was 62.0 +/-15.3 years vs. 61.9 +/- 17.1 years (p 0.991).

Table 1 Mean age in different groups

	Apical			Non Apical			t	p
	Mean	SD	N	Mean	SD	N		
Male	63.0	21.9	7	60.7	16.5	7	0.22	0.829
Female	61.1	7.3	8	63.0	18.7	8	0.26	0.796
Overall	62.0	15.3	15	61.9	17.1	15	0.01	0.991

Table no 2 shows that in apical group 5 patients were having pacing lead in RV apex and 10 patients in apical septum position and in non apical group 7 patients were having pacing lead in mid septum and 8 patients were having low RVOT pacing. At baseline CHB was present in 8 patients in apical group and in 13 in non apical group, high grade AV block in 2 and 1 respectively and sick sinus syndrome (SSS) in 5 and 1 patients respectively. At follow up 2 patients in apical group and 1 patient in non apical group was in NYHA class 2, others in both groups were in class 1. There was no statistically significant difference in baseline risk factors of coronary artery disease (smoking, Diabetes mellitus: DM, hypertension: HTN, dyslipidemia: DLP, family history of CAD).

Table 2 Basic diagnosis, site of pacing and clinical variables in different groups

		Apical		Non Apical		p value
		Count	Percent	Count	Percent	
Sex	Male	7	46.7	7	46.7	p>0.05
	Female	8	53.3	8	53.3	
Site of PPI	A	5	33.3	0	0.0	----
	AS	10	66.7	0	0.0	
	MS	0	0.0	7	46.7	
	RVOT	0	0.0	8	53.3	
Diagnosis	CHB	8	53.3	13	86.7	p>0.05
	High GR AVB	2	13.3	1	6.7	
	SSS	5	33.3	1	6.7	
NYHA at F/U	Class I	13	86.7	14	93.3	p>0.05
	Class II	2	13.3	1	6.7	
Smoking	Yes	0	0.0	2	13.3	p>0.05
DM	Yes	4	26.7	7	46.7	p>0.05
HTN	Yes	9	60.0	11	73.3	p>0.05
DLP	Yes	5	33.3	9	60.0	p>0.05
F/H of CAD	No	15	100.0	15	100.0	-

Table 3, 4 and 5 show various lead parameters in both groups. Mean follow up in apical and non apical groups was 38.2 +/- 20 months and 32.6 +/- 22.1 months respectively. Percent pacing in apical and non apical groups was 92.9 +/- 8.4 % and 94.6 +/- 7.9 % respectively (p 0.575). There was no significant difference among basal and follow up lead threshold and lead resistance (impedance) in both groups .There was also no significant difference among percent change in lead threshold and percent change in lead resistance at baseline and follow up in both groups (Table no 4 and 5).

Table 3 Comparison of various lead parameters

	Apical			Non Apical			t	p
	Mean	SD	N	Mean	SD	N		
Basal Threshold	0.6	0.2	15	0.6	0.1	15	1.18	0.248
F/U Threshold	0.9	0.4	15	0.8	0.2	15	0.84	0.407
Basal RES	847.7	195.4	15	774.7	112.7	15	1.25	0.220
F/U RES	531.1	147.7	15	537.5	105.3	15	0.14	0.891
% PACING	92.9	8.4	15	94.6	7.9	15	0.57	0.575

Table 4 Comparison of percentage change in threshold

Group	Mean	SD	N	t	p
Apical	51.8	57.0	15	0.05	0.964
Non Apical	50.9	48.2	15		

Threshold change = F/U Threshold - Basal Threshold

Table 5 Comparison of percentage change in resistance

Group	Mean	SD	N	t	p
Apical	34.8	21.1	15	0.81	0.425
Non Apical	29.1	16.9	15		

RES_Change = Basal RES - F/U RES

Table no 6 shows that mean QRS duration was 165.7 +/- 18.7 ms in apical group and 158.7 +/- 15.4 ms in non apical group (*p* 0.273). QTc was 466.1 +/- 22.9 ms and 463.5 +/- 23 ms respectively (*p* 0.759).Mean QRS Axis was -69.46 in apical group and +76.76 in non apical group.

Table 6 Comparison of ECG variables in different groups

	Apical			Non Apical			t	p
	Mean	SD	N	Mean	SD	N		
QRS axis	-69.46	14.86	15	+76.76	40.59	15		
QRSD	165.7	18.7	15	158.7	15.4	15	1.12	0.273
QTc	466.1	22.9	15	463.5	23.0	15	0.31	0.759

Table 7, 8 and 9 show different echocardiography variables prior to PPI and on follow up. The left ventricular ejection fraction was decreased more in apical location (mean drop of 6.7 % from baseline; *p* 0.06*)* than non apical location (mean drop of 1.3 % from baseline, *p 0*.68). But there was no significant difference among percent change in EF when both groups compared to each other (Table no 9; *p* 0.278).

Table 7 Echocardiography variable in apical group

	Stage	Mean	SD	N	Mean Difference	Paired t	p
LVIDD	Pre	51.1	7.0	15	2.8	1.59	0.134
	Post	48.3	6.0	15			
LVIDS	Pre	32.1	5.4	15	1.7	0.84	0.415
	Post	30.4	6.4	15			
EF	Pre	73.1	8.8	15	6.7	2.01	0.064
	Post	66.4	10.0	15			
LA	Pre	35.3	3.6	15	0.4	0.3	0.771
	Post	35.7	3.9	15			

Table 8 Echocardiography variable in non apical group

	Stage	Mean	SD	N	Mean Difference	Paired t	p
LVIDD	Pre	48.7	7.8	15	1.5	1.32	0.209
	Post	47.2	5.6	15			
LVIDS	Pre	31.0	6.0	15	2.2	1.81	0.091
	Post	28.8	5.8	15			
EF	Pre	70.1	8.9	15	1.3	0.41	0.686
	Post	68.9	10.0	15			
LA	Pre	33.7	5.3	15	0.9	0.8	0.438
	Post	34.7	4.3	15			

Table 9 Comparison of percentage change in EF

Group	Mean	SD	N	t	p
Apical	8.0	17.5	15	1.11	0.278
Non Apical	0.5	19.5	15		

EF_Change = EF pre - EF post

Dyssynchrony Indices

Table no 10 and 11 showing various dyssynchrony parameters in both the groups. Intraventricular dyssynchrony was significantly more in the apical location as compared to non apical location

(Radial dyssynchrony >> measured as time difference between peak strain of the anteroseptum and posterior / inferior wall: 108.2 ± 50.2 vs. 50.5 ± 24ms, $p < 0.000$; SLWD 63.5 ±27.5 vs.34 ±10.7 ms, p 0.001, SPWD 112.5 ± 58.1 vs. 62.7 ± 12.1 ms, p 0.003). There was no significant difference between mean peak strain in the 2 groups (25.6 +/- 9.6 vs. 22.7 +/- 10.2; p 0.426) though it was less in non apical group. Interventricular dyssynchrony was also more in apical group but not statistically significant (Qao – Qpo 43.4 ± 21.4 v/s 36.6 ± 36.6 ± 13.8; p 0.30).

Table 10 Comparison of dyssynchrony variables in different groups

	Apical			Non Apical			t	p
	Mean	SD	N	Mean	SD	N		
Radial Dyssynchrony	108.2	50.2	15	50.5	24.0	15	4.02**	0.000
Peak strain	25.6	9.6	15	22.7	10.2	15	0.81	0.426
SPW DELAY	112.5	58.1	15	62.7	12.1	15	3.25**	0.003
SL DELAY	63.5	27.5	15	34.0	10.7	15	3.87**	0.001
Qao	144.8	26.9	15	141.8	22.8	15	0.33	0.744
Qao - Qpo	43.4	21.4	15	36.6	13.8	15	1.04	0.309
RR	968.2	91.5	15	978.0	85.2	15	0.3	0.764

Pearson correlation showed that radial dyssynchrony was positively correlated with SPW delay in apical (r 0.546; p 0.035) and non apical group (r 0.121; p 0.668) though it was significant only

in apical group. It was positively correlated with SL delay in apical (r 0.477; *p* 0.072) and negatively in non apical group (r - 0.011; *p* 0.970) but it was not statistically significant.

Table 11 Pearson correlation between Radial dyssynchrony and

SPW DELAY, SL DELAY

	Apical		Non Apical	
	r	p	r	p
SPW DELAY	0.546*	0.035	0.121	0.668
SL DELAY	0.477	0.072	-0.011	0.970

Figures 1 to 3 showing Echocardiographic images of Radial dyssynchrony and Figures 4 to 6 showing fluoroscopic images various lead locations of RV pacing

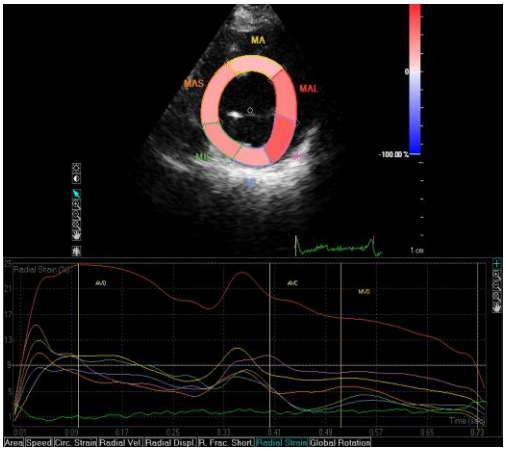


Figure 1: No Significant Radial Dyssynchrony on 2D speckle strain analysis

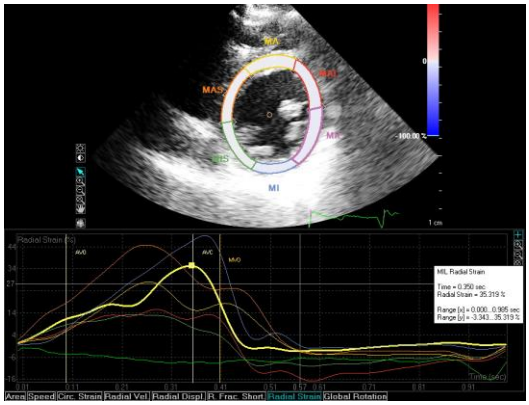


Figure 2: Mild Radial Dyssynchrony on 2D speckle strain analysis

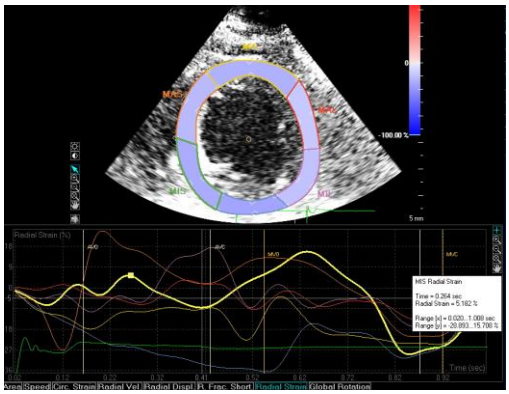


Figure 3: Significant Radial Dyssynchrony on 2D speckle strain analysis

Fig 4: Fluoroscopic image showing RV Apical lead location

AP View RAO 40 LAO 40

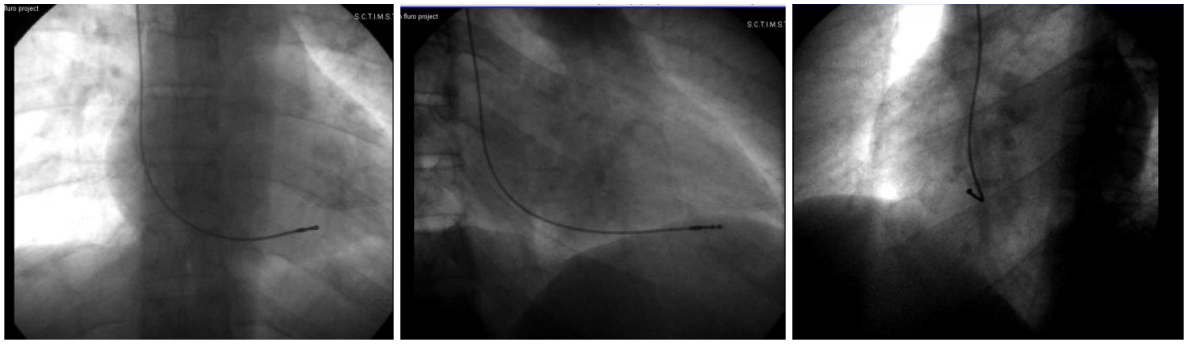


Fig 5: Fluoroscopic image showing RV Mid Septal lead location

AP View RAO 40 LAO 40

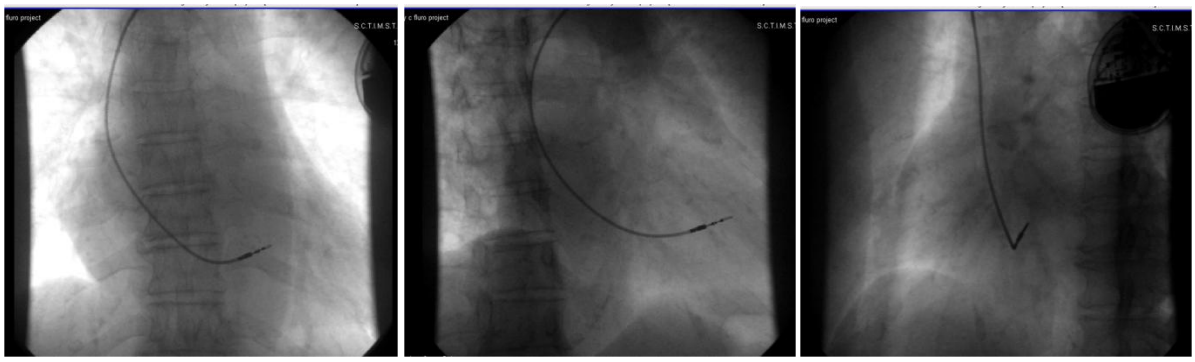
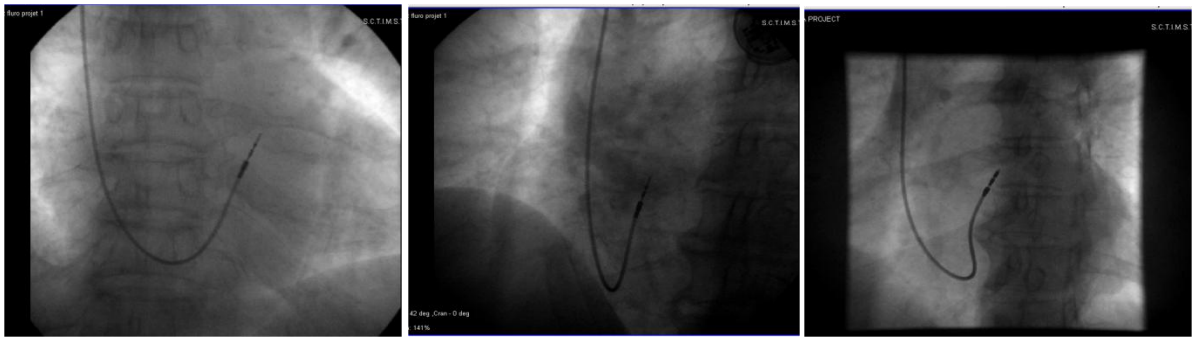


Fig 6: Fluoroscopic image showing RVOT lead location

AP View RAO 40 LAO 40



Discussion

The present study demonstrates a modest but significant beneficial effect of right ventricular outflow-tract pacing compared with apex pacing in a wide range of patients.

Mean age in apical group was 62.0 +/-15.3 years and in non apical group (low RVOT and mid septal) was 61.9 +/- 17.1 years (*p* 0.991).There was no significant difference between 2 groups regarding baseline mean age, DM, hypertension, dyslipidemia, smoking.

One concern in these pacemaker studies is always that how long these trials should be conducted? As stated earlier, most studies (65, 67) were either acute or lasted about six months. Tse et al (68) compared pacing from the RVOT with RV apex and differences were not significant until 18-months post implant. Lewicka-Nowak et al (69) conducted a small 7-year follow up of 27 patients randomized between RVOT pacing and RV apical pacing. There was a significant drop in left ventricular ejection fraction with RV apical pacing whilst no drop was noted with RVOT pacing. The NT-pro BNP levels were also significantly higher and there was more tricuspid regurgitation in the RV apical pacing group. These studies suggest that future studies should be conducted for a minimum of two years. In our study, mean follow up in apical group was 38.2 months and in non apical group 32.6 months.

There was no significant difference in the baseline and follow up lead threshold, lead resistance and also no significant difference in percent change of both parameters in both groups though follow up lead threshold was on lower side in non apical group. Burri H et al (71) reviewed data at implantation and follow-up of 362 consecutive recipients of the same model of active fixation lead (Medtronic 5076-58, Minneapolis, MN, USA) to avoid differences due to lead

characteristics. There were no differences between the septal and apical groups in sensing and pacing thresholds or lead impedance, either at implantation or during a 24-month follow-up. One difference was that our study didn't use the leads of same model. Other larger studies can be done to discuss this issue. As there was no significant difference among lead parameters on baseline and follow up, these alternative sites like RVOT and mid septum can be used in place of RV apical lead once there is clear-cut evidence of favorable hemodynamic and less dyssynchrony with less LV dysfunction in larger trial.

The mean QRS duration (165.7 +/- 18.7 ms in apical group vs. 158.7 +/- 15.4 ms in non apical group; *p* 0.273) and mean QTc (466.1 +/- 22.9 ms vs.463.5 +/- 23 ms respectively; *p* 0.759) were higher in the apical group but not statistically significant. The left ventricular ejection fraction was decreased more in apical location (mean drop of 6.7 % from baseline; *p* 0.06*)* than non apical location (mean drop of 1.3 % from baseline, *p 0.*6). Shorter or near normal QRS duration are usually associated with better LV contraction and less LV dysfunction in RVOT and septal pacing as shown in metaanalysis done by de Cock CC et al (65) and another trial by Victor F et al(70).

Intraventricular dyssynchrony was significantly more in the apical location as compared to non apical location (Radial dyssynchrony: 108.2 ±50.2 vs. 50.5 ±24, $p < 0.000$; SLWD 63.5 ±27.5 vs.34 ±10.7, *p* 0.001, SPWD 112.5 ± 58.1 vs. 62.7 ± 12.1, *p* 0.003).Peak strain was also less in non apical location than apical location, though it didn't reach statistical significance (22.7 +/- 10.2 in non apical vs. 25.6 +/- 9.6 in apical group; *p* 0.426). Interventricular dyssynchrony was also more in apical group but not statistically significant (Qao – Qpo 43.4 ± 21.4 v/s 36.6 ± 36.6 ± 13.8; *p* 0.30). Pearson correlation showed that radial dyssynchrony was positively correlated with SPW delay in apical (r 0.546; *p* 0.035) and non apical group (r 0.121; *p* 0.668) though it was significant only in apical group. It

was positively correlated with SL delay in apical (r 0.477; *p* 0.072) and negatively in non apical group (r - 0.011; *p* 0.970) but it was not statistically significant. There are many trials to discuss on this aspect. Most of the trials (66,68,69,70,72) and one meta analysis (65) showed favorable hemodynamics and less dyssynchrony in RVOT and septal location in comparison to apical and some showed no significant difference between these location(67,73). The favorable effect of RV outflow tract and upper septal pacing may be related to the more physiologic activation pattern, resulting in less LV dyssynchrony. Two recent trials on this aspect are worth mentioning here. One study in Korea (77) done for comparison of Ventricular Dyssynchrony According to the Position of Right Ventricular Pacing Electrode (A Multi-Center Prospective Echocardiographic Study). It showed that despite the marked increase of the QRS duration after pacing, M-mode, Doppler and TDI failed to demonstrate any difference of dyssynchrony indices according to the pacing sites. In this study speckle tracking 2D echo for the dyssynchrony was not used. Another study from Japan (78) showed that Right Ventricular Septal (RVS) Pacing preserves global left ventricular longitudinal function in comparison with RV Apical Pacing (RVA). The 103 patients (74±9 years) with symptomatic bradyarrhythmia and preserved LV ejection fraction, and 50 age-matched control subjects were studied. All patients received a permanent pacemaker and were randomly assigned into 2 groups (RVA: n=51, RVS: n=52). After insertion, patients underwent an echocardiographic study during RV pacing. LV dyssynchrony and global strain parameters were analyzed using speckle tracking echocardiography. The QRS width and dyssynchrony indices by longitudinal and radial strain were significantly greater in RVA than in both the control and RVS. The LV longitudinal dyssynchrony index was significantly related to global longitudinal strain (GLS) among 103 patients receiving RV pacing (R2=0.25, P<0.0001). The GLS in RVA were the lowest among the

3 groups (GLS: Control: –18.2±2.4%, RVA: –14.3±3.1%, P<0.001 vs. control, RVS: –16.8±2.7%, P<0.01 vs. RVA). RVA created heterogeneous LV contraction, which resulted in deteriorated LV longitudinal contraction. RVS could be a better pacing alternative in terms of less LV dyssynchrony and better longitudinal function compared to RVA.

The above study (78) (prospective study of 114 patients) showed good correlation between Color-coded tissue Doppler echocardiography (Septal-to-lateral delay (ms): RVA 62±41 vs. RVS 32±29) and Speckle tracking echocardiography (Longitudinal dyssynchrony index (ms): RVA 87±20 vs. RVS 56±14 and Radial dyssynchrony index (ms): RVA 70±46 vs.RVS 44±27).

Our study also showed less radial dyssynchrony in non apical location which may result in favorable hemodynamics and preserved LV function on long term follow up. Radial dyssynchrony showed positive correlation with SPW delay by M-mode in apical group (*p* 0.035) and non apical group (*p* NS). Correlation with SLW delay was not significant. This can be due to small sample size of the study.

Tissue Doppler imaging and derived strain and strain rate measurements depend on Doppler angle and lack reproducibility, which limit their clinical application. Also regional myocardial velocities are generated by tethering effects from other myocardial segments and by translational motion of the entire heart, which could limit the ability of tissue Doppler imaging to quantify regional function (79). 2D speckle tracking technique for strain measurement has attractions with respect to signal noise, angle dependency, and the ability to monitor strain in two dimensions rather than one dimension (80-83). So this 2D speckle tracking technique can be used for measurement of dyssynchrony indices to predict on long term LV function in various pacing studies to find out optimal pacing site.

To determine the optimal site for RV pacing, two multicenter randomized trials are currently underway (84). These are the Right Ventricular Apical and High Septal Pacing to Preserve Left Ventricular Function (Protect Pace), and Right Ventricular Apical versus Septal Pacing (RASP) trials. In Protect Pace, enrollment is almost complete and the mid septum is the pacing site. The RASP study has the inflow septum as the pacing site. The two studies have different study designs and protocols but all will analyze the long term (24 - 36 months) effects of RV pacing on LV performance indices and functional capacity, with changes in LVEF being the primary outcome. Let us hope that these trials will shed more light on the benefits of RV septal pacing.

Limitations of the Study

This study has several limitations. As sample size is small, this study cannot be extrapolated to the long-term impact on LV function between RV Apical site and RV outflow and mid septal lead location. Ongoing randomized prospective multicenter clinical trials will clarify this issue. Definition of radial strain on a short axis view is difficult in terms of the setting of slice level, which actually can result in poor reproducibility of these parameters. In addition, speckle tracking-based parameters including dyssynchrony and global strain and strain rate depend on the B-mode echocardiographic image quality itself. Three dimensional speckle tracking technology might resolve this issue (85, 86).

Conclusion

Pacing in the non apical location (RV mid septum or low RVOT) is associated with less dyssynchrony by specific measures like 2D radial strain and may correlate with better ventricular function in the long term. The alternate pacing locations are not associated with increased frequency of lead malpositions or lead related complication. These pacing sites should be considered a valid alternative for right ventricular apex pacing particularly in patients with impaired left ventricular function.

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Introduction

Rheumatic heart disease (RHD) is a major health burden in India. Around 25 - 30% of all cardiac visits to hospitals are related to RHD (1). Incidence is 0.7 to 4.5 per 100 children with even higher prevalence among young children (1, 2, 3). There is minimal prevalence of RHD in patients with myocardial infarction in both clinical and autopsy studies (4, 5, 6). In few studies, frequent association of RHD was seen with occurrence of coronary artery disease (CAD) with poor prognosis (7-9). So coronary angiogram is usually performed if there is suspicion of CAD or after a certain age prior to valvular heart surgeries.ACC / AHA recommends routine preoperative coronary angiography in patients with valvular heart disease before valve surgery in men aged ≥35 years, in premenopausal women aged ≥35 years who have coronary risk factors, and in postmenopausal women (10). In India (also in our institute, Sree Chitra Tirunal Institute of science and technology, SCTIMST, Trivandrum), coronary angiography is usually performed routinely in RHD patients prior to valve replacement surgery, if there is any suspicion of CAD or the patient is aged >40 years. Many studies have been done to see prevalence of CAD in various countries, association of the risk factors with CAD in RHD patients, whether CAG is needed prior to valve surgery, if yes at what age (?) (7, 8, 11-25).There are no large studies to see association of inflammation (found in RHD) in causation of CAD in RHD patients .We tried to see this association in our study along with prevalence of CAD in RHD patients and comparison of demographic and CAD risk factor profile of RHD patients with CAD in non RHD patients.

Aims of the study

1. To find prevalence of CAD, CAD patterns and its associations with various CAD risk factors in RHD patients

2. To study any association of inflammation seen in RHD with prevalence of CAD

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Review of literature

Valvular heart disease is a growing problem particularly in developing countries. It is important to consider that spectrum of valve disease in developing world is different from west as the predominant etiology for valve replacement in our part of the world is rheumatic valvular disease whereas degenerative valve diseases are at the top of list in the west. There is minimal prevalence of RHD in patients with myocardial infarction in both clinical and autopsy studies (4, 5, 6). In few studies, frequent association of RHD was seen with occurrence of coronary artery disease (CAD) with poor prognosis (7-9).

Befeler et al (7) studied 26 men with mitral stenosis to assess the importance of obstructive coronary disease in the production of symptoms and the effect upon left ventricular function in England. The patients were studied by cardiac catheterization including selective coronary arteriography and cine ventriculography. Five patients (Group 1) showed severe obstructive coronary lesions, eight patients (Group II) had minor arterial changes and 13 (Group III) had normal vessels. Angina pectoris was confined to the first group who also demonstrated significant left ventricular dysfunction, the consequence of coronary disease. Left ventricular impairment was also found in a significant proportion of those patients without important obstructive coronary disease. In these patients the etiology of the myocardial impairment is poorly understood. Rheumatic involvement of the myocardium or the small coronary vessels has been suggested as an explanation.

Coleman et al (9) (USA) found that 13% of 77 patients who died after surgical treatment to correct valvular dysfunction were having clinically significant coronary artery disease on autopsy. This disorder occurred at all ages but was more common after age 40 years. It was

commoner in aortic valvular disease either alone (17.7 percent) or combined with mitral valvular disease (21.1 percent) than in isolated mitral valvular disease (8.6 percent). This difference might be due to the older age at death of the patients who had aortic lesions. Because clinically significant coronary artery disease complicating valvular heart disease is difficult to recognize on clinical grounds and because it might adversely affect prognosis, coronary cine arteriography and left ventricular angiography are suggested in the overall evaluation of patients for valvular heart surgery. Such studies should be made particularly in those above age 40 years and in those with X-ray evidence of aortic calcification and with atherosclerosis detected during retrograde catheterization of the femoral artery.

Should coronary arteriography be performed routinely before valve replacement? : this concept was first discussed by Lawrence I Bonchek MD et al (11) at the University of Oregon Medical School Hospital, Portland, Ore. The implication that CAD is a common cause of complications and death after prosthetic heart valve replacement, has resulted in the performance of routine preoperative coronary arteriography in many clinics. A review of 4 years' experience with such studies at the University Of Oregon Medical School Hospital indicates that patients with significant coronary obstruction in conjunction with valvular heart disease always had angina pectoris. None of the postoperative deaths or complications was due to demonstrable coronary artery disease without preexisting angina. It is likely that the increased cardiac work load imposed by valvular heart disease increases myocardial oxygen demands. Significant coronary atherosclerosis is therefore unlikely to remain asymptomatic. Coronary arteriography may be safely omitted before valve replacement in many patients with increased myocardial work who have no symptoms of ischemic heart disease, and who lack risk factors known to increase its incidence.

Afterwards many studies in various countries have been done to see the prevalence of CAD and to find out the age at which CAG is needed in RHD patients prior to valve surgery.

Baxter et al (8) found that out of 129 patients with either mitral or aortic valve disease angina was present in 55 (42%). It was more frequent in aortic (60%) than in mitral valve disease (33%). The standard 12-lead electrocardiogram was not helpful in distinguishing underlying occlusive coronary artery disease. Coronary arteriography demonstrated coronary artery disease in 26 patients (20%), only 2 of whom had no angina. The incidence of coronary artery disease was almost identical in both the mitral and aortic groups (22% and 17%, respectively), but the percentage of those with demonstrable coronary artery disease accompanying angina was much higher in the mitral group (67% as against 29%). Angina in mitral valve disorders is thus much more likely to be the result of disease of the coronary arteries. Coronary arteriography is mandatory in all patients in both groups who have angina. Otherwise it seems unnecessary as coronary artery disease was found in only 2 patients who did not have angina.

Chun et al (12) studied 82 patients in USA with mitral stenosis who underwent cardiac catheterization with coronary angiography. Twenty-one patients (26 percent) had coronary artery disease. Characteristics of the mitral valve area, cardiac output, pulmonary artery pressure, pulmonary vascular resistance, left ventricular end diastolic pressure, left ventricular ejection fraction, and atypical chest pain did not correlate with findings of angina pectoris or of coronary artery disease; however, there was correlation with sex, age, and angina. Coronary artery disease occurred only after the age of 40 years and was more frequent in males with angina. Coronary artery disease could not be ruled out in patients with mitral stenosis, especially those over age 40, without coronary arteriography.

Vandeplas A (13) et al studied the frequency of angina pectoris and coronary artery disease in severe isolated valvular aortic stenosis. A consecutive series of 192 patients (121 men and 71 women, mean age 59 years, range 28 to 82) with isolated, severe valvular aortic stenosis was analyzed retrospectively to determine the relation of angina pectoris and coronary risk factors to angiographically significant coronary artery disease (CAD). Significant CAD (diameter reduction ≥50%) was found in 47 patients (24%). Angina was present in 83% of them, but it was also found in 61% of the non-CAD patients. This symptom had as a result a low positive predictive value (31%). Of the patients without angina (n = 65) 12% had significant CAD. The negative predictive value of angina alone was thus 88%. By using multivariate logistic regression, a risk score could be calculated based on angina, age and sex, which increased the negative predictive value to 95%. It was concluded that coronary arteriography can only be omitted in severe aortic valvular stenosis, when patients have no angina and when they are <40 years of age for men and <50 years for women. For all other cases, coronary arteriography should be recommended.

Rangel A et al (14) did study to find out indications for coronary arteriography in heart valve diseases. Among 407 patients with rheumatic heart disease studied, they found 8.3% with coronary atherosclerosis: 2.7% with mitral stenosis and 2.4% with aortic stenosis, lower figures than those reported in the literature. In patients with coronary atherosclerosis, the male to female ratio was 1.6:1. The mean age of men and women with coronary atherosclerosis were 58.9 +/- 8.48 years and 60.33 +/- 5.75 years respectively. The cumulated relative frequency curve of the age was shifted to the right in the patients with coronary atherosclerosis, compared with the age frequency curve of the patients with normal coronary arteries: 50% of the cases with coronary atherosclerosis were < or = 60 years old; on the other hand, 50% of the patients with normal

coronary arteries were < 53 years old. They discovered only 3 patients younger than 50 years old with coronary atherosclerosis. In order of f frequency, the coronary arteries more affected were the anterior descending, right and circumflex. The mean coronary stenosis was 75.2 +/- 21.2%. Disease of one vessel was observed more f frequently. They believe that age is not a good parameter to indicate coronary angiography in patients with valvular heart disease. If coronary angiography would be performed in all patients with valvular disease > or = 30 or 40 years old, would result in a great number of normal studies, with the consequent misspend of supplies and the increased risk of complications. On the other hand, restricting the coronary angiography indication would miss the diagnosis in patients that might need myocardial revascularization. To restrict or to increase the indication of coronary angiography in patients with valvular disease will depend of the frequency between rheumatic heart disease and associated coronary atherosclerosis, and also on the atherosclerosis risk factors present in each patient. They recommended not using the age of the patients as an index to indicate coronary angiography.

Sonmez K et al (15) did the study to find out prevalence and predictors of significant coronary artery disease in Turkish patients who undergo heart valve surgery. The presence of significant atherosclerotic coronary artery disease (CAD) in patients with valvular heart disease is an important predictor of perioperative mortality. CAD prevalence in patients who undergo valvular heart surgery is 20- 40% in industrialized countries. The study aim was to determine the prevalence of CAD in patients undergoing valvular heart surgery, and to identify predictors of its presence. A total of 760 patients (357 males, 403 females; mean age 54.4 ± 18.1 years) who underwent coronary angiography before valvular surgery between 1995 and 2000 were enrolled retrospectively. Significant CAD was present in 15.8% of patients (24% male, 9% females) ($p < 0.001$). The highest prevalence of CAD was found in patients with aortic stenosis ($p < 0.05$).

When correlation between CAD and risk factors was tested, the highest correlation was found with family history of CAD, followed by diabetes mellitus, hyperlipidemia, hypertension and smoking, in decreasing order.

Bozbas H et al (16) did a study to find out prevalence of coronary artery disease in patients undergoing valvular operation due to rheumatic involvement in Turkey. The records of 346 patients who had undergone rheumatic valvular surgery in a university hospital between 1996 and 2002 were evaluated. Coronary angiography was performed in 218 (63%) patients, of whom 41 (18.8%) had CAD. The mean age of the patients having CAD and normal coronary arteries were 57.3 and 50.5 years respectively ($p<0.001$). In the study population patients with CAD had significantly increased prevalence of diabetes mellitus (14.6% vs. 4.5%; $p=0.02$), hypertension (36.6% vs. 16.4%; $p=0.003$), smoking (51.2% vs. 23.2%; $p=0.001$) and family history of CAD (39.5% vs. 20.0%; $p=0.01$) compared to patients with normal coronary arteries. However, the prevalence of dyslipidemia was similar in both groups (45.9% vs. 36.4%; $p=0.1$).These findings suggest that coronary artery disease prevalence in rheumatic valvular disease patients is similar to the normal population of same age. In cases where invasive assessment of valvular lesions is not indicated they suggested coronary angiography to be performed only in patients having clinical suspicion of CAD or multiple risk factors.

Guray Y et al (17)) studied prevalence of angiographically significant coronary artery disease in Turkey patients with rheumatic mitral stenosis. In order to evaluate the prevalence of angiographically significant coronary artery disease (CAD) in patients with predominant mitral stenosis (mitral valve area < 1.5 cm2), coronary angiograms of the 837 consecutive patients with mitral stenosis (482 women and 355 men; median age = 50 years [ranging from 35 to 77]) were

retrospectively analyzed. Significant CAD was defined as at least 50% diameter narrowing of a major coronary artery. Significant CAD was detected in 63 patients (7.5%, 30 men and 33 women). Patients with CAD were significantly older than those without CAD (median: 59 vs. 49 years; $p < 0.0001$, respectively). With respect to coronary risk factors, diabetes mellitus (28.6% vs. 9.4%; $p < 0.0001$), hypertension (46% vs. 16.7%; $p < 0.0001$) and family history of CAD (34.9% vs. 17.3%; $p = 0.001$) were significantly more frequent in the CAD+ group as compared to the CAD- group. Serum levels of cholesterol were significantly higher in CAD+ group as compared to the CAD- patients (median: 199 vs. 176 mg/dl; $p = 0.003$). No significant differences were noted between the two groups in both serum levels of HDL-cholesterol ($p = 0.12$) and triglycerides ($p = 0.08$). Of the 63 patients with CAD, 21 (33.3%) had angina pectoris (AP) and, in patients free of CAD, angina pectoris (AP) was present in 106 (13.7%). The sensitivity and specificity of AP for the presence of significant CAD were 33.3% and 86.3%, respectively. The positive predictive value of AP for the presence of CAD was 16.5% and the negative predictive value of its absence was 94.1%. It was concluded that routine coronary angiography is not necessarily indicated in predominant mitral stenosis particularly in patients who are younger than 40 years and have no coronary risk factors and typical chest pain.

Kruczan DD et al (18) studied the coronary artery disease in patients with rheumatic and non-rheumatic valvular heart disease treated at a public hospital in Rio de Janeiro. This was a cross-sectional study of a series of cases obtained from a pre-defined population, wherein 1,412 patients referred for heart surgery of any etiology were evaluated. Of these, 294 primary heart disease patients aged ≥40 submitted to cinecoronary arteriography (CA) were identified and studied. Patients with RVHD had lower prevalence of CAD (4%) when compared to NVHD (33.61%), $p <0.0001$. The logistic regression analysis showed that age, typical angina-like chest

pain (TACP), systemic arterial hypertension (SAH), diabetes and dyslipidemia were significantly related to CAD, and that the rheumatic etiology was not a disease determinant. Smoking and gender were clinically important in CAD, although not statistically significant. In the whole group, the Log-linear analysis showed that, regardless of the etiology, gender, age ≥55, SAH, TACP, diabetes and dyslipidemia were all related directly to CAD, with the latter three being the most important variables for the disease. They concluded that the prevalence of CAD among RVHD patients is low, whereas it is high among NVHD patients; the rheumatic etiology does not seem to have any beneficial effects on the prevalence of CAD; gender, age, SAH, TACP, dyslipidemia and diabetes were identified as being strongly associated with the presence of CAD. It is possible to define the criteria that indicate the need for pre-surgical CA in heart valve replacements, so that the standard indication after the age of 40 years can be avoided.

All western studies (countries other than South East Asia) have been tabulated in Table A below.

Table A: Reported prevalence of coronary artery disease with rheumatic heart disease in countries other than South East Asia

Study	Country	Year	No of patients	No. of patients with CAD		
				Overall (%)	Mitral (%)	Aortic (%)
Befeler et al. (7)	England	1970	26	50	-	-
Coleman et al. (9)	USA	1970	77	-	-	18
Chun et al. (12)	USA	1982	82	-	26	-
Baxter et al. (8)	England	1978	129	20	22	17
Vandeplas et al. (13)	Belgium	1988	192	-	-	24
Rangel et al. (14)	Spain	1996	407	8	-	-
Sonmez et al. (15)	Turkey	2002	760	16	-	-
Bozbas et al. (16)	Turkey	2004	218	19	-	-
Guray et al. (17)	Turkey	2004	837	-	-	8

Various studies in South East Asia (including India) found the prevalence of CAD less in RHD patients in comparison to western countries mentioned above.

Chu PH et al (19) found low prevalence of coronary arterial disease in Chinese adults with mitral stenosis. They prospectively performed coronary angiography in 119 consecutive Chinese patients older than 40 years old (mitral valve area less than 1.5 cm2) who were about to undergo balloon mitral commissurotomy for significant rheumatic mitral stenosis. The exclusion criteria were the presence of left atrial cavitary thrombi or mitral regurgitation greater than grade 3.There were 32 men (26%) and 87 women (74%) with a mean age of 55 +/- 9.7 years (ranging from 40 to 78). Ninety-two patients (77%) were in atrial fibrillation. The prevalence of risk factors for atherosclerotic cardiovascular disease were hypertension (22%), diabetes mellitus (4%), hypercholesterolemia > or = 240 mg/dL (5%), hypertriglyceridemia > or = 150 mg/dL (13%), and cigarette use (7%). Coronary artery disease on angiography was defined as stenosis of more than 50% of the luminal diameter. They found that only 2 patients (1.7%) had coronary artery disease. The prevalence of coronary artery disease was much lower than in previous reports, some of which, however, had already pointed out the relatively low prevalence of coronary artery disease in rheumatic mitral disease. They concluded that the definite mechanisms require further study in this aspect.

Li B L et al (20) also did study to investigate the prevalence of coronary artery disease (CAD) and the atherosclerotic risk factors in the patients undergoing valvular surgery due to rheumatic heart disease in China. Consecutive 651 patients with rheumatic heart disease aged > 40 who were scheduled for valve surgery underwent diagnostic coronary angiography to delineate coronary arteries. Significant coronary artery disease was considered to be present if one or more single coronary branches showed 50% or more luminal stenosis. Symptoms, such as chest pain, were evaluated. Established risk factors for CAD, such as diabetes mellitus, systemic hypertension, smoking, and dyslipidemia were evaluated. Previous history of myocardial

infarction and coronary artery bypass surgery was also recorded. Seventy-one patients (10.91%), 54 males and 17 females, were detected as with CAD. The mean age of the patients with CAD was (63 +/- 9), significantly higher than that of the patients with normal coronary arteries [(54 +/- 9), $P < 0.01$]. The atheromatous lesion mostly involved the left descending branch (38.12%), and 38 patients (53.52%) showed lesions in 2 or more branches. The prevalence rates of diabetes mellitus and hypertension in the CAD group were 32.39% and 29.58% respectively, both significantly higher than those in the non-CAD group (7.41% and 19.48% respectively; $P < 0.01$ and $P = 0.047$). The smoking rate of the CAD group was 36.62%, significantly higher than that of the non-CAD group (12.93%; $P < 0.01$). However, there were not significant differences in the prevalence rates of dyslipidemia and ECG ST-T changes between these 2 groups (both $P > 0.05$). No relation was found between the rheumatic disease and coronary disease distribution ($P > 0.05$).They concluded that coronary angiography should be performed in all patients clinically suspected with CAD, aged > 50 and the patients with angina and/or coronary risk factors in order to decrease the occurrence of operative complications.

Ayaz Hussain Shaikh (21) et al evaluated the medical records of 144 consecutive patients who underwent mitral, aortic or dual (mitral and aortic) valve replacement surgery at the Tabba Heart Institute, Pakistan during January 2006 to December 2008 retrospectively. All patients underwent coronary angiogram. Significant coronary artery disease (CAD) was defined as coronary stenosis of > 50%.There were 74 (51.4%) males and 70 (48.6%) females in the study. The mean age was 51.64 ± 11 years. Of all, 73 (50.7%) underwent mitral valve replacement, 47 (32.6%) had aortic and 24 (16.7%) had dual valve replacement. Out of 144 patients, 99 (68.8%) had <50% coronary stenosis and remaining 45 (31.3%) had > 50% stenosis. In patients who had undergone mitral valve replacement (MVR), significant coronary disease was found in 32.9%,

whereas in patients who had undergone aortic valve replacement (AVR) and dual valve replacement (DVR) the prevalence of coronary disease was 31.9% and 25% respectively. Their results suggest that the overall prevalence of coronary artery disease in patients undergoing valve surgery in Pakistani population is comparable with prevalence reported in international data.

Few of the Indian studies are also of worth mentioning here.

Ravi K AG (22) at al found CAD in 6% of 106 isolated Aortic stenosis patients.

Gupta KG (23) et al studied the prevalence of significant coronary heart disease in valvular heart disease in Indian patients. Records of 326 patients were analyzed to determine the prevalence of coronary heart disease (CHD) in patients with valvular heart disease (VHD) and to identify the group in whom coronary arteriography is essential. Significant CHD (60% or more luminal narrowing) was found in 7 per cent of cases, and its prevalence was 3 per cent in mitral, 10 per cent in aortic, and 6 per cent in combined mitral and aortic valve disease. Angina was present in 14 per cent of patients with mitral, 39 per cent with aortic and 21 percent with combined mitral and aortic valve disease. 73% of patients with CHD had angina whereas only 19% with angina had CHD. The prevalence of CHD was higher in patients above 50 years (13%) and in males (98%) as compared to those below 50 years (3%) and females (none). They concluded that the prevalence of CHD is low in Indian patients with VHD. Routine coronary arteriography is recommended only in males over the age of 50 years.

Jose VJ (24) et al also studied the prevalence of coronary artery disease in patients with rheumatic heart disease undergoing valve surgery in the current era in India. Consecutive patients with rheumatic heart disease (n=376) who were above the age of 40 years, and

scheduled for valve surgery underwent diagnostic coronary angiogram to delineate coronary arteries. The patients were divided into three groups based on valve involvement (mitral valve, aortic valve, and combined aortic and mitral valve). Significant coronary artery disease was considered to be present if one or more coronaries showed 50% or more luminal stenosis. There were 287 (76.3%) males and 89 (23.7%) females. The mean age of the study population was 51.2+/-8.2 years. 89 (23.8%) patients had typical chest pain, 116 (30.6%) patients had atypical chest pain and 171 (45.5%) patients had no chest pain. Hypertension was noted in 88 (23.4%) patients, 65 (17.3%) patients had diabetes, 98 (26.1%) patients were smoker, and 66 (17.6%) patients had dyslipidemia, and 15 (4.0%) patients gave past history of myocardial infarction. Of the total 376 patients, 46 (12.2%) patients were found to have significant coronary artery disease. In patients with mitral valve disease the prevalence was 13.5% (13/96), while it was 15.3% (19/124) in patients with aortic valve disease and 9% (14/156) in those with combined mitral and aortic valve disease. Their results suggest that the overall prevalence of coronary artery disease in a group of patients with rheumatic heart disease undergoing valve surgery in the current era is 12.2%. This prevalence is much lower than the figures reported earlier in the Western literature.

Rajiv Narang et al (25) did a retrospective analysis of 2,188 consecutive patients (1,319 men, 869 women; mean age 48 ± 7 years) with rheumatic valvular heart disease. The patients underwent preoperative coronary angiography in a tertiary care hospital between 1991 and 2004. The overall prevalence of CAD was 11% (12% in men, 8% in women). The prevalence of CAD in the age groups of 40-44, 45-49, 50-54, 55-59 and >60 years was 4%, 5%, 9%, 15% and 20% in men, and 2%, 2%, 3%, 7% and 10% in women, respectively. Both, age and male gender were independently associated with the occurrence of CAD ($p < 0.01$). The unadjusted odds ratio of having CAD was highest in patients with aortic stenosis (2.08; $p < 0.01$), and lowest in those with

aortic regurgitation (AR) (0.58; p = 0.018). Those patients with AR also showed an independent inverse association with the occurrence of CAD (p = 0.006). The overall prevalence of CAD among Asian Indian patients with RHD was lower than that in patients from western countries. The cut-off age to perform coronary angiographic screening should be maintained at 40 years for men, and 55 years for women. The prevalence of CAD may be lower in those patients with AR.

All South East Asian studies are shown in Table B below.

Table B: Reported prevalence of coronary artery disease with rheumatic heart disease in South East Asian countries

Study	Country	Year	No of patients	No. of patients with CAD		
				Overall (%)	Mitral (%)	Aortic (%)
Chu et al (19)	China	2001	119			2
Li et al(20)	China	2007	651	11		
A H Shaikh et al (21)	Pakistan	2011	144	31.3		
Ravi K et al (22)	**India**	**1988**	**106**			**6**
Gupta et al (23)	**India**	**1990**	**326**	**7**	**3**	**10**
Jose et al (24)	**India**	**2004**	**376**	**12**	**14**	**15**
Narang et al(25)	**India**	**2005**	**2188**	**11**	**10**	**13**

Materials and methods of the study

Patients

The study population consisted of south Indian patients with RHD who underwent CAG prior to scheduled valve surgery at Sree Chitra Tirunal Institute of Science and Technology, SCTIMST, Trivandrum, Kerala. The study involved a **retrospective analysis** of records of 1204 patients of RHD who underwent Coronary angiography (CAG) prior to valve surgery from January 2001 to December 2010. Among them who had significant CAD (stenosis ≥ 50 %) (Group A), were compared with similar number of age and sex matched patients of RHD without CAD (Group B) and CAD in non RHD patients(Group C) selected randomly in the same time period .All RHD patients with embolic acute coronary syndrome (who had previous history of thromboembolism and left atrial thrombus, recanalized coronaries) were excluded. Patients having other inflammatory disorders like COPD, connective tissue disorders, active infection or fever were excluded. All patients with associated congenital heart disease, constrictive pericarditis, ischemic mitral regurgitation, bicuspid aortic valve and degenerative aortic valve disease were excluded from the study.

Coronary angiography

Coronary angiography was performed via a femoral or radial approach. The degree of coronary artery stenosis was estimated visually (confirmed by Quantitative coronary angiography) as the obstructed proportion of each vessel, expressed as a percentage of the vessel diameter. The indicators of atherosclerosis included the presence or absence of any clinically significant CAD,

defined as a ≥50% stenosis of any coronary artery or any major vessel of ≥ 1.5mm in diameter. Multivessel disease was defined as the presence of clinically significant stenosis in ≥2 vessels.

Risk Factors

Hypertension (HTN) was defined as systolic blood pressure ≥140 mm Hg or diastolic blood Pressure ≥90 mm Hg or self reported use of antihypertensive medications.

Diabetes Mellitus (DM) was diagnosed by self reported use of antidiabetic drugs by patients or defined according to American diabetic association guidelines >>

1. Symptoms of DM plus random blood glucose concentration ≥ 11.1 mmol/L (200 mg/dL) *or*

2. Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) *or*

3. Two -hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test

Dyslipidemia (DLP) was defined as Total cholesterol ≥200 mg/dl, low density lipoprotein (LDL-C) level ≥100 mg/dl, or high density lipoprotein (HDL-C) <40 mg/dl in males and <50 mg/dl in females or triglyceride (TG) level ≥150 mg/dl.

Current smoking habit was considered to be a conventional risk factor of CAD.

Family History of CAD (F/H/O CAD) was considered as risk factor if 1st degree relative had CAD <55 years in males and <65 years in females.

Body mass index was calculated as weight (kilograms) divided by height square (meter^2)

Statistical Analysis

Statistical analysis was done using SPSS 14 software (SPSS Inc, Chicago, Illinois). Categorical data were analyzed using chi square or Fisher exact test .Continuous data were analyzed by t test or ANOVA/F tests and presented as mean +/- SD. Univariate analysis done to find out the

predictors of the coronary artery disease in RHD patients. P value < 0.05 was considered as significant.

Observations and Results

Group A, group B and group C in tables are shown for RHD with CAD, RHD with no CAD and CAD in non RHD patients respectively.

Prevalence of CAD in RHD patients who underwent CAG prior to surgery was **9.01%** (109/1204). Males were 65.1% and females were 34.9% in RHD with CAD group as shown in the table no 1. Mean age of the patients was 52.8 ± 8.6 years overall, 52.3 ± 8.9 years for males and 53.6 ± 8 years for the females as shown in the table no 2.These patients were compared with age and sex matched patients of RHD with no CAD group and patient with CAD without RHD group.

Table 1: No (%) of male and females in RHD with CAD patients

	RHD with CAD
Male	71 (65.1%)
Female	38 (34.9%)

Table 2: Mean age of RHD with CAD patients (years ± SD)

	RHD with CAD
Male	52.3 ± 8.9
Female	53.6 ± 8
Overall	52.8 ± 8.6

As shown in the table no 3 >> Mitral valve was involved in 66.1 %, aortic valve in 7.3% cases and both valves were involved in 26.6% cases in RHD with CAD group while in no CAD group these were 56.9%,9.2% and 33.9% respectively with no statistical significant differences (p >0.05).There was no significant difference between presence of significant Aortic stenosis(AS), Aortic regurgitation(AR), Mitral stenosis (MS) in both groups but Mitral regurgitation (MR) was more common in No CAD group (87.2% vs. 71.6%; p <0.01) .

Table 3: comparison of dominant valve disease various groups

		RHD with CAD N (%)	RHD no CAD N (%)	A&B p#
Dominant valve involved	Mitral Valve	72 (66.1)	62 (56.9)	p>0.05
	Aortic Valve	8 (7.3)	10 (9.2)	
	Both	29 (26.6)	37 (33.9)	
Aortic Stenosis	Present	26 (23.9)	30 (27.5)	p>0.05
Aortic regurgitation	Present	44 (40.4)	53 (48.6)	p>0.05
Mitral stenosis	Present	90 (82.6)	90 (82.6)	p>0.05
Mitral regurgitation	Present	78 (71.6)	95 (87.2)	p<0.01

#: Fisher exact test

Table no 4 is showing comparison of various clinical features among the groups. Angina was significantly more in the CAD in non RHD patients while dyspnea and palpitation were more

common in the RHD patients. Patients were more symptomatically in worse NYHA class in the RHD group in comparison to the CAD in non RHD patients.

Table 4: comparison of clinical features in various groups

		RHD with CAD N (%)	RHD no CAD N (%)	Non RHD CAD N (%)	A, B&C P (χ^2)	A&B p#	A&C p#
Angina	Present	29 (26.6)	9 (8.3)	99 (90.8)	p<0.001	p<0.001	p<0.001
Dyspnea	Present	100 (91.7)	109 (100.0)	36 (33.0)	p<0.001	p<0.01	p<0.001
Palpitation	Present	40 (36.7)	54 (49.5)	3 (2.8)	p<0.001	p<0.05	p<0.001
NYHA CLASS	Class II	47 (43.1)	45 (41.3)	74 (67.9)			
	Class III	60 (55.0)	61 (56)	35 (32.1)			
	Class IV	2 (1.8)	3 (2.8)	0 (0.0)			

#: Fisher exact test

Table no 5 is showing comparison of risk factors for CAD in Various groups .Smoking was significantly more in the non RHD CAD patients (group C) and RHD with CAD patients(group A) in comparison with RHD and no CAD patients (group B) but there was no significant difference between group A and C (p >0.05). Diabetes Mellitus (DM), Hypertension (HTN) and dyslipidemia (DLP) were significantly more in group C than group A and B (p <0.001 in all) and more in group A than group B (p <0.05, <0.001, <0.01 respectively).There was no significant

difference in post menopausal status in all 3 groups .BMI was significantly more in group C (24.2 ± 3.1) than the group A (22.2 ± 3.5) and B (21.3 ± 3.6).

Table 5 : comparison of risk factors based on group

Risk factors		RHD with CAD	RHD no CAD	non RHD CAD	A, B&C	A&B	A&C
					P (χ^2)	p#	p#
Smoking	Present	10 (9.2)	1 (0.9)	15 (13.8)	p<0.01	p<0.01	p>0.05
DM	Present	24 (22.0)	11 (10.1)	56 (51.4)	p<0.001	p<0.05	p<0.001
HTN	Present	32 (29.4)	10 (9.2)	68 (62.4)	p<0.001	p<0.001	p<0.001
DLP	Present	56 (51.4)	35 (32.1)	83 (76.1)	p<0.001	p<0.01	p<0.001
F/H/O CAD	Present	7 (6.4)	5 (4.6)	24 (22.0)	p<0.001	p>0.05	p<0.001
Post Menopausal	Present	24 (63.1)	23 (60.5)	28 (73.7)	p>0.05	p>0.05	p>0.05
BMI		22.2 ± 3.5	21.3 ± 3.6	24.2 ± 3.1	0.001	0.052	0.001

#: Fisher exact test; F/H/O CAD: Family History of CAD; BMI: Body mass index

Table no 6 shows that values for hemoglobin (Hb), total cholesterol, High density lipoprotein (HDL), Triglycerides (TG), Low density lipoprotein (LDL) were not significantly different among 3 groups but polymorphs (60.4 ± 10.8 vs. 57.6 ± 9.4; *p* 0.03) and creatinine (1.1 ± 0.2 vs. 1 ± 0.2; *p* 0.002) were significantly more in the RHD CAD (group A) than non RHD CAD patients (group C). Erythrocyte sedimentation rate (ESR) was also high but not significant (22.4 ± 20.7 vs. 19 ± 15.3; *p* 0.173).

Table 6 : comparison of Laboratory investigation in various groups

	RHD with CAD	RHD no CAD	non RHD CAD	A, B&C	A&B	A&C
				P (F test)	P (t test)	P (t test)
Hb	13.5 ± 1.7	13.6 ± 1.8	13.6 ± 1.5	0.963	0.969	0.790
Polymorphs	60.4 ± 10.8	59.8 ± 9	57.6 ± 9.4	0.076	0.633	0.03
ESR	22.4 ± 20.7	19.9 ± 17.9	19 ± 15.3	0.362	0.343	0.173
Creatinine	1.1 ± 0.2	1.1 ± 0.2	1 ± 0.2	0.002	0.833	0.002
Cholesterol	190.2 ± 51.5	195.5 ± 47.9	174.7 ± 50.6	0.110	0.635	0.104
HDL	37.6 ± 10.1	37.5 ± 11.2	36.9 ± 7.9	0.917	0.947	0.673
TG	130.8 ± 61.1	140.1 ± 62.1	132.6 ± 53.5	0.769	0.504	0.870
LDL	127.1 ± 44	130.08 ± 42.54	111.3 ± 45.4	0.075	0.762	0.059

Table no 7 showing % of digoxin and statins used in various groups.

Table 7 : comparison of drug based on group

Drug		RHD with CAD	RHD no CAD	non RHD CAD	A, B&C	A&B	A&C
					p	p	p
Digoxin	Yes	50 (45.9)	63 (57.8)	1 (0.9)	p<0.001	p>0.05	p<0.001
Statin	Yes	32 (29.4)	15 (13.8)	100 (91.7)	p<0.001	p<0.01	p<0.001

Table no 8 shows that ejection fraction (EF) was significantly less in the group A than group C (61 ± 11 vs. 64.5 ± 13.8; *p* 0.040).

Table 8 : comparison of echocardiography variables based on group

		RHD with CAD	RHD no CAD	non RHD CAD	A, B&C	A&B	A&C
					p	p	p
LVIDD		49.6 ± 9.7	51.2 ± 10.5	48.7 ± 7.8	0.127	0.222	0.462
LVIDS		34 ± 9	33.6 ± 8.7	32.8 ± 8.3	0.560	0.754	0.294
EF		61 ± 11	63.4 ± 12.6	64.5 ± 13.8	0.112	0.135	0.040
RWMA	Present	9 (8.3)	1 (0.9)	51 (46.8)	p<0.001	p<0.01	p<0.001

(LVIDD: left ventricular internal diastolic dimension, LVIDS: left ventricular internal systolic dimension, EF: ejection fraction, RWMA: regional wall motion abnormality)

Atrial Fibrillation (AF), non specific ST-T changes and left ventricular hypertrophy (LVH) with strain were more common in electrocardiography (ECG) in RHD patients while normal ECG and ECG suggestive of (s/o) old MI were more commonly seen in the CAD patients with no RHD as shown in the table no 9.

Table 9: comparison of ECG variables based on group

		RHD with CAD	RHD no CAD	non RHD CAD
ECG	Normal	32 (29.4)	28 (25.7)	38 (34.9)
	Suggestive of old MI	0 (0.0)	0 (0.0)	51 (46.8)
	Non specific ST T changes	22 (20.2)	8 (7.3)	19 (17.4)
	AF	45 (41.3)	60 (55.0)	0 (0.0)
	LVH strain	10 (9.2)	13 (11.9)	1 (0.9)

Table no 10 shows that in RHD CAD group single vessel disease (SVD) ,double vessel disease (DVD) and triple vessel disease (TVD) was seen in 58.7%,27.5% and 13.8% respectively while in non RHD CAD patients it was 29.4 %,35.8% and 34.9% .LMCA was involved in 4.6 % vs. 2.8% in both groups respectively. In RHD patients most commonly involved vessel was LAD (left anterior descending artery) (68.9% overall and 29.4% alone) followed by RCA (right coronary artery) (44.1%) and LCx (left circumflex artery) (42.3%).

Table 10: comparison of involvement of coronaries in various groups

		RHD with CAD	non RHD CAD
CAD	Single vessel	64 (58.7)	32 (29.4)
	Two vessel	30 (27.5)	39 (35.8)
	Triple vessel	15 (13.8)	38 (34.9)
CORONARIES involved	LAD	32 (29.4)	19 (17.4)
	LCX	11 (10.1)	3 (2.8)
	RCA	17 (15.6)	10 (9.2)
	LAD + LCX	16 (14.7)	11 (10.1)
	LAD + RCA	12 (11.0)	18 (16.5)
	LCX + RCA	4 (3.7)	10 (9.2)
	All three	15 (13.8)	38 (34.9)
	RI	2 (1.8)	0 (0.0)
LMCA	Present	5 (4.6)	3 (2.8)

Table no 11 and 12 are showing univariate analysis of different groups based on selected variables for predictors of CAD in RHD patients. Univariate analysis (table no 12) showed that SVD was significantly more in RHD CAD patients (*p* 0.001; Odds ratio 5.067 with 95% CI 2.43-10.55) when referenced to TVD in comparison to non RHD CAD patients group which was having significantly more TVD. Two vessel disease (*p* 0.087) or LMCA involvement (*p* 0.65) showed no significant difference between two groups. Diabetes (*p* 0.001), hypertension (*p* 0.001) , dyslipidemia (*p* 0.001), family history of CAD (*p* 0.002) and BMI (*p* 0.01) were significantly less in RHD CAD patients, smoking rates were also less but not statistically significant (*p* 0.29).

Table 11 : Result of univariate analysis on RHD with CAD as compared to RHD no CAD by selected variables for predictors of CAD in RHD patients

Predictors of CAD in RHD patients	B	Sig.	OR (95 % CI)
Mitral Valve involvement	0.393	0.194	1.482 (0.82-2.68)
Aortic Valve involvement	0.020	0.969	1.021 (0.36 – 2.91)
Absence of MR	0.992	0.005	2.696 (1.34 – 5.42)
Angina	1.393	0.001	4.028 (1.80 – 9.00)
Smoking	2.382	0.024	10.829 (1.37 – 85.61)
DM	0.922	0.019	2.515 (1.16 – 5.43)
HTN	1.414	0.001	4.114 (1.91 – 8.87)
DLP	0.804	0.004	2.234 (1.29 – 3.87)
F/H/O CAD	0.356	0.554	1.427 (0.44 – 4.64)
Post Menopausal	0.054	0.869	1.056 (0.55 – 2.01)
BMI	0.076	0.054	1.079 (1.00 – 1.17)
Polymorphs	0.007	0.632	1.007 (0.98 – 1.03)

ESR	0.007	0.343	1.007 (0.99 – 1.02)
Creatinine	0.128	0.832	1.137 (0.35 – 3.72)
Cholesterol	-0.002	0.631	0.998 (0.99 – 1.01)
HDL	0.001	0.947	1.001 (0.96 – 1.05)
TG	-0.002	0.501	0.998 (0.99 – 1.01)
EF	-0.018	0.137	0.983 (0.96 – 1.01)

B: Correlation Cofficient

Table 12 : Result of univariate analysis on RHD with CAD as compared to non RHD CAD patients by selected variables for predictors of CAD in RHD patients

Predictors of CAD in RHD patients	B	Sig.	OR (95 % CI)
Absence of Angina	3.307	0.001	27.31 (12.56 – 59.39)
Absence of Smoking	0.457	0.291	1.58 (0.68 – 3.69)
Absence of DM	1.320	0.001	3.742 (2.08 – 6.74)
Absence of HTN	1.384	0.001	3.991 (2.27 – 7.03)
Absence of DLP	1.106	0.001	3.021 (1.69 – 5.39)
Absence of F/H/O CAD	1.414	0.002	4.114 (1.69 – 10.02)
Post Menopausal	0.202	0.525	1.224 (0.66 – 2.29)
Single vessel	1.623	0.001	5.067 (2.43 – 10.55)
BMI	-0.192	0.001	0.825 (0.75 – 0.91)
Polymorphs	0.028	0.03	1.03 (1.001 – 1.056)
ESR	0.010	0.176	1.010 (1.00 – 1.03)
Creatinine	1.987	0.003	7.295 (1.99 – 26.68)

Cholesterol	0.006	0.107	1.006 (1.00 – 1.01)
HDL	0.009	0.671	1.009 (0.97 – 1.05)
TG	-0.001	0.869	0.999 (0.99 – 1.01)
LDL	0.001	0.550	1.001 (1.00 – 1.01)
EF	-0.023	0.042	0.978 (0.96 – 1.00)

B: Correlation Cofficient

Table no 13 is showing that risk factors were also significantly less in patients with SVD in RHD group as compared to SVD patients in non RHD CAD patients group except smoking and post menopausal status in females (DM p <0.01, HTN p <0.001, DLP p <0.01, family history of CAD p <0. 01, smoking p > 0.05).

Table 13 : comparison of risk factors single vessel disease groups

		RHD with CAD		non RHD CAD		χ^2
		Count	Percent	Count	Percent	
Smoker	Present	5	7.8	4	12.5	p>0.05
DM	Present	11	17.2	16	50.0	p<0.01
HTN	Present	11	17.2	19	59.4	p<0.001
DLP	Present	31	48.4	26	81.3	p<0.01
F/H/O CAD	Present	2	3.1	8	25.0	p<0.01
Post Menopausal	Present	12	18.8	9	28.1	p>0.05

Table no 14 is showing that prevalence of CAD in RHD patients in present study is lower than the western countries and comparable to other Indian studies.

Table 14: comparison of prevalence of CAD in RHD patients between Present study other studies

Study	Country	Year	No of patients	Prevalence of CAD in RHD patients (%)
Befeler et al. (7)	England	1970	26	50
Baxter et al. (8)	England	1978	129	20
Gupta et al (23)	India	1990	326	7
Rangel et al. (14)	Spain	1996	407	8
Sonmez et al. (15)	Turkey	2002	760	16
Bozbas et al. (16)	Turkey	2004	218	19
Jose et al (24)	India	2004	376	12
Narang et al(25)	India	2005	2188	11
Li et al(20)	China	2007	651	11
A H Shaikh et al (21)	Pakistan	2011	144	31.3
Present study	**Kerala, India**	**2011**	**1204**	**9.01**

Discussion

Records of 1204 RHD patients who underwent CAG prior to surgery from 2001 to 2010 were analyzed. Patients of RHD with significant CAD (≥50 % stenosis: as used in most of the similar studies) were compared with age and sex matched patients of RHD with no CAD and atherosclerotic CAD patients. All RHD patients with embolic acute coronary artery syndrome were excluded.

109 **(9.05 %)** RHD patients had significant CAD (males 65.1% and females 34.9%: male – female ratio of 1.86). In western countries this prevalence ranged from 16 to 50 % (7, 8, 15, and 16).Only study from Spain, done by Rangel et al (14) showed prevalence of 8%. In South East Asian countries like China prevalence found to be 11% (20) but in Pakistan it was on higher side 31.3% (21). In previous Indian studies the prevalence found between 7 to 12 % (23, 24, and 25).

Male to female ratio of 1.86:1 matched with other studies which showed ratio between 1.6:1 to 2.6:1 (14, 15, 25).Only study from China, done by Li BL et al showed ratio of 3:1(20).

Mean age of RHD patients who had CAD was 52.8 ± 8.6 years (52.3 ± 8.9 for males and 53.6 ± 8 for females). Mean age of CAD in RHD patient was around 55 to 60 years in western studies(13,14,16) and one of the Asian study from China (20) but comparable to other Indian studies (23,24,25) and study from Pakistan (21). So it is fair enough in India to advise CAG in patients of RHD planned for surgery who are above 40 years of age and definitely in patients with age >40 years with coronary risk factors as significant association was seen with CAD risk factors and CAD in the present study.

In our study the prevalence was similar to other Indian studies but lower than the western countries. This may be due to higher age group in the western countries and partly may be due to the demographic, clinical and environmental characteristics of the different population like race, dietary habits, physical activity etc.

Involvement of mitral valve was seen in 66.1 %, aortic valve in 7.3% and both valves in 26.6% in these patients. Shaikh et al (21) also found that mitral valve involvement was more than the aortic and double valve involvement in RHD patients who underwent for CAG prior to surgery and found to have CAD. This can be explained because of high prevalence of mitral valve disease in RHD patients. Univariate analysis showed significant inverse association between MR and prevalence of CAD (*p* 0.005). Narang et al (25) showed significant inverse association between AR and CAD and no significant association with MR and CAD. It can be concluded that regurgitation lesions are probably less commonly associated with CAD in comparison to AS and MS .Strong association of stenotic lesions with CAD has been found in various studies (15, 25).This may be attributed to more prolonged and ongoing inflammatory process responsible for stenotic lesion leading to micro vascular changes and endothelial dysfunction .Less CAD in regurgitation lesions may be due to larger vessels seen in these lesions. But still more studies needed in this aspect.

Presence of angina was significantly more common in the RHD CAD group than the RHD patients without CAD (*p* 0.005; OR 4.028 with 95% CI 1.8-9.0) .Other studies (8, 13, and 18) also found that presence of angina is a good predictor of the CAD in RHD patients.

Single vessel disease (SVD), double vessel disease (DVD) or Triple vessel disease (TVD) was present in 58.7%, 27.5% and 13.8% respectively. Single Vessel disease was more commonly

seen in the other studies also (14, 25). Left main was involved in 4.6%. LAD was the most common vessel involved (overall 68.9% and 29.4% in isolated cases) followed by RCA (44.1%) and LCx (42.3 %). Rangel A et al (14) also found that LAD was most commonly involved artery followed by RCA and LCx. Li BL et al (20) also found that LAD was the most commonly involved vessel (in 38.12% cases).

Risk factors like smoking, DM, hypertension and dyslipidemia were good predictors of the CAD in RHD patients but not the family history of CAD or BMI. This association was seen in the previous studies also (16-20,24).Mean cholesterol, HDL, triglycerides and LDL levels were not significantly different in CAD and no CAD patients in RHD .It may be due to non availability of lipid profile for all the patients ,so comparison may not be reliable.

Univariate analysis showed that polymorphonuclear leukocyte count was significantly higher (*p* 0.03; OR 1.03 with 95% CI 1.001-1.056) in RHD CAD patients than the non RHD CAD patients. ESR was also higher in these patients but not statistically significant (*p* 0.17). Univariate analysis showed that SVD was significantly more in RHD CAD patients (*p* 0.01; Odds ratio 5.067 with 95% CI 2.43-10.55) in comparison to non RHD CAD group which was having significantly more TVD. Two vessel disease (*p* 0.087) or LMCA involvement (*p* 0.65) showed no significant difference between two groups. Diabetes (*p* 0.001), hypertension (*p* 0.001) , dyslipidemia (*p* 0.001), family history of CAD (*p* 0.002) and BMI (*p* 0.001) were significantly less in RHD CAD patients, smoking was also less but not statistically significant (*p* 0.29). These risk factors were also significantly less in patients with SVD in RHD group as compared to SVD patients in non RHD CAD group except smoking which was less but not significant (DM $p < 0.01$, HTN $p < 0.001$, DLP $p < 0.01$, family history of CAD $p < 0.01$, smoking $p > 0.05$). In

present study mean age of CAD in RHD patients was 52.8 years which is lower than the mean age of atherosclerotic CAD in India (57.5 years) (26) and in Kerala registry (60.2 years) (Abstract: AHA scientific session 2011, Orlando, Florida). So concluding the above discussion, CAD in these patients may be partly attributed to the inflammatory state seen with RHD. But still more studies are required to explain this association.

Limitations of the study

The main limitations of the study were its retrospective nature and single centre study.

To study the association of inflammation with prevalence of CAD, only polymorphonuclear cell counts and ESR may not be sufficient, as CRP levels are usually not done in CAG prior to valvular surgery.

Lipid profiles were not available for all the patients. Information regarding past history of dyslipidemia and self reported use of the lipid lowering drugs was mainly used for the presence or absence of dyslipidemia. So available mean values for different lipids were not reliable and not significant for prediction of CAD in RHD patients.

Comparison may not be valid between RHD CAD patients and patients with CAD and no RHD as latter group are having more angina and history of ACS and natural history of CAD may be different in them.

Though prevalence of AF was not significantly different among RHD CAD group and RHD with no CAD group, still embolic CAD cannot be excluded definitely as most of the patients in RHD CAD group had single vessel disease and none of the patient in CAD with no RHD group had AF.

Conclusion

Prevalence of CAD in patients with RHD is similar to other Indian studies but lower than the prevalence in western countries.

Single vessel involvement, mostly LAD, is more common among these patients.

Coronary angiography should be performed in patients >40 years of age who are undergoing for valvular surgery and it is mandatory in this age group if patients are having CAD risk factors.

CAD risk factors are less common in RHD CAD group than the patients of non RHD CAD group. CAD in these patients may be attributed to the inflammatory state seen with RHD, though further studies are required in this regard with well proven inflammatory markers of CAD like hsCRP.

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