D. M.

RESEARCH PAPERS

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D. M.

RESEARCH PAPERS

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Certificate

This is to certify that **Dr Prashant Shah** enrolled for the academic course of DM (Cardiology) at All India Institute of Medical Sciences, New Delhi has completed a minimum of three years and fulfilled the other requisites including training in various sub-specialities as laid down in the hand book of the All India Institute of Medical Sciences.

This is also to certify that **Dr Prashant Shah** has been actively associated with the projects enclosed and has worked under our direct supervision and guidance.

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Certificate

This is to certify that the clinical and investigative work presented in these papers have been carried out by **Dr Prashant Shah** under our direct supervision and guidance.

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I dedicate this thesis to my parents

Dr Prashant Shah

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Comparison of Rose Angina Questionnaire to Computed Tomographic Coronary Angiography

Shah P, Roy A

Abstract

Introduction: The Rose Angina Questionnaire (RAQ) has been the most common tool of assessing prevalence of coronary artery disease (CAD) burden in community surveys since its introduction in 1962. It has also been used in various Indian epidemiological studies. The abbreviated Shortened WHO Rose Angina Questionnaire (SRAQ) is shown to more sensitive to detect CAD in few studies. However the accuracy of RAQ and SRAQ in Indian population has never been studied. We compared the RAQ and SRAQ to CT coronary angiography (CTCA), which is a non-invasive technique that detects CAD with a high level of accuracy.

Method: This was a prospective observational study where the RAQ and SRAQ were administered in 218 patients, above 25yrs of age, undergoing CTCA for various indications. Patients known to have coronary artery disease and valvular heart diseases were excluded. The conclusion drawn from the RAQ and the SRAQ was then compared with the CTCA findings.

Results: The mean age of studied population was 51.2± 9.25yrs out of whom 52.8% were male and 47.2% female. Coronary risk factors like hypertension, diabetes mellitus, family history of premature CAD, smoking and dyslipidemia was present in 51.4%, 16.5%, 13.3%, 6.9% and 2.3% respectively. When compared to CTCA as a gold standard teat to diagnose CAD, the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and accuracy of RAQ were found to be 51.72%, 92.51%, 51.72%, 92.51%, 6.91, 0.52 and 87.04% respectively and similarly those of SRAQ were found to be 58.62%, 71.66%, 24.29%, 91.78%, 2.07, 0.58 and 69.91% respectively.

Conclusion: We concluded that the RAQ has excellent specificity and negative predictive value, however suffers from very poor sensitivity of about 50% in Indian population. Being commonly used as screening tool of CAD in community surveys, it is likely to reflect only a fraction of population who is actually suffering from CAD. The SRAQ suffers from poor sensitivity, poor specificity and poor accuracy, and doesn't seem to be as useful in Indians as in other studies.

Keywords: Rose Angina Questionnaire, Shortened WHO Rose Angina Questionnaire, CT coronary angiography, Coronary artery disease

Retrospective Study on Outcomes of Radiofrequency Ablation of Intra-atrial Re-entrant tachycardia Following Surgical Repair of Congenital Heart Disease

Shah P, Juneja R, Parikh N

Abstract

Introduction: Intra-atrial re-entrant tachycardia (IART) is a common arrhythmia observed frequently after surgical repair or palliation of congenital heart diseases that carries significant negative impact on patient's clinical outcome. Being resistant to pharmacotherapy, radiofrequency ablation is often the only treatment available, which is also challenging in post-operative patients due to distorted cardiac anatomy and obstacles like baffles and prosthesis. This study was done to find out the efficacy and safety of radiofrequency ablation of IART in post cardiac surgery patients.

Method: This was a retrospective study on outcomes of 58 patients who underwent 78 radiofrequency ablations for post cardiac surgery IART from 1998 to 2014 at our institute. To simplify the description on outcome, we divided our patients into two groups based on their anatomical diagnosis- 1. Simple congenital heart disease: the patients who were operated for ASD, PAPVC, TAPVC, VSD, and TOF and 2. Complex congenital heart disease: those patients who were operated for more complex congenital heart diseases like TGA, single ventricle, DORV with MPGA, DILV etc.

Results: The mean age of our patients was 25.74 ± 15.42 yrs with the youngest patient being 1.5yr of age and eldest patient being 67yrs of age. The mean duration from surgery to the radiofrequency ablation was 10.27 ± 6.58 yrs with a range of 6 months to 28yrs. The mean follow up duration was 4.76 ± 3.85yr with shortest follow up of 2months and longest follow up period of 14yrs after ablation. 54 ablative procedures were performed in 42 patients operated for simple congenital heart diseases-the procedural success rate was 75.92% and the recurrence rate was 26.83%. 71.42% of the patients in this group had no recurrence in follow up.

22 ablative procedures were performed in 16 patients operated for complex congenital heart diseases. The procedural success rate was 72.72% however 56.25% had recurrence of IART on follow up.

Conclusion: Electrophysiological mapping and ablation of IART is safe and effective in surgically corrected or palliated simple and complex congenital heart disease patients. A procedural success rate of up to 75% can be expected in such patients. Recurrence rates are high among patients who are surgically palliated for complex congenital heart diseases. Increasing experience with such patients and procedures is likely to help us in achieving better outcomes in future.

Keywords: Intra-atrial re-entrant tachycardia, congenital heart disease, electrophysiological studies, radiofrequency ablation

COMPARISON OF ROSE ANGINA QUESTIONNAIRE TO COMPUTED TOMOGRAPHIC CORONARY ANGIOGRAPHY

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Abbreviations

- Rose Angina Questionnaire – RAQ
- Coronary artery disease – CAD
- Percutaneous trans luminal coronary angioplasty – PTCA
- Coronary artery bypass grafting - CABG
- Computed tomographic coronary angioplasty – CTCA
- Shortened WHO Rose Angina Questionnaire – SRAQ
- Hypertension – HTN
- Diabetes mellitus – DM

Comparison of Rose Angina Questionnaire to Computed Tomographic Coronary Angiography

INTRODUCTION

The Rose Angina Questionnaire (RAQ) has been the most common tool of assessing prevalence of coronary artery disease (CAD) burden in community surveys since its introduction in 1962. It was developed to obtain a reproducible diagnosis of angina pectoris. It comprises of seven questions that can be answered in one minute. Subsequently, an abbreviated version of RAQ, the shortened WHO Rose Angina Questionnaire (SRAQ) which comprises of only three questions, was found to be more sensitive to detect CAD and also suitable for epidemiological studies. The RAQ has been used in various population surveys as a screening tool for CAD, however its comparison with objective measures has been largely lacking especially for non-Caucasian population. It has also been used in various Indian epidemiological studies; however its accuracy in Indian population has never been studied. We compared the RAQ to CT coronary angiography (CTCA), which is a non-invasive technique that detects CAD with a high level of accuracy.

AIMS:

To compare the Rose Angina Questionnaire to CT coronary angiography in Indian population

OBJECTIVES:

1. To assess the performance of RAQ against CTCA
2. To assess the performance of RAQ against CTCA in women as compared to men
3. To assess the performance of the SRAQ versus RAQ in men and women

REVIEW OF LITERATURE

The RAQ was introduced in 1962 as a screening tool to measure angina in population surveys (1). It was derived from the description of 36 patients, all men, who after full hospital investigation were considered to have unequivocal angina due to ischaemic heart disease. Since its introduction, is has become one of the most common tool to identify patients with

coronary artery disease in population studies. It is composed of seven questions that can be answered in one minute (Appendix 1).

Based on this questionnaire, angina is defined as chest pain or discomfort which: (i) is brought on by exertion, (ii) is situated in the central or left anterior chest, (iii) forces the person to slow down or stop, (iv) is relieved if the subject does so, (v) is relieved within 10 min. The questionnaire further subdivided angina according to severity as grade I (chest pain brought on only by walking uphill or hurrying) or grade II (chest pain brought on by walking at an ordinary pace on the level).

The RAQ has been widely used in its original and modified forms (2). It has consistently been shown to be predictive of mortality and major CAD event (3-13). For example, Lampe et al, in their study comprising of 7735 middle aged men, demonstrated the relative risk (95% CI) of major ischemic heart disease event in those with definite and possible angina was 2.03 compared to those with no chest pain (14). Similarly, Bodegard et al, in their 26 year follow up study, found that men with possible angina had a coronary heart disease mortality of 25% versus 13.8% among men with no symptom of angina ($p<0.013$). They also had a higher incidence of coronary artery bypass grafting ($p<0.0004$) and acute myocardial infarction ($p<0.026$)(15).

The RAQ has high specificity and variable sensitivity when compared to physician identification of the symptom complex of angina pectoris. The Rose questionnaire doesn't take into account various angina equivalents, such as dyspnoea, faintness, and fatigue. Inclusion of these symptoms would increase the diagnostic sensitivity of this questionnaire, although with a decrease in the specificity. The RAQ was found to have sensitivity of 81% and specificity of 97% in one study (16). In another study, the RAQ was less sensitive but equally specific in comparison to physician's diagnosis (17). Rehman et al. compared the conclusions derived from RAQ with cardiologist diagnosis in Bangladesh. In their study, they found that RAQ had sensitivity of 53% and specificity of 89% as compared to a cardiologist diagnosis (18). In one study comprising of post myocardial patients, expert's diagnosis and the RAQ predicted total mortality and coronary heart disease mortality to similar extents, and one measure was not superior to the other in that population (19).

Bass et al assessed the performance of RAQ to detect CAD by comparing it to a high sensitivity test, the exercise thallium (20). In their study of 198 patients, they found that the RAQ had 26% sensitivity, 79% specificity, 42% positive predictive value, and 65% negative

predictive value. Supplemental questions designed to identify atypical ischemic pain led to increased sensitivity of up to 68% that was offset by decreased specificity. While the Questionnaire's sensitivity for coronary disease was greater for women than men (57 vs 40%), the overall accuracy was the same because specificity was lower (63 vs 80%).

Garber et al, in their study of 147 male and 97 female patients, also compared the RAQ with exercise thallium myocardial scintigraphy (21). They found that the sensitivity of the RAQ was similar in females (41%) and males (44%). The specificity was 77% in males, while in females it was significantly lower at 56%. The specificity values reflected the higher ($p < 0.05$) prevalence of "false positive" RAQ results in females (75%) compared with males (27%). In addition, males had a greater ($p < 0.05$) number of "false negative" results (53%) as compared to females (29%).

Similarly, the association between RAQ angina pectoris and coronary calcification was investigated in the Rotterdam Coronary Calcification study (22). In men, the presence of RAQ angina pectoris was associated with a 12.9-fold (95% confidence interval: 3.8–43.7) increased risk of a calcium score ≥ 1000 (reference: calcium score 0–100). The corresponding relative risk in women was 4.8 (2.0–11.3). Similar results were found when sex-specific quartiles of the calcium score were computed.

Udol et al. compared the Thai version of the RAQ with exercise treadmill test. In their study, 157 patients were interviewed using Thai version of RAQ prior to exercise treadmill test and the questionnaire responses were compared with the exercise treadmill test. They reported a sensitivity of 30.3%, specificity of 83.9%, a positive predictive value of 35.3%, a negative predictive value of 81.9%, and total accuracy of 72.6%. There were gender differences in the validity of the questionnaire, with higher specificity, higher positive predictive value, and lower negative predictive value in males then in females (23).

In 2003, Lawlor et al. proposed a short version of the WHO-Rose angina questionnaire (SRAQ) that focussed on only three questions dealing with chest pain after exertion (2). The first three questions of the original RAQ were adopted in the SRAQ without any modification. According to the SRAQ, a patient who never had chest pain was labelled as SRAQ negative. Patient who reported to have chest pain on exertion were labelled as having Grade 1 SRAQ positive. Patients who reported to have chest pain while walking at ordinary pace on a levelled ground were labelled as Grade II SRAQ positive. They compared the RAQ with SRAQ in women using data from a primary care consultation for angina symptoms

within the preceding five years as gold standard. The SRAQ was found to be more sensitive (from 33% to 51.8%) and slightly less specific (from 93.8% to 89.4%) than the original version of RAQ. They concluded that the SRAQ version can also be suitable for epidemiological studies. The discriminatory ability of the SRAQ to predict future coronary events was similar to the full questionnaire in the more recent SMART study (24).

Bastos at al. performed a study to validate the SRAQ in Brazil using treadmill test as the gold standard (25). The SRAQ of the 116 subjects submitted to the exercise treadmill test disclosed 89.7% of accuracy, 25% of sensitivity, 92% of specificity, 10.0% of positive predictive value, 97.2% of negative predictive value, and 3.1 of positive likelihood ratio and 0.82 of negative likelihood ratio. They concluded that the Portuguese version of SRAQ was suitable for epidemiological studies.

Almost all validation studies of the Rose questionnaire have been performed in European or North American ethnic groups, and performance of this questionnaire is known to vary across different ethical groups. Despite being the integral part of almost every population surveys and studies of CAD, the applicability of the RAQ in non-Caucasian and Indian population is not known. Its value as an indicator of CAD is questionable in this population. One study done in migrants from the Indian subcontinents in the United Kingdom showed poor performance of RAQ in that population (26).

We compared the RAQ in Indian population with CTCA findings. CTCA is a non-invasive and very powerful too, to detect CAD. No other study to date, to the best of our knowledge, has compared the RAQ against CTCA.

METHODS

This study was a prospective observational study conducted from April 2013 to May 2014 after getting approvals from the local ethical committee. Sample size calculation for this cross-sectional study to assess the diagnostic accuracy of the RAQ was based on an assumed sensitivity 40 ± 10% and specificity of 70 ± 10% (based on previous exercise thallium studies). According to these assumptions, the number of patients required was 200, to calculate the sensitivity and specificity of the RAQ. We tried to enrol all consecutive patients above 25yrs of age, undergoing CTCA for various indications for this study after obtaining informed consent. Patients with hospital diagnosed CAD and those who were known cases of rheumatic heart disease were excluded. After a written and informed consent, patient's

detailed demographic status, co-morbid illnesses, risk factors for CAD, were recorded. A total of 218 patients who underwent CTCA were recruited. The RAQ was administered by the same investigator who was blinded to CTCA findings, for all the patients and the responses were recorded.

Inclusion criteria

1. All consecutive patients above 25yrs of age undergoing CTCA

Exclusion criteria

1. Post PTCA/ CABG
2. Definite previous MI based on hospital discharge
3. Patients with known Rheumatic Heart Disease
4. Patients not willing to participate

Ethical approval and Consent for study

Permission was obtained from the Institute Ethics Committee and a written informed consent was obtained from the patients at the time of their enrolment. Copy of ethical clearance has been attached in the annexure (Annexure-1).

Statistical analysis

Data were collected on structured Performa and managed on Microsoft Excel spread sheet. The correctness of entries was checked and mistakes and omissions rectified. Statistical processing and analysis were performed using SPSS version 17. Descriptive statistics were conducted by frequency tables. Continuous variables were expressed as mean ± SD. The chi-squared test and Fisher's exact test were used to check the association between categorical variables.

The Sensitivity (the proportion of those with CAD in CTCA identified by the questionnaire; specificity (the proportion of those with no CAD in CTCA who were defined by the questionnaire as not having angina); positive predictive value (the proportion identified by the questionnaire as having angina who actually have CAD on CTCA), negative predictive value (the proportion identified by the questionnaire as not having angina who did not have CAD on CTCA) and accuracy (the proportion of true results on CTCA identified by the questionnaire) were expressed in percentage.

RESULT

We identified 218 patients undergoing CT coronary angiography at AIIMS who satisfied the inclusion and exclusion criteria of our study. The mean age of our study population was 51.17±9.25yrs out of which 52.8% (n=115) were male patients and 47.2% (103) were female patients. 72% of the patients belonged to 40-60yrs age group. Majority of our patients were from Delhi (n=95; 43.6%) followed by Uttar Pradesh and Bihar (n=46; 21.1% and n=44; 20.18% respectively). The demographic characteristics of the patients enrolled are given in detail in table 1.

Table 1: Demographic characteristics

Age Distribution Mean age Range	n=218 51.17 ± 9.25yrs 29-75yrs
Gender Distribution Male Female	 115 (52.8%) 103 (47.2%)

Age-group wise distribution (yrs)

Age Group (yrs)	Male (n, %)	Female (n, %)	Total (n, %)
25-34	3 (2.6%)	1 (1%)	4 (1.8%)
35-44	34 (29.6%)	18 (17.5%)	52 (23.9%)
45-54	36 (31.3%)	42 (40.8%)	78 (35.8%)
55-64	32 (27.8%)	31 (30.1%)	63 (28.9%)
65-74	9 (7.8%)	11 (10.7%)	20 (9.2%)
75-84	1 (0.9%)	0	1 (0.5%)
Total	115 (52.8%)	103 (47.2%)	218 (100%)

Residence

Residence	n, %
Delhi	95 (43.60%)
Uttar Pradesh	46 (21.1%)
Bihar	44 (20.18%)
Haryana	11 (5%)
Jharkhand	7 (3.2%)
Himanchal	5 (2.3%)
Assam	3 (1.4%)
Rajasthan	2 (0.9%)
West Bengal	2 (0.9%)
Madhya Pradesh	2 (0.9%)
Punjab	1 (0.5%)

Table 2: Educational status, occupation and marital status

Educational Status

Level of Education	Male (n=115)	Female (n=103)
Illiterate	3 (1.4%)	17 (7.8%)
Can write name	4 (1.8%)	24 (11%)
Primary school	13 (6%)	15 (6.9%)
Secondary school	24 (11%)	24 (11%)
Higher secondary school	33 (15.1%)	11 (5%)
Above	38 (17.4%)	12 (5.5%)

(p value: 0.000)

Occupation

Occupation	Male (n=115)	Female (n=103)
Farmer	21 (9.6%)	2 (0.9%)
Service holder	50 (22.9%)	22 (10.1%)
Business	32 (14.7%)	1 (0.5%)
Housewife	NA	78 (35.8%)
Others	12 (5.5%)	0

(p value: 0.000)

Marital status

Marital status	Male (n=115)	Female (n-103)
Unmarried	1 (0.5%)	0
Married	114 (52.3%)	103 (47.2%)

9.2% of the study population were illiterate out of which 85% were women. Education up to higher secondary school and above this level was significantly lower in women. 75% of women were housewives. Among men, government or private service was the most common occupation with about 44% having some form of government or private service. All the study subjects, except one male, were married. Table 2 describes the marital status, level of education and occupation of the study population in detail.

Table 3: Presence of risk factors for coronary artery disease

Coronary risk factors (total frequency and percentage)	Male (n=115)	Female (n=103)	p value
Hypertension (n=112; 51.4%)	57 (49.6%)	55 (53.4%)	0.590
Diabetes mellitus (n=36; 16.5%)	21 (18.3%)	15 (14.6%)	0.584
Smoking (n=15; 6.9%)	15 (13%)	0	0.000
Dyslipidaemia (n=5; 2.3%)	4 (3.5%)	1 (1%)	0.373
Family history (n=29; 13.3%)	23 (20%)	6 (5.8%)	0.002

As shown in table 3, the most common cardiovascular risk factor prevalent in our study population was hypertension. It was seen in 51.4% of our study population with equal frequency among both genders. Diabetes mellitus was present in 16.5% and dyslipidaemia in 2.3% and there was no significant difference between men and women. 13% of the total study population were smokers; all of them were men. Family history of coronary artery disease was found to be more common in men (20%) than women (5.8%) and the difference was statistically significant.

Table 4: Drug history at the time of screening for coronary artery disease

Drug history at the time of screening	Male (n=115)	Female (n=103)	p value
Aspirin (n=17; 7.8%)	12 (10.4%)	5 (4.9%)	0.138
Statin (n=21; 9.6%)	15 (13%)	6 (5.8%)	0.106
Beta-blockers (n=18; 8.3%)	12 (10.4%)	6 (5.8%)	0.324
ACE*-Inhibitors/ ARB** (n=35; 16.1%)	21 (18.3%)	14 (13.6%)	0.363
Nitrates (n=19; 8.7%)	12 (10.4%)	7 (6.8%)	0.472

***ACE**-Angiotensin converting enzyme; ****ARB** –Angiotensin receptor blockers

ACE-Inhibitors and ARBs were the most common drugs being taken by our study population followed by statins (16.1% and 9.6% respectively). There was no significant difference in the prescribed drugs between two genders.

The indications for CTCA were noted for every patient. The most common indication was atypical chest pain present in 68.3% of patient in whom CTCA was done to rule out

CAD. 15.6% of the study population were thought to have typical angina chest pain and CTCA was ordered to confirm the diagnosis of CAD. Unexplained dyspnoea, equivocal TMT test, and pre-operative clearance were other indications as shown in table 5.

Table 5: Indications for undergoing CTCA

Indication	Male (n=115)	Female (n=103)
Atypical Angina (n=149; 68.3%)	75 (65.2%)	74 (71.8%)
Typical Anginal (n=34; 15.6%)	17 (14.8%)	17 (16.5%)
Unexplained dyspnoea (n=24; 11%)	15 (13%)	9 (4.1%)
Equivocal TMT (n=9; 4.1%)	6 (5.2%)	3 (2.9%)
Pre-operative work up (n=2; 0.9%)	2 (1.7%)	0
		(p=0.488)

After noting down the details of demography, comorbid illnesses, drugs being taken and clinical indication for CTCA, the Rose Angina Questionnaire was administered on the same day. The RAQ was administered in Hindi by the same person (the principle investigator) for all the patients. The investigator was blinded for CTCA findings at the time of RAQ administration.

Out of 218 patients interviewed, 29 (13.3%) never had any form of chest pain, at rest as well as on exertion and hence further Rose questions which describe the character of chest pain were not applicable. In remaining 189 patients (86.7%), some form of chest pain was present. In 156 patients (71.6%), chest pain was present in typical site and in remaining 33 patients (15.1%), chest pain was present at atypical sites. 44 patients (20.2%) reported that they develop chest pain while walking even on a levelled ground and 63 patients (28.9%) reported that they develop chest pain while walking uphill and while hurrying up. On developing pain, 20 patients (9.2%) had to stop, 21 patients (9.6%) had to slow down and 56 patients (25.7%) continued at the same pace. 34 patients (15.6%) told that pain got relieved on stopping, however 151 patients (69.3%) reported that their pain continued even when they stopped walking. Pain was relieved within 10mins in 86 patients (39.4%), however 103 patients (47.2%) reported to have longer episodes of chest pain. There was no significant difference in response to the individual RAQ between men and women, as described in detail in table 6.

Table 6: The responses to the Rose angina questionnaire (RAQ)

RAQ	Male	Female	p value
RAQ 1			
Yes (n=189; 86.7%)	96 (83.5%)	93 (90.3%)	
No (n=29; 13.3%)	19 (16.5%)	10 (9.7%)	0.164
RAQ2			
Typical sites (n=156; 71.6%)	76 (66.1%)	80 (77.7%)	
Atypical sites (n=33; 15.1%)	20 (17.4%)	13 (12.6%)	
Not applicable (n=29; 13.3%)	19 (16.5%)	10 (9.7%)	0.154
RAQ3			
Yes (n=44; 20.2%)	18 (15.7%)	26 (25.2%)	
No (n=157; 72%)	88 (76.5%)	69 (67.0%)	
Unable (17; 7.8%)	9 (7.8%)	8(7.8%)	0.205
RAQ4			
Yes (n=63; 28.9%)	31 (27.0%)	32 (31.1%)	
No (n=133; 61%)	72 (62.6%)	61 (59.2%)	
Unable (n=22; 10.1%)	12 (10.4%)	10 (9.7%)	0.806
RAQ5			
Stop (n=20; 9.2%)	9 (7.8%)	11 (10.7%)	
Slow Down (n=21; 9.6%)	10 (8.7%)	11 (10.7%)	
Continue at same pace (n=56; 25.7%)	31(27.0%)	25 (24.3%)	
Not applicable (n=121; 55.5%)	65 (56.5%)	56 (54.4%)	0.823
RAQ6			
Yes (34; 15.6%)	16 (13.9%)	18 (17.5%)	
No (151; 69.3%)	78 (67.8%)	73 (70.9%)	
Not applicable (33; 15.1%)	21 (18.3%)	12 (11.7%)	0.352
R**AQ7**			
Less than 10 mins(86; 39.4%)	47 (40.9%)	39 (37.9%)	
More than 10 mins(103; 47.2%)	49 (42.6%)	54 (52.4%)	
Not applicable (29; 13.3%)	19 (16.5%)	10 (9.7%)	0.224

RAQ1-Do you ever have any pain or discomfort in your chest? **RAQ2**-Where do you get this pain or discomfort? **RAQ3**-When you walk on an ordinary pace on the level, does this produce the pain? **RAQ4**-When you walk uphill or hurry does this produce the pain? **RAQ5**-When you get any pain or discomfort in your chest on walking, what do you do? **RAQ6**-Does the pain or discomfort goes away if you stand still? **RAQ7**-How long does it take to go away?

Table 7: Conclusion of Rose Angina Questionnaire

RAQ	Male (n=115)	Female (n=103)	Total (n=218)
RAQ Negative	99 (86.1%)	89 (86.4%)	188 (86.2%)
RAQ Grade I Positive	14 (12.2%)	8 (7.8%)	22 (10.1%)
RAQ Grade II Positive	2 (1.7%)	6 (5.8%)	8 (3.7%)

(p=0.182)

188 patients (86.2%) were RAQ negative, among whom, 99 were men and 103 were women. 30 patients (13.8%) were RAQ positive. There was no significant difference between men and women in terms of RAQ positivity.

We also classified our patients using Shortened WHO Rose Angina Questionnaire according to which 147 (67.4%) were Short RAQ negative and 71 (32.6%) were Short RAQ positive as shown in table 8.

Table 8: Conclusion of Shortened WHO Rose Angina Questionnaire

Shortened RAQ	Male (n=115)	Female (n=103)	Total (n=218)
Shortened RAQ Negative	81 (70.4%)	66 (64.1%)	147 (67.4%)
Shortened RAQ Grade I Positive	16 (13.9%)	11 (10.7%)	27 (12.4%)
Shortened RAQ Grade II Positive	18 (15.7%)	26 (25.2%)	44 (20.2%)

(p=0.194)

When analysed for the agreement between the conclusions of the RAQ with that of Shortened WHO RAQ, there was a significant difference between the conclusions derived from the two questionnaires with the rates of angina positivity being statistically much higher with the Shortened WHO RAQ as compared to the original RAQ as described by table 9.

Table 9: Comparison of RAQ conclusion versus Shortened WHO RAQ conclusion

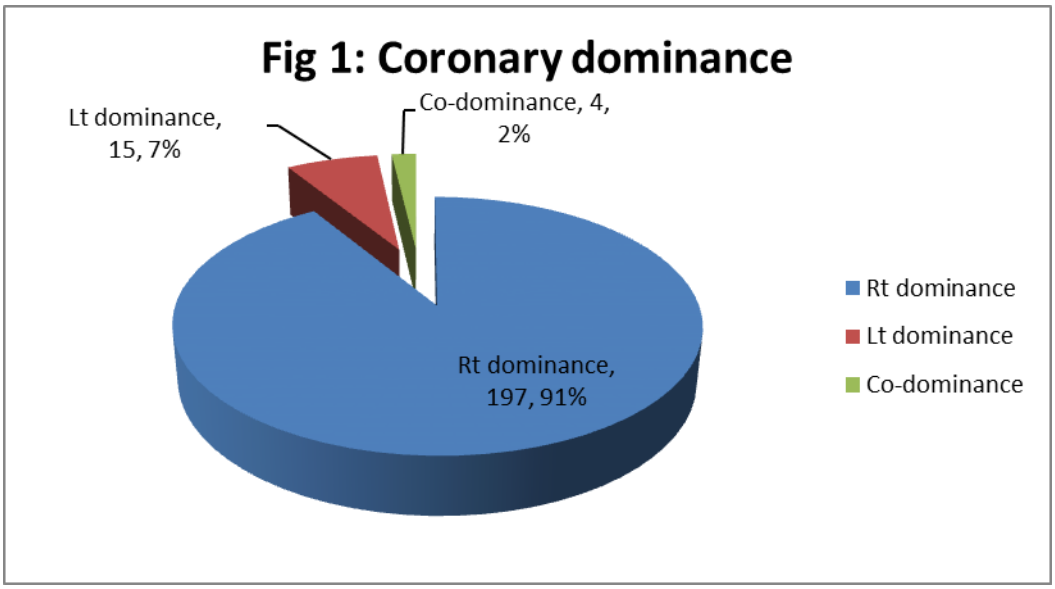
Gender		**Shortened RAQ Negative**	**Shortened RAQ Positive**	Total
Male	**RAQ Negative**	81	18	99
	RAQ Positive	0	16	16
Female	**RAQ Negative**	66	23	89
	RAQ Positive	0	14	14
Total				218

(p=0.000)

All the enrolled, except two patients, underwent CTCA without any complication. In two patients, CTCA couldn't be done due to technical reasons. Hence, analysis of CTCA findings could be done in 216 patients only.

CT coronary angiographic findings

Out of 216 patients who underwent CTCA, 197 patients (91%) had right dominant system, 15 (7%) had left dominant system and 4 (2%) had co-dominance as shown in figure 1.



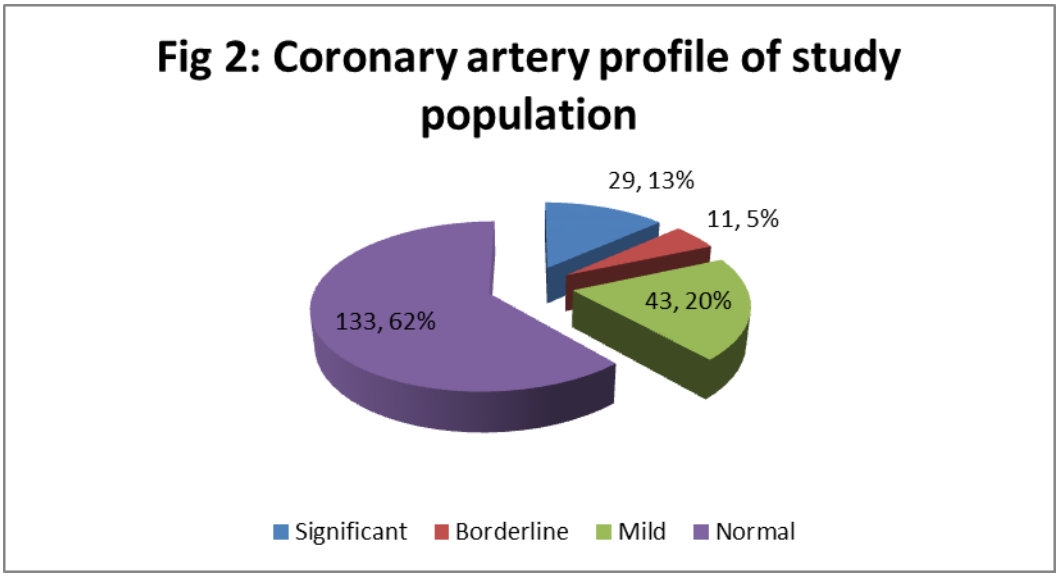


Table 10: Coronary artery disease profile of patients who underwent CTCA

Coronary Artery	Male (n=115)	Female (n=101)	Total (n=216)
Left Main (LM)			
Normal	105 (91.3%)	99 (98%)	204 (94.4%)
Mild disease (<50%)	7 (6.1%)	2 (2%)	9 (4.2%)
Significant disease (≥50%)	3 (2.6%)	0	3 (1.4%)
			*(p=0.086)
Left Anterior Descending Artery (LAD)			
Normal	72 (62.6%)	71 (70.3%)	143 (66.2%)
Mild disease (<50%)	24 (20.9%)	20 (19.8%)	44 (20.4%)
Borderline disease (50-70%)	5 (4.3%)	2 (2%)	7 (3.2%)
Significant disease (≥70%)	14 (12.2%)	8 (7.9%)	22 (10.2%)
			*(p=0.521)
Left Circumflex Artery (LCx)			
Normal	82 (71.3%)	94 (93.1%)	176 (81.5%)
Mild disease (<50%)	17 (14.8%)	3 (3%)	20 (9.3%)
Borderline disease (50-70%)	4 (3.5%)	3 (3%)	7 (3.2%)
Significant disease (≥70%)	12 (10.4%)	1 (1%)	13 (6%)
			*(p=0.000)
Right Coronary Artery (RCA)			
Normal	86 (74.8%)	85 (84.2%	171 (79.2%)
Mild disease (<50%)	12 (10.4%)	13 (12.9%)	25 (11.6%)
Borderline disease (50-70%)	7 (6.1%)	2 (2%)	9 (4.2%)
Significant disease (≥70%)	10 (4.6%)	1 (1%)	11 (5.1%)
			*(p=0.022)

*Statistical comparison between the two genders

As shown in figure 2, 133 patients (63%) had normal coronary arteries, 43 patients (20%) had mild coronary disease, 11 patients (5%) had borderline coronary disease and 29 patients (13%) had significant coronary artery disease.

Among the patients who had significant coronary disease, LAD was the most common artery involved (n=22; 10%) followed by LCx (n=13; 6%) and RCA (n=11; 5.1%). Significant LM disease was seen in 3 patients only (2.6%) and all of them were men. There was no significant difference between men and women, with respect to the disease involvement of LM and LAD. However, significant coronary artery disease involving LCx and RCA was found to be more common in men as compared to women, and this difference was statistically significant. The coronary artery disease profile is described in detail in table 10.

The comparison of RAQ conclusion with that of CTCA is shown in table 11 and the comparison of Shortened WHO RAQ conclusion with that of CTCA findings is made in table 12. The number of patients who were Shortened WHO RAQ positive were more than twice the number of RAQ patients (70 Shortened RAQ positive patients versus 29 RAQ positive patients), when applied to the same population.

Table 11: Comparison of RAQ conclusion with that of CTCA findings

RAQ Conclusion	**CTCA Conclusion**				
	Normal	**Mild CAD**	**Borderline CAD**	**Significant CAD**	**Total**
RAQ Negative	124	39	10	14	187
RAQ Grade I Positive	5	3	1	12	21
RAQ Grade II Positive	4	1	0	3	8
Total	133	43	11	29	216

Table 12: Comparison of Shortened WHO RAQ conclusion with that of CTCA findings

RAQ Conclusion	CTCA Conclusion				
	Normal	**Mild CAD**	**Borderline CAD**	**Significant CAD**	Total
Short RAQ Negative	96	30	8	12	146
Short RAQ Grade I Positive	9	3	1	13	26
Short RAQ Grade II Positive	28	10	2	4	44
Total	133	43	11	29	216

To calculate the sensitivity and specificity of the RAQ, taking CTCA findings as Gold standard, we divided our patients into those with insignificant CAD (<50% stenosis on CTCA) and those with significant CAD (≥50% stenosis on CTCA) and compared with the conclusion derived from the RAQ as shown in table 13. The sensitivity and specificity when applied to entire study group was 40% and 92.61% respectively.

Table 13: Performance of RAQ against CTCA assuming ≥50% stenosis of coronary artery as significant coronary artery disease

	Insignificant CAD on CTCA (<50%)	Significant CAD on CTCA (≥50%)	Total
Men			
RAQ Negative	81	18	99
RAQ Positive	5	11	16
Women			
RAQ Negative	82	6	88
RAQ Positive	8	5	13
Total	176	40	216

Sensitivity of RAQ = 37.93% (men); 45.45% (women); 40% (overall)

Specificity of RAQ = 94.18% (men) ; 91.11% (women); 92.61% (overall)

Positive predictive value = 68.75% (men); 38.46% (women); 55.17% (overall)

Negative predictive value = 81.82% (men); 93.18% (women); 87.17% (overall)

Positive Likelihood Ratio = 6.52 (men); 5.11 (women); 5.41 (overall)

Negative Likelihood Ratio = 0.66 (men); 0.59 (women); 0.65 (overall)

Accuracy = 80.00% (men); 86.14% (women); 82.87% (overall)

The same statistical parameters were calculated for the Shortened WHO RAQ and following results were obtained as tabulated in table 14.

Table 14: Performance of Shortened RAQ against CTCA assuming ≥50% stenosis of coronary artery as significant coronary disease

	Insignificant CAD on CTCA (<50%)	Significant CAD on CTCA (≥50%)	Total
Men			
Short RAQ Negative	64	17	81
Short RAQ Positive	22	12	34
Women			
Short RAQ Negative	62	3	65
Short RAQ Positive	28	8	36
Total	176	40	216

Sensitivity of RAQ = 41.38% (men); 72.72% (women); 50% (overall)

Specificity of RAQ = 74.42% (men) ; 68.89% (women); 75.90% (overall)

Positive predictive value = 35.29% (men); 22.22% (women); 33.33% (overall)

Negative predictive value = 79.01% (men); 95.39% (women); 86.30% (overall)

Positive Likelihood Ratio = 1.61 (men); 2.34 (women); 2.07 (overall)

Negative Likelihood Ratio = 0.79 (men); 0.39 (women); 0.66 (overall)

Accuracy = 66.08% (men); 69.31% (women); 67.59 % (overall)

Subsequently we analysed the performance of RAQ and Shortened WHO RAQ using ≥70%stenosis as a cut-off for significant CAD and we got the following results (table 15 & table 16).

Table 15: Performance of RAQ against CTCA assuming ≥70% stenosis of coronary artery as significant coronary disease

	Insignificant CAD on CTCA (<70%)	Significant CAD on CTCA (≥70%)	Total
Men			
RAQ Negative	89	10	99
RAQ Positive	6	10	16
Women			
RAQ Negative	84	4	88
RAQ Positive	8	5	13
Total	187	29	216

Sensitivity of RAQ = 50% (men); 55.56% (women); 51.72% (overall)

Specificity of RAQ = 93.68% (men); 91.30% (women); 92.51% (overall)

Positive predictive value= 62.50% (men); 38.46 % (women); 51.72% (overall)

Negative predictive value = 89.89% (men); 95.45% (women); 92.51% (overall)

Positive Likelihood Ratio = 7.91 (men); 6.39 (women); 6.91 (overall)

Negative Likelihood Ratio = 0.53 (men); 0.49 (women); 0.52 (overall)

Overall Accuracy = 86.09% (men); 88.12% (women); 87.04% (overall)

Table 16: Performance of Shortened WHO RAQ against CTCA assuming ≥70% stenosis of coronary artery as significant coronary disease

	Insignificant CAD on CTCA (<70%)	Significant CAD on CTCA (≥70%)	Total
Men			
Short RAQ Negative	71	10	81
Short RAQ Positive	24	10	34
Women			
Short RAQ Negative	63	2	65
Short RAQ Positive	29	7	31
Total	187	29	216

Sensitivity of Short RAQ = 50% (men); 77.78% (women); 58.62% (overall)

Specificity of Short RAQ = 74.74% (men); 68.48% (women); 71.66% (overall)

Positive predictive value= 29.41% (men); 19.44 % (women); 24.29% (overall)

Negative predictive value = 87.65% (men); 96.92% (women); 91.78% (overall)

Positive Likelihood Ratio = 1.98 (men); 2.47 (women); 2.07 (overall)

Negative Likelihood Ratio = 0.67 (men); 0.32 (women); 0.58 (overall)

Accuracy = 70.43% (men); 69.31% (women); 69.91% (overall)

We studied the effect of gender, literacy and presence of diabetes and hypertension on the accuracy of both RAQ and Shortened RAQ. For this analysis, we assumed ≥70%

coronary artery stenosis as significant coronary artery disease. RAQ and Shortened WHO RAQ was designated to be accurate if it was either true positive or true negative as compared to CTCA finding. False positive and false negative RAQ and Shortened WHO RAQ were designated as inaccurate. Effect of gender, literacy and presence of hypertension and diabetes on the accuracy of the RAQ and Shortened WHO RAQ is shown in table 17 & table 18.

Table 17: Effect of gender, literacy and presence of hypertension and diabetes on the accuracy of the Rose Angina Questionnaire assuming ≥70% coronary stenosis as significant CAD

	RAQ Accuracy		Total	p value
	Accurate * (TP + TN)	Inaccurate * (FP+FN)		
Gender				
Men	99(86.1%)	16(13.9%)	115	
Women	89(88.1%)	12(11.9%)	101	0.690
Literacy				
Illiterate/ Can sign	39(83%)	8(17%)	47	
Literate	149(88.2%)	20(11.8%)	169	0.336
Hypertension				
Yes	91(82.7%)	19(17.3%)	110	
No	97(91.5%)	9(8.5%)	106	0.068
Diabetes mellitus				
Yes	30(85.7%)	5(14.3%)	35	
No	158(87.3%)	23(12.7%)	181	0.785

*__TP__-True positive; __TN__-True negative; __FP__-False positive; __FN__-False negative

Table 18: Effect of gender, literacy and presence of hypertension and diabetes on the accuracy of the Shortened WHO Rose Angina Questionnaire assuming ≥70% coronary stenosis as significant CAD

	Short WHO RAQ Accuracy		Total	p value
	Accurate *(TP+TN)	Inaccurate *(FP+FN)		
Gender				
Men	77(67.0%)	38(33%)	115	
Women	73(72.3%)	28(27.7%)	101	0.460
Literacy				
Illiterate/ Can sign	32(68.1%)	15(31.9%)	47	
Literate	118(69.8%)	51(30.2%)	169	0.859
Hypertension				
Yes	71(64.5%)	39(35.5%)	110	
No	79(74.5%)	27(25.5%)	106	0.139
Diabetes mellitus				
Yes	22(62.9%)	13(37.1%)	35	
No	128(70.7%)	53(29.3%)	181	0.423

*__TP__-True positive; __TN__-True negative; __FP__-False positive; __FN__-False negative

Gender, literacy, presence of hypertension and diabetes did not have statistically significant impact on the accuracy of both RAQ and Shortened WHO RAQ.

Other important findings that were incidentally detected during the CTCA and their corresponding RAQ and Shortened WHO RAQ interpretation are described in table 19. 13 out of 216 patients (6.02%) had myocardial bridge, all involving the left anterior descending artery. Malignant right coronary artery course was discovered in 4 patients (1.85%).

Table 19: Incidental findings on CTCA and their corresponding RAQ and Shortened WHO RAQ interpretations

Incidental findings on CTCA	**RAQ**	**Shortened RAQ**
Proximal LAD myocardial bridge (n=1)	All negative	All negative
Mid LAD myocardial bridge (n=6)	All negative	All negative
Distal LAD myocardial bridge (n=6)	Negative-5, Positive-1	Negative-5, Positive-1
Re-canalized LAD with evidence of old MI (n=3)	Positive-2, Negative-1	Positive-3
Malignant RCA course (n-4)	All negative	All negative

DISCUSSION

Our study is the only study done on Indian population comparing the RAQ and SRAQ with a very objective and accurate method of detecting CAD, which is CTCA. We conducted this study because RAQ is being used in various epidemiological studies in India as well and there is paucity of robust and comprehensive data on its performance, in this population. To the best of our knowledge, no other study has ever been conducted to assess the performance of RAQ and SRAQ in Indian population.

Table 20: Summary of the study titled "Comparison of Rose Angina Questionnaire to Computed Tomographic Coronary Angiography"

		Men (n=115)	Women (n=101)	Total (n=216)
RAQ	Sensitivity	50%	55.56%	51.72%
	Specificity	93.68%	91.30%	92.51%
	Positive Predictive Value	62.50%	38.46%	51.72%
	Negative Predictive Value	89.89%	95.45%	92.51%
	Positive Likelihood Ratio	7.91	6.39	6.91
	Negative Likelihood Ratio	0.53	0.49	0.52
	Accuracy	86.09%	88.12%	87.04%
SRAQ				
	Sensitivity	50%	77.78%	58.62%
	Specificity	74.74%	68.48%	71.66%
	Positive Predictive Value	29.41%	19.44%	24.29%
	Negative Predictive Value	87.65%	96.92%	91.78%
	Positive Likelihood Ratio	1.98	2.47	2.07
	Negative Likelihood Ratio	0.67	0.32	0.58
	Accuracy	70.43%	69.31%	69.91%

We observed poor sensitivity of RAQ and SRAQ, 51.72% and 58.62% respectively, when compared to CTCA as the gold standard. Although SRAQ was apparently more sensitive as compared to RAQ (58.62% vs 51.72%); this finding was exclusive to the women only and the sensitivities of the two questionnaires were same in men. Moreover, the slight improvement in sensitivity of SRAQ was at an expense of marked fall in specificity which also gave rise to its poorer accuracy as compared to RAQ. The positive predictive values were poor for both the questionnaires. However both the questionnaires were excellent in terms of negative predictive values as shown in table 20.

Table 21: Comparison of performance of RAQ in different studies

	Bass et al (n=198)	**Garber et al** (n=244)	**Udol et al** (n=157)	**This study** (n=216)
Gold standard	Exercise Thallium	Exercise Thallium	Treadmill test	CTCA
Sensitivity	26% (overall)	41%(women) 44% (men)	30.3% (overall)	55.56% (women) 50% (men)
Specificity	79% (overall)	56% (women) 77% (men)	83.9% (overall)	91.30% (women) 93.68% (men)
Positive predictive value	42% (overall)		35.3% (overall)	38.46% (women) 62.50% (men)
Negative predictive value	65% (overall)		81.9% (overall)	95.45% (women) 89.89% (men)
Accuracy		29%	72.6%	88.12% (women) 86.09% (men)

As compared to the study conducted by Bass et al. (20), in which they compared the RAQ with Stress Thallium, we found higher sensitivity, specificity, positive and negative predictive values of the RAQ. The sensitivity and specificity of RAQ in our study was higher than those of Garber et al, who also compared RAQ with Stress Thallium (21). We also observed higher sensitivity, specificity, positive and negative predictive values and total accuracy of RAQ as compared to the study of Udol et al. who compared the Thai version of RAQ with exercise treadmill test (22). The comparison of our study with other similar studies is shown in table 21.

Table 22: Comparison of performance of SRAQ in different studies

	Lawlor et al (n=3987)	**Bastos et al** (n=116)	**This study** (n=216)
Gold Standard	Medical record of angina	Exercise treadmill	CTCA
Sensitivity	51.80%	25%	58.62%
Specificity	89.4%	92%	71.66%
Positive predictive value	22.5%	10%	24.29%
Negative predictive value	96.9%	97.2%	91.78%
Accuracy		89.7%	69.91%

We observed low sensitivity of the SRAQ albeit comparable with the findings of Lowlor et al (2). However the specificity of SRAQ was markedly low in our study. Bastos et al observed even lower sensitivity of SRAQ, but excellent specificity. As stated before, we observed that slight improvement in sensitivity of SRAQ was associated with marked fall in its specificity and hence its accuracy, as compared to RAQ. Conceptually the SRAQ, by excluding four vital questions of the RAQ, is bound to have higher rates of 'false positives' and lower rates of 'false negatives' and hence higher sensitivity and lower specificity as compared to RAQ. However the observation made by Lower et al was somewhat paradoxical as they demonstrated improved sensitivity without loss of specificity, when they compared SRAQ with RAQ.

The sensitivity of SRAQ was slightly higher only for women in our study. This finding probably reflects higher preponderance of non-cardiac chest pain in women. With the RAQ, the atypical nature of chest pain can be defined more accurately as compared to the SRAQ which concludes the diagnosis of CAD on the basis of presence of absence of chest pain only. As a result, patients with non-cardiac chest pain are more likely to be reported as SRAQ positive as compared to RAQ; and hence increasing the sensitivity of SRAQ with fall in its specificity. Due to poor sensitivity, poor specificity and poor accuracy of the SRAQ in our population, we conclude that SRAQ doesn't seem to be as useful in Indians as in other studies.

Our results are not very different from similar other studies. Although widely used, both RAQ and SRAQ, suffer from extreme lack of sensitivity. However, the specificity and negative predictive value of both questionnaires are excellent.

RAQ is a convenient screening tool to detect CAD. For a clinician, a screening tool should have high sensitivity so that the disease in question is not missed. High sensitivity is achieved at the expense of lower specificity, which means larger number of 'false positives' from initial screening test. This often doesn't matter to a clinician, who often sees a very small fraction of total population, and the 'false positive' ones are subsequently ruled out.

However, for an epidemiological studies, where millions and billions of population is screened, a test with high sensitivity would let to extremely high number of 'false positive' patients. It is impractical to refer thousands of 'false positive' patients for cardiologist assessment and more specific diagnostic testing. For this reason, epidemiologists use more

restricted definitions of diseases which provide high specificity allowing them to compare their results and data obtained in different places and periods.

Hence, RAQ appears to have unacceptably low sensitivity as a screening tool; however remains one of the favourite screening tool for epidemiologists.

CONCLUSION

We conclude that the RAQ has excellent specificity and negative predictive value, however suffers from very poor sensitivity of about 50%. Being commonly used as screening tool for CAD in community surveys, it is likely to reflect only a fraction of population who is actually suffering from CAD. Most of the epidemiological surveys for CAD used in India have used the RAQ as one of the screening tools and such surveys are likely to reflect only the tip of the iceberg of the real CAD burden. The SRAQ suffers from poor sensitivity, poor specificity and poor accuracy, and doesn't seem to be as useful in Indians as in other studies.

STRENGTH AND LIMITATIONS

Use of CTCA, which is a very accurate and objective method to diagnose CAD, to validate RAQ and SRAQ is the main strength of this study. The CTCA were ECG gated and were reviewed for accuracy by two separate experts before their final conclusion. The sample size was also larger than that of any other study comparing RAQ and SRAQ with objective diagnostic modality. Another main strength of our study is the standardized way in which it was performed. All the demographic details including literacy rates, presence of co-morbid illness etc. were recorded. Every questionnaire was filled by the same principle investigator on the day of CTCA before the reports of CTCA were available.

37 out of 216 patients (17.13%) were on some form of anti-anginal therapy when being allotted into the study. This might have further lowered the sensitivity and accuracy of RAQ and SRAQ in our study, albeit not to a great extent.

A limitation is that we had very few patients who actually had CAD on CTCA, i.e. 'true positive' patients. Another limitation is that we performed this study in a tertiary care referral centre, despite the fact that RAQ was introduced purely for community studies and surveys. Our patients were fully evaluated clinically and were thought to have indication for CTCA by experts, and hence they didn't represent a community.

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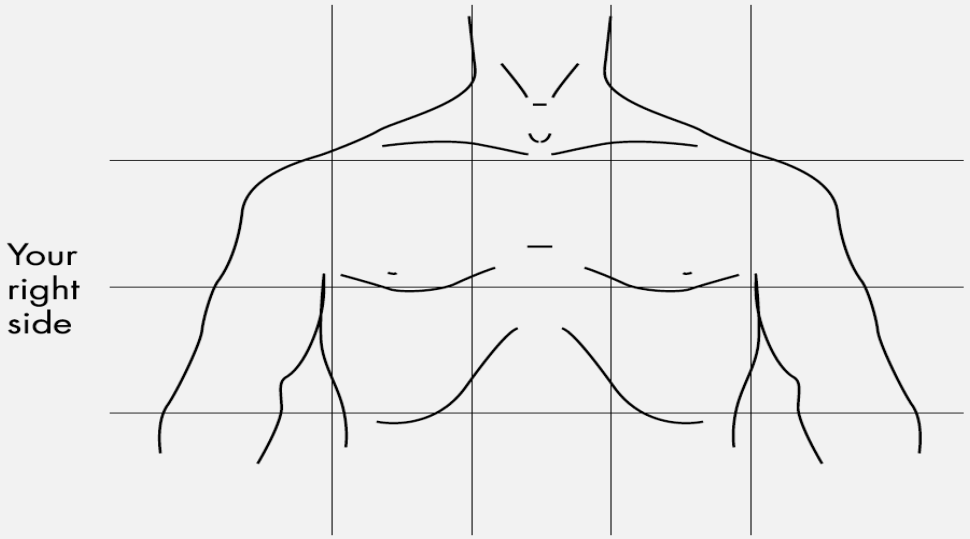
1 Do you ever have any pain or discomfort in your chest?

Yes/No

2 Where do you get this pain or discomfort?
Please mark **X** on the appropriate places



3 When you walk at an ordinary pace on the level does this produce the pain?

Yes/No/Unable

4 When you walk uphill or hurry does this produce the pain?

Yes/No/Unable

5 When you get any pain or discomfort in your chest on walking, what do you do?

Stop Slow down Continue at same pace Not applicable

6 Does the pain or discomfort in your chest go away if you stand still?

Yes/No

7 How long does it take to go away?

10 minutes or less
more than 10 minutes

Figure 1 Complete WHO Rose Angina questionnaire.

RETROSPECTIVE STUDY ON OUTCOMES OF RADIOFREQUENCY ABLATION OF INTRA-ATRIAL RE-ENTRANT TACHYCARDIA FOLLOWING SURGICAL REPAIR OF CONGENITAL HEART DISEASE

Thesis submitted to the faculty of

All India Institute of Medical Sciences, New Delhi

In partial fulfilment of the requirement

For the degree of

DOCTORATE OF MEDICINE

(CARDIOLOGY)

AUGUST, 2014

AIIMS, NEW DELHI **DR PRASHANT SHAH**

Abbreviations

IART- Intra-atrial re-entrant tachycardia

IDAF- Isthmus dependent atrial flutter

CHD- Congenital heart disease

Os-ASD- Ostium secundum atrial septal defect

Op-ASD- Ostium primum atrial septal defect

SV-ASD- Sinus venosus atrial septal defect

VSD- Ventricular septal defect

PDA- Patent ductus arteriosus

TOF- Tetralogy of Fallots

TGA- Transpositions of great arteries

DORV- Double outlet right ventricle

PAPVC- Partial anomalous pulmonary venous connection

TAPVC- Total anomalous pulmonary venous connection

EP/ EPS –Electrophysiological study

RFA- Radiofrequency ablation

BDG/ BD Glenn- Bidirectional Glenn

IDAF- Isthmus dependent atrial flutter

LV/ RV –Left ventricle/ right ventricle

Retrospective Study on Outcomes of Radiofrequency Ablation of Intra-atrial Re-entrant Tachycardia following Surgical Repair Of Congenital Heart Disease

BACKGROUND

Intra-atrial re-entrant tachycardia (IART) is a common arrhythmia in patients with surgically repaired or palliated congenital heart diseases. It often has significant negative impact on the morbidity as well as mortality of these patients. Being resistant to pharmacotherapy, radiofrequency ablation is often the only treatment available. However, access to ablation targets for radiofrequency ablation in post cardiac surgery patients may be limited by distorted anatomy and by surgically created obstacles such as baffles and prosthesis. With improved understanding of the mechanisms of these tachycardias, improvement in the mapping and ablation techniques and with increasing experience, the outcome of radiofrequency ablation in patients with post cardiac surgery IART is rapidly improving. To the best of our knowledge, the efficacy and safety of radiofrequency ablation of IART in post cardiac surgery patients is not well described from our region.

AIM OF THE STUDY

This study was a retrospective evaluation of the safety and efficacy of radiofrequency ablation of intra-atrial reentrant tachycardia following surgical repair of congenital heart disease.

OBJECTIVES OF THE STUDY

1. To describe the clinical profile of patients who developed post cardiac surgery IART
2. To study the success rates of radiofrequency ablation in post cardiac surgery IART patients
3. To study the complications of radiofrequency ablation in post cardiac surgery patients

STUDY POPULATION

This study included all the patients with traceable records who developed IART after various corrective or palliative cardiac surgery for congenital heart diseases and underwent radiofrequency ablation at our institute, All India Institute if Medical Sciences, New Delhi, from 1998 to 2014.

METHODOLOGY

This was a retrospective study. All patients of IART post cardiac surgery, who received radiofrequency ablation at our institute, were identified from our Cardiac Electrophysiology and Radiofrequency ablation register (EP-RFA register), maintained by our cardiology department. Their clinical details of the underlying diagnosis, age at which corrective/ palliative surgeries were performed including the nature of surgery, interval from surgery to the first occurrence of IART, duration of IART, the technical details of the electrophysiological study and ablative procedure including its immediate procedural outcome and complications and long term outcome data were retrieved from their Outpatient/ Inpatients records.

Inclusion Criteria

1. All post corrective/ palliative cardiac surgery patients who underwent radiofrequency ablation for IART in our department from 1998 to 2014.

Exclusion Criteria

1. No patient was excluded.

Statistical analysis

This was a retrospective descriptive study. All the clinical, surgical and radiofrequency ablation procedural details and the long term follow up findings will be entered in Excel sheet for statistical analysis. Continuous variable were analysed using t test and categorical variables were analysed using chi squared test, using SPSS version 17 software.

REVIEW OF LITERATURE

Intra-atrial re-entrant tachycardia (IART) is an important and potentially lethal arrhythmia commonly affecting patients who have undergone corrective or palliative cardiac surgery for various congenital heart diseases (CHD), and its prevalence increases over time (1-7). This arrhythmia is mainly seen after complex cardiac surgery, like atrial switch operation and Fontan operation, which involve extensive atrial incision. Surgical scarring, fibrosis and hypertrophy of the atrial myocardium are likely to be implicated in its pathogenesis (8-10). Sinus node dysfunction and prolonged intraatrial conduction, commonly seen after Fontan repair, may play an important role, or at least be an additional marker for likely occurrence of this arrhythmia (11-13). Presence of atrial wall stress in disordered hemodynamic states may also contribute to onset and maintenance of such arrhythmia. Less commonly, IART may occur after simpler cardiac surgery like repair of atrial septal defect (ASD), ventricular septal defect (VSD) or tetralogy of Fallot's (TOF) (7,14). A steadily increasing prevalence of atrial tachyarrhythmias has been reported in survivors following CHD surgery, with rates approaching or exceeding 50% at 10yrs (15).

Although most of the tachyarrhythmia having supraventricular origin are considered benign as compared to those arising from ventricles, IART often has significant negative effect on the morbidity and mortality, especially in post cardiac surgery patients(16-19). Frequent episodes of IART have a significant impact on the lives of young children, including frequent visits to the emergency room, frequent absenteeism from school, or need for daily medication that may have significant side effects, beside undue anxiety among the parents and family members. Loss of synchronous atrial activity has a significant hemodynamic impact in patients who have undergone palliative single ventricular repair like Glenn or Fontan operation, leading to symptoms of congestive heart failure and worsening cardiac output. IART, if left uncontrolled, can lead to tachycardia induced cardiomyopathy and progressive worsening of ventricular function (20). 1:1 atrio-ventricular conduction can lead to syncope and may even pose high risk of death. Thromboembolism is another feared complication of IART carrying significant morbidity and mortality (18-19).

Management of IART is often problematic. The underlying congenital lesions and the surgical procedures that create the substrate for the development of this arrhythmia are often associated with a marginal hemodynamic status, which often limit the role of antiarrhythmic therapy. Moreover, this arrhythmia is often refractory to most of the currently available anti-

arrhythmic agents and may aggravate sinus node dysfunction or cause deterioration of ventricular function (21,22).

Prior to 1990, pharmacotherapy was the only treatment available, beside open heart surgery for elimination of accessory pathways. With the advent of catheter based electrophysiological studies and radiofrequency ablation technology in adults in the early 1990s, many arrhythmias can be permanently cured with high success rates. Atrioventricular reciprocating tachycardias are now managed with high success and low complication rates by the use of catheter based radiofrequency ablative techniques to eliminate their anatomical substrates for more than past two decades (23-25). Ectopic atrial tachycardias, type I atrial flutter as well as IART in patients with normal cardiac anatomy are ablated with high success rates as well and is well established modality of treatment for such arrhythmias (26-29). Adaptations to perform these procedures are increasing being utilized to cure patients with post cardiac surgery arrhythmias as well.

Catheter based electrophysiological studies and radiofrequency ablation often has high success rates with very rare complications, however mapping and ablation of IART has its own challenges. Often multiple IART circuits coexist in same patients, some of which may be important while other circuits may simply be innocent bystanders. Selective localization and ablation of critical areas of important re-entrant circuits, which may be unstable, is a major challenge. The variant anatomy and surgically created obstacles such as baffles or prosthesis may limit access to ablation sites. In congenital heart disease patients, the right atrium may be markedly enlarged with areas of low blood flow which may hamper the cooling of ablation catheter tip and hence reducing its efficiency. Furthermore, this group may include patients with complex congenital heart disease or ventricular dysfunction, which may further complicate the procedure and have a negative impact on its outcome.

Ablation of IART, although challenging, is gradually evolving with improved success rates due to improved understanding of its mechanism and due to improvement in the mapping techniques like high density electroanatomical mapping and due to improved efficacy of self-irrigating catheters.

Two approaches were initially explored for catheter ablation for IART occurring post cardiac surgery. In one approach, mapping focuses on identifying an isolated diastolic atrial potential, presumably originating from an isolated zone of slow conduction (30-31). Entrainment pacing is used to confirm participation of that site in the re-entrant circuit which

is then ablated. In one study, this approach successfully ablated at least one tachycardia in 73% of the patients (14). However, atrial tachycardia recurred in 53% of the patients with acute ablation success with mean time to recurrence being 4.1months (31). The second approach is based on the concept that atrial tachycardia in patient following atriotomy results from re-entry around the atriotomy scar (14, 32). Catheter ablation is used to create a linear transmural lesion between the atriotomy scar and an anatomical barrier (such as the tricuspid annulus or inferior venacava) to interrupt the re-entrant circuit (14,32). The atriotomy scar is identified as an area without an atrial potential or with double atrial potentials separated by an isoelectric baseline, indicating a line of conduction block. The direction of re-entry around the scar is determined by identifying the timing of atrial activation at several sites around the scar, or sweeping Halo technique (33). In two earlier studies using this approach, ablation acutely eliminated at least one atrial tachycardia in 83% and93% of patients, with recurrence of atrial tachycardia in 33% and 46% of the patients with acute ablation success, respectively (14,32). In another study by Annie et al, using the same sweeping Halo technique, in 45 post cardiac surgery patient, 94% of the circuits were successfully ablated. With a mean follow up of 24months, 31% of those with IART had recurrence (33).

Reconstruction of the re-entrant circuit with conventional catheter mapping techniques (including fluoroscopy and sweeping Halo technique) is challenging, especially in patients with multiple surgical scars and multiple IART circuits. Without the ability to store and display the timing of activation at each of the mapped sites, only an approximate estimation of the re-entrant circuit is achieved. The less than optimal long term success of ablation may relate to the inability to localize multiple scars and multiple re-entrant circuits.

The more recently developed catheter electroanatomical mapping system (CARTO), which combines anatomical recreation of the cardiac chambers with local activation times, is uniquely suited for identifying the re-entrant circuits in macroreentrant right atrial tachycardia (34-36). High density (250-400 mapped points) electroanatomical maps have demonstrated that the substrate for macroreentrant atrial tachycardia is a very large area of low voltage (involving almost all of the right atrial free wall) containing two or more adjacent scars. Narrow channels between the scars are the critical component of the re-entrant circuit (36). The re-entrant impulse propagates around one of the scars and through the channel between the scars. The areas of scars and lines of double potentials identified during tachycardia are also present during sinus rhythm or atrial pacing, indicating these scars are fixed anatomical structures and are not functional blocks related to the rapid rate of the

tachycardia. Therefore, unmappable non-sustained macroreentrant atrial tachycardia can be effectively ablated by targeting all of the channels between scars identified from a high density electroanatomical map obtained during one stable tachycardia or during atrial pacing. Hence, the outcome of IART ablation should improve with the use of electroanatomical mapping, at least in theory.

In one study, by Tanner at el, using electroanatomical mapping system (CARTO) for mapping and radiofrequency ablation using irrigated-tip catheter, for ablation of IART in post cardiac surgery patients, acute success rate of 94% for all targeted tachycardia and 87% for all tachycardias was achieved with 92% of the patients being free of recurrence at mean follow-up of 17 +/- 7 months(37).

Although the western literature on the outcome of catheter ablations of IART in post cardiac surgery patients appear impressive, patient selection and operator experience also has a significant impact on acute and long term outcomes of such procedures which have a long learning curve. We have very limited data on the outcome of radiofrequency ablation in post cardiac surgery patient from our region. Hence we decided to study the outcome of radiofrequency ablation for IART in our post cardiac surgery patients.

RESULTS

We performed 78 procedures in 58 patients who had developed IART/ Atrisl flutter following surgery for congenital heart diseases. The mean age of our patients was 25.74 ± 15.42 yrs. Our youngest patient was of 1.5yr of age and our eldest patient was 67yrs of age. 40 out of 58 (68.97%) patients were male and 18 (31.03%) were female. Mean duration from surgery to the radiofrequency ablation was 10.27 ± 6.58 yrs with a range of 6 months to 28yrs. The mean follow up duration was 4.76 ± 3.85yr with shortest follow up of 2months and longest follow up period of 14yrs after ablation.

To simplify the description on outcomes, we divided our patients into two groups based on their anatomical diagnosis- 1. Simple congenital heart disease: the patients who were operated for ASD, PAPVC, TAPVC, VSD, and TOF and 2. Complex congenital heart disease: those patients who were operated for more complex congenital heart diseases like TGA, single ventricle, DORV with MPGA, DILV etc.

Description of Atrial flutter patients with simple congenital heart disease

Table 1: Summary of ablation outcome in patients with simple CHD

Diagnosis	No. of patients	No. of procedures	Procedural success	Long term success	Procedure failure
Os-ASD	15	17	12	12	5
Op-ASD	3	3	2	2	1
PAPVC + Os-ASD	2	2	1	1	1
Sinus venosus ASD + PAPVC	3	3	1	1	2
TAPVC	2	4	3	2	1
ASD/VSD/PDA	2	3	3	2	0
VSD	2	2	2	2	0
Cor triatriatum with Os-ASD	1	2	1	1	1
TOF	12	18	16	7	2
Total	42	54	41	30	13

As shown in table 1, 42 out of 58 patients were operated up to for simple congenital heart diseases. They underwent 54 ablative procedures. 41 out of 54 (75.92%) procedures were successful and 13 procedures failed. 30 out of 41 patients (71.42%) had no recurrence in long term follow up after their successful ablative procedure. In 11 patients (26.83%), recurrence was observed after initially successful procedure.

We encountered 15 patients who developed atrial fluter after Os-ASD closure. All of them had isthmus dependent atrial flutter. They underwent 17 procedures. We had 5 procedural failures out of which two were successfully ablated in second attempt. Two patients lost to follow up after failure of the first ablation attempt. Second attempt using CARTO also failed in the remaining one patient who was reverted to sinus rhythm by overdrive pacing. He had severe left ventricular dysfunction with LVEF of 25% pre-procedure and was put on beta-blocker therapy. He was found to be mostly in sinus rhythm with occasional junction escape rhythm during follow up and LVEF normalized over the course.

We took 3 patients of atrial flutter following repair of Op-ASD. 2 out of three had procedural and long term success. The procedure failed in one patient, who was put on beta-blocker therapy and on follow up was found to be mostly in sinus rhythm with occasional junctional escape rhythm. She had undergone atrial septation with BD glenn 8yrs back for large Op-ASD and had tachycardia of 1-2months. CS couldn't be cannulated as it was on left side. We kept a decapolar catheter at SVC-RA junction and another decapolar catheter in upper RA like a Halo, however our reference EGM wasn't very stable. Isthmus ablation didn't terminate the flutter.

Out of 2 patients of post Os-ASD with PAPVC repair, both studied under CARTO, one had immediate procedural success and long term success. In the other patient, atrial flutter was of 2yr duration. Ablation couldn't be completed as the child became restless and reference patch got dislocated. She was continued on Sotalol with which she remained in sinus rhythm mostly with occasional junctional escape rhythm. She had severe LV dysfunction pre-procedure that became normal in follow up.

We had 3 patient post sinus venosus ASD and PAPVC repair. Procedural success could be achieved only in one of them. In one patient, the procedure couldn't be done as he was found to have interrupted IVC. CARTO mapping and ablation was planned from IJV route, however it got delayed due to financial constraints and the patient lost to follow up.

2 patients of ASD with VSD with PDA repair were treated with conventional mapping and ablation. One had procedural and long term success and the other had recurrence within 1month. This patient also had tachycardia induced severe LV dysfunction. His atrial flutter was successful ablated in second attempt with no subsequent recurrence. The LV function normalised during follow up.

2 patients of post TAPVC repair atrial flutter underwent four procedures. One of the patients had successful fist procedure with long term success. The other had recurrence the very next day after a seemingly successful ablation. The second procedure was unsuccessful and patient was cardioverted under anesthesia, however flutter recurred the same day. He subsequently underwent a third ablation attempt, which was successful and he remained in sinus rhythm in long term follow up. All these 4 procedures were done using conventional mapping and ablation.

2 patients of VSD closure underwent radiofrequency ablation, one conventional and the other under CARTO. Both had successful procedure and long term results.

One patient of cor-triatriatum and ASD repair underwent successful conventional ablation of isthmus dependant atrial flutter when he was 1.5yrs of age. Later at 8yrs of age, he had recurrence of tachycardia which was found to be left sided. Attempt to map and ablate failed as left atrium couldn't be entered through the ASD patch. He was continued on Sotalol therapy and because of frequent sinus bradycardia and juctional escape rhythm with sotalol, a permanent pacemaker was implanted for back-up pacing. He experiences short and rare episodes of tachycardia on medical management.

12 patients of TOF correction underwent 18 procedures. 6 patients had successful ablation in the first attempt. One patient underwent 3 ablations with all procedure being successful; however all were followed by recurrences 1month, 1 day and 1.5yr respectively. Another patient also underwent 3 ablation procedures. He had recurrences on the same day of the first 2 successful ablations. He had no recurrence after his third ablation. One patient of corrected TOF had severe RV dysfunction and huge RA. Conventional mapping revealed isthmus dependent atrial flutter. Several lines of burn were made across the isthmus, however flutter kept on recurring and the procedure had to be aborted. He expired of congestive heart failure few months later. In remaining 2 patients, we failed to induce tachycardia and performed empirical cavo-tricuspid ablation. They had no recurrence on diltiazem in follow up.

Table 2: Description of IART patients with complex congenital heart disease

S.N.	Surgery	Age	Sex	Surgery to RFA (Yrs)	Tachycardia duration (Yrs)	Attempts	IART no	Isthmus ablation	Success	Recurrence	Others
1	TOF with multiple VSD P/ Fontan	20	F	14	0.4	1CARTO	2	Yes	No	DCC→Sotalol + AAI	Normal
2	DORV with MPGA P/Fenestrated TCPC	23	M	12	0.3	1CARTO	2	Yes	Yes	No	45%-->45%
3	l-TGA with VSD P/ Fontan	32	F	10	1	1CARTO 1CARTO	1	Yes Yes	Yes Yes	1yr after 1st No after 2nd	
4	SS/ DC/ dTGA with VSD and PS P/ Fontan	17	M	13	0.8	1CARTO	2	Yes	Yes	No	30%-->55%
5	SA, RA isomerism, TAPVC, TGA, MPGA P/ BDG after failed Fontan	34	M	12	5	1CARTO 1CARTO 1CARTO	8	Yes Yes Yes	No No Yes	No On sotalol	30%-->30% Expired after cardiac catheterisation
6	lTGA with VSD P/ Fontan	18	M	7	2	1CARTO retrograde mapping	2	Yes	Yes	After 1yr	FU lost
7	dTGA with VSD and PS P/ Senning	13	F	9	3	1CARTO 1EnSite	1	Yes Yes	Yes Yes	After 2yrs and 6months→ On Amio + Flec	30%-->30% Lost FU
8	dTGA with ASD with PAPVC P/ Senning	16	F	7	0.7	1Conventional 1CARTO 1CARTO	3	Yes No	Yes No No→DCC	Yes after 2yr	Mostly jxn rhythm lost FU
9*	SS, DC, AV discordant, Pul atresia P/ Fontan	18	F	10	7	RA overdrive pacing	1	No	Yes	No	On Sotalol +Digoxin Normal LV
10	d/TGA with ASD P/ Senning	18	M	5	0.67	1Conventional 1 EnSite	2	No	Yes Yes	After 0.75yrs CHB after 2nd attempt	Doing well on PPI and betablocker

S.N.	Surgery	Age	Sex	Surgery to RFA (Yrs)	Tachycardia duration (Yrs)	Attempts	IART no	Isthmus ablation	Success	Recurrence	Others
11	dTGA with IVS P/ Senning	14	F	3	1	1CARTO	1	Yes	Yes	After 0.5 yr Overdrive→mostly junctional rhythm	On PPI with Sotalol
12	Ebstein aomaly P/TV replacement + BDG + atrial septectomy	10	M	6	2	1 Conventional isthmus ablation	IDAF	Partial line, child become restless	No Overdrive →NSR	No On Beta-blocker	50%-->50%
13*	dTGA with IVS P/ Senning	17	M	8	0.1	Overdrive Pacing-1 DCC-1	1	No	 No Yes	Not after DCC, mostly in junctional rhythm	Severe systemic RV dysfunction. No keen in getting treated
14	DILV, PS, MPGA P/ Fontan	14	M	7	3	1 Conventional, retrograde approach	IDAF	No	Yes	Recurred same day	On Sotalol, rare short episode
15	DORV with VSD and PS, MPGA P/ Fontan	37	M	19	1	1 CARTO 1 CARTO	4	Yes	Yes No	Yes after 4yrs No after 2nd ablation	LVEF 30%--> No recovery
16	SI with LC, DORV with VSD with PS and MPGA P/ Fontan	41	M	16	0.25	1CARTO	1	Yes	Yes	No	LV normal at baseline

* Not ablated, not included for outcome analysis.

Description of IART patients with complex congenital heart disease

16 out of 58 patients (27.58%) had been operated for complex congenital heart diseases as shown in table 2. 2 patients out of them had isthmus dependent atrial flutter and all the others had IART.

They underwent 22 ablation procedures. CARTO technology was used for 16 procedures (72.72%), 2 procedures were done using EnSite (9.09%) and 4 procedures (18.18%) were done using conventional mapping and ablation technique. Among 22 ablations, 16 procedures were successful (72.72%) out of which 9 (56.25%) had recurrence during follow up. Procedure failed in 6 patients (27.27%).

We had 9 Fontan patients and on one of them we performed overdrive pacing which restored his normal sinus rhythm. He had no recurrence thereafter on Sotalol and Digoxin. On remaining 8 patients, we performed 10 ablative procedures. Procedural success was highest in Fontan patients (80%) however recurrence rate was 50% even after successful ablation. All fontan patients had IART, except one who had isthmus dependent atrial atrial flutter. Conventional ablation was attempted in this patient via retrograde route, however child became restless and needed high doses of sedation following which induction of tachycardia became difficult and procedure had to be aborted. Subsequently he was put on sotalol and had rare short episodes of palpitations.

5 patients had undergone Sennings repair for TGA. On one patient, we tried overdrive pacing, failing which we gave DC shock that successfully aborted the tachycardia. She had severe systemic RV dysfunction with recurrent congestive heart failure and the family members were not keen on ablative therapy and then they lost to follow up. In the remaining 4 patients of post Senning IART, we performed 8 ablation procedures out of which 6 procedures were successful and 2 failed. 5 out of 6 patients had recurrences after successful IART ablation (83.33%). 2 patients ultimately needed sotalol and permanent pacemaker implantation. The outcome of IART ablation was worst in post Senning patient with the rate of recurrence of 83.33%.

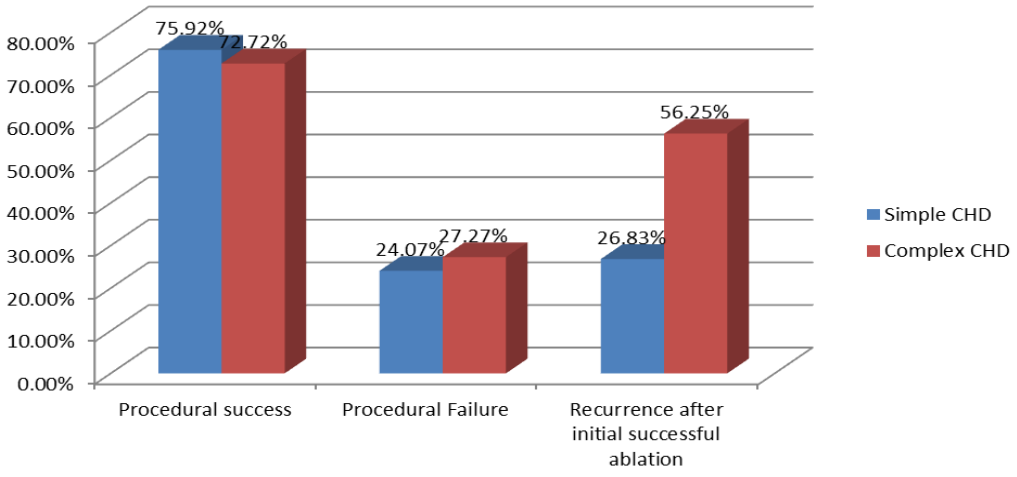
We had two post BD Glenn patients- one was a case of Ebstein's anomaly who had undergone tricuspid replacement and BD Glenn and the other was a Fontan failure patient. Conventional mapping revealed isthmus dependent atrial flutter. Entrainment lead to termination of flutter. Subsequently child became very restless and needed high doses of

sedation. However, thereafter tachycardia couldn't be induced and procedure had to be aborted as child failed to cooperate despite heavy sedation. He was put on beta-blocker and had no recurrence thereafter. The other one with failed Fontan had huge atrium with at least 8 different IART. CARTO mapping and ablation failed twice but third attempt was successful. Unfortunately he suffered a sudden cardiac death following cardiac catheterization which was done to evaluate his Glenn circuit 9 yrs after his successful IART ablation. The summary of outcome of IART in patients following complex congenital heart disease repair is shown in table 3.

Table 3: Outcome of IART ablation in complex congenital heart disease patients

Surgery done	Attempts	Procedural success	Procedure failed	Recurrence after successful ablation
Fontan (n=8)	10	8 (80%)	2 (20%)	4 (50%)
Senning (n=4)	8	6 (75%)	2 (25%)	5 (83.33%)
BD Glenn	4	2 (50%)	2 (50%)	0
Total	22	16 (72.72%)	6 (27.27%)	9 (56.25%)

Figure 1: Comparison of various outcome measures of IART ablation procedure in post-operative patients with simple congenital heart diseases (no of procedures- 42) versus complex congenital heart diseases (no of procedures- 22)



Discussion

We identified 42 patients operated for simple congenital heart diseases who were suspected to have atrial flutter/ IART. All of them had isthmus dependent atrial flutter, except three patients, who had non-isthmus dependent atrial flutter. The procedural success rate was about 76% in this group and the recurrence rate was about 27%. In majority of them, isthmus could be ablated and bidirectional blocks could be achieved.

We analysed the procedural details of patients in whom the initial procedure failed and their clinical outcome (Figure 2 and table 2). 2/3 of these patients (n=12) either had successful subsequent ablation or had stable sinus rhythm on medical management. 1 patient, who was a non-residential Indian couldn't extend her stay in India and got treated abroad. 4 patients lost to follow and 1 patient with intractable atrial flutter expired.

Figure 2: Clinical outcome after Procedural failure

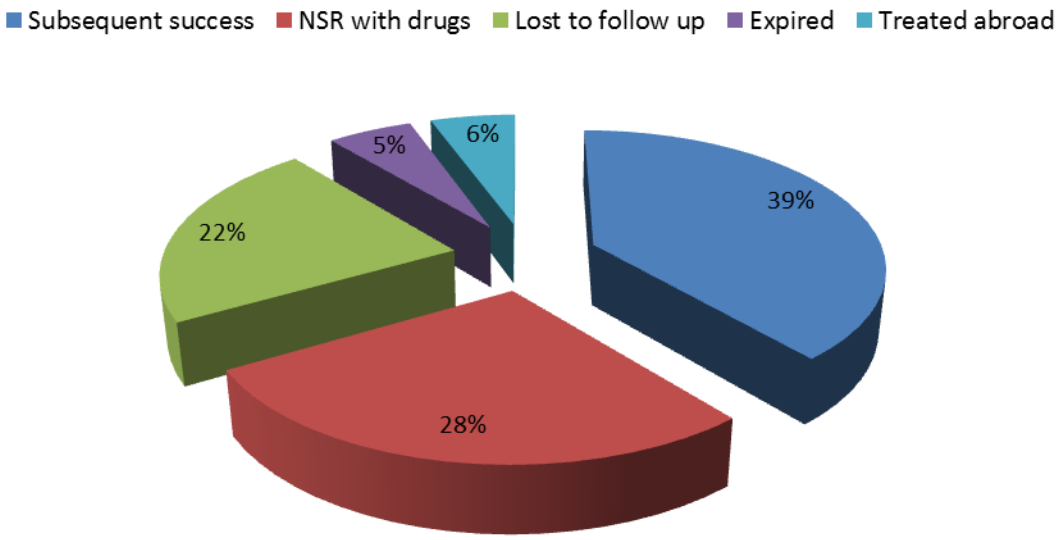


Table 4: Clinical course of patients whose ablation failed (Simple congenital heart disease)

Anatomical diagnosis	No of procedural failures	Clinical course and outcome
Os-ASD	5 Procedural failures	2 successfully ablated in second attempt 1 normal sinus rhythm on beta-blockers 2 lost to follow up
Op-ASD	1 Procedural failure Non-Isthmus dependent atrial flutter	Reason: CS couldn't be entered being left sided, High RA deca-polar gave unstable reference EGM NSR on beta-blocker
PAPVC	2 failure	1 Child became restless and reference patch got dislodged; NSR on Sotalol 1 Interrupted IVC→ procedure aborted; planned for ablation via SVC route under CARTO, but patient had financial issues, lost to follow up.
ASD/VSD PDA	1 procedural failure	Successful second ablation, no recurrence
TAPVC	2 initial attempts failed	CARTO advised but couldn't be performed due to financial reasons, 3rd conventional mapping and ablation→successful with no recurrence
Cor-triatriatum	1 Procedural failure	Tachycardia arising from LA, LA couldn't be entered because of atrial septal patch; mostly NSR on Sotalol
TOF	6 Procedural failures	2 patients- successful on 3rd attempt 1 patient – severe RV dysfunction with huge RA and CHF; kept recurring despite isthmus ablation 1 patient – got treated abroad 1 patient- sinus rhythm on beta-blocker 1 patient- lost to follow up.

No major complication was observed in any of the patients.

We concluded that most of the patients who develop atrial flutter after cardiac surgery for simple congenital heart disease have isthmus dependent atrial flutter. Majority of these patients benefit from radiofrequency ablation and have excellent success rates with no major complications.

Most of the patients who develop atrial tachyarrhythmia after surgical correction of complex congenital heart disease have IART on electrophysiological studies, 14 out of 16 in our study (87.5%) in our study. Only 2 out of 16 patients (12.5%) had isthmus dependent atrial flutter. 8 patients (50%) had more than 1 IART and hence 3 dimensional mapping systems, like CARTO or EnSite, are often required to map these complex IART circuits. We used 3 dimensional mapping for 18 out of 22 patients (81.81%); CARTO in 16 patients and EnSite in 2 patients. Procedural success rates are almost same as those of IDAF ablation in post-operative simple congenital heart disease, however the major problem observed in thic group was alarmingly high recurrence rates (56.25%). Recurrence was universal in patients with Senning's repair and about 50% on Fontan patients.

Table 5: Clinical course of patients whose ablation procedure failed or had recurrence (Complex congenital heart disease group)

Surgery	**Clinical course after procedural failure or recurrence**
Fontan patients	1.Failed 1st ablation→started on Sotalol + AAI: No recurrence 2.Recurrence after 1yr→Successful 2nd ablation: No recurrence 3.Recurrence after 1yr→Planned for 2nd ablation: Lost to follow up 4.Recurrence same day→started on Sotalol: Rare short episodes of palpitation 5.Recurrence after 4yrs→Successful 2nd ablation: No recurrence
BD Glenn (after failed Fontan takedown)	1.Failed 1st 2 attempts: Had severe ventricular dysfunction with huge atrium→ Successful 3rd ablation: No recurrence for 9yrs Sudden cardiac death after Cardiac catheterization done to evaluate Glenn failure (9yrs after ablation)
Senning's Repair	1. Recurrence after 2yrs and 6 months of successful ablations→Started on Amoidarone: severe systemic RV dysfunction+ CHF , lost to follow up. 2. Recurrence after yrs of successful ablation→2nd and 3rd attempts failed had severe systemic RV dysfunction: lost to follow up. 3. Recurrence after 9months of successful ablation→2nd ablation successful but developed CHB: Received DDDR, no recurrence

We had observed only one complication in our study which was complete heart block after second successful ablation of IART in Post Senning's repair patient. He was given a dual chamber pacemaker and remained asymptomatic and had no recurrence of IART.

Baker et al reported a success rate of 93% in their study of IART ablation in 14 patients (32). However, in their study only 10 were post-operative congenital heart disease. 2 of their patients had undergone surgical transection of accessory pathway, one patient was post mitral valve replacement patient and one was cardiac transplant recipient. The arrhythmia substrate after repair of congenital heart disease is logically different from patients who undergo other cardiac surgery. Outcome of same arrhythmia may be different in patient who had undergone congenital heart disease repair versus those who undergo surgery for other heart conditions, the most important reason being more extensive scarring and difficult to reach and ablate the desired spot due to septal patches and baffles in post CHD surgery patient. They reported a recurrence rate of 46% over a mean follow up of 7.5±5.3 months. We reported almost similar rates of recurrence but over much longer period of time.

Triedman et al reported similar success rates and recurrence rates of 73% and 53% respectively in their study of 45 patients (20). They used conventional mapping and ablation for all their patients. Kalman et al also reported success rates and recurrence rates, which were comparable to our findings (14). Anee et al reported higher procedural success rates of 94% in their study of 45 post-operative CHD patients (13). They described a new technique called sweeping Halo technique in their report. All these studies had short period of follow up which may lead to under estimation of recurrence rates.

The largest study of IART ablation in post cardiac surgery was reported by Triedman et al (39). They reported their experience in 134 patients with IART following surgical correction/ palliation of congenital heart diseases. They used both conventional and CARTO mapping system. They reported success rate and recurrence rates which were similar to our study, 66% and 42% respectively.

Peichl et al reported 100% procedural success rate in their study of 7 patients, all of complex congenital heart diseases. They used CARTO mapping and intra-cardiac echocardiography to aid in ablation. The rate of recurrence was much less in their patients; 28% over a period of 23 ± 13months follow up.

Table 6: Other similar studies and their main outcomes

Study	Study group	Success rates	Recurrence rate	Comment
1.Baker et al. 1996 (32)	n=14, procedures=17, 5- Complex CHD patients, 5- Simple CHD repair, 2-surgical transection of acc. pathway, 1-MVR+CABG, 1-cardiac transplant; conventional mapping and ablation.	93%	46%	Follow up 7.5±5.3months; 17 out of 31 tachycardia selectively ablated
2.Triedman et al 1997 (20)	n=45, procedures 55, 30-Complex CHD patients, 10-simple CHD patients, 5-non surgical patients (10%), conventional mapping and ablation	73%	53%	Follow up 17.4±11.3months
3.Kalman et al 1996 (14)	n=18; procedures 26, 9-Complex CHD patients, 9-Simple CHD patients, conventional mapping and ablation	80%	33%	Follow up 17± 8months
4.Anee et al. 2002 (13)	n=45; procedures 51. 19-simple CHD patients, 9 complex CHD patients,17-acquired heart disease, conventional mapping and ablation	94%	29%	Follow up 24months
5.Jospeh et al. 2001 (38)	n=16; procedures 24. 12-simple CHD patients, 4-complex CHD patients. Conventional mapping	90%	4.2%	Follow up 24months
6.Triedman et al. 2002 (39)	n=134; procedures, 47-simple CHD patients, 85-complex CHD patients, 2-not post- operative patients. Conventional and CARTO	66%	42%	Follow up 25 ± 11months
7. Peichl et al. 2008 (48)	n=7; all complex congenital heart diseases. CARTO and intracardiac echocardiography for mapping	100%	28%	Follow up 23 ± 13months

The main strength of our study was the number of patients. Only one similar published study has more number of patients than we had (39). Our follow up period was 4.76 ± 3.85yr which is much longer any other study that we found. Our limitation was unavailability of resources- most of our patients get treated from 'out-of-pocket' expenses and almost none of our patients are covered by insurance or any other funding group. Many of our patients couldn't afford 3 dimensional mapping and ablation, which could have improved the outcome.

CONCLUSION

We conclude that electrophysiological mapping and ablation of IART or atrial flutter is safe and effective in surgically corrected or palliated simple and complex congenital heart disease patients. A procedural success rate of about 75% can be expected in such patients. Failure rates are less common in patients with simple congenital heart diseases. The recurrence rates are high in patient who is surgically palliated for complex congenital heart diseases. Increasing experience with such patients and procedures is likely to help us in achieving better outcomes in future.

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ALL ABOUT FRACTIONAL FLOW RESERVE

Thesis submitted to the faculty of

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In partial fulfilment of the requirement

For the degree of

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(CARDIOLOGY)

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All About Fractional Flow Reserve

Multivessel disease is commonly encountered during coronary angiography. In the CASS registry, among patients with definite angina, 72% men and 53% women had multivessel disease (1). Intermediate lesions, defined as 50-70% diameter stenosis of an epicardial coronary artery, are also not infrequent. Determining the lesion responsible for the symptoms in a given patient is difficult. Careful selection of ischemia inducing stenosis is essential for deriving greatest benefit from revascularization. Restricting angioplasty to lesions associated with reversible ischemia is logical and improves symptoms. Angioplasty of non-ischemic lesion is of no proven benefit; not an evidence based medical practice, and is not just only unnecessarily expensive but may be potentially harmful (2). Fractional flow reserve is the gold standard for assessment of ischemia in the catheterization lab.

ANGIOGRAPHY IS A POOR DISCRIMINATOR

Although angiographic finding has always been regarded as the gold standard for diagnosis of CAD against which other diagnostic modalities are compared, it suffers several limitations. Histopathological studies have demonstrated that angiographic evidence of stenosis is usually not detected until the cross-sectional area of plaque approaches 40% to 50% of the total cross-sectional area of the vessel (3-5). Atherosclerosis in its initial stages, leads to positive re-modelling of the involved vascular segment; that is the external elastic lamina enlarges to accommodate the growing plaque. The plaque begins to encroach upon the lumen only after the expansive capacity of the external elastic lamina is exceeded. It is only then that an angiogram might reveal minimal luminal narrowing (6-7). In addition, significant intra- and inter-observer variability exists in the assessment of coronary stenosis (8). A recent study investigated the relationship between angiographic and functional severity of coronary artery stenosis and concluded that angiography is inaccurate in assessing the functional significance of coronary stenosis as shown in the figures given below (Figure 1 & 2) (9).

Figure 1: Number of functionally diseased vessels (0-, 1-, 2-, 0r 3-VD) as proportions of all patients with angiographic 3-VD (n=115)

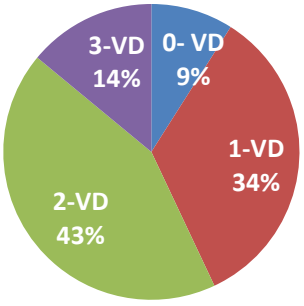
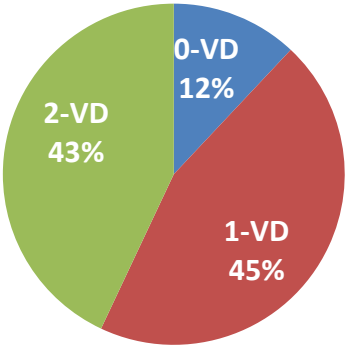


Figure 2: Number of functionally diseased vessels (0-, 1-, 2-) as proportions of all patients with angiographic 2-VD (n=394)



Unfortunately, non-invasive test of ischemia may not always be available and is performed in less than one-half of the patients undergoing elective angioplasty. Moreover, non-invasive tests for ischemia cannot identify the ischemia causing lesion in patients with multivessel disease. FFR is the only test that precisely identifies the ischemia producing lesions with highest degree of accuracy. Due to its unmatched spatial resolution, it not only identifies the ischemia producing artery in patients with multivessel disease, but also tells the exact location of functionally significant obstruction in a diffusely diseased artery. Deferring percutaneous intervention (PCI) in non-ischemic stenotic lesions as assessed by FFR is associated with annual rate of death or myocardial infarct of about 1%, which is lower than routine stenting (2). Hence, FFR is an indispensable tool for managing patients with multivessel disease and intermediate coronary lesions in the cardiac catheterization lab.

FFR: BASIC CONCEPTS

FFR is the ratio of maximal myocardial blood flow in the case of a diseased artery to maximum myocardial blood flow if that same artery were to be normal. Understandably, FFR in a normal coronary artery is 1. FFR of ≤ 0.80 means maximum myocardial blood flow reaches only 80% of its normal value and this cut-off is used to define physiologically significant stenosis. Similarly, FFR of $\geq$ 0.80 means maximum myocardial blood flow is more than 80% of normal, and the stenosis is physiologically insignificant. Although practically, FFR involves measuring pressures proximal and distal to a stenotic lesion, it actually reflects flow, as explained in box 1.

FFR not only differentiates functionally significant lesions from non-significant ones, it also reflects the extent of increase in myocardial blood flow that can be achieved if the lesion gets stented as depicted in figure 3.

Box 1 Simplified theoretical explanation illustrating how a ratio of two flows can be derived from a ratio of two pressures provided these pressures are recorded during maximum hyperaemia (11)

1. FFR is the ratio of hyperaemic myocardial flow in the stenotic territory (Q_s^{max}) to normal hyperaemic myocardial flow (Q_N^{max})

$$FFR = \frac{Qs\ max}{QN\ max}$$ (Empirical definition)

2. Since the flow (Q) is the ratio of pressure (P) difference across the coronary system divided by its resistance (R)

$$FFR = \frac{(Pd-Pv)/Rs\ max}{(Pa-Pv)/RN\ max}$$

3. Since the measurements are obtained under maximum hyperaemia, resistances are minimal and therefore equal, and thus they cancel out:

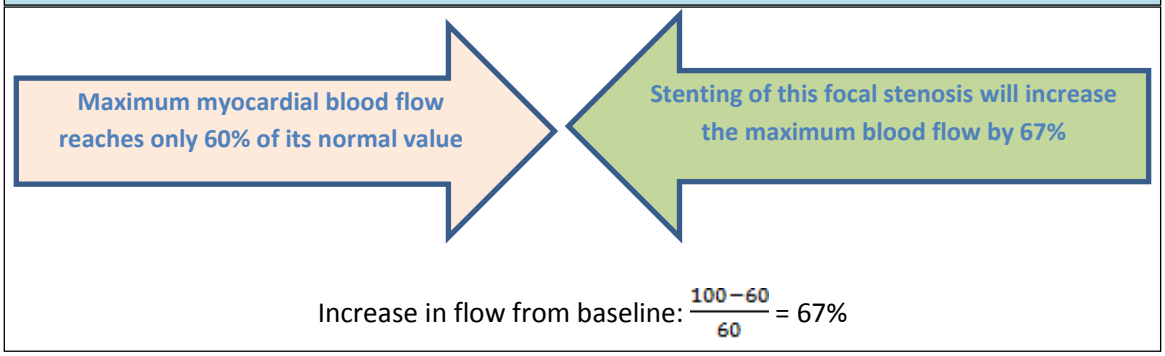
$$FFR = \frac{(Pd-Pv)}{(Pa-Pv)}$$

4. In addition Pv is negligible as compared to Pa or Pd, therefore

$$FFR = \frac{Pd}{Pa}$$

Pa, aortic pressure; Pd, distal coronary pressure; Pv, venous pressure; QSmax, hyperaemic flow in stenotic territory; QNmax, hyperaemic flow in normal territory; RSmax, hyperemic resistance in stenotic territory; RNmax, hyperaemic resistance in normal territory

Figure 3: FFR is 0.60, what does that mean?



FFR: PRACTICAL ASPECTS

Catheters

Guiding catheter is preferred because of its larger lumen which not only minimizes the resistance to wire manipulation but also provides more accurate pressure recording. Another benefit of using a guiding catheter is the ability to perform ad hoc percutaneous intervention (PCI), if a significant lesion is encountered.

Wires

Two major types of wires are commercially available for measurement of intracoronary pressures, namely the PressureWire (RadiMedical Systems Inc, Sweden), and the Volcano Wavewire (Volcano Inc, California, USA). The pressure sensor is located at the junction between the 3cm long radiopaque tip of the wire and the remainder of the wire. Current generation pressure wires are 0.014 inch wires, and have handling characteristics similar to most of the work-horse wires. The recently introduced wireless FFR system (PressureWire Aeris, St Jude Medical) makes the procedure less cumbersome as compared to the traditional system.

Anticoagulation

The anticoagulation protocol need not be different from standard practices adopted during any PCI. Unfractionated heparin adjusted to the body weight and with the target of activated clotting time of around 250s is generally adequate.

Hyperaemic stimuli

Achieving maximum vasodilatation of the epicardial and microvasculature is the most essential part for accurate FFR assessment, because it is only at the maximum hyperaemia, at which coronary pressure-flow relationship becomes linear (as explained before in box 1). The lack of a maximum hyperaemic response produces a lower pressure gradient across the lesion and therefore underestimates its severity (12).

Box 2: Drugs used to achieve maximum hyperaemia during FFR assessment

Epicardial vasodilation

Isosorbide dinitrate at least 200mcg ic bolus, at least 30s before the first measurement

Microvascular vasodilation

Adenosine ic	50mcg ic bolus
Papaverine ic	8mg in RCA,12mg in LCA
Nitroprusside ic	0.6mcg/kg in bolus
Adenosine	140mcg/kg/min (via femoral vein)

ic- intra-coronary; RCA – right coronary artery; LCA-left coronary artery

A bolus of 200mcg intracoronary nitroglycerine often abolishes epicardial vasoconstriction. It should be given at least 30s before the first measurement. Adenosine, either as intracoronary boluses or as continuous systemic infusion via femoral vein, is often the most preferred drug to achieve microvascular vasodilation, although intracoronary nitroprusside and intracoronary papaverine are other alternatives (13-15). One problem of giving intracoronary boluses of any vasodilator is the artefact that it produces in FFR tracings.

In our opinion, intravenous adenosine infusion at 140mcg/kg/min administered via central vein generally provides a constant and reliable maximum hyperaemia, due to which the operator gets more time to optimally position the catheter and the pressure-wire.

FFR: OPTIMIZATION OF SYSTEM FOR PRESSURE MEASUREMENTS

Before any hemodynamic study performed in a cardiac catheterization lab, the pressure recording system must be checked for internal accuracy to avoid erroneous results, and same rule applies for FFR assessment also. During FFR assessment, two different pressures are measured simultaneously – the pressure proximal to the lesion being interrogated that is the central aortic pressure, and the pressure distal to the lesion of interest. The central aortic pressure is the pressure transmitted to the transducer from the tip of the guiding catheter. Air must be purged out thoroughly from the pressure monitoring system before it is connected the guide catheter. Contrast medium must be flushed out repeatedly from the catheter because it damps the pressure traces. Zeroing of the catheter tubing system and the pressure wire sensor must be done before the procedure, and may be repeated whenever the consistency of the two pressure recordings is in doubt (Box 3).

Box 3: Vital steps before starting FFR assessment

1. Purging air from the system.
2. Zeroing of the catheter tubing system and pressure wire sensor.
3. Frequent flushing of contrast medium from catheter.
4. Equalization of the two pressures in vivo (Figure 4).
5. Disengagement of the guiding catheter from ostium to prevent damping of proximal pressures.
6. Repeating the above manoeuvres whenever its accuracy is in doubt.

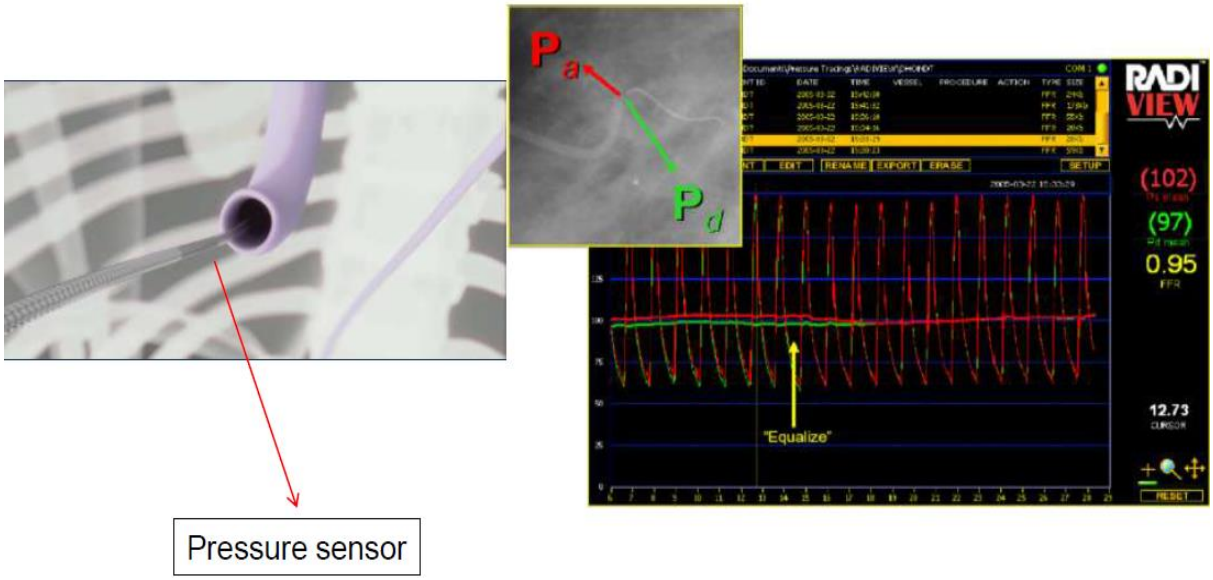


Figure 4: In vivo equalization of pressures of catheter tubing system and pressure wire sensor.

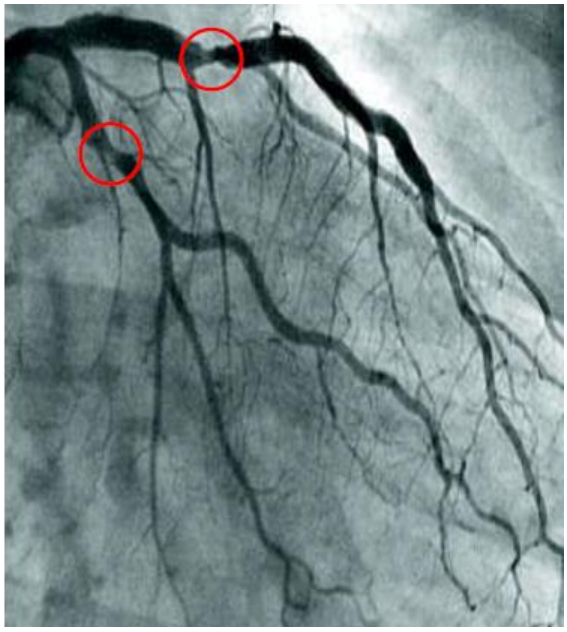
Not infrequently, the proximal pressure may get damped due to inadvertent deep engagement of guide catheter, ostial disease or ostial spasm. This may lead to underestimation of functional severity of a lesion. This problem can be identified by careful observation of pressure wave-forms and can easily be corrected by unhooking the guide catheter.

FFR: APPLICATION IN VARIOUS CONDITIONS

Intermediate lesions

One of the most important indications of FFR is to assess the functional significance of an intermediate lesion. Five-year outcome after deferral of PCI of an intermediate coronary stenosis based on FFR $\geq$ 0.75 is excellent. The risk of cardiac death or myocardial infarction related to this stenosis is < 1% per year and decreased by stenting. The percentage of patients free from chest pain at follow is also not different between the patients in whom PCI is not performed on the basis of FFR as compared to those on whom PCI is performed (2). Hence, there is absolutely no benefit of PCI of intermediate lesions in which FFR is $\geq$ 0.75.

Figure 5: Should I treat these intermediate lesions?



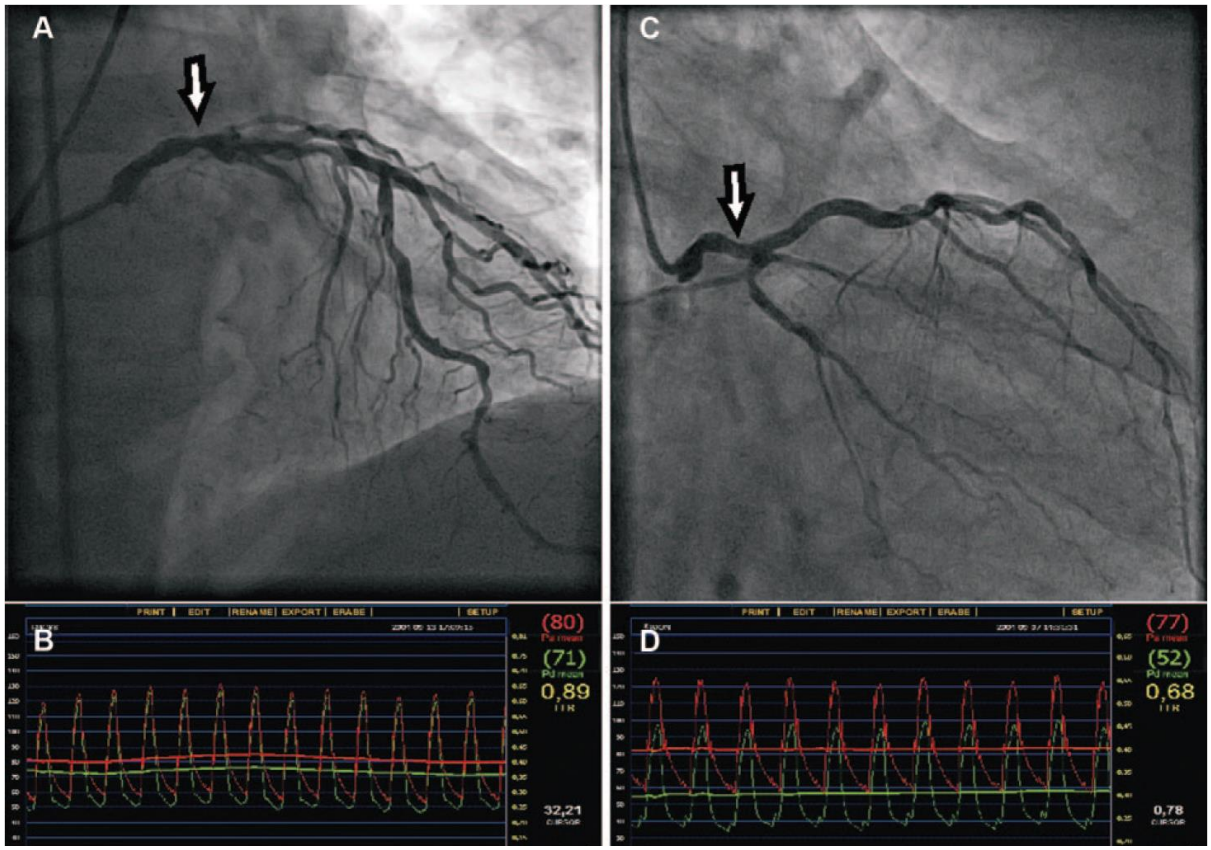


Figure 6: Examples of discordance between the angiographic appearance and FFR values of LMCA lesions. A, An angiographically tight LM stenosis with an FFR value of 0.89 (B). C, An angiographically mild LM stenosis with an FFR value of 0.68 (D) (17)

Left main disease

Assessment of severity of left main coronary artery (LMCA) disease can be one of the most challenging lesion subset for angiographers (Figure 6). LMCA can be short and diffusely diseased with no reference disease free reference segment to compare and quantify the lesion severity. The proximal portion of LMCA often gets obscured by contrast filled aortic sinuses, making its assessment even more difficult. A FFR of > 0.75 is associated with excellent 3 –year outcome and freedom from major adverse cardiovascular events (16). In a study of 213 patients with angiographically equivocal LMCA disease, patients with FFR ≥ 0.80 were treated medically and those with FFR < 0.80 were treated with coronary artery bypass grafting. The 5-year survival estimates were 89.8% in the nonsurgical group (n=138) and 85.4% in the surgical group (n=75, p=0.48) (17). In another study comprising of fifty-one patients with intermediate left main coronary artery disease, 27 patients (53%) received coronary artery bypass surgery and remaining 24 patients were treated non-surgically. The event free survival after 4 years of follow up was 66% in the surgical group and 69% in the nonsurgical group (18).

The technique of FFR measurement for LMCA disease is no different; however, care must be taken to retract the guide catheter from the ostium of LMCA before pressure measurements are taken.

Bifurcation lesions

Angiographic assessment of the severity of bifurcation lesions is hampered by the inherent limitations of angiography, especially overlap of adjacent vessels, angulation, and foreshortening of the origin of the side branch (19). Physiologic determination of the hemodynamic significance of bifurcation lesions can also be reliably addressed with FFR. Separate FFR analysis of each branch can be performed to assess the hemodynamic significance of each stenosis. Koo et al. evaluated the feasibility and safety of physiological assessment of jailed side branches with FFR in 97 patients (20). The study demonstrated that no lesion with <75% stenosis by quantitative coronary angiography (QCA) had FFR < 0.75 and among 73 lesions with >75%stenosis only 20 were functionally significant. Ziaee et al showed that 80% of patients with >70% stenosis of the side branch had FFR > 0.75 in their cohort (19). Hence, most of the lesions involving the jailed side branch might not have functional significance and do not require revascularization. The use of FFR in the assessment of bifurcation lesions might prevent unnecessary interventions in lesions that are not functionally restrictive (Figure 7)

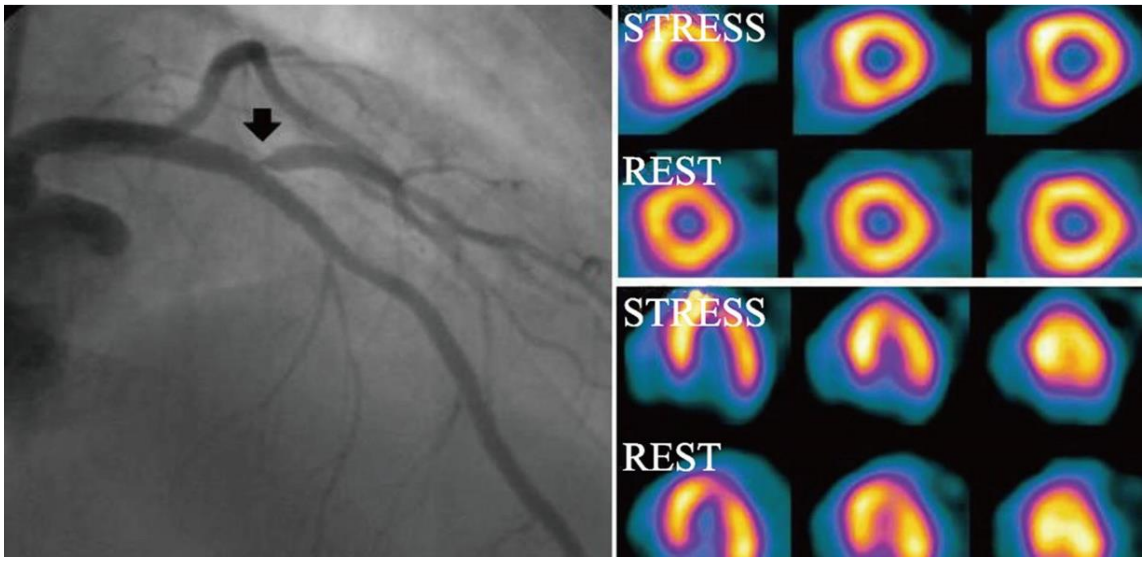


Figure 7: Mismatch between angiographic severity and functional significance. Despite the tight angiographic stenosis, no perfusion defect was found on myocardial SPECT scan. FFR at this jailed diagonal branch was o.81. (Ref 21)

FFR can be easily measured in bifurcation lesions both before and after the intervention. However, when FFR if a side branch (SB) lesion is measured, the influence of proximal and distal stenotic lesions should be taken in to account. If a significant stenosis exists at the proximal main branch (MB), SB FFR overestimates the functional severity of the SB lesion. On the contrary, if a significant stenosis exists distal to a SB ostial lesion, FFR underestimates the lesion severity by submaximal flow through the SB ostial lesion.

Sequential lesions in the same artery

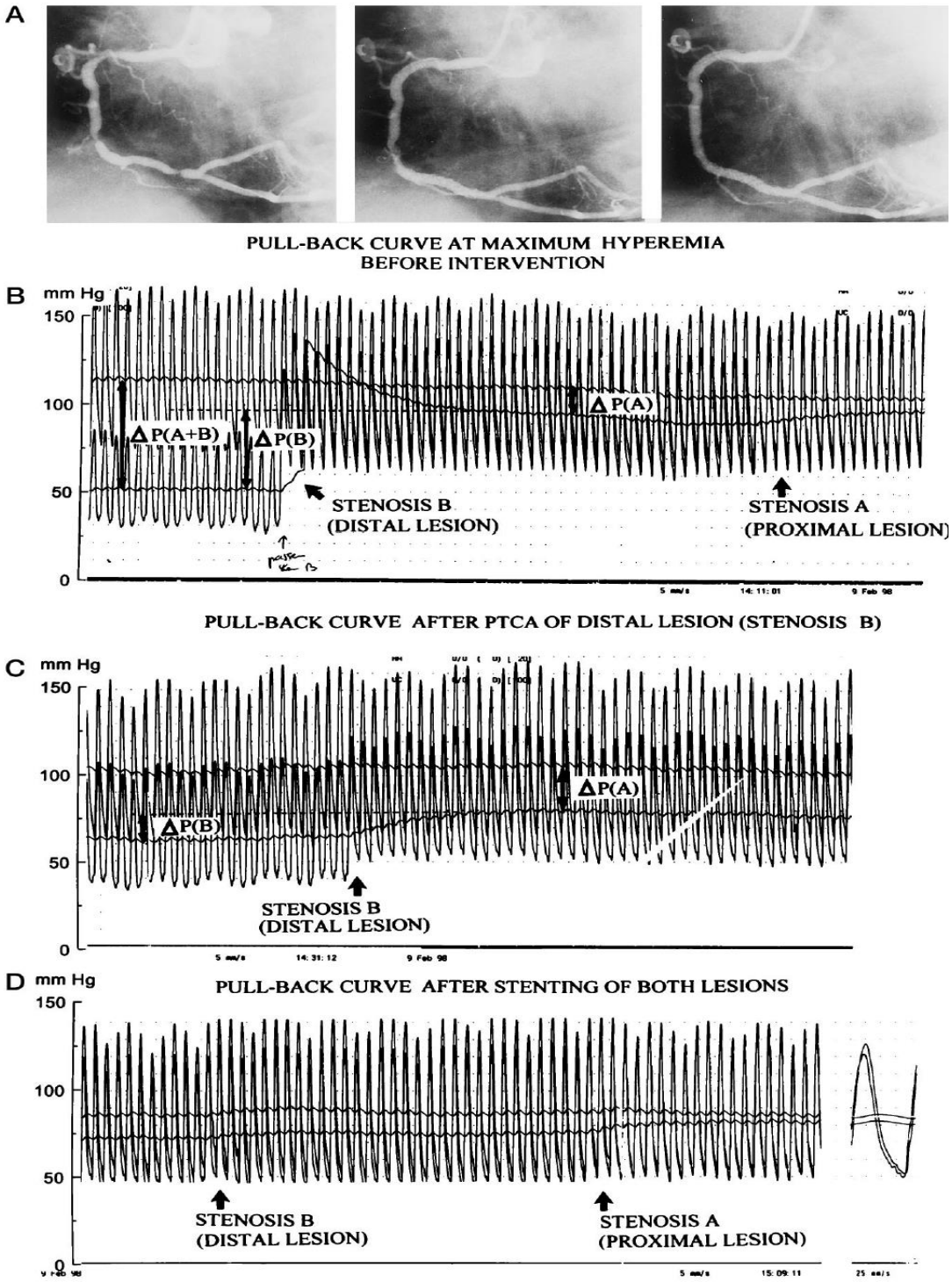


Figure 8: Increase of hyperaemic gradient across a proximal stenosis. Panel A shows the RCA with 2 severe stenoses in the mid and distal part (stenoses A and B) before PTCA (left), after stenting of the distal lesion (middle) and after stenting of both lesions (right). B, The pressure wire is positioned distal to stenosis B and pulled back slowly to the ostium of the RCA during maximum hyperaemia. A large pressure drop, ΔP (B) is observed when the sensor crosses the distal stenosis, and a much smaller pressure drop, ΔP (A), is present across stenosis A, which suggests that stenosis A is not functionally severe. After PTCA of stenosis B, the blood flow through artery has increased unmasking the true severity of stenosis A. Panel D shows the final pull-back curve after stenting both lesions. (Reference 24)

The hemodynamic effect of multiple sequential lesions in the same coronary artery is very complex and cannot be adequately assessed by visual interpretation on the coronary angiogram (22). However, coronary pressure measurements made using a pressure guidewire can uniquely determine the separate hemodynamic effects of the individual stenosis in sequence. The FFR can theoretically be calculated for each stenosis individually but remains academic, as the coronary wedge pressure (during coronary balloon occlusion) is needed to perform these calculations (23, 24). This is neither practical nor easy to perform and therefore of little use in the catheterisation laboratory. Practically, a pull-back manoeuvre under maximum hyperaemia is the only way to appreciate the exact location and physiological significance of sequential stenosis. The stenosis with the largest gradient can be treated first, and the FFR can be re-measured for the remaining stenosis to determine the need for further treatment as shown in figure 8 above.

Generally, distal lesions have more effect on assessment of proximal lesions and reverse is less significant. It is also said that when the distance between 2 lesions is >6 times the vessel diameter, the stenosis generally behave independently (25). For quick practical tips, refer to box 4.

Box 4: Practical tips for using fractional flow reserve in sequential stenoses

1. Insert a pressure guidewire past the most distal stenosis.
2. Measure the FFR of all stenosis together under maximum hyperaemia.
3. If FFR is insignificant (FFR > 0.80), defer revascularization in the serial stenotic lesions and treat with optimal medical therapy.
4. If FFR is significant FFR ≤ 0.80, perform a pressure pullback tracing under maximum hyperaemia.
5. Perform PCI in the lesion with the largest pressure step-up first. Do not miss anatomical considerations around the target lesion.
6. Repeat the decision making process for each stenosis in the series.

Diffuse disease and long lesions

Considerations similar to those for patients with several discrete stenoses in 1 coronary artery can be applied to patients with diffuse diseases and long lesions. The only way to demonstrate the haemodynamic impact of diffuse disease is to perform a careful pull-back manoeuvre of the pressure sensor under steady state maximal hyperaemia. The location of a focal pressure drop superimposed on the diffuse disease can be identified as an appropriate location for treatment. In some cases, the gradual decline of pressure along the vessel occurs over a very long segment, such that interventional treatment is not possible. Optimal medical therapy or bypass surgery can be offered to such patients.

Previous myocardial infarct

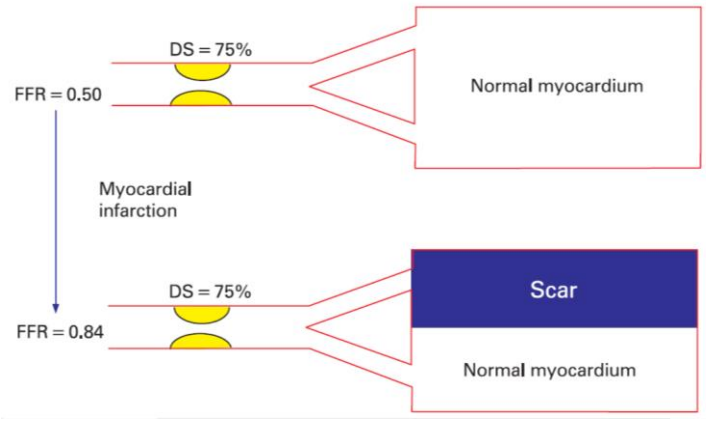


Figure 9: Relationship between fractional flow reserve and myocardial mass

After a myocardial infarction, previously viable tissue is partially replaced by scar tissue. Therefore, the total mass of functional myocardium supplied by a given stenosis in an infarct related artery will tend to decrease. The reduced flow in the diseased infarct related artery still may be sufficient for the remaining viable myocardium, which is reflected by FFR. Figure 9 illustrates that mere presence of stenotic segment doesn't necessarily reflect its functional significance.

Conversely FFR also takes collateral blood supply into account. Maximum blood flow in a given coronary artery is proportional to the mass of viable myocardium supplied by that artery. Any increase in the mass of myocardium supplied, for example as a result of development of collateral branches to an alternative myocardial territory, will increase blood flow in the artery giving rise to the collaterals. Because the flow in the artery supply collaterals to alternative territory increases, pressure gradient across any lesion in the feeding artery will get overestimated. Re-establishing normal blood flow in that ischemic territory will attenuate the FFR of the lesion in the initial feeding artery, and represent its true functional significance as shown in figure 10 (26).

Acute coronary syndromes

Although FFR provides critical physiological assessment of coronary artery stenosis in various conditions, its utility in patients with acute coronary syndrome (ACS) is limited. Severe microvascular dysfunction that occurs in ACS causes FFR to greatly underestimate the pressure gradient across potentially flow limiting lesion (27).

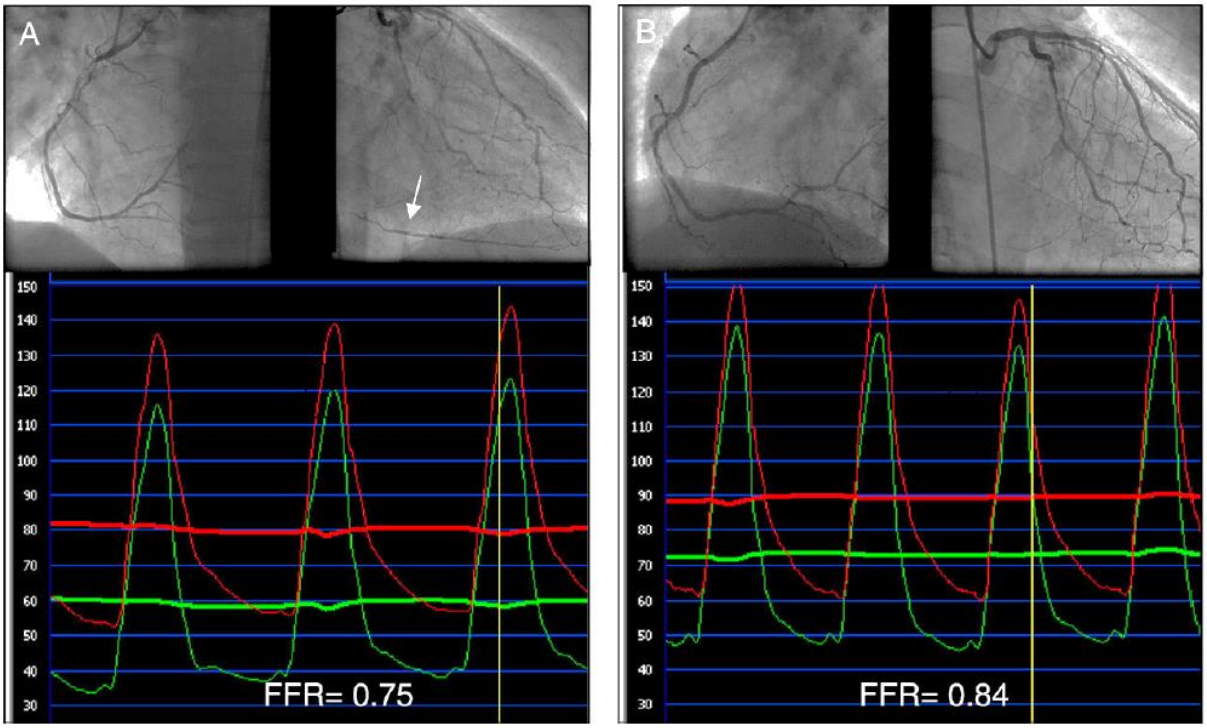


Figure10. Example of the influence of collaterals on FFR measurements in 77yr old man with critical stenosis in proximal RCA and collaterals supplied by the left coronary artery. Proximal (red trace) and distal (green trace) pressure traces in the LAD artery and corresponding angiographic images before (Panel A) and after (Panel B) successful PCI to the RCA. When antegrade flow was restored in the RCA, the LAD had no longer to supply blood to the territory of the RCA. The hyperaemic flow in the LAD was lower than before nd the FFR increased form 0.75 to 0.84. This illustrates the relationship between FFR and the myocardial mass supplied by the artery; the larger the myocardial mass, the greater the hyperaemic flow, and the lower the FFR for a given stenosis.

Coronary artery bypass grafting

FFR has important role for assessing functional severity of lesions before sending a patient for coronary artery bypass surgery (CABG) and well as for assessment of native vessel and grafts for patients who presents with symptoms of ischemia post CABG.

Bypassing non-critically diseased coronary arteries leads to a high rate of disease progression in the grafted native artery and is associated with a high rate of graft atresia (28.29). A prospective study of 153 patients with 525 stenoses accepted for CABG revealed significantly lower arterial and venous graft patency if put on native vessels with functionally insignificant stenosis as compared to those put on vessels with functionally significant disease, at 1 year (30, Figure 11). FFR can be used to objectively assess the functional severity of CAD before subjecting any patients to the morbidities and mortalities associated with CABG.

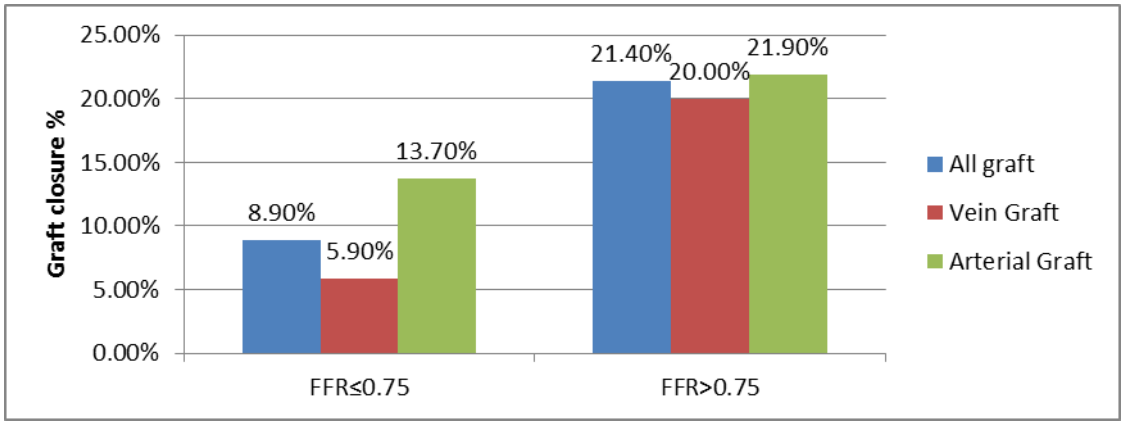


Figure 11: Graft closure rate at 1yr for functionally non-significant versus significant native vessel disease

FFR also has important role in deciding therapy in post CABG who present with symptoms suggestive of ischemia. If the native artery is occluded, pressure wire is passed distal to the bypass graft and FFR interpretation is done as in a regular routine case (Figure 12, panel A). If FFR is ≤ 0.80, one may decide to do PCI of native vessel or graft, whichever is feasible.

If both native vessel and graft are patent, the pressure wire is advanced distal to the graft and FFR is estimated after achieving maximum hyperaemia (Figure 12, Panel B). If FFR is > 0.80, no intervention is needed. However if FFR is ≤ 0.80, both native and bypass graft are significantly diseased and PCI of native vessel or graft can be planned according to the feasibility.

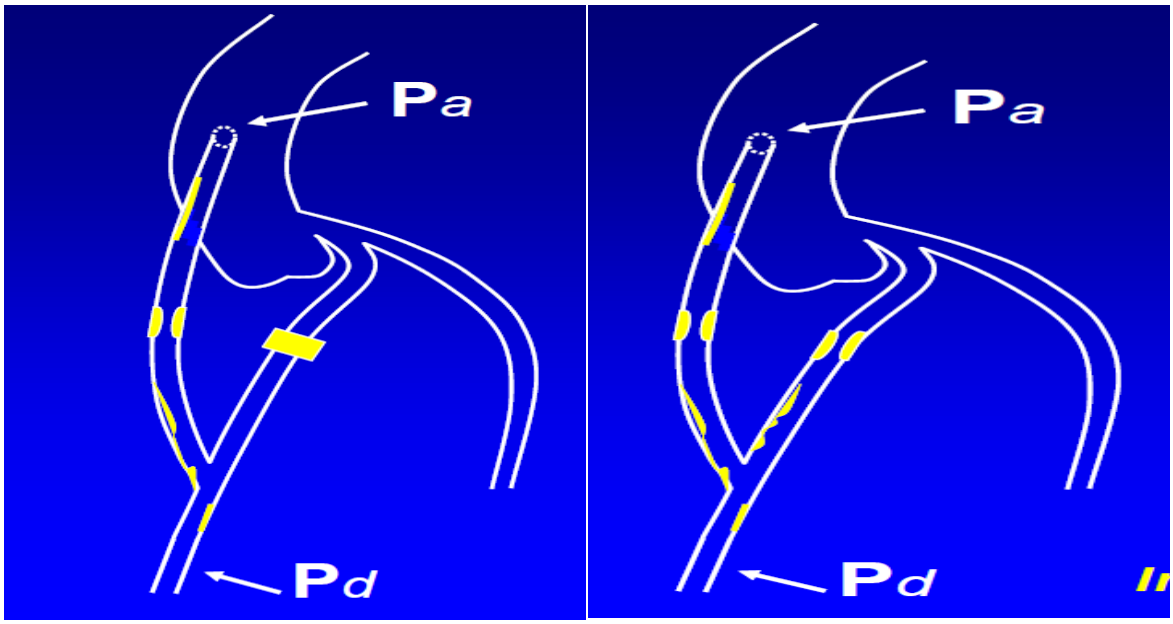


Figure 12.Panel A. Native artery occluded: Interpretation done as in regular routine case. **Panel B.** Both vessels patent, no intervention needed if FFR > 0.80; if FFR ≤ intervene in native artery or graft whichever is feasible.

TRICKS TO ENSURE ACCURACY

The functional significance of a lesion can be reconfirmed by "Pull back and Advance" manoeuvre which not only re-confirms the functional severity of the lesion but also gives detailed spatial information about distribution of lesions along the complete artery, as shown in figure 13, panel A. Similarly, check for "signal drift" must also be performed periodically to ensure consistent pressure measurement of the catheter and the pressure wire, as shown in figure 13, panel B. A signal drift > 5mmHg mandates repeat measurement of the last measurement.

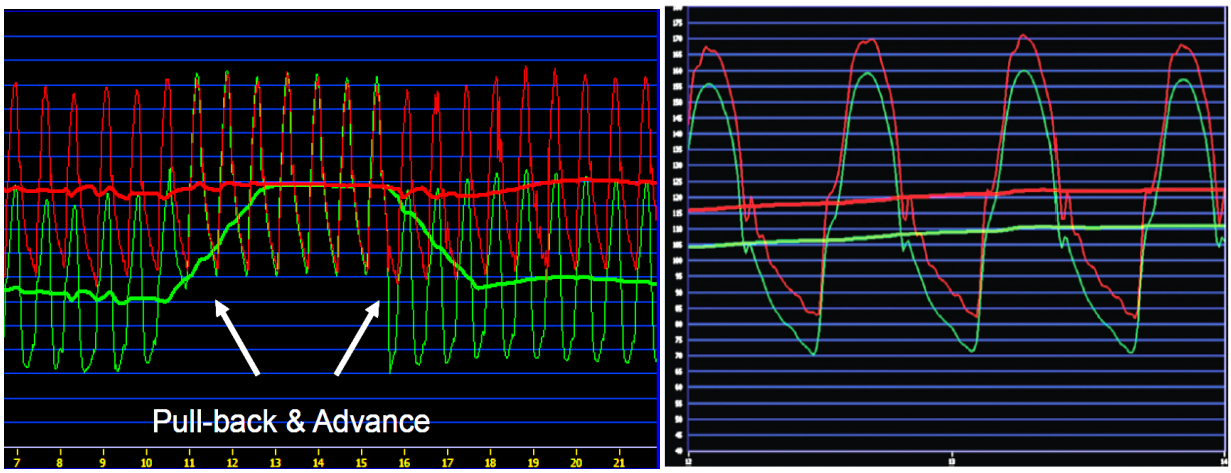


Figure 13, Panel A : "Pull Back and Advance Manoeuvre" for detailed spatial information about distribution of lesions, **Panel B:** Signal drift during FFR measurement.

COMMON TRAPS AND PITFALLS

FFR never lies, if its technical aspects are understood. The following segment describes common pitfalls which if unrecognized can lead to erroneous results (Figures 14-17).

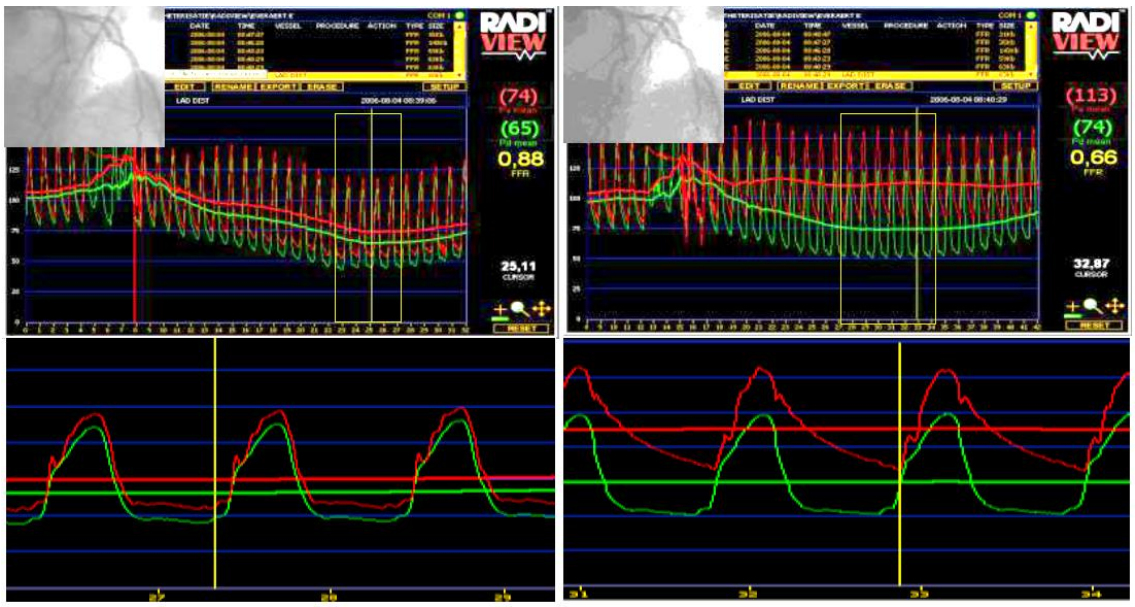


Figure 14: Presence of the guiding catheter in the ostium. **Trick→** Disengage the guiding from the ostium

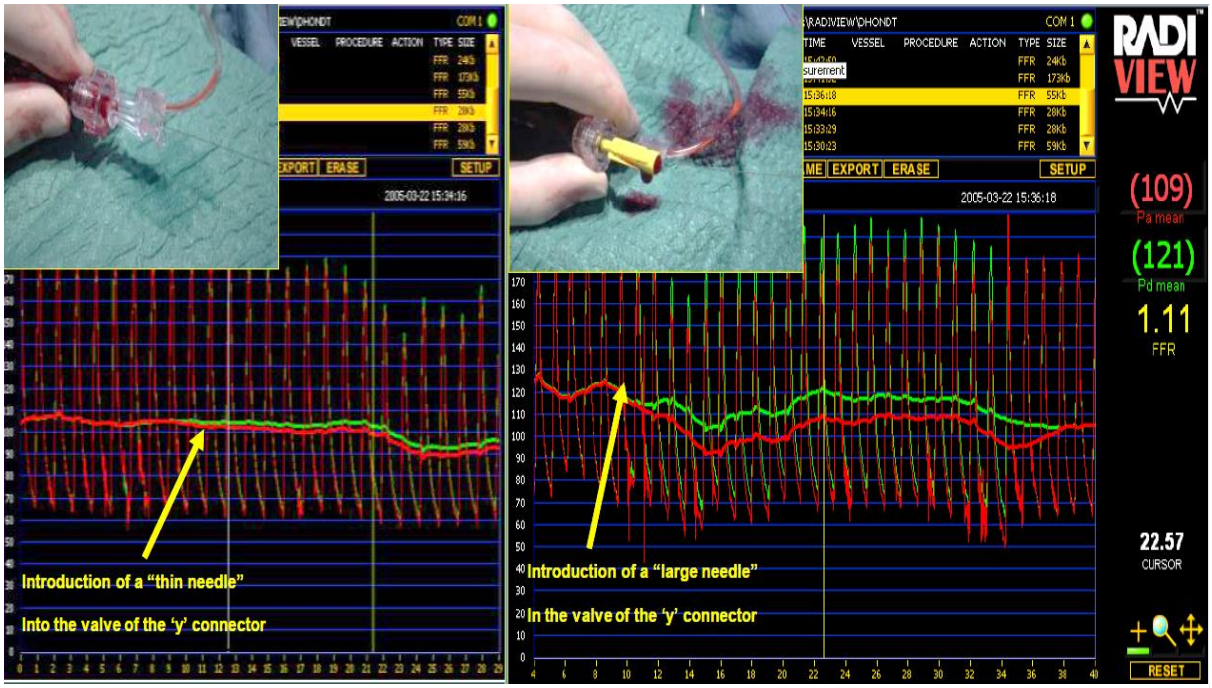


Figure 15: Effect of large introducing needle**. Trick**- Recognise the artefact, distal pressure can never be higher than proximal pressure. Use the recommended introducing needle.

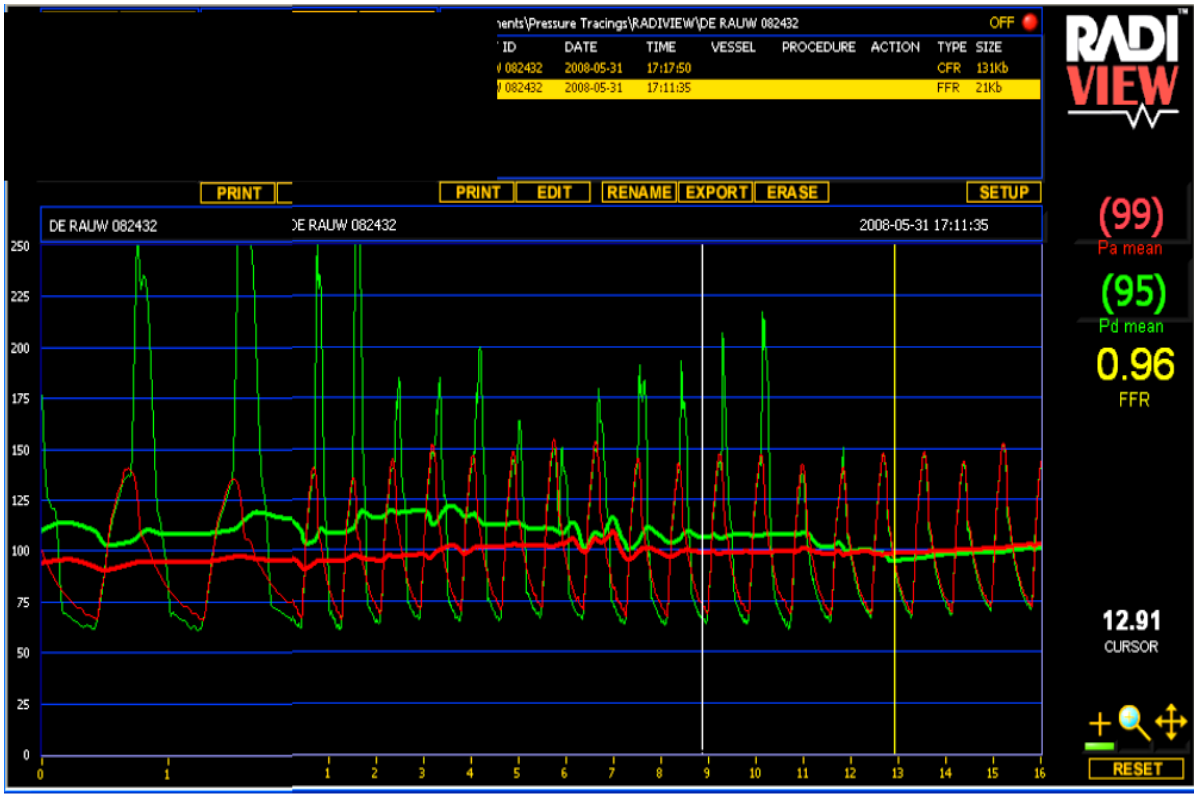


Figure 16: Wire whipping effect as a result of oscillation of pressurewire within the coronary artery. **Trick-** Advance or pull the wire.

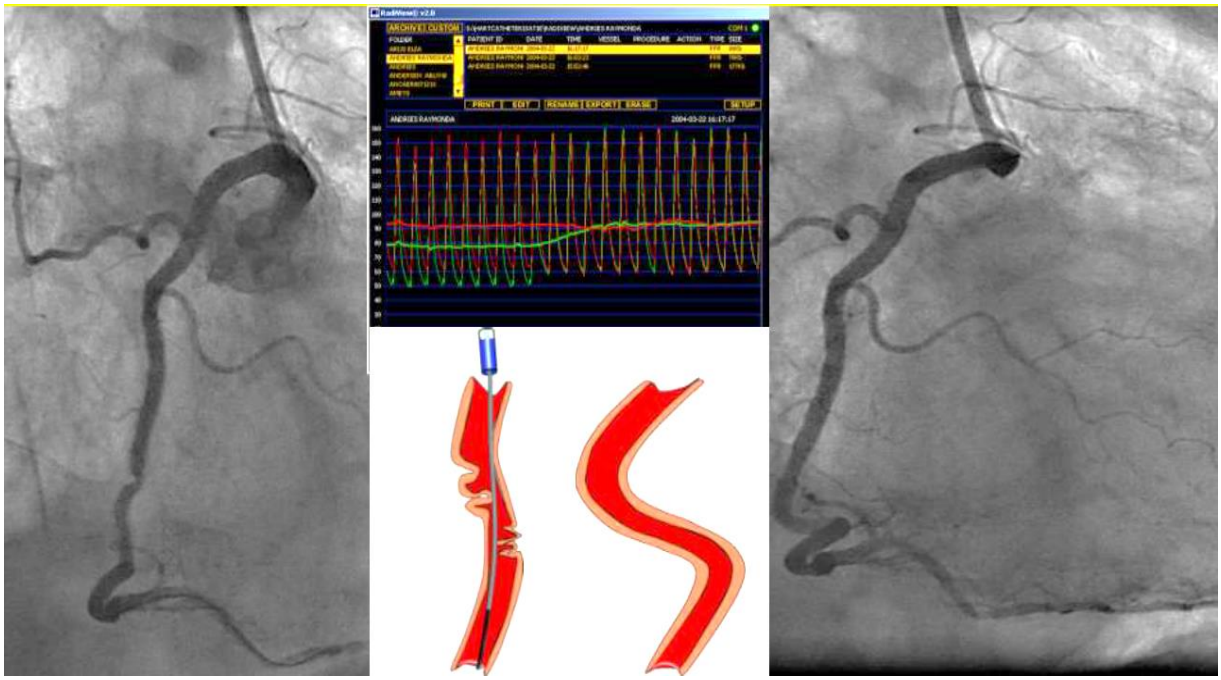


Figure 17: Accordion effect. Trick- Recognize the artefact. Pull back the wire.

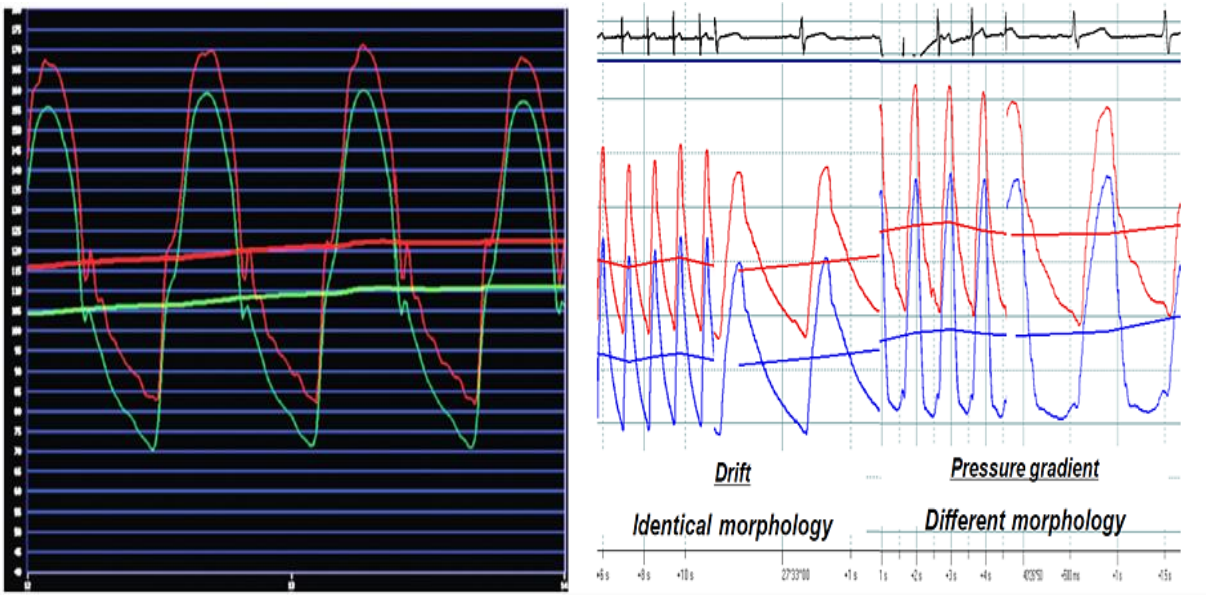


Figure 18: Pressure drift. **Trick -** Check for it periodically. Re-equalize the pressures.

Figure 19: Flush artefact: Intracoronary bolus of adenosine or papaverine produces this artefact. Analyzer selects the artefact and calculates FFR as 0.59, when it is 0.83 in reality**. Trick –** Identify the artefact, use of adenosine infusion via central vein abolishes this problem.

Conflict of Interest

The authors do not have any conflict of interest.

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MEASUREMENT OF QT INTERVAL: REVISITED

Thesis submitted to the faculty of

All India Institute of Medical Sciences, New Delhi

In partial fulfilment of the requirement

For the degree of

DOCTORATE OF MEDICINE

(CARDIOLOGY)

AUGUST, 2014

AIIMS, NEW DELHI **DR PRASHANT SHAH**

Measurement of QT Interval: Revisited

The QT interval on the electrocardiogram (ECG) has gained clinical importance, primarily because any perturbation of this measure beyond its narrow safety limits is associated with an increased risk for life-threatening ventricular arrhythmias and sudden cardiac death. It is one of the most important parameter checked rigorously in every patient visiting an arrhythmia clinic. However, a very small fraction of patient actually gets referred to arrhythmia clinics, and the abnormalities of QT interval can easily be missed at the first point of medical care. The objective of this review is to sensitize the medical professionals in various medical fields to the abnormalities of QT interval. We will focus on the methods for clinically relevant visual and manual assessments of QT interval durations in various conditions from ECG, which can be utilized in day-to-day medical practice.

The Cardiac Cycle

Cardiac muscles are different from skeletal muscle as they do not need any external stimuli to contract. Each beat is initiated by the spontaneous depolarization of pacemaker cells in the sino-atrial (SA) node. These cells trigger the adjacent atrial cells by direct atrial contact and a wave of depolarization spreads out over the atria, eventually exciting the atrio-ventricular (AV) node. Contraction of the atria precedes that of the ventricles, forcing extra blood into the ventricles and eliciting the Starling response. The electrical signal form AV node is carried to the ventricles by a specialized bundle of conducting tissue (the bundle of His) which divides into several bundle branches within the interventricular system. The conducting tissues are derived from modified cardiac muscle cells, and are known as Purkinje fibres. They have reduced content of contractile proteins, and a much higher conduction velocity, than ordinary cardiomyocytes. The conducting bundles divide repeatedly as they spread out through the myocardium to coordinate electrical and contractile activity across the heart.

In response to the propagating electrical wave-front in the cardiac conducting tissues, each myocardium undergoes the four phases of action potential, brought about by orchestrated activity of various ion channels, which causes cardiac contraction and relaxation as illustrated in figure 1.

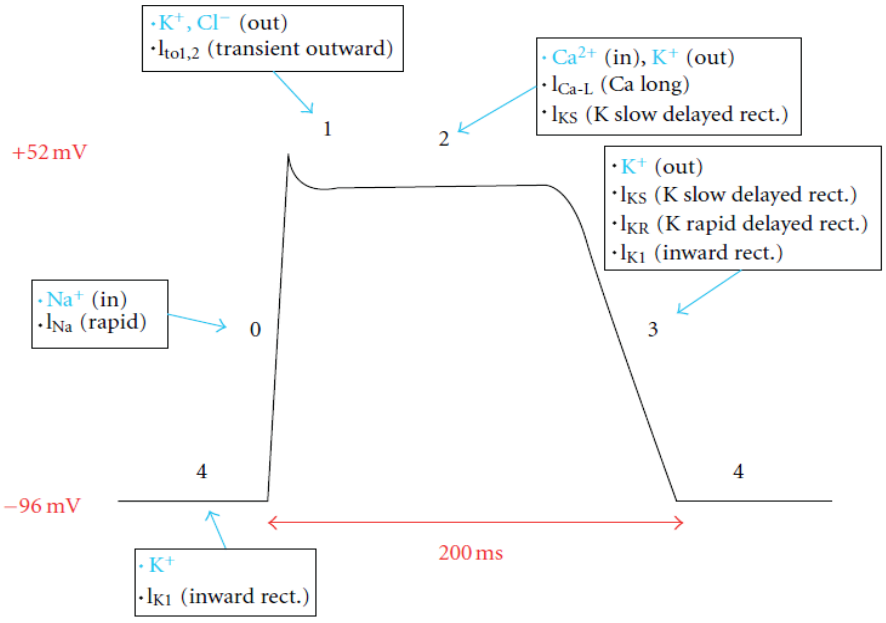

Figure 1. Ventricular action potential and major ion currents: Initial depolarization of cardiac myocytes through gap junctions (cell-to-cell connection) activates the inward Na^+ current that depolarizes myocytes rapidly (Phase 0). Transient outward K^+ current (Phase 1) creates a notch during the early phase of repolarization (I_{to}). Balance of the inward depolarizing Ca^+ current ($_{Ica-L}$) and outward rectifier K+ currents (I_{Ks} and I_{kr}) forms a plateau phase (Phase 2). Deactivation of the inward current and increase of the outward current (I_{Ks}, I_{Kr}, I_{K1}) complete repolarization (Phase 3) and the membrane potential returns to its resting potential (Phase 4).

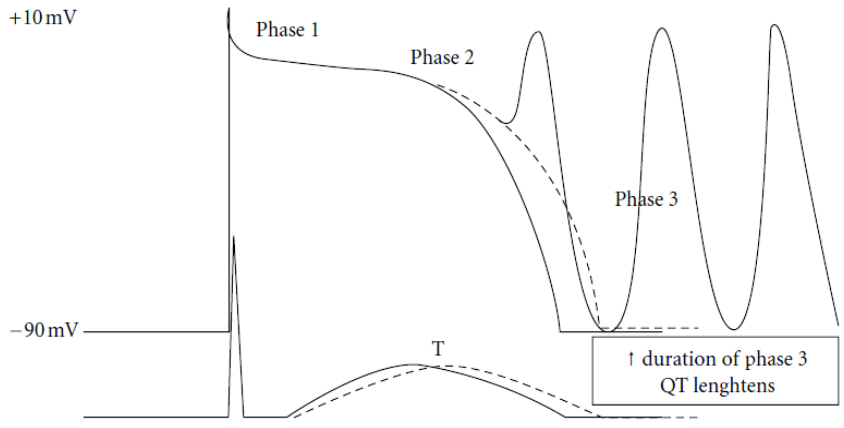

Figure 2. Multiple early afterdepolarizations (EADs) from progressively more negative transmembrane potential.

QT Interval

The QT interval of the surface electrocardiogram (ECG) consists of the QRS complex, which represents depolarization within the His-Purkinje system and ventricles, and the JT interval, which reflects ventricular repolarization. The QR interval is measured from the initiation of the QRS complex to the termination of the T wave. It represents the duration of the ventricular action potential. Because of the inverse relationship to heart rate, the measured QT interval is routinely transformed by various heart rate correction formulae into a variable known as the corrected QT interval (QTc) that is intended to be independent of the heart rate.

Molecular basis of QT prolongation and shortening

As explained in figure 1, rapid inflow of positively charged ions (sodium and calcium) leads to normal depolarization of myocardium. When this inflow is exceeded by outflow of potassium ions, myocardial repolarization occurs. Any malfunction of ion channels, which either leads to inadequate efflux of potassium ions or excess influx of sodium channel from myocardium, can result in excess intracellular positively charged ions. This malfunction of channel may be caused by mutations in genes encoding specific channels (congenital LQTS), by metabolic abnormalities, or by drugs (acquired LQTS). This intracellular excess of positively charged ions extends ventricular repolarization and results in QT interval prolongation. The ensuing intracellular surplus of positive causes early after-depolarisations (EADs). Lengthening of repolarization further delays the inactivation of calcium channels and the resulting late inflow of calcium contribute to the formation of EADs. The EADs may reach threshold amplitude and trigger ventricular arrhythmias (1-3) (Figure 2). Some regions of the ventricle, specially the deep sub endocardium, are most likely to show prolonged repolarization and EADs (4). The resulting heterogeneity of repolarization allows the onset of a distinctive re-entrant arrhythmia-torsade de pointes (4,5). Torsade de pointes often leads to syncope and may even lead to sudden cardiac death.

Short QT syndrome (SQTS) is a rare entity only about 30 cases of SQTS been reported till date (6-8). Mutations that lead to gain of function of potassium channels (I_{Kr} and I_{Ks}) or loss of function of calcium channel ($I_{Ca, L}$) shorten the QT interval. These patients have QTc interval of less than 320ms and a high risk if sudden death due to ventricular fibrillation.

Measuring the QT interval

Measurement of the QT interval is subject to substantial variability, which can cloud interpretation (9,10). This variability in QT interval measurement results from biological factors, such as diurnal effects, differences in autonomic tone, electrolytes, and drugs; technical factors, including the environment, the processing of recording, and the acquisition of the ECG recording; and interobserver and intraobserver variability, resulting from variations in T wave morphology, noisy baseline, and the presence of U waves. A recent survey of health care practitioners demonstrated that only 61% of the respondents were able to identify what the QT interval represented on an ECG and only 36/5 could correctly measure it (11). Another study found that >80% arrhythmia experts but <50% of cardiologist and <40% of non-cardiologist could calculate QTc correctly (12). The following section of this review will describe the standard practice to measure the QT interval in various conditions.

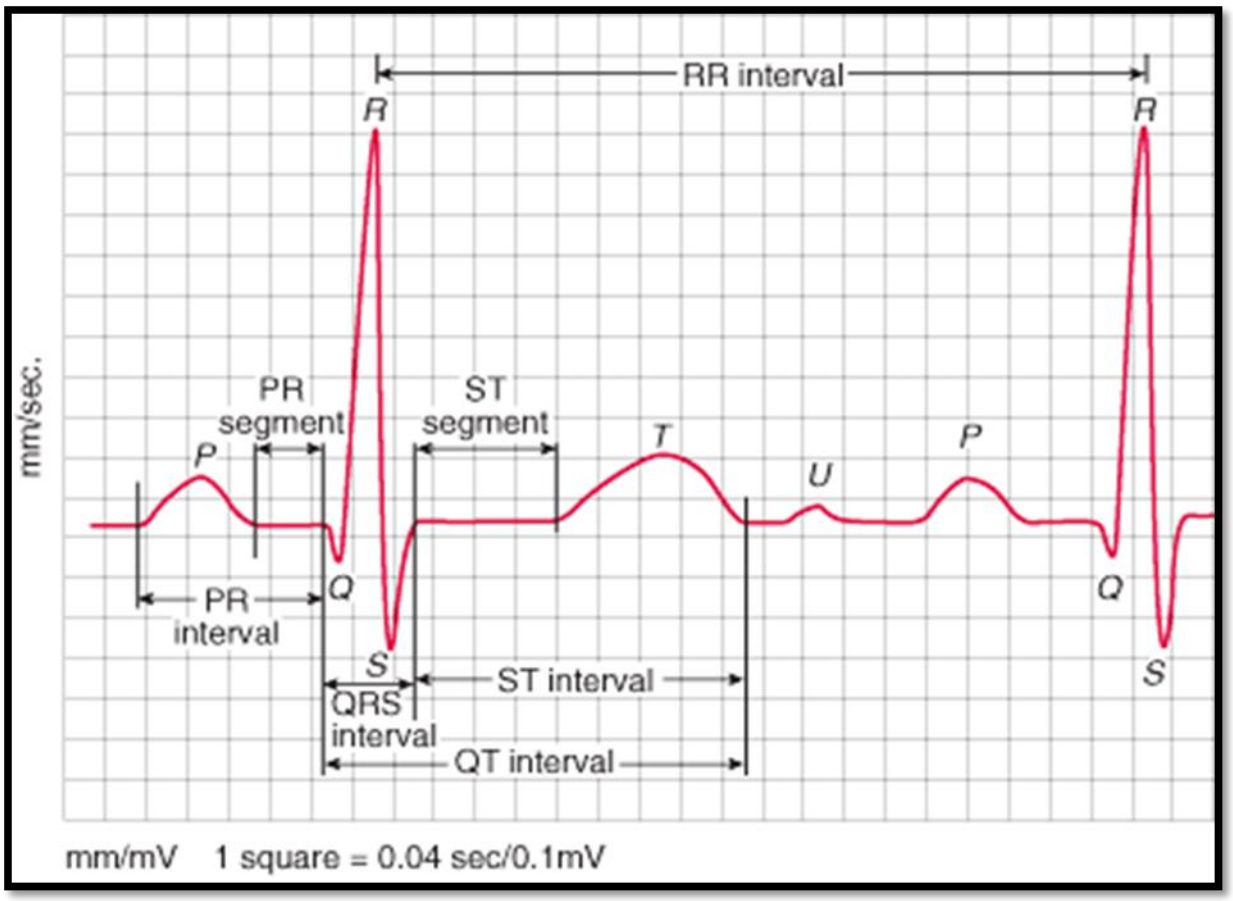

Figure 3: Calculation of QT interval from surface ECG

1. Which lead should be used to calculate QT?

The QT interval on the surface ECG is measured from the beginning of the QRS complex to the end of the T wave. It should be determined as a mean value derived from at least 3-5 cardiac cycles (heart beats). However the onset of QRS and the end of T wave do not occur simultaneously in all leads. It is a well-known fact that QRS begins earlier in the chest leads V1-V3 than in leads V4-V4 or in the limb leads (13). The most exact values of QT can therefore be obtained in leads V2-V3, if the T wave can be adequately measured in these leads. In a 12 lead ECG, where two or more leads are registered synchronously, the point corresponding to the earlier beginning of QRS in any of these three leads must be taken as the beginning of the QT interval. In most cases, the difference in the beginning on QRS in different leads does not exceed 20ms (14).

The end of the T wave may vary by up to 40ms in different leads. In leads where the T wave is very low, its terminal portion may be indistinguishable from the baseline. It is therefore advisable to measure the QT duration in leads showing the highest voltage of T. These are usually the leads V2-V4. If the leads are synchronized, then the latest point on the T wave in any lead must be taken for QT calculation.

2. How to identify offset of T wave in presence of a U wave?

The main difficulty lies in identifying correctly the point where the descending limb of T wave intersects the isoelectric line. When the T wave is of normal morphology and is not followed by a U wave, then the T wave offset is identified when the descending limb returns to the TP baseline (Figure 4 A). When the T wave is followed by a distinct U wave, the T wave offset is identified when the descending limb of the T wave returns to the TP baseline before the onset of the U wave (Figure 4 B). When the T wave is biphasic with T1 and T2 waves of similar amplitude, the T wave offset is identified at the time when T2 returns to baseline; and when a second low amplitude repolarization wave interrupts the terminal portion of the larger T wave, the T wave offset should be measured both at the nadir of the two waves (QT interval) and at the final return to baseline (QTU interval) (Figure 4 C and D).

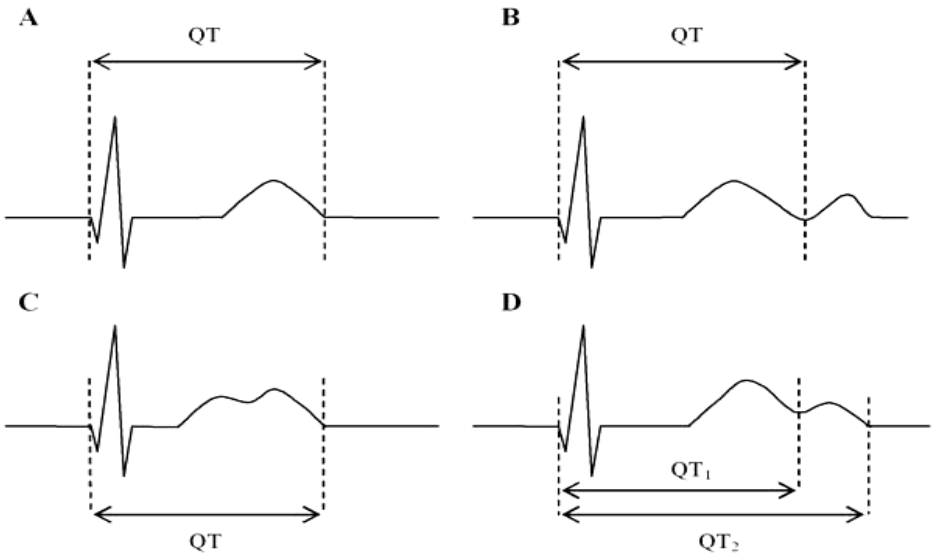

Figure 4 (A-D): QT calculation in presence of different T wave morphology (15)

3. How to differentiate a notched T wave from a T and a U wave?

Not infrequently a notched T can be mistaken for U waves. A synchronous lead with a well-defined T wave may be used to mark the end of T in such cases.

Table 1: Clues to differentiate a notched T wave from T wave and U wave

1. The terminal portion of T following the notch is usually of short duration (less than 150ms), while a U wave is longer.
2. The slope of T wave exceeds 1microvoit per ms while that of the U wave usually does not.
3. The distance between the summits of a true notched T wave doesn't exceed 40% of the distance between the beginning of QRS and the second summit, while that between sumits of T and U wave generally 40% of the distance between beginning of QRS and summit of U wave.
4. The notch of T wave is situated at least 40ms earlier than the S2 whereas the notch between T and U is situated within 40ms of S2.

(adapted from L Eugene and Surawicz B. Circulation 1952;6:378-388.)

4. Where to take T wave offset if T wave and U wave are fused?

The T wave almost always retains the steep slope of its descent. A tangential line drawn from the steepest slope of terminal down sloping portion of T wave is drawn. The point where it crosses the isoelectric line is used to mark the end of T wave as shown in figure 5(16).

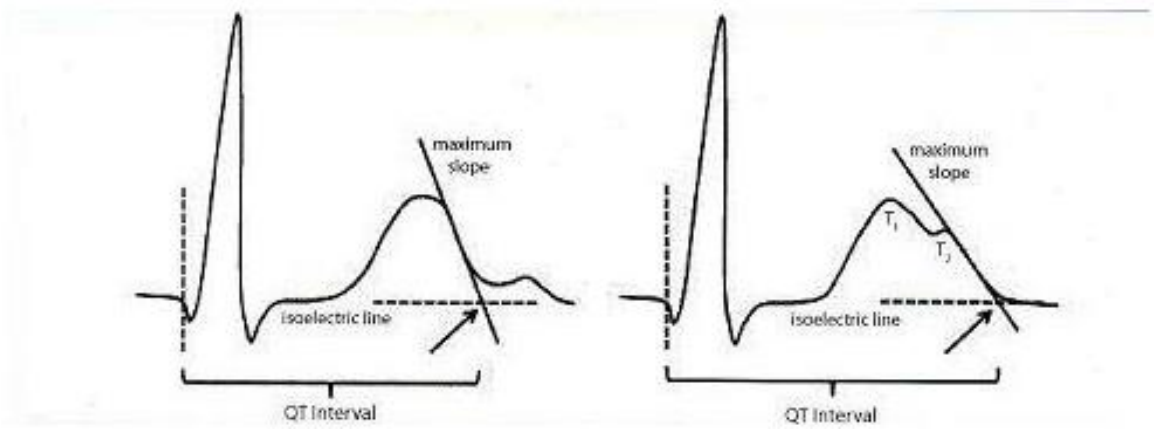

Figure 5: Tangential line drawn from steepest slope from downsloping portion of T wave marks the end of T wave.

5. Where to take T wave offset if T wave and U waves are fused?

Fusion of the T waves with P waves is not uncommon in A-V conduction disturbances, in A-V dissociation and in supraventricular tachycardia. In the cases where P wave mprphology is known (as in 2:1 AV block), it can be geopmetrically subtracted from the area of the merged T and P wave. If P wave morphology is unknown (as in supraventricular tachycardia) QT must be calculated from left precordial leads as the P wave in these leads is usually very small (13).

6. QT interval adaptation to changing heart rate- the concept of hysteresis.

On the surface ECG, complete adaptation of the QT interval to a sudden change in heart rate is associated with a time delay (16-19). This phenomenon is called ‘QT delay’ or ‘hysteresis’, which in humans may take approximately two to three minutes (20). The QT hysteresis may have an important impact on the QTc if the QTc is evaluated during significant changes in RR interval. For example, if haert rate changes quickly to a new

sustained higher rate during sudden exertion, it may take several minutes before the QT interval adapts to the new steady-state heart rate. The converse is also true, such that as heart rate slows, the QT interval will require will require several minutes to fully prolong to its new steady state value. QT hysteresis must be taken into consideration before calculating QTc in any individual.

7. Applying correction for heart rate

Normally the QT interval gets prolonged at slower heart rates and shortened at faster heart rates, many formulas have been proposed to adjust for these variations. Yet differences of opinion exist regarding the most useful correction for heart rate (21-24). One of the most commonly used formulas is the Bazett formula, however this formula has been criticized for overcorrecting QT at higher rates and undercorrecting it at lower heart rates (25). Other formulas has been shown in table 2. Framingham linear regresion equation is the most sound because it is based on empirical data from a large population sample rather than on hypothetical reasoning. Unfortunately, non of these corrections has been examined comparatively to determine the most effective formula in predicting which patients are at greatest risk for torsades de pointes.

Table 2: Various formulas to derive QTc

Method	Formula	Comment
Exponential		
Bazett	$QTc = QT/RR^{1/2}$	Widely used; may give erroneous results at both slow and fast heart rates
Fridericia	$QTc = QT/RR^{1/3}$	Widely used; may give more consistent results at fast heart rates
Linear		
Framingham	$QTc = QT + 0.154(1\text{-}RR)$	May have more uniform rate correction over a wide range of heart rates
Hodges	$QTc = QT + 1.75(HR\text{-}60)$	
Rautaharju		May have more uniform rate correction over a wide range of heart rates
Females and males <15	$QTI = (QT[HR + 100])/656$	
and >50 years	$QTI = (QT[HR + 100])/656$	
Males 15–50 years	$QTI = 100(QT)/([656/(1 + 0.01HR]) + 0.4–25)$	
Logarithmic		
Ashman	$QT = K1 \times \log(10 \times [RR + K2])$	At low heart rates, the values are too low
Adult men	$K2 = 0.07$, and $K1 = 0.380$	
Adult women	$K2 = 0.07$, and $K1 = 0.390$	

Bazett's formula has been most frequently used in the medical literature and the reported criteria for normal and abnormal values are given in table 3 (26)

Table 3. Normal and abnormal values of QTc

	Adult male	Adult female
Normal	< 430	<450
Borderline	430-450	450-470
Prolonged	>450	> 450

8. Problem of QTc estimation when the QRS is wide

The QT is less reliable when the QRS duration (QRSd) is ≥ 120ms, as the increased QRSd which measures the duration of ventricular depolarization contributes to prolongation of the QT interval. The JT interval (defined as QT – QRSd) has been proposed as a more valid way to assess ventricuar repolarization in such circumstances (27). This is justified, because in normal conduction, the QT interval is largely determined by the duration of repolarization, and that corresponds to the JT interval (28). Additionally, several investigators have reported that JT is independent of QRSd and suggest the the JT interval better represents the specific repolarization time than does the QT interval (29,30). The JTc can be determined by subtracting QRSd from QTc. The accepted normal value of JTc is 310ms (31). A single parameter formula was derived for the JT prolongation index of the form JTI = JT (HR + 100) / 518, with a JTI ≥ 112 identyfying repolarization in all patients with intraventricular conduction delay (29).

9. QTc estimation in atrial fibrillation

The QT interval varies from beat to beat. There is no single consensus on how to measure the QT interval in atrial fibrillation. One method is to average the measured QT intervals over 10 beats. The other method is to calculate the average of QT intervals with shortest and longest preceding R-R intervals as shown in figure 6 (31).

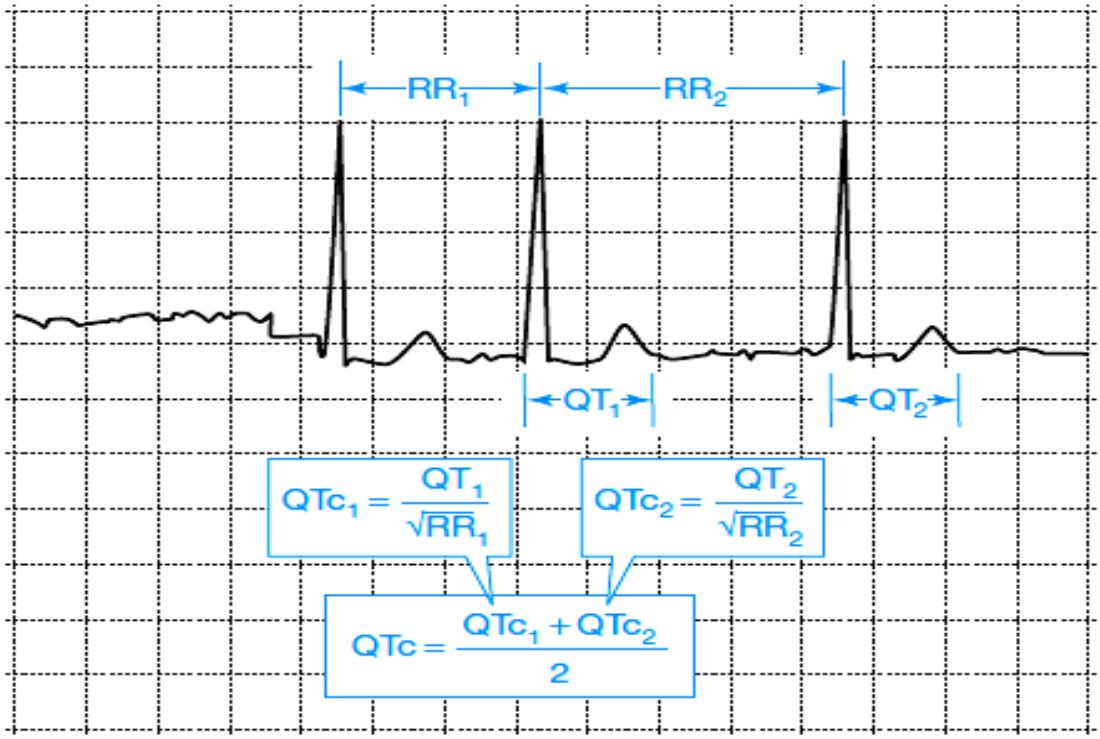

Figure 6. QTc calculation in atrial fibrillation. QT interval is caluclated by taking the average of QT intervals with shortest and longest preceding RR intervals.

10. QT estimation in ventricular paced rhythm

Ventricular pacing (VP) from the right ventricular apex causes abnormal ventricular acticvation and contraction resulting in both widened QRS complex and altered ventricular repolarization. As the intrisic ventricular repolarization may be hidden withim the deformed ventricular paced QT interval, there has been unresolved difficulty in assessing the QT interval during VP rhythm, which is reflected by the lack of a specific guideline in this group of patients (32). According to a Chiladakis et al. the Framingham and Nomogram correction methods perform most reliabily in assesssing the underlying QT interval in patient's with ventricular paced rhythm. Bazett's formula should be avoided because of the produced heart rate-dependent variability of the ventricular paced QT intervals (33).

Box. QT Interval measurement summary

1. Always record of 12 lead ECG.
2. Use multichannel synchrous leads.
3. Allow a few minutes for QT to adapt to a new heart rate.
4. Meaurre QT from leads with longest QT interval.
5. Take earliest point of QRS to most late point of T.
6. Measureat least 3-5 cardiac cycles and take maximum QT interval.
7. Tangential line drawn from steepest slope from downsloping portion of T wave marks the end of T wave.
8. For serial QTc measurement in same individual, measure at the same time of the day, use same kind of ECG, same correciton formula and preferably a single observer.

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D. M.

RESEARCH PAPERS

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RESEARCH PAPERS

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D.M. [CARDIOLOGY]

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This is to certify that the clinical and investigative work presented in these papers have been carried out by **Dr Prashant Shah** under our direct supervision and guidance.

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I dedicate this thesis to my parents

Dr Prashant Shah

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