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PROJECT REPORT

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DECLARATION

I , Dr. VENKATESHWARAN .S, hereby declare that the project in this book were undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute of Medical Sciences and Technology.

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GENERAL CONTENTS

Report I

INTERMEDIATE AND LONG-TERM OUTCOMES AND PREDICTORS OF OUTCOMES IN PATIENTS WITH FONTAN SURGERY

CONTENTS

Introduction

The Fontan operation is a palliative procedure for patients with a congenital heart defect that precludes biventricular repair. The significant evolution of the Fontan procedure and perioperative care has been associated with improvement in life expectancy. So increasing number of Fontan patients are now entering adulthood. The second natural history in this population is different from that of their basic congenital heart disease. Patients are prone to developing arrhythmias, heart failure, and progressive rise of their pulmonary vascular resistances. Information on midterm and longterm outcomes after Fontan operation are emerging, because these patients are only just reaching adolescence and adulthood. Valuable data on longer-term actuarial survival are likewise emerging, with a focus on particular surgical techniques or a particular congenital heart disease (1; 2; 3; 4). Therefore, we assessed long-term survival, predictors of mortality and morbidity in a large single-center cohort of patients with diverse forms of complex congenital heart defects that preclude biventricular repair, who had undergone Fontan procedure.

Aims & Objectives

1. To investigate intermediate and late outcomes after the Fontan operation.

2. To identify the predictors of mortality and morbidity outcomes.

Review of Literature

The Fontan operation- evolution

The Fontan operation is a palliative procedure for patients with a congenital heart defect that precludes biventricular repair. It was first introduced by Fontan and Baudet in 1971 in patients with tricuspid atresia (5). The Fontan circulation results from routing of the systemic venous blood to the pulmonary circulation without a hydraulic source of a ventricle. The procedure has been modified since its introduction. The earliest method of atriopulmonary connection resulted in a high incidence of re-operation and arrhythmias and is generally considered to be obsolete (6). Total cavopulmonary connection (TCPC) is now considered the method of choice and is usually performed using a two-stage operation. Connection of the superior vena cava to the right pulmonary artery (Glenn procedure or hemi-Fontan) is generally performed at 3 to 9 months of age, with TCPC being performed at approximately 1 to 5 years of age. TCPC can be achieved using two different techniques, intracardiac TCPC (lateral tunnel) and extracardiac TCPC to join the inferior vena cava to the pulmonary artery (7). Modifications of atriopulmonary connection to TCPC and staging with bidirectional Glenn shunt [BDG] have extended the indications for this operation to a wide range of congenital heart defects (8; 6). The spectrum of congenital heart disease, for which Fontan surgery was offered, has also changed in last 3 decades. Earlier

it was mainly confined to Tricupid atresia, thereafter heterotaxy and now hypoplastic left heart syndrome constitutes the majority of Fontan palliation (9; 10). Since the late 1990's prosthetic tube grafts have been used as an alternative in some centers to accomplish an extracardiac connection between the IVC and the pulmonary artery, the so-called 'extracardiac Fontan'. Theoretical advantages include the avoidance of aortic cross clamping and the avoidance of atrial suture lines with the complete exclusion of the atrial wall from high venous pressures. This could potentially result in a lower incidence of atrial arrhythmias. Potential disadvantages include the lack of growth potential of the circumferential conduit, conduit stenosis resulting from intimal peel formation, an increased risk of thromboembolism, and the need for formal anticoagulation. Satisfactory mid-term results have been reported with the extracardiac Fontan (9; 11; 12; 13). However in the absence of randomised evidence the debate over the lateral tunnel versus the extracardiac Fontan remains unresolved. Furthermore, creation of fenestration in Fontan pathway has led to a significant drop in early mortality and morbidity in the high-risk individual (14; 15). It is also beneficial in standard risk Fontan patients (shorter hospital stay, decreased pleural drainage and fewer additional procedures) (16). The disadvantages of the fenestrations have been reported to be the ongoing risk for a paradoxical embolus, persistent cyanosis, and an increased incidence of late catheter intervention for device closure of the fenestration. Therefore, the overall benefit of routine fenestration in Fontan

patients remains uncertain (17). In addition, improvements in perfusion strategy, anesthesia and intensive care management over the past decade have probably made important contributions. The significant evolution of the Fontan procedure has been associated with improvements in early mortality from 20% to 40% in the late 1970s to below 6.6% currently (18). In earlier studies, midterm and long-tem survival revealed the potentially finite life span of a Fontan circulation, with the overall 1-, 5-, and 10-year survivals found to be 77%, 70%, and 60%, respectively, in the Mayo Clinic study (19). Follow up also often suggested a poor functional capacity. At 5 years, only 26% of patients were free from significant cardiac symptoms (20).

Despite improvements in surgical techniques that reduce perioperative mortality (21; 22; 16), late deterioration in functional status can be observed with longer duration of follow-up (23). Late morbidity is mainly defined by pathway obstruction (24), atrial arrhythmia (25; 26; 27), and cyanosis because of systemic venous collateralization (28), thrombus formation (29), protein-losing enteropathy (30), plastic bronchitis and pulmonary arteriovenous malformations (31). Postoperative morbidity with the need of hospitalization also includes surgical and catheter based re-interventions. Somatic growth failure was documented after Fontan operation.

FONTAN FAILURE: Mortality and reoperation

Gentles et al showed a late failure rate of 9% in their series of 500 patients and identified heterotaxy and atriopulmonary type connections as significant risk factors for failure (22). Stamm et al had a late failure rate of 6% in their series of 220 patients with a lateral tunnel Fontan (32). Weipert et al determined risk factors for late failure and for intra-atrial re-entrant tachycardia at 15 to 20 years' follow-up. They found that at 15 years, Kaplan-Meier estimated survival was significantly better for patients with tricuspid atresia (93%) compared with that for patients with complex congenital malformation (71%). The sole multivariable risk factor for Fontan failure was the type of underlying diagnosis (27). Masamichi found overall survival in Fontan circulation was 87% at 20 years after Fontan operation. Actuarial survival in patients with APA was 75% at 10 years, which was significantly lower than that of TCPC (90%) and f-TCPC (90%) ($p = 0.04$) (33). Khairy et al concluded that, in perioperative survivors of Fontan surgery, gradual attrition occurs predominantly from thromboembolic, heart failure–related, and sudden deaths. Independent predictors of heart failure death were protein-losing enteropathy, single morphologically right ventricle and higher right atrial pressure (34).

VENTRICULAR FUNCTION:

Deterioration of systolic or diastolic ventricular function results in a rise of venous pressures. Failure of the Fontan circulation may then occur. Thus, the assessment of cardiac volumes, mass, and Ejection Fraction (EF) yields valuable diagnostic, prognostic, and therapeutic implications. Fogel et al found decreased systolic ventricular function after Fontan operation. Previous pulmonary arterial banding had no impact on ventricular function (35). Robbers-Visser et al studied clinical outcome 5 to 18 years after the Fontan operation performed on 34 children younger than 5 years. At median follow-up of 7.8years, patients were in acceptable clinical condition, with preserved global ventricular function, moderately decreased exercise capacity, and NT-pro-BNP levels within reference range (36). Strategies to preserve ventricular function, such as the use of angiotensin-converting enzyme inhibitors, have not shown benefit in limited study (37). Anderson et al reported abnormal diastolic function in 72% of children who had undergone a Fontan, which has not been previously reported and is concerning. Ventricular diastolic function was assessed with measures derived from pulsed Doppler interrogation: E' (cm/s), E/A ratio and E/E'. These indices are dependent on cardiac loading conditions and are unable to distinguish between enhanced chamber compliance and impaired relaxation (38).

FUNCTIONAL STATUS AND EXERCISE CAPACITY:

Maximal exercise performance in Fontan patients is lower than normal subjects more so in older individuals (38; 39). The mechanisms proposed are, absence of a subpulmonary pumping chamber, abnormal endothelial cell function, increased systemic vascular resistance, decreased muscle mass, and deconditioning. Blaufox et al found that in 521 pediatric patients (6–18 years) after the Fontan procedure, a lower resting heart rate and a higher peak heart rate are each independently associated with better physical function as measured by anaerobic threshold and Child Health scores (40). Brian et al studied the associations of Child Health Questionnaire Physical and Psychosocial Functioning Summary Scores (FSS) with standardized measurements from prospective with cardiopulmonary exercise, echocardiography, magnetic resonance imaging, and measurement of brain natriuretic peptide. They concluded that in relatively healthy Fontan patients, Laboratory Measures are weakly associated With Functional Health Status After Fontan Procedure (41). Improved exercise capacity has been noted with exercise training programs, but the impact on functional health status and activity levels is not known (42; 43).

RHTHYM DISTURBANCES:

Hemodynamic decompensation due to loss of sinus rhythm was identified by Fontan in his first report of three cases. Supraventricular arrhythmia is a critical factor in the chain of events leading to failure of a Fontan circulation. The development of intra-atrial re-entrant tachycardia (IART) exposes patients after long-term Fontan circulation to serious morbidity (23; 44; 20; 30). Thus, control of arrhythmia is important to maintain good hemodynamics, prevent thromboembolism, and ventricular dysfunction. Rhythm disorders, such as sinus node dysfunction and atrial tachycardia, are common and potentially important late morbidities of the Fontan operation (45; 20; 46; 26; 25). The incidence of late sinus node dysfunction after the Fontan operation has been reported to be about 15% but may occur in up to 44% of patients in selected series (46). The incidence of atrial tachycardia is 16% to 17% at approximately 5 years after the Fontan procedure (25; 26) and reaches 50% by 12 years (25). The prevalence of arrhythmias after Fontan operation varies with the type of modification. The atriopulmonary connection has been identified as a risk factor by several groups (47; 48) with a prevalence of atrial tachyarrhythmias at long-term follow-up of 29% in these patients (48). Prevalence of atrial tachyarrhythmias in lateral tunnel type TCPC is about 15% to 20% at midterm to long-term follow up (38; 48; 47). Although in theory atrial tachyarrhythmia should be

less frequent with extracardiac conduit TCPC, prevalence has been reported to be as great as 11% in a large cohort at midterm follow-up (1). Rationale of converting atriopulmonary connection to an extracardiac conduit has been advocated initially by the team of Mavroudis and Deal (49; 50). In this initial experience with Fontan conversion only the sickest patients were offered this treatment. Other risk factors for development of atrial tachyarrhythmias are older age at Fontan completion, longer duration of follow-up, heterotaxy syndrome and early postoperative atrial tachyarrhythmias (38; 48; 36; 27; 51). Masamichi et al observed fenestration in Fontan circulation provided better cardiac output and lower incidence of late tachyarrhythmia, suggesting a benefit of fenestration for late outcome even after 20 years (33). Antiarrhythmic drug therapy, antitachycardia pacing, or both offer limited arrhythmia control. A few small series report the use of electrophysiologic mapping and radiofrequency ablation techniques with good acute success rates but high early recurrence rates of arrhythmia (52; 53). Hence an improved risk analysis of patients plays a key role in improving patient selection for the completion Fontan.

The reason why these various morbidities occur after Fontan operation is still unclear. A recent study demonstrated the evidence of progression of pulmonary vascular disease in patients with failing Fontan circulation (54). Pulmonary vascular resistance (PVR) becomes an important determinant of

cardiac output in the Fontan circulation. Even with morphologically 'normal' pulmonary arteries, a dominant single ventricle circulation exposes the pulmonary vasculature to different periods of too much or too little flow. Pulsatile flow is important for shear-stress-mediated release of endothelium-derived nitric oxide (NO) and for recruitment of pulmonary capillaries and to maintain their patency. The systolic pressure rise not only recruits the capillary bed and lengthens the capillaries but also keeps them open during diastole. After total cavopulmonary connection, there is loss of pulsatility in the pulmonary arterioles and capillaries with less recruitment of the pulmonary vascular bed (55). A chronically underfilled pulmonary vascular bed with loss of pulsatility may contribute to pulmonary endothelial dysfunction and consequently increase pulmonary vascular resistance (56). Stasis, polycythemia due to chronic cyanosis, and abnormal coagulation profile in patients with Fontan circulation predispose them to increased incidence of pulmonary thromboembolism (57). Collateral circulation through bronchial and other vessels remains a hidden unaccounted source of pulmonary blood flow that is difficult to quantify (58). Venous channels between systemic and pulmonary veins or hepatic veins and atrium contribute to mixing. Assessment of pulmonary blood flow is incomplete without including the collateral flow in accurate estimation of pulmonary vascular resistance. The impact of vasodilators on early pulmonary vascular dysfunction was clearly demonstrated by Goldman *et al,* in postoperative period after Fontan operation

(59). With the advent of pulmonary vasoactive drugs such as phopshodiesterase inhibitors (sildenafil) and endothelin antagonists (bosentan), manipulation of PVR has been attempted in both early and late postoperative phases in Fontan circulation. They have been used to treat late sequelae such as PLE and plastic bronchitis, wherein elevated PVR and consequently, increased systemic venous pressure may have contributory effects (60; 61). Sildenafil has also been shown to acutely improve exercise performance and hemodynamic response to exercise (62). Despite this, the long-term effect of sildenafil or bosentan on Fontan circulation and their tolerance is not known (63). The splanchnic venous hypertension along with altered flow in the gut vasculature, low cardiac output state, persistent hypoxia, and inflammation contributes to protein-losing enteropathy (PLE) (64). The dominant systemic ventricle may be of right ventricular or indeterminate morphology with unfavorable fiber arrangement that is technically inefficient to sustain systemic cardiac output. From a volume overloaded, dilated, and hypertrophied ventricle, the superior cavopulmonary connection and finally the Fontan completion expose the systemic ventricle to volume unloading at suboptimal preloads. Following total right heart bypass, the preload of the systemic ventricle is reduced to 25-70% with respect to the ventricular size. This leads to systolic and diastolic dysfunction and myocardial dyssynchrony (65). This leads to remodeling and eventually low cardiac output (66).

Patients & Methods

A cross-sectional analysis was performed on 66 early postoperative (30-day) survivors of the Fontan procedure done between August 1993 and May 2009. Medical records were reviewed for medical history and patient characteristics. Patients who died or underwent surgical revision were considered to be instances of failed Fontan circulation and were included in the survival analysis. All patients were reviewed and subjected to pulseoximetry, ECG and echocardiography. Forty four patients (82%) underwent echo tissue Doppler imaging and Holter. Outcome variables studied were failure of the Fontan operation (i.e., death, takedown Fontan, or transplantation), ventricular dysfunction, arrhythmia, heart failure admissions, functional health status and other complications.

The two dimensional echocardiograms and Doppler evaluations of standard short and long-axis views of the ventricle were performed. Systolic function was assessed by ejection fraction (EF). EF was calculated using adequate M-mode tracings for patients with left ventricular morphology and (67). All other patients had EF calculated using a biplane Simpson's rule, with orthogonal images obtained at the cardiac apex or the subcostal window. Doppler examination was performed at the cardiac apex. Pulse wave Doppler interrogation of Atrio Ventricular (AV) valve was performed in accordance with previously published recommendations (68). AV valve flow was

evaluated with the sample volume placed near the tip of the valve leaflets. When 2 AV valves were present, the 1 connected to the PV atrium was evaluated. AV valve peak early diastolic inflow velocity (E); AV valve peak late diastolic inflow velocity (A); deceleration time of the early AV valve inflow (DT); tissue Doppler peak early diastolic velocity (E') and tissue Doppler peak late diastolic velocity (A').

Diastolic ventricular function was assessed by Doppler E: A ratio and TDI derived E/E' and were age adjusted using reference values previously reported (69; 70). Diastolic dysfunction was graded as 1 to 4. Cardiac functional status was determined by New York Heart Association (NYHA) class of patients symptoms. Arrhythmic outcome was considered to present if it was previously documentated or was detected in the holter examination performed during the study.

Statistical analysis:

Data are described as frequencies in percentage, means with standard deviations as appropriate. Data were analyzed using SPSS statistical software. P value was derived by Student `t' test for continuous variables and Chi-square test for categorical variables. A value of $p < 0.05$ was considered to be statistically significant. Estimated actuarial survival and freedom from late morbidities were determined by the Kaplan - Meier method and analyzed with the log-rank test.

Observations & Results

A cross-sectional analysis was performed on 66 early postop (30-day) survivors of the Fontan procedure done between August 1993 and May 2009. There were 36 (55%) males. Patient characteristics are shown in Table 1 and Figure 1, 2.

Mean age was 16.8 years (5–38 years). Mean age at Fontan completion was 8.1 ± 4.8 years. Mean follow-up after Fontan completion was 8.6± 4.3 years. Fifty-eight patients had an intra-atrial lateral tunnel; 7 patients had an extracardiac conduit and 1 had kawashima operation. Nineteen patients (29%) had undergone staged procedures, with a BDG before completion of the Fontan circulation. Mean interval between BDG and Fontan completion was 48.8 ± 23.6 months. Eleven patients (16.6%) had aortopulmonary shunt prior to TCPC. Forty nine patients (74%) had fenestrated TCPC.

Figure 1- Patient distribution on duration of Follow up

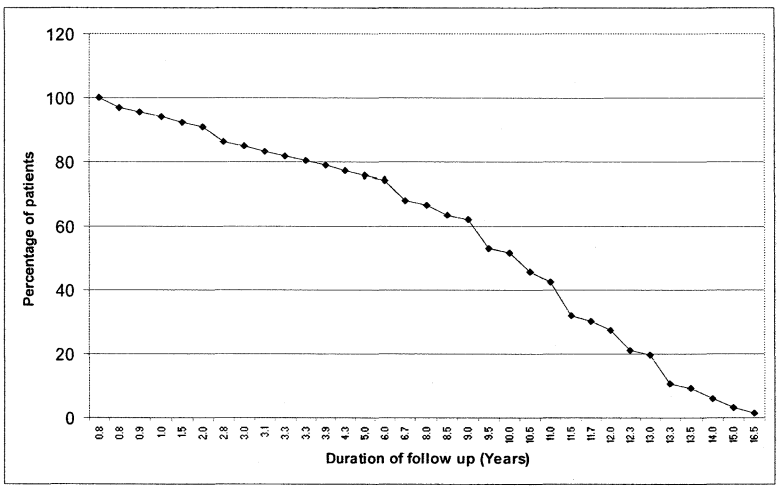
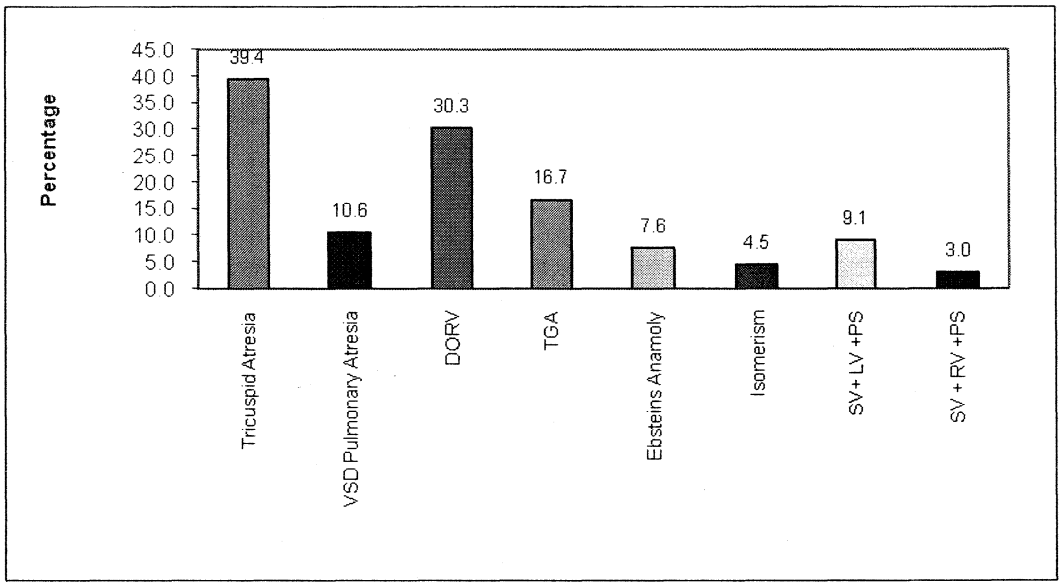


TABLE 1. Patient Characteristics

CHARACTERISTIC	n (%)
Demographics	
Male gender	36 (55)
Age at Fontan in years,	
Less than 4	7 (10.6)
4 to 8	33 (50)
More than 8	26 (39.4)
Diagnosis	
Tricuspid Atresia	26 (39.4)
VSD Pulmonary Atresia	7 (10.6)
DORV	20 (30.3)
TGA	11 (16.7)
Ebsteins Anamoly	5 (7.6)
Isomerism	3 (4.5)
Single ventricle of LV type + PS	6 (9.1)
Single ventricle of RV type + PS	2 (3.0)
Predominant ventricle	
Left	38 (57.6)
Right	2 (3)
Biventricular	26 (39.4)
Other morphological characteristics	
Bilateral SVC	10 (15.2)
Interrupted IVC	1 (1.5)
Atrial isomerism	8 (12.1)
Juxtaposed RA appendage	14 (21.2)
Common AV valve	3 (4.5)
Prior staging with bidirectional Glenn, n (%)	19 (28.8)
Prior Aorto pulmonary shunt, n (%)	11 (16.7)
Interval between BDG and Fontan (mean ± S.D.) in months	48.8 ± 23.7
Duration of follow up (mean ± S.D.) in years	8.6 ± 4.3
Type of Fontan operation, n (%)	
Lateral tunnel	58 (87.9)
Extracardiac	7 (10.6)
Kawashima	1 (1.5)
Fenestration created, n (%)	49 (74.2)

Figure 2 : Frequency distribution of Diagnosis



Hemodynamic data from preop cardiac catheterization was available in 60 patients and is shown in Table 2. Distribution of patients based on duration of follow up is shown in Fig 2.

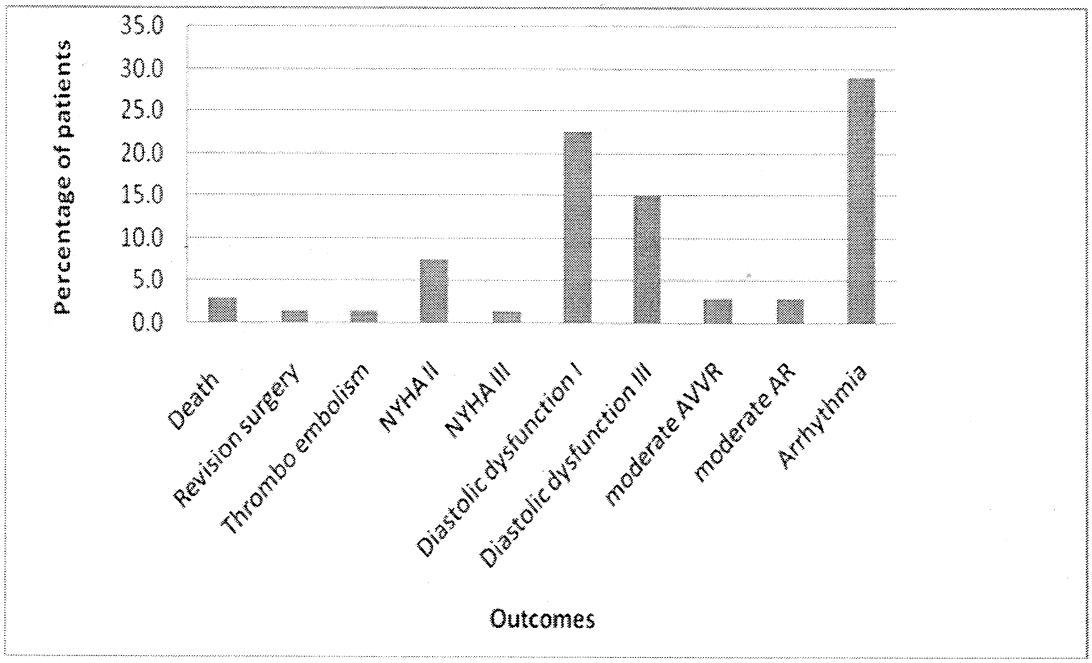
Table 2 Hemodynamic data before Fontan operation: Based on fenestration

Variable	Total n= 60	Fenestration No	Fenestration Yes	P value
	Mean ± SD	Mean ± SD	Mean ± SD	
PAP (mm Hg)	10.7 ± 2.9	10.8 ± 2.9	6.4 ± 2.8	0.879
LA Pressure (mm Hg)	6.6 ± 2.7	6.4 ± 2.8	9.1 ± 3.3	0.733
SV EDP (mm Hg)	9.4 ± 2.9	9.1 ± 3.3	4.2 ± 3.1	0.686
TPG (mm Hg)	4.3 ± 3	4.2 ± 3.1	4.3 ± 3	0.907

Outcomes :

Outcome variables studied were failure of the Fontan operation (i.e., death, takedown Fontan, or transplantation), heart failure rehospitalizations, arrhythmia, functional health status and other complications. Frequency of various outcomes is shown in Fig 3.

Figure 3. Frequency of outcomes

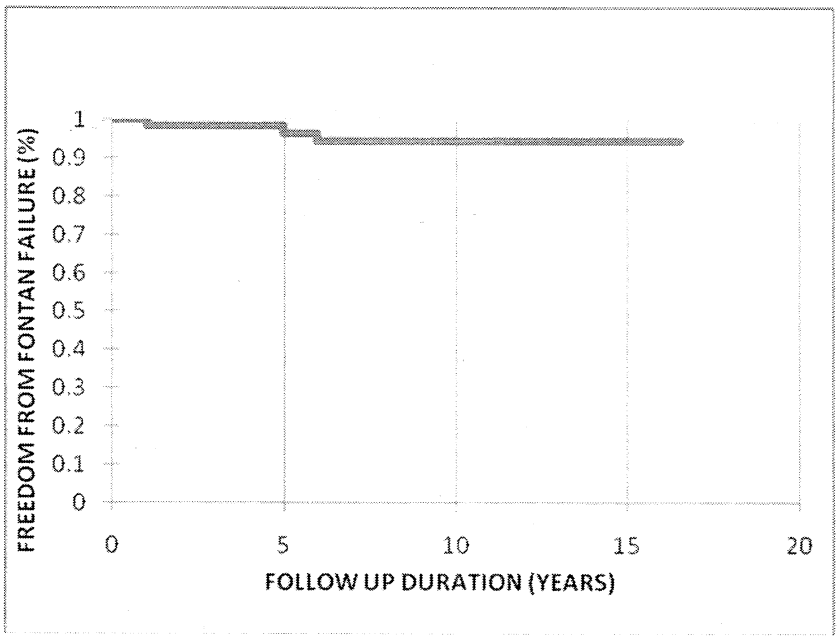


Fontan failure

Two patients (3%) died of heart failure at 60 and 72 mths after surgery. Of this one patient had desaturation due to baffle leak and other had atrial tachycardia. One patient underwent take down Fontan to BDG at 12 months of

follow up. Actuarial freedom from death or revision is 95% at a mean follow up of 8.6 years. Kaplan-Meier estimated freedom from Fontan failure was 98.4% at 5 years and 94.4 at 10 and 14 years as shown in Fig 4.

Figure 4. Kaplan Meier- Freedom from Fontan failure



Morbidities

1. Ventricular dysfunction

Two out of 66 patients (3%) had systolic ventricular dysfunction. Diastolic function by tissue Doppler was analysed in 53 patients. Echocardiographic parameters are shown in Table 4. Diastolic dysfunction was present in 20 (37.7%). Age-adjusted diastolic function was worse in lateral tunnel group than extracardiac Fontan. But it was not statistically

significant. Single ventricular morphology, preop ventricular EDP, transpulmonary gradient and fenestration did not significantly influence diastolic function as shown in Table 5. Moderate AV valve regurgitation and aortic valve regurgitation was noted in 2 patients each.

Table 4 : Echocardiographic parameters

Characteristic	**Observation**
Tissue Doppler variables	
E' cm/s	0.1 ± 0
E/A ratio	1.2 ± 0.3
E/E' ratio	5.7 ± 2.
Diastolic dysfunction grade (n = 53)	
Normal	33 (62.3)
Impaired relaxation	12 (22.6)
Restrictive	8 (15.1)
Overall AV valve regurgitation	
None	14 (21.2)
Mild	50 (75.8)
Moderate	2 (3)
Aortic valve regurgitation	
None	48 (72.7)
Mild	16 (24.2)
Moderate	2 (3)

Table 5 : Diastolic dysfunction based on selected variables

Predictors		Diastolic dysfunction				p value
		Total	Absent	I	III	
Type of Fontan	Lateral tunnel	48	30 (62.5)	12 (25)	6 (12.5)	0.172
	Extracardiac	**5**	**3 (60)**	**0 (0)**	**2 (40)**	
Fenestration details	No	14	10 (71.4)	3 (21.4)	1 (7.1)	0.587
	Yes	**39**	**23 (59)**	**9 (23.1)**	**7 (17.9)**	
SV morphology	LV	34	21 (61.8)	8 (23.5)	5 (14.7)	0.977
	Both	**19**	**12 (63.2)**	**4 (21.1)**	**3 (15.8)**	
Age of surgery in mean ± SD		7.8 ± 4.4	7 ± 4.1	8.3 ± 3.4	10.1 ± 6.2	0.648
Duration of FU in yrs mean ± SD		8.7 ± 4.4	8.7 ± 4.2	11.2 ± 2.9	4.8 ± 4.8	0.454
PAP (mm Hg) in mean ± SD		10.5 ± 2.9	10.4 ± 2.6	10.8 ± 3.9	10.8 ± 2.8	0.767
SV EDP (mm Hg) in mean ± SD		9.9 ± 2.7	9.6 ± 2.2	11 ± 3.4	9.3 ± 3	0.676

2. Arrhythmia

Nineteen (29%) patients developed a new supraventricular arrhythmia during follow-up. Frequency distribution of rhythm is shown in figure 5. Mean time to onset of arrhythmia after Fontan operation was 7.6 years. Kaplan-Meier estimated freedom from arrhythmia was 89.5%, 81% and 58.6% at 5,10 and 14 respectively, as shown in Fig 6.

Figure 5. Rhythm distribution

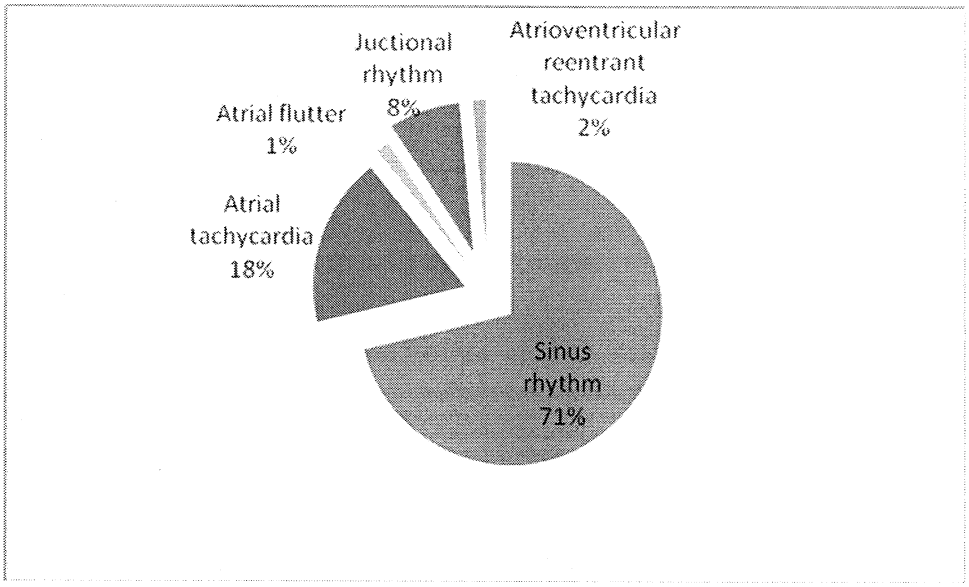


Figure 6. Kaplan-Meier curve- Freedom from arrhythmia

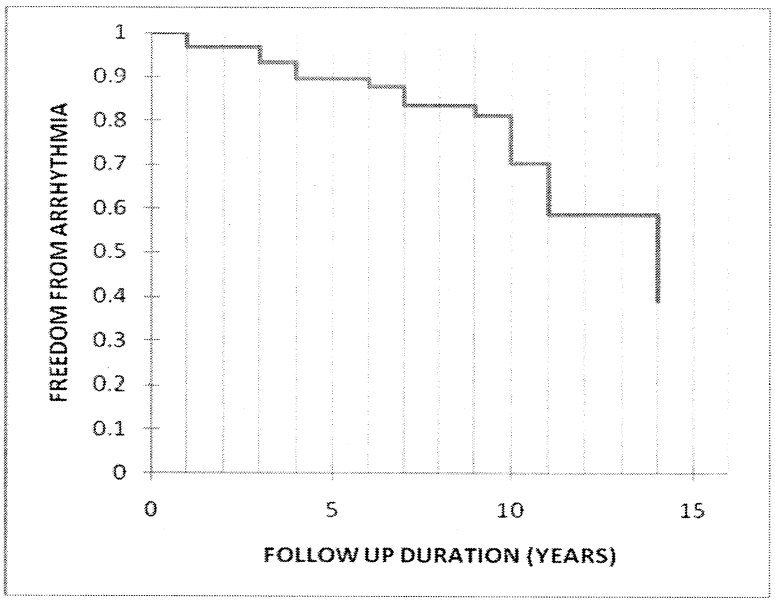


Table 6 : Predictors of Arrhythmia

Prediction variable		Arrhythmia			p value
		Total	No	Yes	
Type of Fontan	Lateral tunnel	58	41 (87.2)	17 (89.5)	0.202
	Extracardiac	7	6 (12.8)	1 (5.3)	
	Kawashima	1	0 (0)	1 (5.3)	
Fenestration details	No	17	12 (25.5)	5 (26.3)	0.947
	Yes	49	35 (74.5)	14 (73.7)	
SV morphology	LV	37	26 (55.3)	11 (57.9)	0.755
	RV	2	1 (2.1)	1 (5.3)	
	Both	27	20 (42.6)	7 (36.8)	
Juxtaposed RA appendage	No	52	39 (83)	13 (68.4)	0.190
	Yes	14	8 (17)	6 (31.6)	
Common AVV	Absent	63	45 (95.7)	18 (94.7)	0.859
	Present	3	2 (4.3)	1 (5.3)	
Isomerism	Absent	63	46 (97.8)	17 (89.5)	0.138
	Present	3	1 (2.2)	2 (11.5)	
	Yes	2	0 (0)	2 (10.5)	
Diastolic dysfunction	Absent	33	25 (65.8)	8 (53.3)	0.505
	I	12	7 (18.4)	5 (33.3)	
	III	8	6 (15.8)	2 (13.3)	
AVVR	Absent	14	10 (21.3)	4 (21.1)	0.797
	1+ and 2+	50	36 (76.6)	14 (73.7)	
	3+ and 4+	2	1 (2.1)	1 (5.3)	
Age of surgery (mean ± S.D.)		8.1 ± 4.8	7.4 ± 3.9	10 ± 6.3	0.459
Duration of FU in years (mean ± S.D.)		8.6 ± 4.3	8.3 ± 4.4	9.6 ± 4	0.107
Interval between BDG and Fontan completion in months (mean ± S.D.)		48.8 ± 23.7	56.8 ± 26.7	37.8 ± 13.6	0.329
PAP (mm Hg) (mean ± S.D.)		10.7 ± 2.9	10.8 ± 3.1	10.6 ± 2.7	0.543

Six patients (9%) were on antiarrhthymic drug treatment. Pacemaker therapy or radiofrequency ablation was not required in any of the patients. There was trend towards higher incidence of arrhythmia with older age at surgery, longer duration of follow up, presence of isomerism, juxtaposed atrial appendages and diastolic dysfunction. But they did not reach statistical significance. There was no statistically significant difference in arrhythmia incidence between the patients with fenestration and those without fenestration. See Table. 6

3. Functional limitation

Sixty (90%) patients were in NYHA 1. Predictors of functional limitation were single ventricle of RV morphology (p- 0.041), SV EDP (mm Hg), TPG (mm Hg) and systemic saturation as shown in Fig 7.

Table 7 : Comparison of the NYHA class based on selected variables

Variable	Total	I	II or more	P value
	Mean ± SD	Mean ± SD	Mean ± SD	
SV EDP (mm Hg)	9.4 ± 2.9	9.3 ± 2.8	10.8 ± 5.1	0.012
TPG (mm Hg)	4.3 ± 3	4 ± 2.7	6.5 ± 4.8	0.049
Systemic saturation (%)	93 ± 6.5	93.8 ± 4.8	84.5 ± 13.5	0.001

There was no statistically significant difference in functional class and systemic saturation between the patients with fenestration and those without fenestration.

4. Heart failure rehospitalisation

Seven patients (11%) had heart failure requiring rehospitalisation. Weak predictors for heart failure admission were single ventricle of RV morphology, common AV valve, single ventricle EDP, TPG and presence of diastolic dysfunction.

5. Other morbidities and observations

Thromboembolic complications occurred in 1 patient. Antiplatelet medication was provided in 22 patients (33.3%) and anticoagulation with warfarin sodium in 18 (27%). None of our patients had protein losing enteropathy.

Discussion

In this study of 66 early postoperative Fontan survivors, mean follow-up after Fontan completion was 8.6 ± 4.3 years. It is comparable to the previously reported trials (38; 33; 10; 34). Freedom from death or revision is 95%. This confirms the good postoperative survival reported earlier (22; 32; 34; 27). However, significant proportions of them do develop atrial arrhythmias and ventricular diastolic dysfunction on long-term follow up. Nineteen (29%) patients developed a new supraventricular arrhythmia during follow-up. Mean time to onset of arrhythmia after Fontan operation was 7.6 years. Twelve (18%) patients had atrial tachycardia. Earlier studies have shown that, incidence of atrial tachycardia is 16% to 17% at approximately 5 years after the Fontan procedure (25; 26) and reaches 50% by 12 years (25). There was trend towards higher incidence of arrhythmia with older age at surgery, longer duration of follow up, presence of isomerism, juxtaposed atrial appendages and diastolic dysfunction. Several studies have shown older age at Fontan completion, longer duration of follow-up, heterotaxy syndrome and early postoperative atrial tachyarrhythmias as risk factors for development of atrial tachyarrhythmias are (38; 48; 36; 27; 51). Diastolic dysfunction was present in 20 (37.7%). Anderson et al reported abnormal diastolic function in 72% of children who had undergone a Fontan (38). The difference can be attributed to shorter duration of follow up and load dependent diastolic

indices: E' (cm/s), E/A ratio and E/E'. These indices are unable to distinguish between enhanced chamber compliance and impaired relaxation (38). No significant risk factor could be identified for diastolic dysfunction. Masamichi et al observed that at 20 years of follow up fenestration in Fontan circulation provided better cardiac output and lower incidence of late tachyarrhythmia (33). In contrast, this study did not find any difference in arrhythmia incidence between the patients with and without fenestration. Long duration of follow up may be needed to show the benefit of fenestration. Sixty (90%) patients in this study population were in NYHA 1. Kim et al showed, that at median follow-up of 6 years 95.2% patients were in NYHA class I or II (51). Similarly, others have reported good cardiac functional class in majority of their patients (10; 71).

The number of surviving young adults with a single ventricle physiology continues to increase. So there is an increasing urgency to either find appropriate future therapy, or at least optimize the Fontan procedure. At follow-up, late survival is satisfactory, but there is a relevant late morbidity to be observed after Fontan procedure. An improved risk analysis for these patients plays a key role in improving patient selection for the completion of Fontan.

Study Limitations

1. The subjects represented a subgroup of available current survivors. The study population was relatively well, and this may have contributed to the lack of strong associations noted. Many interventions proposed for study in Fontan patients have been aimed at primary prevention of late complications. Thus the population we studied would be the target population, and the associations explored would be the ones of interest.
2. Functional health status was determined from patient reporting. Some would have underestimated their symptoms. Few variables, such as diastolic function, may have been less valid and reliable, although no gold standard currently exists for use in a heterogeneous group of functional single-ventricle patients.
3. The incidence of arrhythmias is likely to be underestimated because of their transient and intermittent nature.

Conclusion

In this study, we have shown that late postoperative survival and functional outcome are excellent in patients who had Fontan procedure. However, significant proportions of them do develop atrial arrhythmias and ventricular diastolic dysfunction on long-term follow up. Long-term consequences of Fontan circulation merit further investigation and proper management to avoid morbidity and Fontan failure. Future efforts should concentrate on randomized evaluation of different surgical techniques and early re-intervention of the failing Fontan.

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GLOSSARY

A - peak late diastolic inflow velocity

A'- tissue Doppler peak late diastolic velocity

AVVR- Atrio ventricular valve regurgitation

BDG - Bidirectional Glenn

E- peak early diastolic inflow velocity

E'- tissue Doppler peak early diastolic velocity

EDT- deceleration time of the early diastolic inflow velocity

EF- Ejection Fraction

f- TCPC- fenestrated Total cavopulmonary connection

IART - Intra-atrial re-entrant tachycardia

IVC – Inferior venacava

NT-pro-BNP – N-terminal pro Brain natriuretic peptide

NYHA - New York Heart Association

PLE- Protein-losing enteropathy

PS – Pulmonary stenosis

PVR - Pulmonary vascular resistance

SV EDP – Single ventricle end diastolic pressure

SVC – Superior venacava

TDI – Tissue Doppler Imaging

TPG – Transpulmonary gradient

Master Chart

S.N.	NAME	AGE(YRS)	SEX (1-Male, 2- female)	H.N.	age of Sx in years	AGE OF SX.(MTHS.)	DURATION OF FU in YRS	DURATION OF F/U (MTHS)	Type of Fontan (1= Lateral tunnel, 2= Extracardiac, 3= Atriopulmonay)	Fenestration details (0= no, 1= yes)	Previous BTS (0- no, 1= yes)	Previous BDG(0- no, 1= yes)	Interval between BCPS and Fontan completion(mths)	Pre-operative arrhythmia (0- absent, 1- present	SV morphology (LV- 1/RV- 2/ Both- 3/ 4- Indeterminate)	PAP (mm Hg)	LA PRESSURE (mm Hg)	SV EDP (mm Hg)	TPG (mm Hg)	Juxtaposed RA appendage (0-no, 1- yes)	Common AVV (0- absent, 1- present)	heterotaxy (0- ABSENT,LEFT- 1, RIGHT- 2, Indeterminate- 3)	Presence of bilateral SVC (0- NO, 1- yes)
1	NEFSIA	5	2	231745	1.83	22	3.25	39	1	0	0	0	0	0	1				0	0	0	0	0
2	SAROKRISH	6	2	237135	4.5	54	2	24	1	1	0	0	0	0	1	11	7	8	4	0	0	0	0
3	FATHIMA	6	2	218741	5.5	66	0.75	9	2	0	0	1	50	0	1	6	5	8	1	0	0	0	0
4	VAISHNU	6	1	9502538	5.5	66	0.75	9	1	1	0	0	0	0	1	10	5	5	5	0	0	0	0
5	RAHUL	8	1	195304	7	84	1	12	2	1	0	1	89	0	3	11	6	10	5	1	0	0	0
6	AKASH	8	1	207897	5	60	3	36	1	1	0	1	52	0	1	14	10	13	4	0	0	0	0
7	MANYA	8	2	220354	6.5	78	1.5	18	2	1	0	1	49	0	1	8	6	8	2	1	0	0	0
8	MEENA	8	2	210755	6.83	82	0.916666667	11	2	0	0	0	0	0	3	10	0	0	10	0	0	1	1
9	PRAJITHA	9	2	215326	6	72	3.083333333	37	1	1	0	1	47	0	1	11	9	12	2	0	0	0	0
10	RISHBANU	9	2	210977	3	36	6	72	1	1	0	0	0	0	3	7	6	10	1	0	0	0	0
11	SHAMIL	9	1	186126	5	60	4.333333333	52	1	1	1	1	26	0	1	14	10	12	4	0	0	0	0
12	SAHAYA MELBIN	9	1	199164	7	84	2	24	2	1	0	1	79	0	3	12			12	0	0	0	0
13	RAJA	10	1	8602498	10	120	15	180	1	0	0	0	0	0	1	10	6	16	4	0	0	1	1
14	VISHNU	11	1	9709719	10	120	0.833333333	10	2	1	1	1	98	0	3	9	5	6	4	0	0	1	1
15	SANDRA	11	2	9801261	8	96	3.333333333	40	1	1	0	1	84	0	3	8	6	10	2	0	0	0	1
16	MINIKUTTY	11	2	5988	5	60	6	72	1	1	1	0	0	0	3	15			15	0	0	1	0
17	SIYAD	13	1	256846	11	132	2	24	2	1	0	0	0	0	1	9	7	8	2	0	0	0	0
18	ABDUL AYUB	13	1	9801489	3.5	42	9.5	114	1	1	0	0	0	0	3	10	5	10	5	0	0	0	0
19	SUHAIL	13	1	9804823	4.5	54	8	96	1	0	0	1	48	0	1	10	3	10	7	0	0	0	0
20	ARJUN	13	1	9608214	9	108	3.916666667	47	1	1	0	0	0	0	1				0	0	0	0	0
21	LEXSHMY	14	2	9509899	3.5	42	10.5	126	1	1	0	0	0	0	1	7	4	6	3	0	0	0	0
22	MOHAMMED RUSSEL	14	1	202442	8	96	6.666666667	80	1	1	0	0	0	0	1	8	3	8	5	0	0	0	0

23	NIKHIL HARIDAS	15	1	9603792	3.5	42	10.5	126	1	1	0	1	30	0	1	9	4	7	5	0	0	0	0
24	PRABEENA	15	2	9907790	7	84	8	96	1	1	0	0	0	0	1	8	7	8	1	0	0	0	0
25	NAIZAB	15	1	9608340	6	72	9	108	1	1	0	0	0	0	3	7	3	5	4	0	0	0	0
26	FEREENA FRANCIS	15	2	9408318	3.5	42	11	132	1	1	0	1	38	0	1	9	7.5	10	1.5	0	0	0	0
27	ASWIN	15	1	9607186	4	48	11	132	1	1	1	0	0	0	3	17	10	9	7	1	0	0	1
28	BARAKATH JAMIL	16	2	9701311	10	120	6	72	1	1	0	1	31	0	1	10	6	13	4	0	0	0	0
29	MANU MATHEW	16	1	9306978	5	60	11	132	1	0	0	0	0	0	1	6	5	10	1	0	0	0	0
30	AJITH	16	1	9900154	6	72	10	120	1	0	0	0	0	0	1	8	6	10	2	1	0	0	1
31	VISHESH	16	1	9309206	4.5	54	11.66666667	140	1	1	0	0	0	0	1	11	9	10	2	0	0	0	0
32	JINCEMON GEORGE	16	1	9409070	4	48	12	144	1	1	0	1	26	0	1	9	3	6	6	0	0	0	0
33	RAGHUNA DEVI	16	2	208380	10	120	6	72	1	1	0	0	0	0	1				0	0	0	0	0
34	BALAMANIKANDAN	16	1	9710558	2.5	30	11	132	1	1	0	0	0	0	3	10	7	8	3	0	0	0	1
35	CHRISTO MONISHA	17	2	202546	14	168	2.833333333	34	1	1	0	1	54	0	1	16	11	14	5	1	0	0	0
36	SUFAIJA	17	2	9507723	9	108	8.5	102	1	1	0	1	28	0	3	16	8	10	8	0	0	0	0
37	KRISHNA PRIYA	17	2	9303453	4.5	54	12.33333333	148	1	1	0	0	0	0	3	10	10	14	0	0	0	0	0
38	GANESH KUMAR	18	1	9205811	4	48	14	168	1	0	0	0	0	0	1	11	10	10	1	1	0	0	0
39	LIJIN JOSE	18	2	9302652	5	60	13	156	1	1	0	1	20	0	1	10	7	12	3	0	0	0	0
40	SANTHUMON	18	1	9205571	4	48	13.33333333	160	1	0	0	0	0	0	1	13	10	10	3	1	0	0	0
41	SANTHANA KUMAR	18	1	9800142	9	108	9	108	1	1	0	0	0	0	3	8	4	10	4	0	0	0	0
42	CHANSON THOMAS	18	1	9303423	5	60	5	60	1	1	0	0	0	0	2	9			9	0	1	0	0
43	SARATH	19	1	9500635	5.5	66	13.5	162	1	1	0	0	0	0	3	11	7	7	4	0	0	0	0
44	MANIMARAN	19	1	9400054	10	120	9	108	1	1	0	0	0	0	1	9	6	10	3	1	0	0	0
45	AKASH	19	1	9109304	5.5	66	13	156	1	0	0	0	0	0	3	10	8	12	2	0	0	0	0
46	SELVA VADIVU	19	2	9503037	6	72	13	156	1	0	0	0	0	0	1	14	9	9	5	1	0	0	0
47	FASEELA	19	2	184755	10	120	9	108	1	1	0	0	0	0	2	9	6	8	3	0	1	1	1
48	RAMESH	19	1	9005228	6	72	13	156	1	1	0	0	0	0	1	12	4	6	8	0	1	1	0
49	SUKUMAR	20	1	9006973	8	96	12	144	1	1	0	1	22	0	3	15	4	6	11	0	0	0	0
50	SANOOP	20	1	9006622	9	108	11	132	1	1	0	0	0	0	3	10	5	10	5	1	0	0	1
51	STEPHY MATHEW	20	2	9204281	7	84	13	156	1	1	0	0	0	0	3	10	8	10	2	1	0	0	0
52	LIJI	20	2	9608330	11.5	138	9	108	1	1	0	0	0	0	1	20	16	18	4	0	0	0	0
53	NEETHU	21	2	8900631	11	132	10	120	1	1	1	0	0	0	3	10	5	9	5	0	0	0	0
54	LIJISHA	21	2	8909209	7	84	13.5	162	1	0	0	0	0	0	1	15	5	10	10	0	0	0	0
55	PRANAVYA	21	2	9402050	9	108	11.5	138	1	0	0	0	0	0	3	11	6	10	5	0	0	0	0
56	REMYA	21	2	8905556	10	120	11	132	1	1	1	0	0	0	3	8	7	10	1	1	0	1	0
57	SHIMNA MOL	22	2	8902009	10	120	12	144	1	1	1	0	0	0	3	12	6	12	6	1	0	0	0
58	SREEJA	22	2	9101722	10	120	11.66666667	140	1	1	0	0	0	0	1	13	8	14	5	0	0	0	0

59	MOHAMMED RIYAZ	22	1	9909189	12	144	9	108	1	1	0	0	0	0	1	8	3	12	5	0	0	0	0
60	MANOSH	22	1	8801477	11	132	11	132	1	1	1	0	0	0	1	16	12	10	4	0	0	0	0
61	SATHU THIRUMALAIAF	29	1	9905433	19	228	10	120	4	0	0	0	0	0	3	16	9	6	7	1	0	1	1
62	VIBIN PRABHAKARAN	31	1	8709111	14	168	16.5	198	1	0	1	0	0	0	1	12	10	10	2	0	0	0	0
63	KUMARAN	33	1	9407469	19	228	14	168	1	0	0	0	0	0	3	12	6	6	6	0	0	0	0
64	MANJU	34	2	9307750	22	264	12	144	1	1	0	0	0	0	1	8	4	5	4	0	0	0	0
65	BIJU	36	1	696	23	276	13	156	1	0	1	0	0	0	3	9	4	9	5	0	0	0	0
66	SHEELA	38	2	1328	25	300	10	120	1	1	1	1	56	0	3	8	6	8	2	0	0	0	0

S.N.	NAME	Presence of interrupted IVC (0-no, 1- yes)	basal Systemic saturation (%)	basal AVVR (0- absent, 1- 1+ and 2+, 2- 3+ and 4+)	basal Ejection fraction (%)	Anti-coagulation (0- no, 1- yes)	Anti-platelets(0- no, 1- yes)	Death (0- no, 1- yes)	[illegible] 1- yes)	HEART FAILURE EPISODES (0-5)	NYHA class (1 to 4)	Basal saturation (%)	Ejection fraction (%)	e velocity (m/sec)	a velocity (m/sec)	e decelaration time (msec)	Ea	Aa	DIASTOLIC DYSFUNCTION (0- absent, 1- I, 2- II, 3- III, 4-IV)	AVVR(0- absent, 1- 1+ and 2+, 2- 3+ and 4+)	*AR(0- absent, 1- 1+ and 2+, 2- 3+ and 4+)*	time of onset	Arrhythmia (0- absent, 1- AT, 2- AF/AFL, 3- JR, AVRT-4, AVNRT-5, VT/VF)
1	NEFSIA	0	80	1	60	0	0	0	0	0	1	96	62	0.6	0.5	160	0.09	0.05	0	1	*0*	NA	0
2	SAROKRISH	0	80	0	60	1	0	0	0	0	1	95	63	0.6	0.5	160	0.08	0.15	0	0	*0*	NA	0
3	FATHIMA	0	86	0	65	0	0	0	0	0	1	95	80	0.7	0.5	160	0.16	0.09	0	1	*0*	NA	0
4	VAISHNU	0	75	0	74	0	0	0	0	0	1	95	67	1	0.7	180	0.11	0.07	3	1	*0*	NA	0
5	RAHUL	0	77	1	70	1	0	0	0	0	1	98	70	0.5	0.6	160	0.11	0.07	0	1	*0*	NA	0
6	AKASH	0	83	0	85	1	0	0	0	0	1	98	70	0.6	0.5	180	0.12	0.08	0	0	*0*	NA	0
7	MANYA	0	88	0	75	1	0	0	0	0	1	96	57	0.5	0.5	210	0.12	0.07	0	0	*1*	1	1
8	MEENA	0	70	0	65	1	0	0	0	0	1	95	65	NA	NA	NA	NA	NA	NA	1	*0*	NA	0
9	PRAJITHA	0	88	0	70	0	0	0	0	0	1	93	62	0.6	0.5	200	0.14	0.06	0	1	*0*	NA	0
10	RISHBANU	0	82	0	64	0	1	0	0	0	1	86	64	0.5	0.4	140	0.12	0.08	0	1	*0*	NA	0
11	SHAMIL	0	80	0	65	0	1	0	0	0	1	99	76	1.3	0.7	260	0.11	0.05	3	1	*0*	4	1
12	SAHAYA MELBIN	0	88	1	60	1	0	0	0	0	1	95	60	NA	NA	NA	NA	NA	NA	1	*1*	NA	0
13	RAJA	1	76	1	56	1	0	0	0	2	2	82	50	0.5	0.6	220	0.14	0.05	1	1	*1*	14	1
14	VISHNU	0	91	1	79	1	0	0	0	0	1	96	70	0.5	0.5	160	0.07	0.04	3	1	*0*	NA	0
15	SANDRA	0	97	1	79	0	1	0	0	0	1	96	73	0.8	0.9	220	0.08	0.04	3	1	*0*	NA	0
16	MINIKUTTY	0	87	0	65	0	0	1	0	0	3	60	65	NA	NA	NA	NA	NA	NA	0	*0*	NA	0
17	SIYAD	0	85	0	65	1	0	0	0	0	1	95	70	0.7	0.6	140	0.08	0.16	3	1	*0*	NA	0
18	ABDUL AYUB	0	83	0	76	0	1	0	0	0	1	98	60	0.8	0.6	210	0.11	0.06	0	2	*0*	NA	0
19	SUHAIL	0	82	0	74	0	0	0	0	0	1	93	63	0.8	0.5	200	0.17	0.06	0	1	*0*	NA	0
20	ARJUN	0	66	1	60	1	0	0	0	0	1	92	58	0.6	0.4	180	0.15	0.09	0	1	*1*	NA	0
21	LEXSHMY	0	91	0	65	0	1	0	0	0	1	98	58	0.5	1.3	160	0.07	0.05	1	0	*0*	NA	0
22	MOHAMMED RUSSEL	0	70	0	60	0	1	0	0	0	1	96	70	0.7	0.5	300	0.1	0.05	0	1	*0*	NA	0

23	NIKHIL HARIDAS	0	90	0	74	0	0	0	0	0	1	95	71	0.5	0.4	200	0.14	0.04	0	1	0	NA	0
24	PRABEENA	0	78	0	66	0	1	0	0	0	1	94	58	0.7	0.6	320	0.1	0.05	0	0	0	NA	0
25	NAIZAB	0	66	0	69	0	0	0	1	0	2	82	56	0.6	0.5	290	0.14	0.06	0	1	0	NA	0
26	FEREENA FRANCIS	0	86	1	64	0	1	0	0	0	1	92	61	0.6	0.8	220	0.09	0.05	1	1	0	13	2
27	ASWIN	0	80	0	61	0	1	0	0	0	1	96	55	NA	NA	NA	NA	NA	NA	1	2	NA	0
28	BARAKATH JAMIL	0	88	1	64	1	0	0	0	0	1	97	59	0.6	0.7	130	0.09	0.08	1	1	1	6	1
29	MANU MATHEW	0	73	1	68	0	0	0	0	0	1	93	58	0.5	0.6	160	0.12	0.05	1	0	0	NA	0
30	AJITH	0	86	0	73	1	0	0	0	0	1	98	63	0.6	0.5	250	0.15	0.06	0	1	0	10	1
31	VISHESH	0	76	0	69	0	0	0	0	0	1	92	75	0.9	0.8	270	0.08	0.04	3	0	0	NA	0
32	JINCEMON GEORGE	0	89	0	64	0	0	0	0	0	1	90	66	0.7	0.4	160	0.16	0.06	0	1	0	1	3
33	RAGHUNA DEVI	0	80	0	68	0	1	0	0	0	1	92	70	NA	NA	NA	NA	NA	NA	1	0	NA	0
34	BALAMANIKANDAN	0	82	0	65	0	0	0	0	1	1	96	60	NA	NA	NA	NA	NA	NA	1	0	10	3
35	CHRISTO MONISHA	0	66	1	63	1	0	0	0	1	2	96	55	0.6	0.7	270	0.07	0.04	3	1	1	3	1
36	SUFAIJA	0	80	0	65	0	0	0	0	0	1	95	66	0.6	0.6	220	0.11	0.08	1	1	0	NA	0
37	KRISHNA PRIYA	0	74	0	62	0	1	0	0	0	1	91	51	0.6	0.4	160	0.09	0.06	0	1	1	NA	0
38	GANESH KUMAR	0	60	0	69	0	0	0	0	0	1	95	63	0.6	0.4	140	0.12	0.08	0	1	1	NA	0
39	LIJIN JOSE	0	83	0	55	0	0	0	0	0	1	88	66	0.7	0.5	250	0.15	0.07	0	1	0	NA	0
40	SANTHUMON	0	56	0	72	0	0	0	0	0	1	96	69	0.6	0.5	270	0.12	0.05	0	1	0	NA	0
41	SANTHANA KUMAR	0	70	1	66	0	0	0	0	1	1	96	80	NA	NA	NA	NA	NA	NA	0	0	NA	0
42	CHANSON THOMAS	0	70	1	68	0	1	1	0	1	2	94	65	NA	NA	NA	NA	NA	NA	2	0	4	1
43	SARATH	0	93	1	58	0	1	0	0	1	1	97	67	0.5	0.7	180	0.12	0.07	1	1	0	NA	0
44	MANIMARAN	0	88	1	68	0	1	0	0	0	1	93	58	0.5	0.5	180	0.15	0.08	0	1	1	9	1
45	AKASH	0	62	0	60	0	0	0	0	0	1	90	63	0.6	0.5	260	0.15	0.06	0	1	1	11	1
46	SELVA VADIVU	0	72	0	70	0	0	0	0	0	1	95	60	0.6	0.4	160	0.13	0.08	0	1	0	NA	0
47	FASEELA	0	69	1	73	1	0	0	0	0	1	97	72	NA	NA	NA	NA	NA	NA	1	0	NA	0
48	RAMESH	0	70	1	64	0	1	0	0	0	1	96	60	NA	NA	NA	NA	NA	NA	1	1	NA	0
49	SUKUMAR	0	85	0	73	0	0	0	0	0	1	95	78	0.8	0.5	160	0.16	0.04	0	1	0	11	1
50	SANOOP	0	80	0	70	1	1	0	0	0	1	92	63	0.6	0.8	220	0.1	0.05	1	1	0	10	3
51	STEPHY MATHEW	0	82	0	75	0	0	0	0	0	1	91	56	0.7	0.8	230	0.09	0.09	1	1	0	NA	0
52	LIJI	0	70	0	45	0	0	0	0	0	1	83	62	0.4	0.6	230	0.12	0.09	1	0	0	NA	0
53	NEETHU	0	82	0	65	0	1	0	0	0	1	97	70	0.7	0.4	150	0.14	0.08	0	0	1	10	1
54	LIJISHA	0	82	1	78	1	0	0	0	0	1	90	63	0.7	0.5	130	0.12	0.07	0	1	0	NA	0
55	PRANAVYA	0	72	0	65	0	0	0	0	0	1	95	57	0.6	0.5	230	0.09	0.06	0	1	2	NA	0
56	REMYA	0	85	0	65	0	1	0	0	0	1	93	66	0.7	0.7	180	0.1	0.06	0	1	1	NA	0
57	SHIMNA MOL	0	89	0	60	0	1	0	0	0	1	95	59	0.8	0.7	200	0.11	0.07	0	1	0	NA	0
58	SREEJA	0	71	0	62	0	1	0	0	0	1	90	61	0.6	0.6	160	0.21	0.07	0	1	0	NA	0

59	MOHAMMED RIYAZ	0	72	1	73	1	0	0	0	0	1	90	58	0.6	0.9	300	0.12	0.07	1	1	*0*	NA	0
60	MANOSH	0	60	0	59	0	1	0	0	0	1	94	59	0.5	0.5	170	0.15	0.07	0	1	*1*	NA	0
61	SATHU THIRUMALAIAF	1	78	0	57	1	1	0	0	0	1	66	62	NA	NA	NA	NA	NA	NA	1	*0*	3	2, 3
62	VIBIN PRABHAKARAN	0	82	0	65	0	0	0	0	0	1	98	71	0.5	0.8	190	0.11	0.07	1	0	*0*	7	1
63	KUMARAN	0	81	0	72	0	0	0	0	1	1	97	72	NA	NA	NA	NA	NA	NA	0	*0*	NA	0
64	MANJU	0	86	1	68	0	0	0	0	0	1	98	65	NA	0.6	200	0.15	0.1	NA	1	*0*	11	3
65	BIJU	0	77	0	53	0	0	0	0	0	1	95	68	0.6	0.8	140	0.06	0.09	3	1	*1*	NA	0
66	SHEELA	0	89	0	75	0	0	0	0	0	2	93	65	0.5	0.4	220	0.15	0.06	0	0	*1*	7	3

CONTENTS

Introduction

Historically, quantitative coronary analysis (QCA) has been the reference method for the angiographic assessment of coronary arteries. (1; 2; 3; 4; 5) However the limitations of coronary angiography, particularly with respect to underestimation of coronary diameter and disease severity are well described. (6; 7; 8; 9) Accurate reference segment and lesion site lumen dimension measurements are essential for assessing acute and late results of coronary interventions. However reference diameter as measured by QCA may be misleading. The 3D-reconstruction system has been developed to improve visualisation and diagnostic information of QCA. Three dimensional QCA (3D QCA) has provided additional insight on QCA, especially with respect to length of lesion. (10) However for reference luminal diameter, 3D QCA studies have shown conflicting results. (11; 12; 13) Intravascular ultrasound (IVUS) is an invasive imaging technique used to visualize coronary cross-sectional anatomy and is superior to coronary angiography for the assessment of vessel size, calcium content, and lesion severity. Although time consuming, IVUS is an accurate method of sizing the reference diameter (14; 15; 16; 17; 18; 19). So we compared and correlated the IVUS reference lumen diameter with QCA and 3D QCA.

Aims & Objectives

1. To compare the coronary artery reference diameter as measured by intravascular ultrasound (IVUS), 3 Dimensional coronary angio reconstruction (3D QCA) and Quantitative Coronary Angiogram (QCA).
2. To compare the Left main coronary artery luminal diameter as measured by IVUS, 3D QCA and QCA.

HYPOTHESIS:

1. QCA coronary artery reference diameter needs to be confirmed by better imaging modalities.
2. Three dimensional reconstruction of angiogram with 3D QCA software will give more reliable reference segment lumen diameter than 2D QCA.
3. IVUS, an universally accepted gold standard for in-vivo coronary analysis will validate the QCA and 3D QCA measurements. Through linear equation, IVUS diameter can be derived from QCA and 3D QCA.
4. Angiographically normal Left main lumen diameter (IVUS) is not reported in Indian population. It can be compared with that of western population.

Review of Literature

The importance of the severity of a coronary artery stenosis was shown in the Coronary Artery Surgery Study (CASS). In this study, the risk of myocardial infarction (MI) over a period of 3 years was 2% for patients with a coronary artery stenosis of less than 50%, 7% for a stenosis of 50%–70%, 8% for a stenosis of 70%–90%, and 15% for a stenosis of greater than 90%. (20) Conversely, other studies have shown that 80% of all MIs occur in lesions with a diameter stenosis less than 50%. (21; 22) There are two potential explanations for this discrepancy. First, patients with coronary artery disease have a large number of angiographically "insignificant" lesions, but only a few "significant" stenoses. Thus, while the more significant stenosis is more likely to lead to an MI, the shear number of "insignificant" lesions makes it more likely that a culprit lesion will have started out as "insignificant." Second, IVUS and physiologic lesion assessment studies have questioned the ability of angiography to define the critical stenosis. (23)

Quantitative coronary analysis (QCA):

Visual interpretation of coronary artery remains the standard for clinical diagnosis and treatment of CAD. However, the need for an objective, accurate, unbiased, and reproducible assessment of stenosis severity and vessel size led to the development of QCA. QCA is an inexpensive, fast, and reproducible

technique that can be used during the procedure (on-line), after the procedure, or at a core laboratory. As compared to QCA measurements, visual angiographic inter-pretation overestimates lesion severity prior to percutaneous transluminal coronary angioplasty (PTCA) and underestimates lesion severity after the procedure. (24; 25) QCA measurements are reproducible; as a result, these techniques have been used in most major interventional trials. (26; 27; 28)

Limitations of QCA:

QCA is only a lumenogram and is confounded with numerous limitations. Studies correlating angiographic and histopathologic anatomy concluded that angiography usually underestimates severity of a lesion, especially with a 51% to 75% histolopathologic cross-sectional area narrowing [4, 5] and in patients with multivessel disease. (29) An important explanation for the discrepancy between pathologic and angiographic findings is the presence of compensatory dilation of the arterial wall in direct response to the accumulation of atherosclerotic plaque (the Glagov phenomenon). An absolute reduction in lumen dimensions typically does not occur until the lesion occupies approximately an estimated 40%–50% of the area within the internal elastic membrane. As a result, most of the atherosclerotic burden is contained within angiographically normal reference segments. Although many lesions occur in the setting of positive remodelling (which eventually fails to

compensate for plaque growth), others are produced by negative remodelling, implying that vessel shrinkage (and not plaque accumulation) accounts for most of the lumen narrowing. (30)

Another major factor contributing to this discrepancy is the assumption that the segment of the artery adjacent to the lesion is normal; in fact, it is typically involved in the atherosclerotic disease process. (23) In addition, there are a number of QCA systems with different performance characteristics. In one study, most QCA systems overestimated smaller luminal diameters and underestimated larger lumens. (31) Some of these errors have been resolved by recalibration of the QCA software. Nevertheless, these systems are still confounded by a number of potential sources of error: overlapping side branches, emergence of a side branch immediately before or after a stenosis, foreshortening of the stenotic segment, poststenotic dilatation, and marked irregularities of the segment adjacent to the lesion. (32; 33) Furthermore, debate still exists regarding the relative merits of the two quantitative coronary angiography techniques more frequently used, namely edge-detection (ED QCA) and videodensitometry (VID QCA). (31; 34) In edge-detection quantitative coronary angiography the boundaries of the selected coronary segment are automatically detected by an algorithm using the weighted sum of the first and second derivative functions of the brightness profile. The reference segment is either selected by the operator or automatically

interpolated by the system. The catheter, used as a scaling device, allows absolute measurements. Eventually, lumen cross-sectional areas are 'calculated' from orthogonal projections or from the worst view. Conversely, videodensitometry is based on the relationship between the optical density of the contrast filled lumen and absolute vessel dimensions. The cross-sectional area function is obtained from values calibrated for the amount of X-ray absorption after subtracting the brightness background contribution. Calibration of videodensitometric images are performed by equalizing the reference area to that calculated from the edge-detection algorithm. (34) Therefore, this technique measures vessel dimensions independent of lesion contour and luminal shape. It requires, however, homogeneous complete opacification of the lumen and may be less reliable in calcified vessels. Whereas edge-detection quantitative coronary angiography has gained widespread acceptance, the clinical value of videodensitometry remains controversial.

Intravascular Ultrasound (IVUS):

IVUS provides transmural tomographic images of coronary arteries in vivo. The coronary artery is selectively cannulated by a catheter incorporating a miniature transducer which emits high frequency ultrasound (usually in the range of 20 to 50 MHz). As the transducer is moved through the artery, ultrasonic reflections are electronically converted to cross sectional images. It

has the unique ability to provide direct visualization of the atherosclerotic plaque on the coronary vessel wall. (35; 36; 17) The echo reflectivity of the plaque may be used as a surrogate to determine its underlying histology. It provides the pathophysiological mechanism, causing coronary narrowing. It gives accurate measurements of both lumen area and total vessel area. This comprehensive information has represented a major breakthrough in our understanding of coronary artery disease, a disease of the vessel wall. IVUS studies have confirmed the pathologic observations that atherosclerosis is commonly present in angiographic, apparently normal, reference segments. (36) In a series of 73 patients studied pre-intervention, IVUS minimum lumen cross sectional area correlated strongly with coronary flow reserve measured by Doppler Flow wire (EndoSonics Corp, Rancho Cordova, CA) velocimetry ($r = 0.831$, $p < 0.0001$). (37) In addition, a pre-intervention minimum lumen area greater than or equal to 4.0 mm2 had a diagnostic accuracy of 92% in predicting a coronary flow reserve greater than or equal to 2.0. Von Birgelen et al. demonstrated that plaque progression as measured by IVUS was associated with a significantly increased risk of clinical events as predicted by established risk-scoring systems. (38) In addition, IVUS had shown that despite an apparently satisfying angiographic result, stents are often insufficiently deployed, and high-pressure balloon inflation may be necessary to achieve complete stent expansion. (39) IVUS, is the present standard for the evaluation of optimum stent deployment. Qualitative and quantitative IVUS

analyses are usually performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies. (40) Lumen cross-sectional area (CSA) is quantified by planimetry of the leading edge of the blood-intima acoustic interface. The outer vessel border (external elastic membrane [EEM] CSA) is detected as the interface between media and adventitia. Atheroma-CSA is calculated as the difference between EEM-CSA and lumen-CSA. However, IVUS is expensive, requires exchange of the balloon for the IVUS catheter, and can be time consuming. (41)

Comparison of IVUS versus QCA:

Previous studies comparing coronary angiography and IVUS have consistently shown disparities between the presence, location, distribution, composition, and severity of coronary artery atherosclerosis. (14; 17; 36; 42; 43; 35) There are systematic differences between IVUS and QCA in the measurement of reference and lesion lumen dimensions. In patients with intermediate lesions QCA correlates poorly with IVUS. Alfonso et al found a moderate correlation between both techniques at sites which were angiographically normal, but contained plaque on IVUS. However the correlation deteriorated in complex lesions or following intervention. (35) Peters et al. evaluated the correlation between edge-detection quantitative coronary angiography, videodensitometry and intravascular ultrasound in 161

patients after successful balloon angioplasty. They concluded IVUS derived lumen dimensions corresponded more closely to videodensitometry than to edge-detection quantitative coronary angiography measurements. However, minimal lumen area, as obtained by IVUS, was significantly larger than that measured by videodensitometry and edge-detection QCA. (44) In a detailed study, Ozaki et al concluded that the agreement between IVUS and QCA progressively deteriorated according to the degree of vessel damage, but this finding was less evident with videodensitometry. (45) De Scheerder compared IVUS and QCA for measurement of luminal diameters in normal and moderately diseased coronary arteries; the correlation was excellent ($r= 0.92$, $p <0.0001$) in angiographically normal coronary arteries, but only moderate for mild stenosis ($r=0.467$, $p < 0.001$). (14) Abizaid et al noted that, IVUS reference segment measurements are consistently larger than QCA with an average (but not predictable) difference of 0.5 mm. (46) Hoffmann et al concluded that reference lumen dimensions measured by IVUS were consistently larger than measured by QCA. (47) Reiber et al reported a long-term variability of 0.36 mm for measurement of minimum lumen diameters and 0.66 mm for measurement of reference diameters. (28) Accuracy and precision vary among QCA systems, with only a moderate correlation in the measurement of reference and lesion lumen diameters. (48) Fernandes et al study in Intermediate Coronary Lesions revealed a significant underestimation of the reference segment luminal diameter by angiography as compared to

IVUS. Linear regression analysis showed a weak correlation between the two methods for the assessment of reference segment luminal diameter ($r = 0.4$; $p < 0.001$). (49)

Discrepancy between IVUS and QCA:

With increasing vessel damage and increasing luminal complexity after intervention, a progressive deterioration in the relationship between the IVUS and QCA measurements was seen. Thus, the cross-sectional shape of the vessel lumen postintervention may be a significant factor in the discrepancy between IVUS and ED QCA measurements. MLD obtained from ED QCA depends on the angiographic projection. Even when calculated from two orthogonal views, the chances of obtaining the exact minimal and maximal diameters using ED QCA would be small. IVUS and VID are not projection dependent, and both would provide a measure of the "depth" as well as the "width" of the lumen cross section. ED, however, provides only a measure of one diameter (the "width") of the lumen. Consistent with this, most studies showed that VID QCA provided a better agreement in relation to IVUS measurements than ED QCA. While IVUS is not universally available and involves additional time and expense, QCA is more widely available and less time-consuming. VID QCA may thus be the "poor man's" IVUS, especially in lesions with complex morphology. Two additional IVUS related factors may also have contributed to the observed discordance between IVUS and quantitative angiographic

measurements. Elliptical angulation of the ultrasound catheter within the longitudinal axis of the vessel may have led to overestimation of reference luminal dimensions by IVUS. Additionally, introduction of the ultrasound catheter may have itself resulted in tacking back of dissection flaps, with a resultant larger lumen during IVUS examinations postintervention compared with the less invasive technique of contrast angiography. However, at times QCA may yield larger luminal measurements than IVUS, this increase in the apparent angiographic diameter may be caused by extraluminal contrast within fissures, cracks, and dissection as seen around the true lumen. (45)

Three dimensional QCA: 3D QCA

Conventional angiography provides only two-dimensional image of the vessel lumen. It is limited by vessel foreshortening, interobserver variability and out- of-plane magnification error. Furthermore, it has been shown to poorly correlate with vessel dimensions obtained by IVUS. 3D QCA based on routine angiographic projections has emerged as a new tool to increase the assessment capabilities for both diagnostic and interventional cardiology. (11) Studies comparing QCA and 3D QCA have shown good agreement between 2 modalities in terms of lesion and reference segment assessment. Rittger et al compared 3D QCA and QCA in 61 patients and concluded, coronary artery diameter at lesion and reference segment were comparable. They also found

that, stenosis length measurements were more accurate using 3D system as compared to QCA, with respect to true balloon length.

Comparison between 3D QCA and IVUS:

It was thought that the 3D QCA could resolve limitations of standard 2D QCA. 3D QCA has been shown to be effective in measuring in vivo dimensions of coronary stent deployment and phantom stenosis. (50; 51) Further studies have demonstrated that the use of three-dimensional reconstruction rather than of two-dimensional angiography of coronary vessels is capable of optimizing appropriate stent selection in clinically treated lesions. (11; 12) Studies comparing 3D QCA and IVUS had yielded mixed results. Collingwood et al studied 34 patients with intermediate lesions. They found minimal CSA by 3D QCA significantly correlated in a linear fashion with minimal CSA by IVUS. But no correlation was noted in MLD, % diameter stenosis and % area stenosis. They concluded that, further study is necessary to evaluate the reproducibility and clinical application of three-dimensional angiography. (52) Gollapudi et al analysed role of 3D QCA in optimizing length of DES in 38 lesions. They concluded that 3D reconstruction can help choose the appropriate stent length and number during DES implantation. (11) Tu et al compared coronary artery segment length by 3D QCA and IVUS in 20 patients. They concluded that, 3D QCA software package can accurately assess the actual arterial segment length. The difference in segment lengths measured from 3D QCA and IVUS was

correlated with the accumulated curvature of the segment. (53) Yong et al investigated whether 3D and 2D-QCA measurements differed in their accuracy in predicting reduced fractional flow reserve (FFR), and how this varied with stenosis severity and the FFR cut-off used. They found that, 3D-QCA showed a non-significant trend towards more accurate prediction of FFR < 0.75 than 2D QCA. (54) However 3D-QCA is still 'luminography' and cannot overcome the limitations involved in angiography image resolution. (51) Tsuchida et al, in a phantom lesion model indicated that both three-dimensional angiography and two-dimensional quantitative angiography systematically underestimate true vessel diameter, as measured by optical coherence tomography. (13) Furthermore, underestimation was more severe with three-dimensional reconstruction rather than with two-dimensional angiography. Such work suggests that angiography in general and three-dimensional angiography in particular may have limitations in measuring absolute vessel dimensions. Although IVUS currently yields the most accurate measurements of vessel geometry and lesion severity, 3D-QCA measurements can be performed on existing standard coronary angiography images without the need for additional time or equipment during the procedure. (50)

Studies on angiographically normal Left mains:

Many studies have shown that angiographically normal left main (LM) may harbor significant atheroma burden with or without luminal stenosis.

QCA assessment of left main may underestimate LM reference diameter and stenosis. Hermiller et al showed that, IVUS detected plaque in 24 of 27 (89%) angiographically normal LM arteries. (55) These findings were confirmed in studies by Yamagishi and Gerber. (56; 57) They also showed that in patients with angiographic disease, there was no correlation between QCA and IVUS percent area stenosis. Similarly, Riccardi et al in 107 patients with angiographically normal LM found 30% area stenosis by IVUS. They concluded that angiographically silent, LM disease detected by IVUS is an independent predictor of cardiac events and may serve as a marker for future events. (58) Abizaid et al correlated IVUS and QCA in 122 patients with normal and intermediate LM lesion (<50%). The QCA reference diameter 3.91 ± 0.76 mm, correlated moderately with IVUS diameter of 4.25 ± 0.78 mm, r = 0.492, p = 0.0001. The lesion site MLD by QCA correlated less well with IVUS. (59) Fassa et al found that the lower range of normal LM minimal lumen area (MLA) is 7.5mm^2. Deferring intervention for lesions with MLA > 7.5 mm^2, did not increase adverse events in their mean follow up of 3 years. (60) Sano et al evaluated 115 patients with angiographically intermediate LM by IVUS. They used an MLA by IVUS <6.0 mm^2 as the criterion for a significant LM stenosis because it has been shown to correlate with a fractional flow reserve <0.75. (61) The main reasons for the discrepancy between angiography and necropsy or IVUS appear to be the following: 1) diffuse atherosclerotic involvement affects the diameter stenosis calculation

because of the lack of a normal reference segment, 2) a short LM also makes identification of a normal reference segment difficult, 3) there is compensatory enlargement (positive remodeling) of the vessel as plaque burden increases to preserve lumen size as shown by Glagov et al. (62) Coronary artery size in Indians has been reported to be significantly smaller when compared to that of the western population. (63; 64) This has been attributed to their low body surface area. In contrast, Saikrishna et al reported normal coronary artery diameter in Indians by QCA. Mean LM diameter in their study was 3.72 ± 0.65 mm. They concluded that at least some branches of the left coronary system are similar to that reported in the West and RCA dimensions are greater than west. (65)

Patients & Methods

A cross sectional study was performed on 24 patients who underwent both angiographic and IVUS examinations during percutaneous coronary intervention. Detailed retrospective review of medical records, coronary angiogram and IVUS study was made with standardized forms. Angiographic images were recorded at 15 frames/sec by a monoplane X-ray angiogram (AXIOM-Artis, Siemens, Germany). IVUS scans were performed at operator discretion by manual pullback with a 40 MHz transducer catheter and 2.2 F imaging sheath (Volcano s5, Volcano Corporation, USA). The decision to intervene on a lesion is frequently made in the catheterization laboratory based on the visual estimation of the lesion's severity. Lesions with more than 70% stenosis on visual quantification are usually considered hemodynamically significant and submitted to intervention. In majority of cases, IVUS examination was done after balloon modification the plaque to facilitate IVUS catheter advancement. Three dimensional angio reconstructions were done with the 3D QCA software. The same vessel segments of interest were identified and measured on QCA, 3D QCA and IVUS images.

Two-dimensional quantitative coronary angiography (2D QCA) –

2D QCA was performed offline using standard commercial soft ware on workstation (Quant, Siemens), which is derived from the CAAS II system (Pie Medical Imaging, Maastricht, Netherlands). Automated distance

calibration was used to determine pixel size. All analyses were performed during the ECG-gated end-diastolic frame. Angiographic views with the least foreshortening and yielding the best depiction of the stenosis were used. Edge detection correction was performed if required.

Three-dimensional quantitative coronary angiography (3D QCA) –

Three-dimensional quantitative coronary angiography was performed offline using 3D reconstruction software on the Leonardo workstation (IC3D, Siemens), which is derived from the Cardio-op B system (Paieon Medical, Rosh Ha'ayin, Israel). The contrast-filled non- tapered part of the guiding catheter was used to calibrate pixel size. The two best orthogonal angiographic views of the target lesion in the ECG-gated end-diastolic frame were used for 3D-QCA reconstructions. The site of minimum luminal diameter, proximal and distal coronary artery reference segments were manually identified on the first angiographic plane, and repeated in a second image, at least 30° orthogonal to the first. Proximal and distal planes were derived automatically, and after the centre of the arterial lumen was manually identified, the software automatically generated a 3D representation of the arterial lumen (as shown in Figure 1). Minimum luminal diameter (MLD), percentage area stenosis, percentage diameter stenosis and reference segment diameter were measured using both 3D- and 2D-QCA. All measurements were performed twice and averaged.

Quantitative IVUS :

Validation of cross-sectional measurements of external elastic membrane (EEM), stent, lumen and plaque plus media (P+M) CSAs by IVUS have been previously reported (40). The term EEM is shorthand for the media–adventitia border, which is a reproducible measure of the total arterial CSA. Because media thickness cannot be measured accurately, percentage Plaque + Media (P+M) was used as a measure of atherosclerotic plaque burden. The target lesion and reference segments were assessed before stenting by measuring: 1) EEM CSA (mm^2); 2) lumen CSA (mm^2); 3) MLD (mm); 4) EEM (mm) and 5) P+M CSA (mm^2).

The reference segments were identified as the most normal-looking cross sections <10 mm proximal and distal to the lesion, but before any side branch. This method of reference segment selection has been previously published. IVUS images at lesion and reference segment of a study subject is shown in Figure 2.

Figure 1. 3D reconstruction of an LAD lesion

a) QCA b) 3D QCA

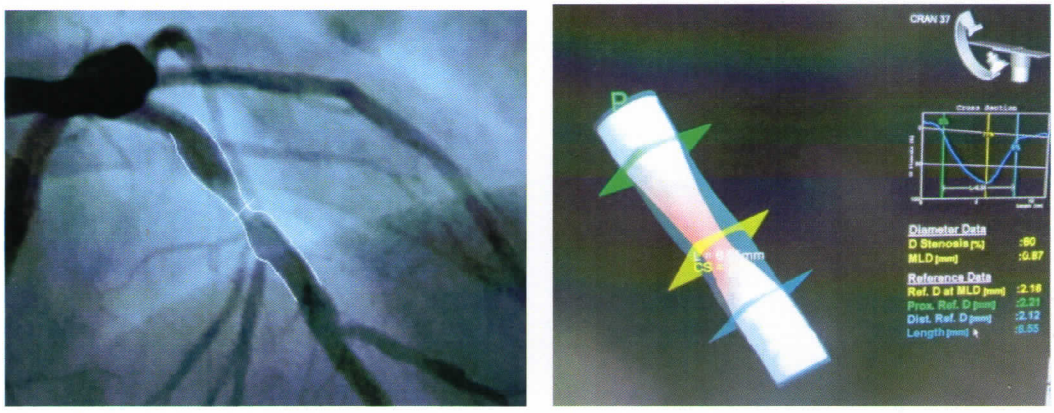
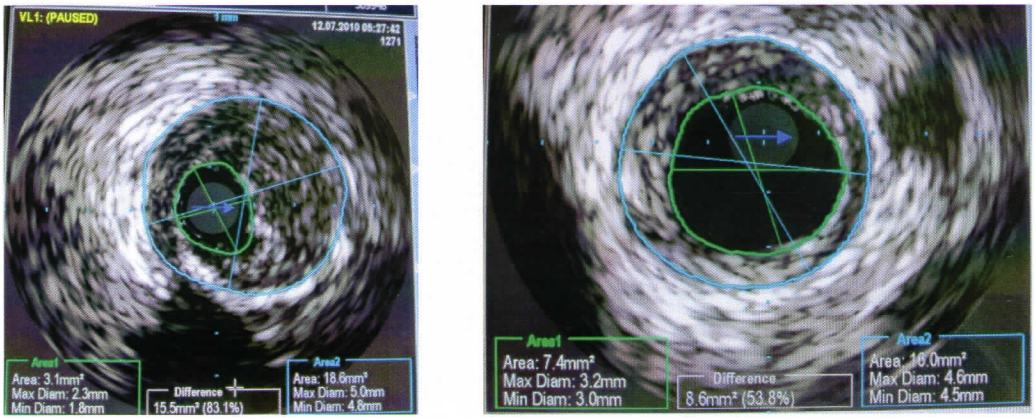


Figure 2. IVUS cross sectional images:

a) At lesion b) At distal reference segment



IVUS, 3D QCA and 2D QCA were compared in their measurements of reference diameter and left main diameter. The 3D QCA and 2D QCA assessment were made prior to balloon dilatation of lesion. As IVUS assessment of lesion was temporally different, it was not compared with 3D QCA and QCA. The 3D QCA and 2D QCA were compared in their measurements of minimum luminal diameter (MLD), percentage area stenosis and percentage diameter stenosis.

Statistical analysis :

Data were analyzed using SPSS statistical software (SPSS Inc., Chicago, IL). Continuous variables were expressed in mean ± standard deviation and categorical variables were expressed in percentages. The luminal parameters were compared between IVUS and 3D QCA, IVUS and QCA and QCA and 3D using student `t' test. A value of $p < 0.05$ was considered to be statistically significant. The relations between IVUS and 3D QCA, IVUS and QCA and 3D QCA and 2D QCA were analyzed with use of the Pearson correlation and linear regression analysis.

Observations & Results

A cross-sectional analysis was performed on CAG and IVUS images of 24 patients, who had undergone IVUS-guided PCI between May 2009 and July 2010. Mean age was 52.8 ± 9.1 years, 23 were males. Risk factors of CAD were smoking in 13 (54.2%), hypertension in 15 (62.5%), diabetes mellitus in 13 (54.2%), Dyslipidemia in15 (62.5%) and Family h/o CAD in 4 (16.7%). Prior myocardial infarction was present in 11 patients. Multivessel disease was seen in 14 (58%) patients. Coronary artery studied was LAD in 17 (70.2%), RCA in 3(12.5%), OM 2 in (8.3%), LCX and LM in 1 each. Left main ostium was studied in 21 patients. Patient characteristics are shown in Table 1 and Figure 3.

Table 1. Patient characteristics

Characteristic	n (%)
Male	23 (95.8%)
Smoking	13 (54.2%)
Hypertension	15 (62.5%)
Diabetes mellitus	13 (54.2%)
Dyslipidemia	15 (62.5%)
Family h/o CAD	4 (16.7%)
Prior MI	11 (47.8%)
Three vessel disease	3 (12.5%)
Study vessel LAD RCA OM LCX LM	17 (70.2%) 3 (12.5%) 2 (8.3%) 1 (4.2%) 1 (4.2%)

Figure 3. Study vessel

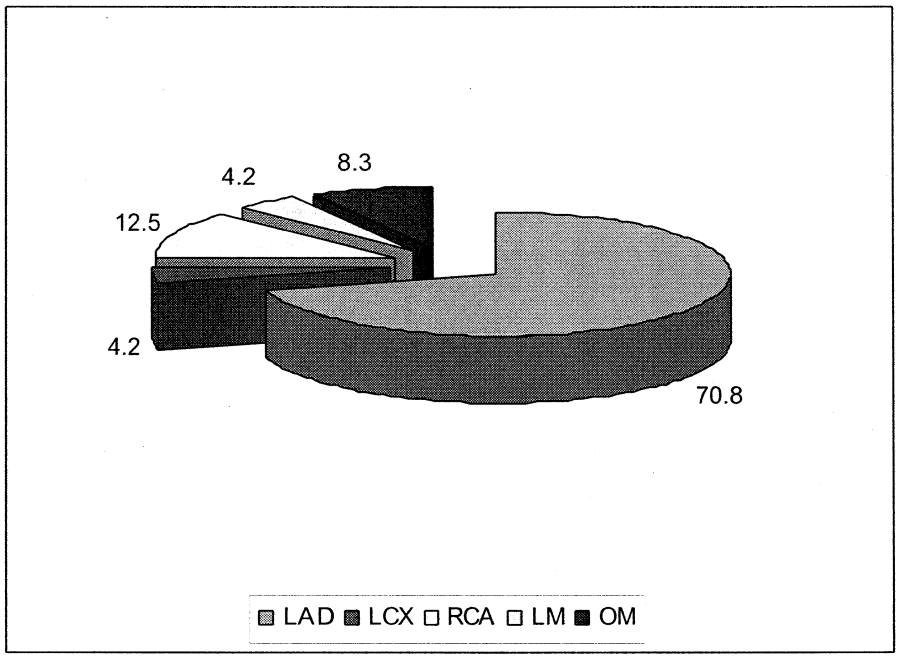


Table 2. 3D QCA, QCA and IVUS parameters : At lesion

Variable	3D QCA		QCA		IVUS (after balloon modification of plaque)	
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median
MLD at lesion (mm)	0.99 ± 0.41	0.93	0.98 ± 0.35	1.0	2 ± 0.4	1.9
% Diameter Stenosis	59.2 ± 12.3	61.5	60.0 ± 13.8	59.5	28.6 ± 12.4	32.7
% Area Stenosis	78.9 ± 12.7	84.5	80.4 ± 11.4	84.0	48.7 ± 18.5	51.6

Comparison between IVUS, QCA and 3D: At the lesion

At the lesion, mean MLD (mm) as measured by 3D and QCA were 0.99 and 0.98 respectively, p =0.91 as shown in Table 2. Percentage diameter stenosis at lesion as calculated by 3D and QCA were 59.2% and 60%

respectively, p =0.83. Percentage area stenosis at lesion as calculated by 3D and QCA were 78.9% and 80.4% respectively, p =0.66. The correlation between 3D QCA and QCA in diameter and area stenosis were excellent r= 0.97, and r= 0.93 respectively. The correlation between 3D QCA and QCA in diameter stenosis was good (r= 0.74), as shown in Table 3. IVUS measured MLD, percentage diameter stenosis and percent area stenosis at the lesion (after initial balloon dilatation) were 2 mm, 28.6% and 48.7% respectively, as shown in Table 2.

Table 3. Comparison and correlation between 3D QCA and QCA : At lesion

Variables	3D QCA Vs QCA	
	r	p
MLD	0.89	0.91
Diameter Stenosis	0.97	0.83
Area Stenosis	0.93	0.66

Comparison between IVUS, QCA and 3D QCA: At reference segments

Mean luminal diameter at proximal reference segment as measured by IVUS, 3D and QCA were 2.8, 2.3 and 2.5 respectively, as shown in Table 4. Mean luminal diameter at distal reference segment as measured by IVUS, 3D and QCA were 2.7, 2.3 and 2.4 respectively. Reference diameter for a lesion was calculated as mean of proximal and distal reference diameters. Mean reference diameter as measured by IVUS, 3D and QCA were 2.9, 2.4 and 2.5

respectively. The difference in reference luminal diameter as measured by IVUS and 3D QCA was significant ($p < 0.01$) and there was a positive correlation ($r= 0.73$), as shown in Table 5. A linear correlation was observed between IVUS and 3D QCA reference diameter as shown in Figure 4. Formula for computing IVUS diameter from 3D QCA diameter is, **IVUS DIA (mm) = 1.523 + 0.560 X 3D QCA DIA (mm)**

The difference in reference luminal diameter as measured by IVUS and QCA was significant ($p < 0.01$) and there was a positive correlation ($r= 0.745$), as shown in Table 5. Similarly a linear correlation was observed between IVUS and QCA reference diameter as shown in Figure 5. Formula for computing IVUS diameter from QCA diameter is, **IVUS DIA (mm) = 0.931 + 0.781 X QCA DIA (mm)**

Table 4. Comparison of IVUS, 3D and QCA-
At reference segments and left main

Variable	IVUS		3D		QCA	
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median
Proximal reference lumen diameter (mm)	2.8 ± 0.8	2.9	2.4 ± 0.8	2.3	2.5 ± 0.7	2.4
Distal reference lumen diameter (mm)	2.7 ± 0.5	2.6	2.3 ± 0.6	2.2	2.4 ± 0.4	2.2
Reference Diameter (mm)	2.9 ± 0.5	2.8	2.4 ± 0.6	2.2	2.5 ± 0.4	2.4
Left main lumen	3.5 ± 1.5	3.9	3.2 ± 1.3	3.6	3.2 ± 1.4	3.6

Table 5. Comparison and Correlation of IVUS with 3D and QCA- At reference segment and Left main ostium

Variables	IVUS Vs 3D		IVUS Vs QCA	
	r	p	r	p
Proximal reference lumen diameter	0.787**	<0.01	0.85**	<0.01
Distal reference lumen diameter	0.732**	<0.01	0.683**	<0.01
Reference Diameter	0.73**	<0.01	0.745**	<0.01
Left main lumen	0.973**	<0.01	0.967**	<0.01

Figure 4. Correlation between IVUS and 3D QCA reference diameter

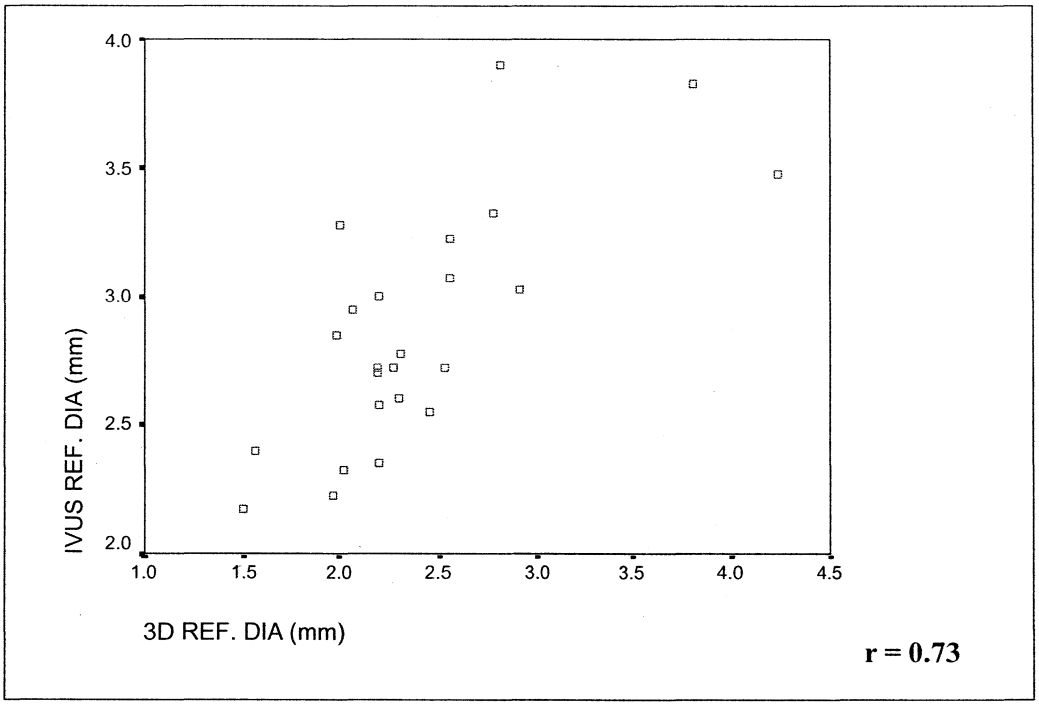
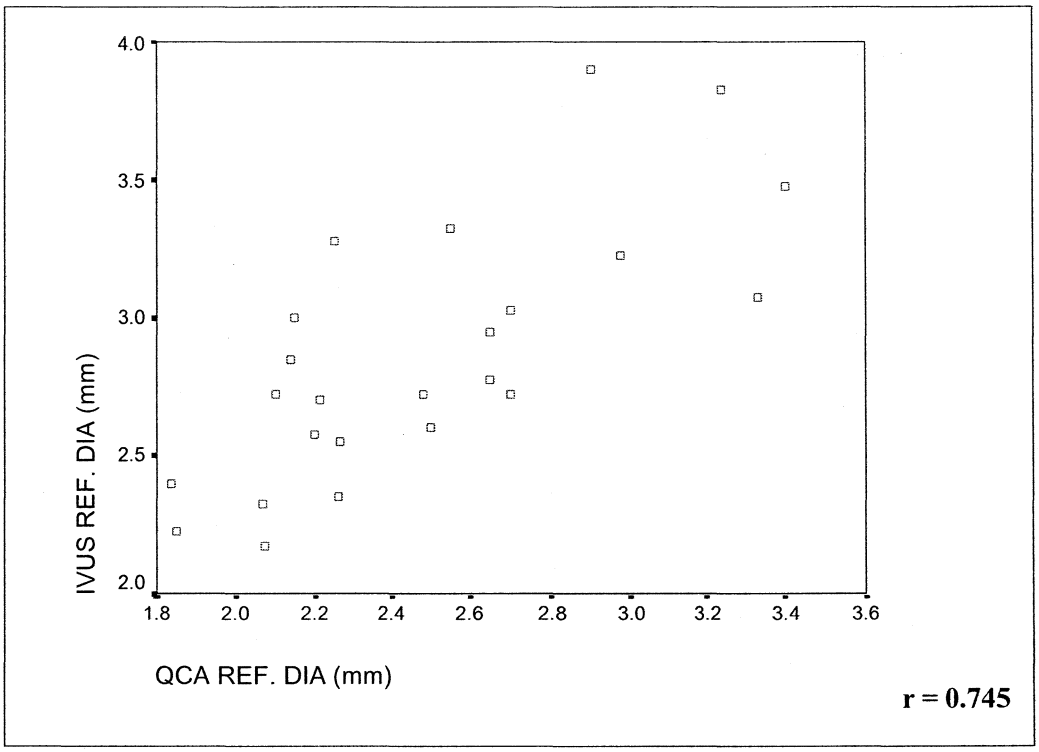


Figure 5. Correlation between IVUS and QCA reference diameter



Comparison between IVUS, QCA and 3D: At Left main ostium

Left main ostium was studied in 21 patients. Mean luminal diameter at Left main ostium as measured by IVUS, 3D and QCA was 3.5, 3.2 and 3.2 respectively, as shown in Table 4. The difference in left main luminal diameter as measured by IVUS and 3D QCA was significant ($p < 0.01$) and there was a positive correlation ($r= 0.97$). The difference in left main luminal diameter as measured by IVUS and QCA was significant ($p < 0.01$) and there was a positive correlation ($r= 0.97$), as shown in Table 5.

Vessel characters by IVUS:

Vessel wall characteristics by IVUS are shown in Table 6. At the lesion, mean EEM diameter as measured by IVUS was 4 ± 0.7 mm. Mean EEM diameter at proximal reference and distal reference segments were 4 ± 1.2 and 3.8 ± 0.7 respectively. Remodelling index was calculated as a ratio of EEM diameter at lesion to EEM diameter at reference segment. Mean remodeling index was 1, implying no significant negative or positive remodeling. Patients with diabetes also showed no significant remodeling. Mean plaque burden at lesion, proximal reference and distal reference segments were 72%, 47% and 45% respectively. See Table 6. Mean EEM diameter at left main ostium was 4.5 ± 1.9 mm. Mean plaque burden at left main ostium was 31%.

Table 6. Vessel wall characteristics by IVUS

Variable	Mean ± SD	Median
Minimum Lumen area (MLD) in mm2 in IVUS	3.4 ± 1.7	2.9
IVUS reference area	6.7 ± 2.2	6.4
Proximal reference lumen area in mm2 (IVUS)	6.8 ± 2.8	6.4
Distal reference lumen area in mm2 (IVUS)	6.2 ± 2.3	5.8
EEM or TV diameter (mm) in lesion	4 ± 0.7	4.1
EEM or TV diameter (mm) in proximal	4 ± 1.2	4.2
EEM or TV diameter (mm) in distal	3.8 ± 0.7	3.6
EEM or TV area in lesion	12.9 ± 4.5	12.7
EEM or TV area in proximal	13.7 ± 5.9	13.5
EEM or TV area in distal	11.3 ± 4.4	10.2
Plaque plus media CSA in lesion	9.6 ± 4.3	8.9
Plaque plus media CSA in proximal	6.9 ± 3.7	6.2
Plaque plus media CSA in distal	5.2 ± 2.6	4.7
Plaque burden (% area : P+M/ EEM) in lesion	72.4 ± 13	75.3
Plaque burden (% area : P+M/ EEM) in proximal	46.8 ± 14.1	50.4
Plaque burden (% area : P+M/ EEM) in distal	44.7 ± 9.2	45.4
Reference EEM area	12.9 ± 4.6	12.2
Remodeling index : Lesion EEM CSA/ Reference EEM CSA.	**1 ± 0.2**	**1.0**
Left main EEM- IVUS	**4.5 ± 1.9**	**4.9**
Left main lumen area	11.4 ± 5.4	11.7
Left main EEM area	18 ± 8.7	18.6
Left main plaque burden	31.4 ± 15.6	30.8

Discussion

The accurate assessment of lesion severity and reference diameter are crucial for a successful coronary revascularization procedure. Present study represents the direct comparison between 3D and 2D QCA in predicting IVUS reference dimension. Although widely used, 2D QCA has several limitations. (33) IVUS and optical coherence tomography are more accurate in depicting vessel anatomy.

Three-dimensional quantitative coronary angiography is relatively new technology that allows the fusion of two or more angiographic views to enable 3D reconstruction of the coronary artery of interest. Although 3D-QCA is still 'luminography' and cannot overcome the limitations involved in angiography image resolution, it may be able to better account for vessel tortuosity and lesion asymmetry in the assessment of coronary artery. (50; 51; 11) 3D-QCA can be quickly obtained from existing coronary angiographic images during cardiac catheterization or offline, and only requires that two or more orthogonal, non overlapped images of the target lesion are taken.

The main observation of the study is, both QCA and 3D QCA underestimate the reference luminal diameter of coronary artery, as measured by IVUS. At the reference segments, QCA and 3D QCA systematically underestimated the IVUS luminal diameter. The observed difference was

approximately 0.5 mm, but it was statistically significant. However, there was a linear correlation between QCA and 3D QCA diameter with IVUS diameter. Linear equations can be derived for estimating IVUS diameter from QCA and 3D QCA. Previous studies comparing QCA and IVUS have consistently shown similar observation. (14; 17; 36; 42; 43; 35). Reference lumen dimensions measured by IVUS were consistently larger than measured by QCA. They found a moderate correlation between both techniques at sites which were angiographically normal, but contained plaque on IVUS. Abizaid et al noted that, IVUS reference segment measurements are consistently larger than QCA with an average (but not predictable) difference of 0.5 mm. (46) At the lesion, MLD, percentage of diameter stenosis and percentage of area stenosis as measured by QCA and 3D QCA were similar and had good correlation.

Discrepancy between IVUS and QCA:

Even when calculated from two orthogonal views, the chances of obtaining the exact minimal and maximal diameters using QCA would be small. IVUS is not projection dependent, and would provide a measure of the "depth" as well as the "width" of the lumen cross section. (45) Two additional IVUS related factors may also have contributed to the observed discordance between IVUS and quantitative angiographic measurements. Elliptical angulations of the ultrasound catheter within the longitudinal axis of the vessel

may have led to overestimation of luminal dimensions by IVUS. Additionally, introduction of the ultrasound catheter may have itself resulted in tacking back of dissection flaps, with a resultant larger lumen during IVUS examinations postintervention compared with the less invasive technique of contrast angiography. (45)

Discrepancy between IVUS and 3D QCA:

Underestimation was also seen with three-dimensional QCA. Tsuchida et al also in a phantom lesion model indicated that 3D QCA underestimate true vessel diameter. (13) Such work suggests that angiography in general and three-dimensional angiography in particular may have limitations in measuring absolute vessel dimensions. Accuracy and precision vary among 3D QCA systems.

Mean plaque burden at lesion, proximal reference and distal reference segments were 72%, 47% and 45% respectively. This observation is similar to the other IVUS studies, that although angiographically normal, the reference segments do have significant plaque burden. Remodelling index was calculated as a ratio of EEM area at lesion to EEM area at reference segment. Mean remodeling index was 1, implying no significant negative or positive remodeling. Patients with diabetes also showed no significant remodeling. This is contrary to the common belief that coronary artery remodelling occurs

with atherosclerosis. This can be explained by the fact that, reference segments also had plaque burden and would have also remodeled. This would have led to nullification of any change in EEM at lesion.

Both QCA and 3D QCA underestimate the Left main ostium luminal diameter, as measured by IVUS. Mean luminal diameter at Left main ostium as measured by IVUS, 3D and QCA was 3.5, 3.2 and 3.2 respectively. The observed difference was statistically significant and positively correlating. This is similar to the previously published studies, that QCA underestimates LM lumen diameter. (59; 55; 58) The absolute diameter is lesser than the previously published studies in western population, probably due to low BSA. (63; 64) Abizaid et al study showed QCA reference diameter of 3.91 mm, IVUS diameter of 4.25 mm. (59) Mean EEM diameter at left main ostium was 4.5 ± 1.9 mm, as compared to 6.1 mm of western population. (61) Mean plaque burden at left main ostium was 31%. This is similar to 35% plaque burden reported by western studies. (59)

Study Limitations

1. A relatively small number of patients were included in this retrospective study.
2. The coronary sites compared by IVUS and QCA may not have been exactly identical. Although we tried to ensure that this was the case by using landmarks such as side branches to guide us, there is no guarantee that we analyzed exactly the same point of the coronary artery in IVUS and QCA measurements. This is, however, a generic problem of any IVUS-QCA study that would be very difficult to overcome, as the presence of the IVUS catheter at the lesion site during coronary arteriography would interfere with the QCA measurements. (17; 66)
3. It is also possible that ultrasound image analysis fails to see the true leading intimal edge, especially if the plaque has a low fibrous component and appears relatively hypoechoic, thus overestimating luminal dimensions.
4. IVUS analysis was done with manual pull-back. Although it will not affect the cross sectional analysis, it would have guided us that the reference segment is within 10 mm of the lesion, as recommended.

Conclusion

1. QCA and 3D QCA systematically underestimate the IVUS reference luminal diameter. Through linear equations, IVUS reference diameter can be derived from QCA and 3D QCA diameters.

2. 3D QCA dimensions were not different from QCA. It does not overcome the discrepancy between QCA and IVUS.

3. No positive or negative remodelling of coronary artery at the lesion noted in either Diabetics or non- diabetics

4. Angiographically normal Left main harbors atherosclerotic plaque burden as detected by IVUS. Left main reference segment - lumen and EEM diameter in Indians is lesser than that of western population and needs larger studies to confirm the same.

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GLOSSARY

3D QCA- Three Dimensional Quantitative Coronary Angiogram

CAD- Coronary artery disease

CAG- Coronary arteriogram

CASS- Coronary Artery Surgery Study

CSA- Cross-sectional area

DES- Drug eluting stent

DIA- diameter

ED- Edge-detection

EEM- External elastic membrane

FFR- Fractional flow reserve

IVUS- Intravascular ultrasound

LAD- Left anterior descending

LCX- Left circumflex

LM- Left main

MI- Myocardial infarction

MLA- minimal lumen area

MLD- Minimum lumen diameter

OM- Obtuse marginal

P+M- Plaque + Media

PTCA- Percutaneous transluminal coronary angioplasty

QCA- Quantitative Coronary Angiogram

RCA- Right coronary artery

TV- Total vessel

VID- Videodensitometry


Master Chart

Serial No.	NAME	AGE(YRS)	SEX (1-Male, 2-female)	Number	CATH NO	IVUS DATE	RISK FACTOR-SMOKING=1,HYPERTENSION=2, DM=3,DYSLIPIDEMIA=4,FAMILY CAD=5	ACS (0-nil, AWMI-1, IWMI- 2, PLMI-3, UA- 4)	NUMBER OF VESSELS	LV dysfunction (o- nil, 1-mild, 2-moderate, 3-severe)	NYHA class-(1, 2, 3, 4)	others (MR 3-4+-1, PAH-2, CHF- 3, VT-4)	STUDY VESSEL (LAD-1, LCX-2, RCA-3, LM-4, OM-5)	MLD (mm) in IVUS	MLD (mm) in 3D
1	RADHAKRISHNAN	46	1	292260	46063	10.08.09	1,4	1	1	1	2	0	1	1.75	1.37
2	ARAVINDAKSHAN	58	1	307959	47810	16.03.10	1,4	1	2	1	2	0	1	1.85	0.9
3	BABU	42	1	294277	47112	15.12.09	1,2,3	1	1	0	2	0	1	1.85	1.06
4	RAVISUTH	52	1	305962	47478	3.2.10	1,2,3,4	2	2	0	2	0	1	1.85	1.21
5	BAHULEYAN	54	1	305599	47394	22.1.10	2, 4	0	1	0	2	0	1	1.75	0.4
6	MOHANAN	51	1	304522	47867	22.3.10	3,4	2	2	0	2	2	1	1.65	0.8
7	MATHEW	66	1	300631	46350	15.9.9	2, 3	1	3	0	2	0	3	2.25	1.3
8	SIDDHARTHAN	54	1	302994	47771	12.3.10	1	4	1	0	3	0	1	1.75	1.1
9	GEORGE THOMAS	52	1	309746	48154	30.4.10	2,3,4,5	3	2	0	2	0	5	1.75	0.68
10	SAMAD	45	1	227736	48247	12.5.10	2,3,4,5	1,2	3	1	2	0	5	1.75	1.1
11	KUMARAN	43	1	308885	47964	7.4.10	1,3,4	1	1	0	2	0	1	2.3	1
12	NEELAKANDA PILLA	52	1	293917	47949	6.4.10	1	4	2	0	2	0	2	1.8	0.2
13	KRISHNAN KUTTY	63	1	195028	48075	21.4.10	2, 3	0	1	0	2	0	1	3.2	0.95
14	SANTHA	60	2	295310	46787	3.11.2009	4	4	3	0	2	0	1	2.4	1.2
15	JAYAN	30	1	298770	46283	8.9.9	1,2,3	1	1	0	2	0	1	2.25	2.1
16	SIVASANKARAN	55	1	291111	46964	25.11.09	1,2	0	2	0	2	0	1	1.7	0.8
17	CHALEY	44	1	311280	48372	26.5.10	1,2,3,4	0	0	0	2	0	4	3.4	1.8
18	SOMAN	57	1	290977	45444	28.5.9	2,4	4	2	0	2	0	1	1.95	0.8
19	VIKRAMAN	57	1	302167	46740	30.10.09	2,5	4	2	0	2	0	1	1.95	0.8
20	KOCHUKUNJU	75	1	299962	46109	18.8.09	1,2,3,4	0	2	0	2	0	1	1.95	1.29
21	SALISAM	51	1	295587	45454	28.5.9	2,4,5	1	2	1	2	0	3	1.85	0.55
22	SIVANKUTTY	56	1	310250	48008	13.4.10	3	4	1	0	2	0	1	1.95	0.9
23	GOPI	58	1	309531	48585	23.6.10	1,2,3,4	4	2	0	2	0	3	2.2	0.7
24	SUNDARAN	46	1	309846	48738	13.7.10	1,4	1	1	0	2	0	1	2	0.8

MLD (mm) in QCA	IVUS REF. DIA (mm)	3D REF. DIA (mm)	QCA REF. DIA (mm)	%diameter stenosis	% Diameter Stenosis in 3D	% Diameter Stenosis in QCA	% lumen Area in IVUS	% Area Stenosis in IVUS	% Area Stenosis in 3D	% Area Stenosis in QCA	Proximal reference lumen diameter in mm (IVUS)	Proximal reference lumen diameter in mm (3D)	Proximal reference lumen diameter in mm (QCA)
1.35	2.725	2.52	2.48	35.7798165	46	49	30.3797468	69.6202532	76	74	2.85	2.62	2.86
0.8	3.025	2.905	2.7	38.8429752	68	70	35.2112676	64.7887324	90	92	3.05	3.04	2.8
1.12	2.6	2.3	2.5	28.8461538	55	58	52.8301887	47.1698113	80	84	2.8	2.36	2.9
1.15	2.725	2.275	2.1	32.1100917	47	49	43.8596491	56.1403509	66	70	2.6	2.33	2
0.3	3.275	2	2.25	46.5648855	80	85	26.9005848	73.0994152	95	98	3.55	2.2	2.4
0.75	2.35	2.2	2.26	29.787234	64	66	52.2727273	47.7272727	85	88	2.3	2.2	2.27
1.6	3.825	3.805	3.24	41.1764706	64	60	33.6283186	66.3716814	77	74	4.25	4.25	3.68
1	3.075	2.55	3.33	43.0894309	60	66	31.7241379	68.2758621	84	86	3.25	2.66	3.4
0.77	2.225	1.965	1.85	21.3483146	66	59	59.7402597	40.2597403	88	84	2.5	2.13	2.05
1.22	2.325	2.02	2.07	24.7311828	45	41	54.1176471	45.8823529	57	69	2.75	2.1	2.2
1.12	2.7	2.195	2.215	14.8148148	44	42	56.9230769	43.0769231	69	66	3.1	2.25	2.34
0.21	2.4	1.555	1.835	25	86	90	57.4712644	42.5287356	96	98	2.4	1.61	2.01
0.98	3.225	2.55	2.975	0.7751938	63	68	90.6976744	9.30232558	90	88	3.3	2.6	3
1.2	2.575	2.2	2.2	6.7961165	47	42	88.4615385	11.5384615	49	62	2.55	2.3	2.3
1.5	3.475	4.225	3.4	35.2517986	53	57	40.625	59.375	76	80	3.25	4.45	3.6
0.67	2.55	2.45	2.265	33.3333333	68	70	46	54	86	85	2.55	2.6	2.43
1.5	3.9	2.8	2.9	12.8205128	34	32	76.6666667	23.3333333	57	54	0	0	0
1	2.175	1.5	2.075	10.3448276	48	50	82.1917808	17.8082192	68	67	2.15	1.53	2
0.7	3	2.2	2.15	35	65	69	44.7552448	55.2447552	88	90	3.05	2.4	2.4
1.17	3.325	2.765	2.55	41.3533835	53	54	33.7209302	66.2790698	68	75	3.85	2.81	2.5
0.6	2.85	1.98	2.14	35.0877193	72	70	40	60	90	88	2.85	2.02	2.27
1.1	2.95	2.065	2.65	33.8983051	60	57	42.3357664	57.6642336	87	86	3.4	2.05	2.6
0.9	2.725	2.19	2.7	19.266055	68	66	59.8290598	40.1709402	86	82	2.8	2.24	2.9
0.8	2.775	2.305	2.65	27.9279279	65	70	50.8196721	49.1803279	85	90	3.05	2.35	2.7

Distal reference lumen diameter in mm (IVUS)	Distal reference lumen diameter in mm (3D)	Distal reference lumen diameter in mm (QCA)	Minimum Lumen area (MLD) in mm^{2} in IVUS	IVUS REF AREA	Proximal reference lumen area in mm2 (IVUS)	Distal reference lumen area in mm2 (IVUS)	EEM or TV diameter (mm) in lesion	EEM or TV diameter (mm) in proximal	EEM or TV diameter (mm) in distal	EEM or TV area in lesion	EEM or TV area in proximal	EEM or TV area in distal	Plaque plus media CSA in lesion
2.6	2.42	2.1	2.4	7.9	6.4	9.4	2.9	3.7	3.1	6.7	10.6	7.5	4.4
3	2.77	2.6	2.5	7.1	7.2	7	4.2	4.2	4.8	13.6	13.6	16.5	11.1
2.4	2.24	2.1	2.8	5.3	6.3	4.3	3.9	4	3.25	11.8	12.4	8.3	9
2.85	2.22	2.2	2.5	5.7	5.3	6.1	3.5	4.35	3.55	9.5	15	9.9	7
3	1.8	2.1	2.3	8.55	9.9	7.2	5	5.3	4.35	19.9	22.1	14.9	17.6
2.4	2.2	2.25	2.3	4.4	4.2	4.6	3.7	3.4	2.9	10.6	8.9	6.6	8.3
3.4	3.36	2.8	3.8	11.3	13.9	8.7	4.35	5.5	4.45	14.1	23	15.4	10.3
2.9	2.44	3.26	2.3	7.25	8.1	6.4	4.45	5.3	3.8	15.5	22.2	11.4	13.2
1.95	1.8	1.65	2.3	3.85	4.8	2.9	3.7	3.65	2.85	9.7	10.4	6.2	7.4
1.9	1.94	1.94	2.3	4.25	5.7	2.8	2.75	3.1	2.7	6	7.3	5.8	3.7
2.3	2.14	2.09	3.7	6.5	7.5	5.5	4.05	4.15	3.35	12.5	13.5	8.7	8.7
2.4	1.5	1.66	2.5	4.35	4.3	4.4	4.1	3.5	3.65	12.9	9.6	10.4	10.4
3.15	2.5	2.95	7.8	8.6	9.4	7.8	4.95	5.05	5	18.8	19.5	19.2	11
2.6	2.1	2.1	4.6	5.2	5.1	5.3	3.2	3.25	3.25	7.9	8.4	8.3	3.3
3.7	4	3.2	3.9	9.6	8.4	10.8	5.25	5.4	5.3	21.4	22.4	21.4	17.4
2.55	2.3	2.1	2.3	5	5.1	4.9	3.25	3.35	4.2	8.1	8.8	9.5	5.8
3.9	2.8	2.9	9.2	12	0	12	4.35	0	5.1	14.5	0	20.2	5.4
2.2	1.47	2.15	3	3.65	3.6	3.7	3.15	3.1	2.95	7.5	7.6	6.6	4.5
2.95	2	1.9	3.2	7.15	7.4	6.9	4.95	5	3.85	19	19.4	11.2	15.8
2.8	2.72	2.6	2.9	8.6	10.9	6.3	4.65	4.7	3.9	16.9	17.1	11.9	13.9
2.85	1.94	2.01	2.5	6.25	6.2	6.3	3.45	3.6	3.4	9.7	10.1	9.1	7.2
2.5	2.08	2.7	2.9	6.85	8.9	4.8	4.45	4.5	3.6	15.5	15.9	10	12.6
2.65	2.14	2.5	3.5	5.85	6.2	5.5	3.7	4.15	3.6	10.8	13.5	10.4	7.9
2.5	2.26	2.6	3.1	6.1	7.4	4.8	4.7	4.55	3.7	17.7	16.5	10.6	14.6

Plaque plus media CSA in proximal	Plaque plus media CSA in distal	Plaque burden (% area : P+M/ EEM) in lesion	Plaque burden (% area : P+M/ EEM) in proximal	Plaque burden (% area : P+M/ EEM) in distal	REFERENCE EEM AREA	Remodeling index : Lesion EEM CSA/ Reference EEM CSA.	Left main lumen- IVUS	Left main lumen- 3D	Left main lumen- QCA	Left main EEM- IVUS	LM lumen area	LM EEM AREA	LM PLAQUE BURDEN
4.2	2.3	65	40	31.1	9.05	0.7403315	3.45	3.64	3	4.15	9.4	13.4	29.5
6.4	9.4	82	47	57	15.05	0.9036545	4	3.66	3.48	4.7	12	16.8	29.6
6.1	4	76.4	48.9	48	10.35	1.1400966	4.1	3.93	3.75	4.9	13.1	18.4	28.7
9.7	3.7	73.6	64.8	37.7	12.45	0.7630522	3.75	4	3.6	5.45	11.2	22.6	50.5
12.2	7.7	88.4	55.3	51.6	18.5	1.0756757	4.4	3.43	3.85	5.7	15.6	24.8	36.9
4.7	2	78	53	30	7.75	1.3677419	3.8	3.01	3.6	4.7	10.5	16.8	38
9.1	6.7	73	40	44	19.2	0.734375	NA	NA	NA	NA	NA	NA	NA
14	5	85	63.3	44	16.8	0.922619	4.4	4.06	4.85	6	14.8	28.2	47.4
5.6	3.3	76.4	53.6	53.3	8.3	1.1686747	5.3	4.5	4.4	6.35	21.4	30.3	29.4
1.6	3	61.2	22.4	51.7	6.55	0.9160305	4.2	3.69	3.1	4.65	14.4	17.6	18.3
6	3.2	70	44.4	36.9	11.1	1.1261261	3.9	3.42	3.56	5.2	11.6	20.8	44.4
5.3	6	80.9	54.8	57.8	10	1.29	3.65	3.36	3.15	4.4	10.4	15.2	31.9
10.1	11.4	58.4	51.9	59.5	19.35	0.9715762	3.7	3.05	3.8	5.1	10.8	20	46
3.2	3	41.5	38.8	36.3	8.35	0.9461078	3.75	3.2	2.75	4.8	11.1	18	38
14	10.6	81.6	61	49.7	21.9	0.9771689	4.8	4.6	4.75	5.65	17.8	24.6	27.7
3.7	4.6	71.6	42.5	29	9.15	0.8852459	3.5	3.6	3.5	4.2	9.8	13.8	29
0	8.2	37	0	40.4	20.2	0.7178218	3.25	4.78	4.42	4.15	8.1	13.5	40
4	2.9	60.1	52.5	44.3	7.1	1.056338	4.6	4.08	4.05	5.35	16.3	21.7	25
11.9	4.3	83.3	61.7	38.5	15.3	1.2418301	3.95	3.25	3.3	5.75	11.8	24.8	52.4
6.2	5.6	82.6	36.2	46.8	14.5	1.1655172	3.85	4.09	4.1	4.9	10.9	18.7	48.2
3.9	2.9	74.2	38.4	31.4	9.6	1.0104167	NA	NA	NA	NA	NA	NA	NA
7	5.3	81	44	52.4	12.95	1.1969112	4.45	4.1	4.2	6.15	15.1	28.4	47
7.2	4.8	73.3	53.6	46.5	11.95	0.9037657	NA	NA	NA	NA	NA	NA	NA
9.1	5.7	82.5	55.4	54	13.55	1.3062731	4.2	3.5	3.85	5.3	13.3	21.5	38