P78

1. **ANOMALOUS LEFT CORONARY ARTERY FROM PULMONARY ARTERY CLINICAL, HEMODYNAMIC AND ANGIOGRAPHIC PROFILE**

2. **ORAL DIPYRIDAMOLE TEST IN SYNDROME X.**

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CERTIFICATE

I, Dr. JYOTHI P. hereby declare that I have actually performed all the procedures listed / carried out the project under report.

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Name in JYOTHI P.
capital letters

Date: 4.11.94

Forwarded. He has carried out the minimum requirement of procedures / etc.

Signature

Head of the department

PROJECT REPORT

TITLE OF THE PROJECT: **ANOMALOUS LEFT CORONARY ARTERY FROM PULMONARY ARTERY CLINICAL, HEMODYNAMIC AND ANGIOGRAPHIC PROFILE**

NAME: DR. JYOTHI P.

PROGRAMME: DM CARDIOLOGY

MONTH & YEAR OF SUBMISSION: OCTOBER 1994

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ANOMALOUS LEFT CORONARY ARTERY FROM PULMONARY ARTERY CLINICAL, HEMODYNAMIC AND ANGIOGRAPHIC PROFILE

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INTRODUCTION

ALCAPA is a rare congenital anomaly of the coronaries occurring in approximately one in 3,00,000 live births[1]. The anomaly was first described by Abott[2] in a 60 year old woman and later Abrikosoff reported it is a 5 month old infant. The clinical syndrome was described by Bland and co-workers and is often referred to as the Bland-White Garland syndrome[3]. Gouley has used the terms adult type and infantile type to distinguish between patients who survived for many years with with few or no symptom and those who died in infancy with profound symptoms[4]. The report of pericardial poudrage by Paul and Robin first proposed surgical therapy in 1955[5].

In ALCAPA there is a low perfusion pressure in the left coronary artery. In fetal and neonatal life the RV is the systemic ventricle and hence the LV is well perfused. With the tendency for PA pressures to fall decreased perfusion of the LV develops at a time when the LV has to develop high intramural tension associated with the production of systemic pressures. Decreased LV perfusion leads to low output with elevation of LA pressures and PAH. This reactive PAH prevents perfusion pressure in the LCA from dropping precipitously and allow time for development of

collaterals. There collaterals may be life saving and patients with adequate collaterals may never show symptoms large intercoronary anastamosis have opposing effects.

1) Re-establishment of coronary perfusion

2) Undesirable effect of acting as low resistance channels that bypass the capillary bed - coronary steal- thus depriving the myocardium and promoting ischaemia.[6,7,8,9,10]

3) Cause L->R shunt with volume overhead

MR results from secondary endocardial fibroelastosis, contraction of the chrodac tendinae and infarction of the papillary muscle secondary to ischaemia of the LV.

Optimally operation should be undertaken in all patients with the idea of constructing a two coronary system whereas transfer of the anomalous artery into the aortic root is the most direct and advisable procedure it is not always possible. In critically ill infants a case may still be made for simple ligation of the anomalously connected coronary artery. When the distance between the empty left aortic sinus and posterior aspect of the pulmonary artery from where the anomalously connected coronary artery originates is long, and tunnel repair may be necessary[12].

MATERIAL AND METHODS

The clinical presentation, investigation hemodynamic echocardiographic profile, surgical results and follow up of the cases of ALCAPA encountered at SCTIMST for a 7 year period from 1986-1993 were analysed.

The case records were studied in detail with special reference to age at presentation, mode of presentation and clinical diagnosis made at initial presentation. The echocardiographic reports were reviewed. These echocardiograms were done using ATL ultramark 8 machine. All patients except one underwent cardiac catheterisation and review of hemodynamic and angiographic data were done with special reference to PA pressures, LVEOP and degree of MR. The type of surgical procedure and follow up after surgery were analysed.

RESULTS

11 cases of ALCAPA were encountered in the 7 year period. Their age ranged from 4 months to 40 years. Five of them were infants. These were six males and five females.

The presenting symptoms included recurrent upper respiratory infections in 5, shortness of breath in 6, feeding difficulty in 6, failure to thrive in 4 and excessive sweating in 4. Angina was the presenting symptom of the patient who presented at 40 years of age. Clinical examination revealed cardiomegaly and LVS3 in the majority of patients. 54% had a systolic murmur suggestive of MR Continuous Murmur was seen in only one adult patient. (Table No.1).

Electrocardiogram revealed anterolateral Mi in 9 (81%). LAE was present in the six who had clinical evidence of MR. The mean frontal QRS axis was distributed between a normal axis or a left axis deviation in the majority whereas an extreme right axis deviation was observed in 3 patients all 3 were infants.

Echocardiography revealed increased LV dimension in 90% of patients, RWMA EFE and MR were observed in 3,4 and 7

patients respectively. The diagnossi of ALCAPA was stronglysuspected in 64% of patients with LCA visualisation in short axis view. A precath diagnosis of RCA to RVOT fistula was made in one patient.

Cardiac catheterisation was performed in 10/11 patients. LVED was mildly elevated in 1 and moderately elevated in 4 patients. A calculable L-R shunt was seen in 2/11 patients both of whom had good LV function and normal LVEDP with mild MR. The two adult patients had a normal LVEjection Fraction. 4/5 infants had poor LV function with LVEF <25%. Secondary EPE was seen in 3 of them (Table No.2).

Surgical correction undertaken in 6 patients 3 patients had tunnelling operation and 2 underwent aortocoronary saphenous vein grafting. There were 2 death following tunnelling operation one due to VF and the other due to low cardiac output. A 27 year old female underwent re implantation of the left coronary artery and is doing well after surgery. Post operative TMT showed 11 mets with 2mm ST depression in V4 which normalised in early recovery. Two post operative deaths were both in children with poor LVEF.

On post operative follow up all survivors were in NYHA Class I. No late post operative deaths. Follow up ranged from 3 months to 6 years.

Table No.1

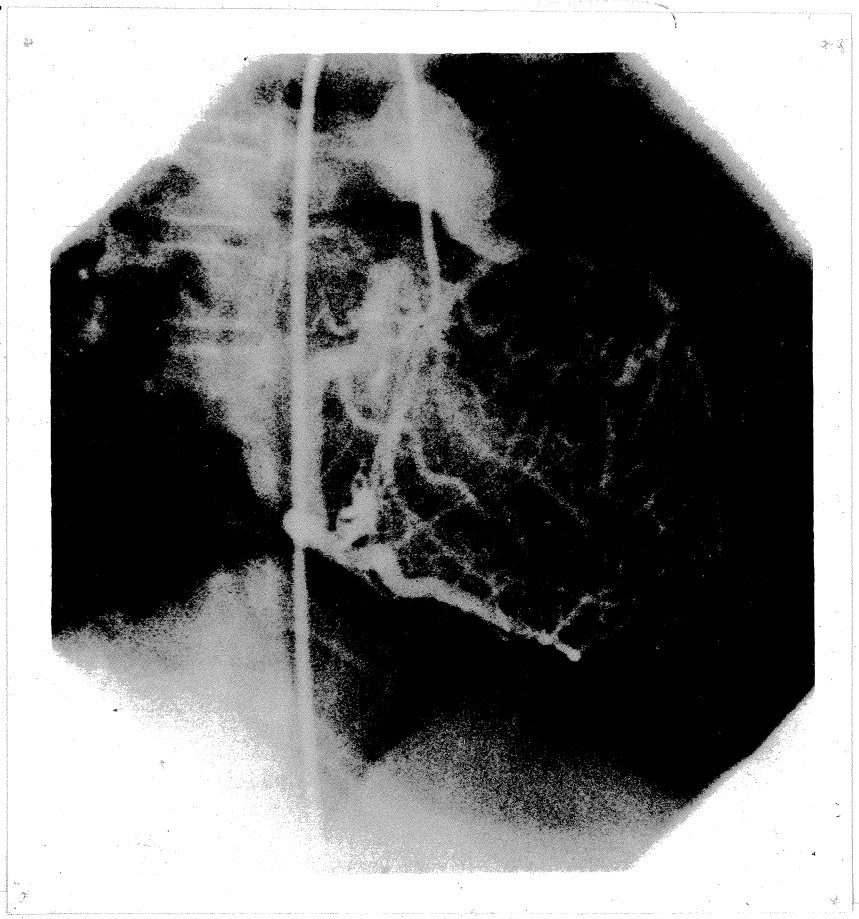
Presenting symptoms		Clinical Examination	
Recurrent URI	- 5	Cardiomegaly	10
Shortness of breath	-6	LVS3	- 9
Feeding difficulty	6	Systolic murmur	-6
Angina	1		
Excessive sweating	4		
Failure to thrive	4		

Table No.2

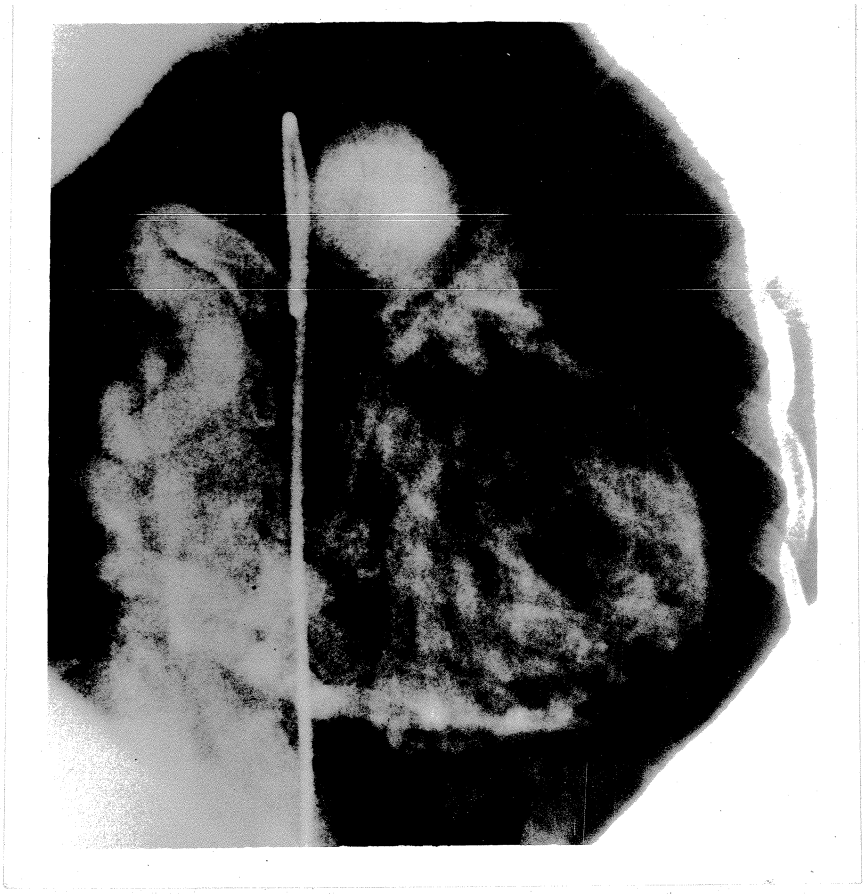
CARDIAC CATHETERISATION DATA IN THE 10 PATIENTS

Sl No.	Age & Sex	Ao	PA	LVED	PAW	Qp/Qs	LV ej. fraction	MR grade
1.	7 M yrs	120/80 M(100)	40/15 M(20)	9	m (12)	1.5:1	46%	Grade 1
2.	9 F yrs	100/80 M(80)	32/14 M(20)	16	m (21)	1:1	57%	
3.	40 F yrs	96/50 M(74)	20/10 M(14)	5	m (8)	1.6:1	78%	Grade 2
4.	4 1/2M yrs	90/50 M(70)	28/13 M(20)	18	m (13)	-	20%	nil
5.	4 M months	64/32 M(42)	20/8 M(12)	10	m (12)	-	13%	Grade 2
6.	4 M months	87/50 M(62)	-	22	-	-	20%	Grade 2
7.	6 M months	73/88 M(44)	-	17	-	-	24	Grade 2
8.	6 1/2 M yrs	88/60 M(70)	40/20 M(30)	24	m (26)	Nil	20	Grade 4
9.	27 F yrs	110/60 M(75)	22/12 M(15)	8	m (11)	Nil	61%	Nil
10.	10 months	74/44 M(58)	20/15 M(18)	12	m (8)	Nil	60	Nil

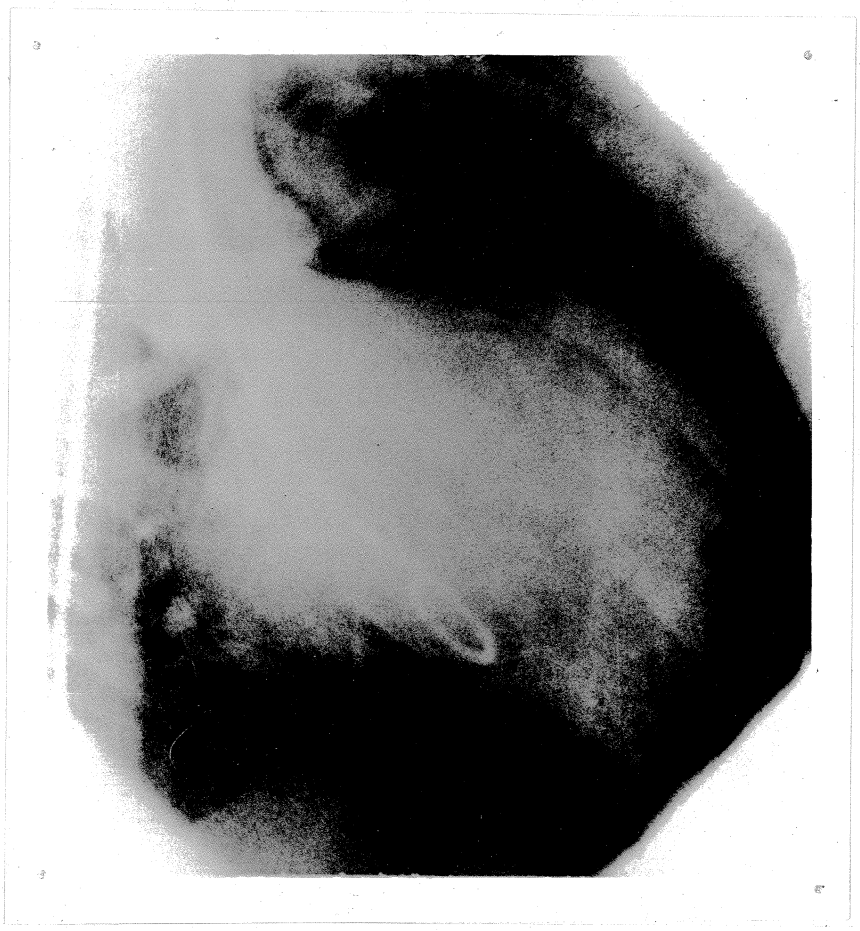
Aortic root angio in LAO cranial view showing the dilated and tortuous RCA filling the LCA through collaterals. The PA is seen enhancing from the LCA.



Selective RCA injection in RAO view showing retrograde filling of LCA by collaterals from RCA, with PA enhancement.



RCA injection in RAO view showing filling of LCA and PA enhancement.



LV Angio in Rao view showing the dilated hypocontractile LV.

DISCUSSION

ALCAPA is a rare anomaly of the coronaries with varying spectra of presentation depending on the coronary perfusion. The present study is a retrospective analysis of 11 cases of ALCAPA. The slight male preponderance in this series was commonly noted by others.[4] Wessel[13] Hoft had divided patients into 4 groups based on clinical presentation.

Gr. I:Infant syndrome which constituted 5 pts in the present series.

Gr. II:Mitral insufficiency - 5 pts

Gr. III:continuous murmur - 1 pt

Gr. IV:Sudden death in adult nil

In their series the proportion of patients presenting with continuous murmur in the 140 patients was nil in infants and 37% in children and adults. In the present series only one patient had a continuous murmur. This may be due to the younger age of patients at presentation. The continuous murmur was observed in the 40 year old female patient. An absence of continuous murmur was observed in the series of 15 patients reviewed by Askenazi probably because of the high proportion of infants in that series. The incidence of cardiomegaly and CHF in our series closely

corresponds to theirs probably signifying the lack of adequate collateral development in the majority of patients leading to ischaemic LV dysfunction, dilatation and MR.

ECG evidence of anterolateral MI in 81% of our patients is comparable to the 92% reported by Askenazi and 80%. By Wesselhoft and 88.8% by Buziash Villi whereas Moodie [15]. had reported an incidence of 50%. Absence of myocardial infarction pattern may be due to adequate perfusion of the anamolously arising LCA from the hypertensive PA or through collaterals. Absence of significant PAH or a calculable L-R shunt in the majority of our patients correlates with the ECG pattern of MI. The 40 year old and the 27 yr old patient had q in 1, AVL but no evidence of MI. The left axis deviation in ECG has been observed earlier by Askenazi and Nadas [4].

The diagnosis is supsected on echocardiography when the anomalously connected LCA cannot be demonstrated to arise from the usual site in the left coronary sinus in the short axis of the aortic root. A firm diagnosis can be made if the anomalous origin of LCA is identified on cross sectional view of MPA [16]. The diagnosis was confirmed by Doppler echo in 64% of our patients.

Cardiac catheterization can reveal the hemodynamic

spectrum of this disorder. Tiraboschi had observed an adult type in 2/10 patients[17]. The observation in the present study were similar to theirs as well as those made by Askenazi. Our patients had less of PAH although MR was more common. Four of the five infants who were catheterised had a poor LV function, with LVEF by planimetry less than 25%. The two adult patients had preserved LV function. The two patients with calculable L-R shunt on catheterisation had preserved LV function.

The surgical option available such as ligation alone or ligation + SVG was compared by Wilson et al[18] in his review of all cases reported 13 years or older which included 29 cases. During the mean follow up of 9.2 yrs in Group A (ligation) and 5 years in group B (ligation + SVG), there were no late deaths in group B Vs 3 late sudden death in Group A. In view of the trend for improved survival in the latter group a combined approach was suggested. No patient in the present series had undergone simple ligation of the coronary artery. Those who underwent ligation and SVG had a good result. Creation of a two coronary system by direct re-implantation is currently recommended[19]. One of our patients underwent the same and had a good result. The 2 post operative deaths in the tunnelling operation is probably related to the learning curve or very poor LV function.

Perfection of newer techniques is expected with growing surgical experience with the disorder. The two adult patients with preserved LV function had good result after surgery.

CONCLUSION

ALCAPA is a rare congenital anomaly of the coronaries. 11 cases encountered in 7 years five were infants. ALCAPA identified by echo and confirmed by cath in all patients. Early surgery indicated. Surgical results are still suboptimal. Direct re-implantation of the anomalous LCA to the Aorta remains an attractive option. The infantile type usually has less of collaterals, poorer LV function and do badly even with surgery. The adult type has a preserved LV protected from ischaemia and do well after surgery.

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CERTIFICATE

I, Dr. JYOTHI P. hereby declare that I have actually performed all the procedures listed / carried out the project under report.

Signature.....

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Date: 4. 11. 94

Forwarded. He has carried out the minimum requirement of procedures / etc.

Signature

Head of the department

PROJECT REPORT

TITLE OF THE PROJECT **ORAL DIPYRIDAMOLE TEST IN SYNDROME X**

NAME DR. JYOTHI P.

PROGRAMME DM CARDIOLOGY

MONTH & YEAR OF SUBMISSION OCTOBER 1994

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6. CONCLUSIONS

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INTRODUCTION

I/v dipyridamole imaging has a definitive role in defining the functional significance of anatomic lesions [1-7]. It is especially useful in patients in whom exercise testing cannot be performed. Oral Dipyridamole in doses of 200-400 mg has been found to be as useful as intravenous administration [8-9]. Use of dipyridamole for evaluation of atypical chest pain has been reported [10]. Since dipyridamole acts by inhibiting cellular uptake of adenosine which is a powerful coronary vasodilator oral dipyridamole was given to assess the response in patients with microvascular angina who have defective vasodilatory reserve.

REVIEW OF LITERATURE

Dipyridamole initially developed as a coronary vasodilator agent for treatment of angina pectoris. Later Dipyridamole has proved to be more useful and has been approved by FDA of USA for intravenous use in coronary vasodilatory stress studies.

Efficacy of oral dipyridamole: Oral dipyridamole is better absorbed in the fasting state reaching peak plasma levels at 2 to 2 1/2 hrs [11]. The plasma half life is 11 hrs. Levels similar to I/v dipyridamole 0.56 mg/kg have been achieved with oral suspension of 300 mg dipyridamole [9]. The peak effect was observed in 30 minutes. After overnight fast higher peak blood levels are likely.

Mechanism of Action

Dipyridamole is a purine transport inhibitor and acts by inhibiting cellular uptake of adenosine by erythrocytes and endothelium [11,12]. It potentiates sympathetic beta stimulation by phosphodiesterase inhibition. Adenosine is a potent coronary vasodilator. It selectively dilates the resistance vessels and graded responses to the extent of adenosine removal blockade by varying doses of intravenous Dipyridamole have been observed [10]. Systemic vasodilatation and arterial hypotension occurring after dipyridamole

administration does produce simultaneous sympathetico adrenal activation.

A variety of drugs like beta blockers, Ca channel blockers and nitrates, producing changes in the endogenous vascular tone can alter the dipyridamole test resuts [3,5,10,13]. Hence long periods of drug free interval have been recommended to derive optimum vasodilatory effect. Use of theophylline containing beverages like coffee and tea obviously will interfere with test results.

Mechanism of Dipyridamole Induced Ischaemia

1. Increase in myocardial oxygen consumption of 20-100% has been observed because of an increase in the rate pressure product (20-30%) and sympathetic stimulation induced by Dipyridamole [10,14].

2. Systemic steal: Dipyridamole induced systemic vasodilation can reduce the diastolic perfusion pressure. In presence of critical coronary stenosis and already maximally dilated coronary bed the reduction in perfusion presssure induces ischaemia.

3. Vertical steal:Coronary reserve of subendocardium already exhausted in presence of significant coronary lesion. So on challenge with dipyridamole only

epicardial vessels dilate diverting the subendocardial perfusion thereby inducing subendocardial ischaemia[15].

4. Horizontal steal-collateral vessels are maximally dilated with no myocardial perfusion reserve and they develop only in presence of significant coronary artery disease so the effect of dipyridamole in the normal vessels subserving the collaterals redcues the collateral blood flow. This by reducing perfusion pressure by dilating the normal arteriolar system induces ischaemia in the collateral perfused territory. This forms the basis of Dipyridamole induced ischaemia in the majority[2,5,13].

5. Microvascular angina, Refers to angina occurring in patients with fixed microvascular conductance (disease) involving the blood vessels perfusing the subendocardium[16,17]. In these patients dipyridamole can induce ischaemia by the mechanism of vertical steal. Few studies have highlighted absence of perfusion defects and wall motion abnormalities in presence of chest pain and/or electrocardiographic abnormalities[2,5,18] (Echocardiographically silent ischaemia/super ischaemia). Occurrence of ischaemia in one dimension which manifests in the electrogram and significant improvement in perfusion in other two

dimensions along with sympathetic activation accounts for the echocardiographic silence.

Dipyridamole at times can induce chest pain independently or disproportionate to ischaemia which is basicallymediated by adenosine [2,5,19].

Side effects of Dipyridamole

Reporting on the registry data on intravenous dipyridamole from 64 centres in over more than 4000 patients Baller GA [20] reported major side effects like bradyarrhythmias severe broncho spasm and acute myocardial infarction in 2.6% of the patients with no deaths. Myocardial Infarction occurred in 0.5% of the patients irrespective of prompt aminophylline reversal and use of nitrates on failure of aminophylline. Registry data reported minor side effects like nausea, headache, dizziness hypotension, chest pain and transient ECG changes in 30-60% of patients which promptly reverted with intravenous aminophylline 125 mg [20].

AIM OF THE STUDY

To observe the response to oral dipyridamole in patients with possible microvascular angina ie patients with chest pain syndrome but normal coronary arteries on coronary angiogram. The study assesses whether oral dipyridamole can be used to identify patients with syndrome X.

Subjects & Methods

25 patients aged 25-62 years mean age 46 y (5 females and 20 males) were studied. All patients had chest pain on effort, normal global and regional LV systolic function at baseline and normal coronary arteriographic findings. TMT using Bruce protocol was performed in all patients except in two who had peripheral vascular disease. 2D echocardiography and 12 lead Electrocardiogram were performed 0, 15,20,30,45 min and 1 hour after 300 mg of oral dipyridamole. This dose approximated the dose used in three similar studies in the past [21,22]. All patients were studied after an overnight fast. All drugs were discontinued for 24 hours prior to the test. Caffeinated beverages were avoided for 48 hours. Any adverse reaction to Dipyridamole looked for at frequent intervals. Routine reversal with 250 mg of I/v diluted aminophylline was done in all patients at the end of the study. Echocardiography was performed on a commercially available equipment (ATL ultramark 4). All

values were expressed as mean ± standard deviation. Statistical analysis. The difference in sensitivity of oral dipyridamole was compared with standard treadmill by binomial test of proportions.

RESULTS

There was a total of 25 patients patients of which 80% were male. Age ranged from 25-62 years. All of them had angina or atypical chest pain for which they were investigatedCoronary risk factor HBP (BP >140/90) mm Hg) was present in 8 patients (32%). 2 were diabetic FBS > 120 mg%. H/o smoking present in 8 patients. 7 had a positive family history of CAD. Cholesterol more than 240 mg% was present in 4 patients and a reduced HDL in 1 patient. TMT was positive at high work load in 12 patients. 1 patient had a strongly positive TMT at 4 METS. TMT was not done in two patients due to associated peripheral vascular disease. It was inconclusive in two patients, boderline in one. One patient had chest pain but no ECG changes. The remaining had negative TMT.

Coronary Angiogram was performed in all but 1 patient. All patients had normal coronaries by visual assessment although a quantitative assessment was not performed. Type III LAD was found in 24%. 3 had a left dominant system and 1 had a codominant system. Myocardial bridges were seen in 2 patients.

The Hemodynamic response to DPN is given in Table 1

Table No.1

	Basal	After DPN
Heart rate heats/min	70.4±11.2	84.47±14.14
Systolic BP mmHg	137 ±11.5	127.4 ±9.32
Deastolic BP mmHG	89.3±4.95	80.5 ±5.82
Rate pressure product	9523±1870	10744.6±1970

Dipyridamole echo was negative in all the patients studied. No patient had any new RWMA after dipyridamole 36% patients had chest pain and 32% diagnostic ST segment depression. ECG changes occurred after a mean of 35±20.5 minutes after oral dipyridamole. Changes reverted after a mean of 12±7.4minutes after I/v aminophylline. The ST-T changes involved the lateral leads in all patients. 2 of the patients had additional changes in the inferior leads.

Sensitivity of oral dipyridamole was found to be low. Comparision of sensitivity, with that of TMT by binomial test of proportions showed a $P<.05$ indicating that oral dipyridamole had a much lower sensitivity that treadmill stress test.

DISCUSSION

In patients with syndrome X the chest pain and ST segment depression are typically ischaemic but LV shows the normal hyperkinetic pattern. This paradoxical entity of echocardiographically silent ischaemia is suggestive of normal coronary arteries and is different from the pattern seen in epicardial coronary artery disease. In these patients abnormalities in regional LV function precede the development of diagnostic ECG changes.

The percentage of patients showing chest pain and ST segment depression in this study 32% is much lower than the 84% reported by Picano et al[18]. This may be because of the lower dose of dipyridamole used in the present study (300 mg oral Vs 0.84 mg/kg 1/v). The efficacy of oral dipyridamole Vs a high dose intravenous dose is not certain. Thirdly the group of patients with angina and normal corcnary arteries form a heterogenous group and these patients cannot be expected to react in a homogenous way to different pharmacologic stimuli.

Reproduction of chest pain and ST segment depression by dipyridamole makes any non cardiac etiology of chest pain with normal coronaries unlikely.

The absence of abnormal wall motion appears to relate to the amount of subendocardial tissue rendered ischaemic with minor degrees of transmural involvement less likely to produce regional dysfunction. It may be hypothesized that dipyridamole induced ischaemia is large enough in a horizontal direction to induce angina and electrial abnormalities but not so deep in a transmural or vertical axis to provoke wall motion abnormalities.

In syndrome X-dipyridamole induced chest pain and ST segment depression occur in the absence of regional asynergy or depressed global LV function. This might be explained on the basis of slight reduction in afterload due to systemic vasodilator effects of dipyridamole and activation of the sympathetic nervous system hoth increasing contractility which counter balance the mild subendo cardial ischaemia.

A prearteriolar constriction is postulated [23,24] to account for the reduced vasodilator response and anginal pain observed after administration of dipyridamole in patients with syndrome X. A compensatory production of adenosine could explain the development of angina in the presence of a patchy distribution of ischaemia and even in its absence.

Limitations of the Study

1. Oral dipyridamole was used instead of high dose/iv dipyridamole.
2. Digitised echo image processing of LV was not available.
3. A quantitiative analysis of coronary angiogram was not performed.

CONCLUSIONS

1. Oral dipyridamole test may produce diagnostic ECG changes in patients with Syndrome X.

2. Methods to increase the sensitivity of the test have to be developed.

3. The occurrence of echocardiographically silent ischaemia may provide insight into the mechanism of pain in patients with syndrome X.

4. The minimal increase in rate pressure product observed suggests mechanism other than supply demand mismatch in the production of chest pain in these patients.

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