A REVIEW OF PATIENTS WITH A 'NORMAL' CORONARY ANGIOGRAM OVER A 3-YEAR PERIOD

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ABSTRACT

Over a period of 36 months, we detected 54 patients with normal coronary arteries or non-critical coronary artery stenosis within our study series of coronary angiography. We studied these patients to determine their clinical, electrocardiographic, stress testing and angiocardiographic characteristics. We detected among them a preponderance of female sex and a higher incidence of ethnic Indians. The majority of the patients studied had one or more coronary risk factors. 52% had a normal resting ECG. In those with a positive stress test and reports available for review, there is a near equal distribution of horizontal and J-type ST depression. Those patients with a positive treadmill tend to have a higher left ventricular end diastolic pressure (LVEDP) at cardiac catheterization. We also noted in this group of patients a higher proportion with a small distal left anterior descending artery. These patients also tend to have higher LVEDP even in the presence of normal left ventriculogram. Our current series suggests the possibility of raised left ventricular end-diastolic pressure and the presence of a "small distal left anterior descending artery" syndrome in association with patients with a 'false positive' treadmill test.

Keywords: angina, coronary artery disease, treadmill test, coronary arteriography, left ventricular end diastolic pressure.

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INTRODUCTION

Despite careful patient selection, we do come across in the cardiac catheterization laboratory patients with normal or near normal coronary angiograms. This not only adds to ever increasing health costs, it also subjects the patients to an invasive test with its small risk of morbidity and mortality. Over the period from January 1987 to December 1989, we did a total of 506 coronary angiograms in a study series. We noted a total of 54 patients with normal coronary arteries or non-critical coronary artery stenosis (defined as no lesions causing a coronary luminal diameter reduction of > 50%). We were interested in this group of patients with regards to their clinical and investigational characteristics. We hoped to identify factors that could account for their symptoms or abnormal test results.

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METHOD

Patient selection

We studied retrospectively all consecutive patients who had a coronary angiogram done under one of our consultants over a 36 month period from January 1987 to December 1989. We traced the coronary angiogram reports of these 506 patients and identified 54 with normal coronaries or non-critical coronary artery disease. We then went through the case-notes of these 54 patients to check on their clinical data and reviewed the electrocardiogram and treadmill results. Patients with proven myocardial infarction or known to have cardiomyopathy were excluded even if they fulfilled the coronary selection criteria. One young patient had mild mitral valve prolapse. There were no other patients with valvular lesions.

Data analysis

Electrocardiograms and treadmill results

The electrocardiogram (ECG) done nearest to the coronary angiography date was reviewed for each patient. Treadmill reports, where available, were reviewed with regards to the degree and type of ST changes. In cases where the test was done in another centre, attempts were made to retrieve the information from the referring letter. In cases where the treadmill test was done more than 6 months prior to the coronary angiogram date, or if treadmill was not done at all, these are labelled as 'Not Done'.

Coronary/left ventriculogram and left ventricular end diastolic pressure (LVEDP) measurement

Coronary angiography was carried out via the percutaneous femoral approach using standard Judkin's technique. Five French catheters were used in the majority of patients. In very occasional cases, bigger size or non-coronary seeking catheters had to be used. Arteriograms of the coronary arteries were obtained in multiple views, with varying degrees of cranial and caudal tilting depending on the segment of the artery being imaged. Philips equipment with C-Arm was used so that the patient need not be moved during the study. Left ventriculography was done using five French pigtail catheters. Biplane left ventriculography was done in each case. The LVEDP was determined using the Hewlett-Packard Catheteri-

zation Data Analysis System. In general, the left ventriculogram was done after the coronary injections.

Statistical analysis

Results are reported as the mean ± standard deviation. Student's t test was used for quantitative data and chi-square analysis for qualitative data. One-way analysis of variance was used to compare the groups with different distal left anterior descending (LAD) artery sizes. Results were considered significant at $p<0.05$.

RESULTS

Demographic data

The demographic data is shown in Table I. The mean age of the patients was 48.8±8.6 years (range 29 to 73 years). There were a total of 26 (46%) males and 28 (54%) females. This is noteworthy since coronary artery disease has a male preponderance. There were 34 Chinese, 15 Indians, one Malay, and 4 from other races. This showed an over-representation of Indian race in this sample compared to our population data (according to the 1990 Singapore census figures, only 7.1% of our total population are Indians).

Clinical data

Twenty-six patients (48%) had one coronary risk factor; 24% had 2 or more risks factors (see Table I). We define 'elevated cholesterol' as those whose serum cholesterol was > 5.2 mmol/l. 'Smokers' are patients who were engaged in cigarette smoking at the time when they were admitted for coronary arteriography. Patients who were labelled as 'hypertensives' or 'diabetics' must be diagnosed by qualified medical practitioners and have been advised on nonpharmacological therapy or started on treatment. 'Family history of coronary artery disease' refers to those whose parents or siblings have been diagnosed to have coronary artery disease at age <55 years. Nineteen (35%) patients had typical anginal symptoms, another nineteen (35%) had atypical chest pain and three (5%) had exertional dyspnoea. Six (11%) had no symptoms but had

Table I - Clinical data/ECG/Stress test/Coronary angiogram/Left ventriculogram findings in our patients

S. No	(yr)/Sex	Race	Symptoms	Risk Factors	ECG	Stress Test	Coronary Angiogram	Distal LAD Size	LEVDP (mmHg)	LV
1	34/F	Ch	At	None	Normal	+ (GP)	Normal	Medium	6	N
2	55/M	Ch	None	Chole	Normal	+, H-2 mm	Normal	Medium	3	N
3	63/M	Oth	None	None	Normal	+, H-1.7 mm	Normal	Medium	15	SI
4	49/F	In	At	DM	Normal	No	Normal	Small	13	N
5	42/M	Oth	None	None	T inversion	-	Normal	Large	0	N
6	56/F	Ch	A	Hypt	RBBB	No	Normal	Small	7	N
7	37/M	Ch	At	Chole, Smoker	Early repol	-	Normal	Large	10	N
8	47/F	In	A	HPT, DM, FHO	T inversion	No	Normal	Small	16	N
9	58/F	Ch	At	FHO	ST depress	+, J-3 mm	Normal	Medium	20	N
10	54/F	Ch	At	None	Early repol	+, J-15 mm	Normal	Small	10	N
11	41/M	In	At	HPT, Smoker	LVH	+, J-2.3 mm	Minor LAD	Small	11	N
12	58/M	Ch	At	Smoker	Normal	+, J-1.7 mm	Normal	Medium	5	N
13	53/M	In	A	Chole	Normal	+, J > 2 mm	Normal	Large	14	N
14	57/M	Ch	Dys	HPT, DM, Smk	Normal	-	Normal	Medium	4	SI
15	45/M	Ch	None	HPT, Chole, Smk	LVH ST dep	+, A-2.4 mm	Minor RCA	Medium	8	N
16	45/M	Ch	A	Chole	Normal	+, J-1.7 mm	Minor RCA	Medium	14	N
17	40/M	In	A	Smoker	ST depress	+, H-2 mm	Normal	Large	23	N
18	52/M	Ch	Pal	Chole	Normal	+, J-3.1 mm	Normal	Large	10	N
19	42/F	Ch	At	Chole, FHO	Normal	-	AN Cx	Large	21	SI
20	42/F	In	A	None	T inversion	No	Normal	Medium	18	N
21	40/F	Ch	Pal, Loc	Smoker	LVH	No	Normal	Medium	8	SI
22	48/F	Ch	A	HPT	ST depress	No	Normal	Small	17	N
23	54/F	Ch	At	HPT, Chole	ST depress	No	Normal	Medium	22	N
24	56/F	In	Pre-Op	None	ST depress	No	Normal	Large	10	N
25	39/M	Oth	At	Smoker	LVH	+ (GP)	Normal	Large	13	N
26	35/M	In	A	APT Smoker	Normal	+, J-1.5 mm	Normal	Medium	15	N
27	60/F	Ch	A	Chole	Normal	No	Normal	Medium	8	N
28	39/F	In	Intra-Op	None	T inversion	No	Normal	Large	19	N
29	56/F	In	A	HPT, DM	ST depress	-	Normal	Medium	6	N
30	57/M	Ch	At	HPT	Normal	+ (GP)	Normal	Medium	16	N
31	47/M	Ch	A	Smoker	Early repol	+, ?-2.3 mm	Normal	Large	1	N
32	61/F	Ch	None	HPT	Normal	No	Normal	Large	15	N
33	45/M	Ch	None	None	T inversion	+, J-1.7 mm	Normal	Medium	15	N
34	48/F	In	A	None	ST depress	No	Normal	Medium	5	N
35	58/M	Ch	Pal	Smoker	Normal	+, J-2.3 mm	Minor LAD	Medium	9	N
36	48/F	In	At	None	ST depress	+, J-1.6 mm	Normal	Small	23	N
37	52/M	Ch	A	None	ST depress	+, H-1.7 mm	Normal	Small	14	N
38	50/F	Ch	A	HPT	T inversion	+, H-1.5 mm	Normal	Small	15	N
39	64/F	Ch	At	None	Normal	+ (GP)	Minor LAD	Medium	15	N
40	54/F	Oth	A	HPT	Normal	No	Normal	Small	30	N
41	73/M	Ch	Pre-Op	None	Normal	+, ?-2.3 mm	Minor LAD	Small	15	N
42	45/F	Malay	At	None	Normal	+, H-2.3 mm	Normal	Large	23	N
43	29/F	In	At	HPT, DM, Chole	ST depress	No	Normal	Medium	11	N
44	54/M	Ch	At, Loc	HPT, Smoker	Paroxys AF	+,+ 4.2 mm	Minor RCA	Medium	12	N
45	57/M	Ch	At	FHO	T inversion	+, J-3.1 mm	Normal	Small	13	N
46	47/F	Ch	At	HPT	Normal	+, H-2 mm	Normal	Large	17	N
47	40/M	Ch	At	Smoker, Chole	ST depress	+, H-1.6 mm	Normal	Large	22	SI
48	39/M	Ch	Pre-Employ	HPT	T inversion	No	Normal	Large	15	SI
49	47/F	In	A	DM	T inversion	+ (GP)	Minor LAD	Small	8	N
50	51/M	Ch	A	Smoker	ST depress	No	Normal	Small	18	N
51	45/F	Ch	Dysp	None	ST depress	+ (GP)	Normal	Large	7	N
52	43/M	In	A	HPT	Normal	No	RCA ecta	Medium	12	N
53	44/F	Ch	Dysp	HPT, Chole	Normal	+, ?-2.8 mm	Normal	Medium	9	N
54	41/F	Ch	A	HPT	Normal	No	Normal	Large	6	N

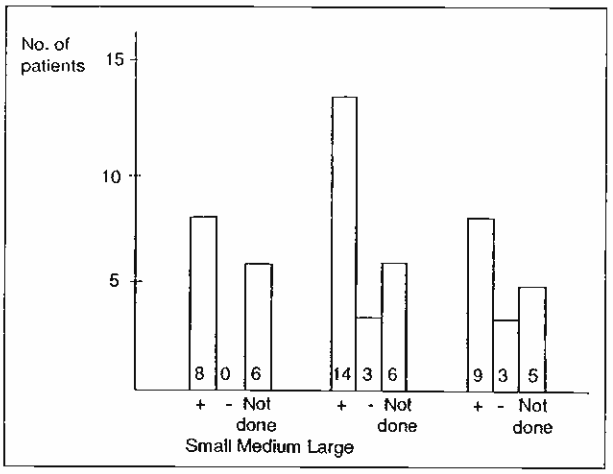
Abbreviations: Ch-Chinese; In-Indian; Oth-Others; At-Atypical chest pain; A-Angina chest pain, Dys-Dyspnoea; Pal-Palpitations, Loc-Loss of consciousness, HPT-Hypertension, DM-Diabetes Mellitus; Chole-Elevated cholesterol; FHO-Family history of ischemic heart disease; depress-depression; H-Horizontal; J-J type ST depression, GP-stress test performed by refering practitioner; +- Positive; - Negative; AN-Aneurysmal Ecta-Ectasia, SI-right LV hypokinesia

a positive treadmill done as part of their health examination or pre-employment check-up. One (2%) asymptomatic patient was a pilot with an abnormal resting ECG. Of the 3 patients with palpitations, 2 had a positive treadmill and one had a history of loss of consciousness. There were 2 patients who had an angiogram done as part of pre-operative assessment, and one had the coronary angiogram done post-operatively because ST segment changes were seen during surgery. The last patient had a coronary angiogram as part of the work-up for syncope. There was one patient with mild mitral valve prolapse. She was also the youngest patient (29 years) and had atypical chest pain and 3 coronary risk factors (hypertension, diabetes mellitus and dyslipidaemia).

12-electrocardiography and treadmill test

Twenty-eight (52%) patients had a normal resting electro-cardiogram. Of these, 3 patients had early repolarization pattern, and all had an abnormal treadmill response. Twenty-one of the remaining 26 patients showed ST-T changes over the inferolateral leads. Four showed anterior T wave inversions, and one had partial right bundle branch block pattern. Three (0.6%) patients had left ventricular hypertrophy based on ECG criteria. Thirty-six (66%) had a stress test done prior to coronary angiography (Table I). Thirty of these were positive by ECG criteria. Non of the negative stress test patients came from the small distal LAD group (Fig 1). Fifteen of the 30 showed ST depression of equal to or more than 2mm. Of the 21 patients with tracings available, 9 showed horizontal and 12 had J type ST depression.

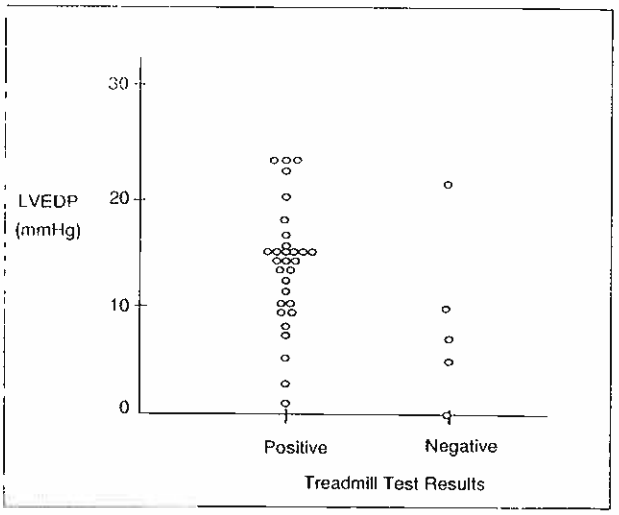
Fig 1 - Stress test results in relation to Distal LAD sizes



Coronary angiography, left ventriculography and left ventricular end diastolic pressure (LVEDP)

Forty-four (82%) of the 54 patients had completely normal coronary angiograms. Seventeen patients had a large distal anterior descending (LAD) artery (defined as distal LAD arteries that are large in calibre, and which supply the distal portion of the posterior septum), 23 medium (defined as medium-sized arteries which also supply part of the posterior septum) and 14 small distal LAD artery (defined as LAD arteries that do not go around the cardiac apex or are diminutive in size). There was only hypokinesia in one of the ten left ventricular segments in 7 (13%) patients in the series. In the 54 patients, the average LVEDP was 13 ± 6.6 mmHg (range 0 to 30 mmHg). It was noted that patients with a positive treadmill tended to have higher LVEDP values (13.5 ± 5.6 mmHg) compared to those with a negative test (8.2 ± 8.0mmHg); this was nearly but not statistically significant (p=0.076)(Fig 2).

Fig 2 - LVEDP in relation to Treadmill Test Results



DISCUSSION

The pathophysiology of angina pectoris is usually related to myocardial ischaemia secondary to significant obstruction of the large epicardial coronary arteries. Occasionally, patients who present with typical angina or angina-like symptoms have entirely normal or near normal coronary arteries during coronary arteriography[1,2]. This combination has been descriptively known as Syndrome X. In fact, one fourth of the patients who entered prospectively into the Coronary Artery Surgery Study fell into this category[3]. It is also known that these patients may exhibit an abnormal ST response during treadmill testing, and this has often been labelled as a 'false positive' response. We reviewed the clinical data and investigational findings in our patients who had proven normal or non-critical coronary artery occlusions over a 3-year-period in our present study. The patients were recruited consecutively from January 1987 to December 1989. During this period, a total of 506 coronary angiograms were done in our study series.

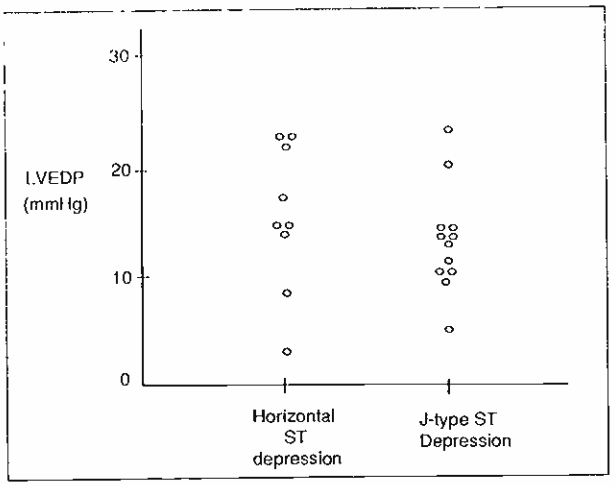
The interesting demographic findings are that slightly more than half of the patients (52%) were female, and there is a high proportion of Indians in this cohort. Coronary artery disease is more prevalent in males. A higher female preponderance in this study is not unlike that described by Kemp et al[4] in 1971 (the male to female ratio was 1:1). The higher incidence of Indians in the study population reflects earlier findings in our local practice. The mean age of the patients was 48.8±8.6 years. This again is akin to Kemp's [4] series, where the average age was 47 years.

Most patients in our study (72%) have one or more coronary risk factors. About half (48%) of the patients also had abnormal resting electrocardiographic changes. These 2 findings may be biased, as in patients who have chest pain, the presence of these features probably influenced their selection for subsequent coronary angiography.

Nineteen patients had typical angina and this accounted for 10 of the 18 patients who did not have a treadmill done. The 'atypical' angina patients are labelled as when the threshold of the pain was variable, when pain occurs at rest or on effort and occasionally nocturnally, and when the pain was variably relieved by nitrates. As expected, the majority of these patients had a stress test done. Of the total of 35 patients with treadmill done, 30 were positive. Although the patients were proven to have normal or near normal coronary arteries subsequently, this group of patients was found to have a higher left ventricular end diastolic pressure (LVEDP) during left heart catheterization. Bush et al[5] noted in an earlier study that patients with elevated LVEDP may have anginal chest pain with angiographically normal coronary arteries. All our patients have normal or only slightly impaired left ventricular function. These patients thus appear to have isolated diastolic dysfunction. Various mechanisms (eg microvascular angina[6], underlying

cardiomyopathic process with increase in diastolic filling pressure[7]) have been suggested but remain unproven. It is possible that the elevated LVEDP impedes circulation to the subendocardial region of the myocardium and causes ischaemia, and hence angina-like symptoms. The type of ST changes during the treadmill test (horizontal or J-type depression) did not correlate with the LVEDP measurement (Fig 3).

Fig 3 - LVEDP in relation to ST changes during Treadmill Testing



We noted an interesting feature during the analysis of the coronary angiogram of this group of patients - a higher than normal number of patients with small distal left anterior descending (LAD) artery (Note: This information is routinely coded during our reporting of coronary angiograms). Our definition of a small distal LAD artery is one that does not wrap around the left ventricular apex and/or one that is diminutive in size (Fig 4). Of the 506 patients with coronary angiography done, 15 patients' distal LAD could not be seen as the LAD artery was totally blocked and there were no visible collaterals supplying it. Another 21 has poorly visualised distal LAD artery and the size could not be ascertained correctly. Of the remaining 470 patients, 241 had a medium-sized, 179 had a large and 50 had a small distal LAD artery. The 50 patients with a small distal LAD in this big group actually included patients with disease in the proximal or mid LAD artery, hence the distal LAD might be underfilled. It also included patients with distal LAD disease and hence the figure of 50 might be an overestimate. Even so, the proportion of patients with a small distal LAD artery in the angiographic population is only 11%. Of the 54 patients in our study series, there were 14 patients (26%) with a small distal LAD. The difference is not statistically significant (p=0.16); however, this might be due to the small sample size of small distal LAD artery patients. Interestingly, this group of patients also had higher mean LVEDP (15.1 ± 6.0 mmHg) as compared with the 2 other groups (11.6 ± 5.4 and 12.7 ± 7.45 for medium and large distal LAD artery respectively)(Fig 5). However, the difference is not statistically significant. This does suggest that the small distal LAD artery in patients with chest pain but normal coronary arteries might not just be a chance observation but there could exist a possible underlying association.

The widespread use of the treadmill test to detect myocardial ischaemia has given a group of patients with positive results but subsequently proven to have normal or near normal coronary artery during coronary angiography. These patients are subsequently labelled to have a false positive stress test and their chest pain is thought to be noncardiac in origin. O Cannon III et al[6,8,9] have done extensive work in these patients and suggested that the underlying pathophysiology is that of an abnormal vasodilator response of small vessels (vessels ranging from 50 - 500 microns in diameter). These are too small to be detected in routine coronary angiography. Also, a normal coronary angiogram does not exclude ischaemia due to these small vessels. Hence, these patients' stress test findings are strictly speaking not 'false positive' for myocardial ischaemia but rather 'false positive for major epicardial stenosis'[10]. In fact, exercise thallium-201 scans have been shown to produce 'false positive' results in this group of patients as well[11]. However, these patients have a rather benign prognosis generally, and their symptoms may be relieved by medications[4,8].

Fig 4 - An example of a small distal LAD Artery

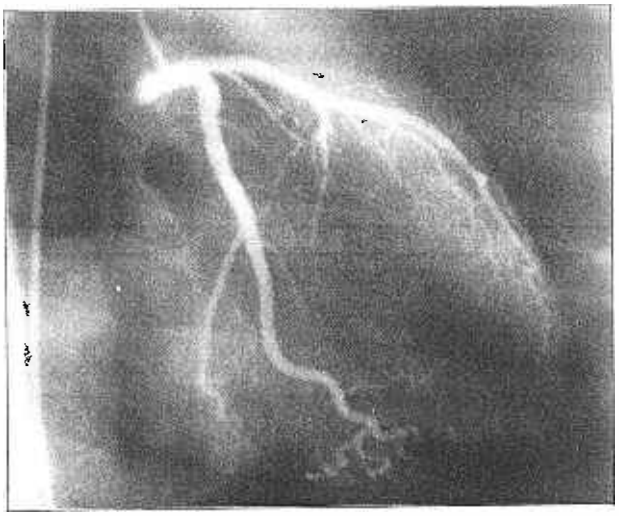
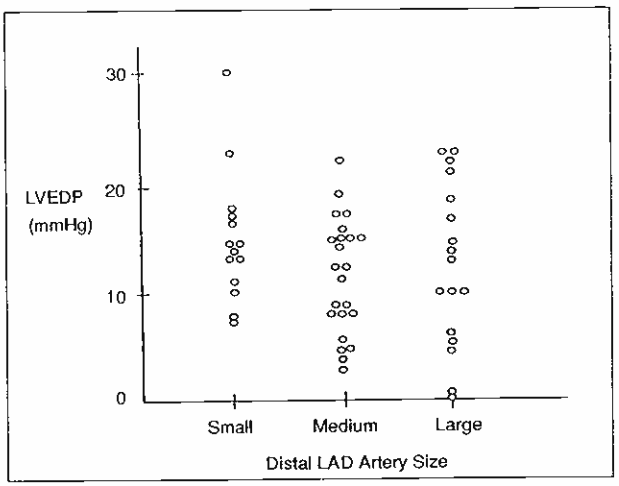


Fig 5 - LVEDP in relation to Distal LAD Artery Size



CONCLUSION

In this small study, we find that neither the symptoms nor treadmill response is helpful to us in defining the subgroup of patients who will have normal or near normal coronary arteries during angiography in a population of patients with angina. However, these patients are more likely to be female. Those with positive treadmills tend to have higher left ventricular end diastolic pressure (LVEDP), as does the group with a small distal left anterior descending (LAD) artery. Although our current series is too small to detect any statistical significance, it suggests the possibility of raised left ventricular end diastolic pressure and the presence of a "small left anterior descending artery" syndrome in association with patients with 'false positive' treadmill test. However, these observations remain to be further studied and proven.

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