The profile of subjects with suspected coronary artery disease who have atypical chest pain symptoms

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DOI: https://doi.org/10.24170/22-1-6738

ABSTRACT

Background: This study describes the risk factor profile of subjects with coronary artery disease (CAD) who present with atypical chest pain.
Method: Hospital records of patients with chest pain who did not satisfy the criteria for typical angina and who underwent both sestamibi nuclear imaging and coronary angiography were evaluated over a 6 year period (2002 - 2008).
Results: Amongst 5 378 subjects referred for evaluation of myocardial ischaemia to a tertiary hospital, the prevalence of atypical / non-anginal pain was 9.9% (531 patients). Of the 173 subjects who underwent both nuclear scans and coronary angiography, 99 (M 66, F 33) (57%) had epicardial CAD at angiography (>50% stenosis) with equal distribution of single, double and triple vessel disease. There was no difference in the pretest probability of CAD in subjects with and without CAD (20.5% vs. 21.9% p=0.891). Neither the number of chest pain criteria nor the individual pain characteristics were associated with the presence of CAD (p>0.05). CAD was more likely in the middle age and older subjects (p<0.001), in males (p<0.001) and in those who smoked (LR 5:2 p=0.001). On multivariate analysis age, smoking, waist circumference and gender emerged as predictors of CAD. Clustering of 3 or more risk factors was associated with the presence of myocardial perfusion deficits (p=0.001).
Conclusion: Characterisation of chest pain symptomatology did not prove to be helpful in the detection of CAD among subjects with a low pretest probability. Decision-making and triage should be supported by a positive smoking history and risk factor clustering.
SA Heart® 2025;22:22-28

INTRODUCTION

Chest pain is a common presenting symptom and raises immediate concerns about coronary artery disease (CAD). In a general practice survey of almost 25 000 subjects presenting with chest pain only 12% of subjects were found to have CAD.[1] The prevalence of "noncardiac" symptoms assessed in the emergency room was 17% in a large registry of 17 737 subjects with acute coronary syndrome.[2] When angina pain is not typical it is not uncommon for subjects to be labelled "atypical chest pain" (ACP) and discharged without a firm diagnosis. Patients with nonspecific chest pain symptoms are not without risk,[3] and continue to seek treatment on a regular basis, imposing a large cost burden for undiagnosed symptoms. In a Mayo Clinic study 49% of subjects who presented to the emergency room were labelled as psychogenic chest pain and during follow up 42% had repeated cardiology evaluations.[4]

Many patients present in a non-acute setting with chest pain symptoms that do not fit the description of typical angina. Typical angina as originally described by the English physician, William Herberden[5] in 1768, comprises distinct criteria that describe a flow of events from onset of pain, its duration and mode of relief. It is characteristically a dull discomfort that is usually brought on by effort and relieved by rest or sublingual nitroglycerine. When evaluating patients presenting with suspected myocardial ischaemia, the clinician's approach is to evaluate the history to assess the typicality of chest pain, and inherently applies conventional risk prediction to estimate the probability (pre-test likelihood) of CAD based on the patient's age, gender and chest pain characteristics.[6,7] However, subjects frequently present with varying symptomatology and severity of chest pain resulting in poor discriminatory power for the diagnosis of coronary disease. While clinicians may appropriately

refer central chest pain with typical angina and avoid referring subjects with musculoskeletal symptoms, they are often faced with the dilemma of unspecified chest pain symptoms with an uncertain diagnosis. In subjects who do not fulfil all the criteria for typical angina the term "atypical chest pain" (ACP) is loosely applied while the subject is being referred or investigated. Chest pain in these subjects should not be disregarded as these symptoms may be associated with a heightened cardiovascular burden. In a Swedish study subjects with nonspecific symptoms were found to have significant morbidity and mortality on long-term follow-up.[3] In this study we describe the clinical and angiographic profile of subjects with atypical chest pain symptoms referred to a tertiary centre for evaluation of suspected ischaemia.

AIMS

We aimed to evaluate whether chest pain categorisation predicts the presence of CAD in a low risk subjects with stable chest pain symptoms. The objectives were to describe the clinical profile of patients who presented to the cardiac clinic with atypical chest pain symptoms, as well as to identify clinical parameters that are likely to suggest the presence of CAD in these subjects.

METHODOLOGY

This was a retrospective study over a 6 year period (2002 - 2008) of subjects with stable chest pain suspected to be of cardiac origin referred to the IALCH cardiac clinic in the Cardiology Department at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa. During this period subjects with atypical symptoms underwent sestamibi scans and coronary angiography. Patients were identified using the Speedminer software programme that was used at the hospital to store data collected on its Medicom database. Data were extracted on age, gender, risk factors, chest pain symptomatology and investigations for CAD (sestamibi, methoxyisobutylisonitrile nuclear scans and coronary angiography). Subjects who did not satisfy the criteria for typical angina were assessed at the cardiac clinic by the senior registrar in consultation with the cardiology consultant. All subjects had stable chest pain symptoms and were initially assessed on history, chest radiograph, electrocardiogram, and exercise stress testing. Troponin estimation was not performed in these subjects as they did not present with acute symptom onset and were stable. Those found to have an extracardiac cause for their symptoms were evaluated and discharged from the clinic. Patients with known established coronary artery disease who underwent coronary artery bypass surgery were excluded. The remaining patients with atypical symptoms constituted the study group.

Typical angina was defined by a set of 3 criteria[8] as follows: (1) onset with effort or emotion, (2) typical nature (retrosternal, crushing, dull), radiation (neck, jaw, left arm, back, epigastrium), duration (2 - 10 minutes) and (3) relief with rest and / or TNT. If all 3 of the criteria for angina were met, the pain was diagnosed as typical angina and the probability for CAD considered high. When 2 criteria were present the pain was classified as "atypical" chest pain and in the presence of only 1 criterion the risk was considered lowest and classified as "non-anginal" chest pain.[8] Exertional dyspnoea and fatigue suspected to be angina equivalents were classified as atypical angina.

Subjects without typical angina (i.e. atypical and non-cardiac pain as defined above) who underwent both coronary angiography and sestamibi scans were selected for study in order to obtain an angiographic as well as a functional assessment of coronary artery disease severity. The end points of this study were obstructive CAD (defined at invasive coronary angiography as >50% reduction in lumen diameter), or inducible myocardial ischaemia on non-invasive stress imaging. The sestamibi study employed a 2-day stress – rest imaging protocol using 15mCi of technetium 99m-sestamibi injected at the peak of stress for stress imaging on the 1st day, and the same dose of technetium 99m-sestamibi for rest imaging study performed at least 24 hours after stress imaging.[9] Single photon emission computed tomography imaging (SPECT) was performed and gated acquisition was done on the stress images. Images were analysed with MPI Siemens Corridor 4DM V501 and the study was interpreted as abnormal if evidence of inducible myocardial ischaemia (reversible defect), and / or infarction (irreversible defect) was present.

Ethical approval for access to the medical records was obtained from the Biomedical Research and Ethics Committee (BREC) - Reference number BR 194/09.

Statistical Package for the Social Sciences (SPSS version 18.0) was used for analysis of data and a 95% level of confidence estimated; a global significance level of $\alpha = 5\%$ was chosen. Chest pain criteria, age and gender were used in a basic model to assess the pretest probability of coronary artery disease.[6, 10] The type of pain as well as the number of criteria were compared with the angiographic findings. The chi-squared test was used for categorical variables and the Student's t-test was used for continuous variables, to assess the significance of any difference in risk between subjects with and without CAD. Binary logistic regression and multivariate analysis was used to control for confounding factors when assessing the independent rela-

tionships between traditional risk factors (age, diabetes, lipid levels, blood pressure and smoking) and the outcome variable (CAD).

RESULTS

During the 7 year study period (2002 - 2008), 5 378 patients were referred to the IALCH cardiac clinic for the evaluation of chest pain of a suspected ischaemic aetiology. Of these, 564 had symptoms that fell short of the classical description of angina (i.e. they satisfied 1 or 2 out of the 3 criteria). Thirty-three patients had previously undergone cardiothoracic surgery and were excluded from the study, leaving 531 subjects for analysis. This yielded a 9.9% (531/5378) prevalence of patients presenting to the clinic for suspected ischaemia in whom chest pain symptoms were not typical for angina. The male to female ratio in this group was 1:1.3 (229/302). The mean pre-test score in these 531 subjects was 20.9%, in keeping with a low risk for ischaemia. After clinical evaluation and non-invasive assessment clinicians attributed the chest pain symptoms to a non-ischaemic cause in 358 subjects, leaving 173 subjects with chest pain symptoms of a possible ischaemic aetiology. These 173 subjects (93M, 80F) had equivocal or negative exercise stress tests and underwent both sestamibi scans and coronary angiography to determine whether there was an ischaemic basis for their symptoms.

The demographic data, clinical and angiographic findings are shown in Table I. The majority of the subjects were of Indian ethnicity (134/173, 77.5%). Subjects with coronary disease were more likely to be male (M:F 2:1) with no racial predisposition. Ninety-one (52.5%) of these 173 subjects presented with a variety of pre-existing conditions which may have contributed to the clinician labelling their symptoms as "atypical" (Table I). The most frequent underlying conditions were gastrointestinal causes, psychiatric conditions and mitral valve prolapse which totalled 49 of the 91 cases. Of the 173 subjects, 22 had atypical chest pain (2 criteria met), 81 had non-cardiac chest pain (1 criterion met) and the remaining 70 subjects met none of the criteria for angina ("zero criteria pain").

Coronary angiography revealed obstructive coronary disease (>50% coronary stenosis) in 99/173 patients with an equal distribution of single, double and triple vessel involvement. This yielded an 18.6% (99/531) prevalence of significant CAD amongst subjects who presented to the clinic with chest pain symptoms that were not typical of angina. There was no difference in the pre-test score (Diamond and Forrester)[6] between those subjects with a normal angiogram and those subjects with coronary CAD (p=0.891) (Table II).

Subjects with a normal angiogram were younger (mean 48 years) than those with CAD (mean 54 years) (p<0.001) and more likely to be of female gender (p<0.001). Obstructive CAD was more likely in middle-aged or older males and smokers (LR 5:2 p=0.001). The number of criteria met (0, 1, or 2) for the diagnosis of angina had no influence on the findings at angiography. Indeed, 42 of the 70 subjects who met none of the criteria for angina ("zero criteria pain") were found to have significant CAD at angiography. Neither the pain characteristics (nature, duration and radiation) nor the relieving factors (rest or sublingual nitroglycerin) showed any association with CAD or with an abnormal sestamibi scan (Table II). Using established cutoff levels,[11] there was a positive association between increased waist circumference (>102cm) and CAD (p<0,001), as well as between obesity (BMI>30kg/m^2) and CAD (p<0,001). After all risk factors were fed into a multivariable predictive model (controlling for age, gender, BMI, waist circumference, hypertension, diabetes, and family history), it was found that only age, gender, smoking and waist circumference emerged as independent predictors of the presence of obstructive CAD (Table III).

There was no difference between the sestamibi and coronary angiographic findings (p=0.127). Smoking (LR 4:1 p=0.028) was the only individual risk factor associated with an abnormal sestamibi scan. Clustering of 3 or more risk factors was present in 78 of the 173 subjects and was significantly associated with the presence of an abnormal sestamibi scan (p=0.001). Of interest, 39 of the 65 subjects with normal angiograms had an abnormal sestamibi findings raising the possibility of micro-vascular disease in these subjects.

TABLE I: Pre-existing disease conditions.

Disease	n=173	%
GIT causes	22	12.7
Psychiatric / Neurological	15	8.7
Valve Disease / ASD	12	6.9
Connective Tissue Diseases	9	5.2
Neck (Joint / bone / muscles) diseases	8	4.6
Thyroid Disease	8	4.6
COPD	7	4.0
HOCM / DCMO	5	2.9
CVA / TIA / PVD	5	2.9
Total	**91**	**52.5**

HOCM / DCOM: hypertrophic / dilated obstructive cardiomyopathy, CVA: cardiovascular accident, TIA: transient ischaemic attack, PVD: peripheral vascular disease.

TABLE II: Clinical features vs. angiographic findings.

Risk parameter	Normal / non-obstructive (n=74) n (%)	CAD on angiogram (n=99) n(%)	Total (n=173)	p-value
Demographic data				
Age (years)	48.5	54.0		<0.001
Female	47 (58.8 %)	33 (41.2 %)	80	<0.001
Male	27 (29.0 %)	66 (71.0 %)	93	
Ethnic Group				
Black	3	4		0.957
Coloured	4	4		
Indian	56	78		
White	11	13		
Clinical characteristics				
Chest pain				
Zero criteria	27 (36)	42	70	
Non-cardiac	35 (247)	46	81	0.415
Atypical	12 (16)	11	22	
Pretest probability*				
Low (0% - 30%)	26 (35)	33	59	0.891
Medium (31% - 70%)	49 (66)	65	114	
Risk Factors				
Diabetes	4 (32)	41	65	0.227
Hypertension	48 (65)	68	116	0.597
Dyslipidemia	45 (60)	71	116	0.131
Family History	43 (58)	50	93	0.321
Smoking**	23 (31)	57	80	0.001
Obesity measures				
Increased WC	54 (73)	48	102	<0.001
BMI >30Kg/m^2	0 (0)	63	63	<0.001
Sestamibi scan				
Smokers**	18/54	61/119	79	0.028

**Pretest probability was calculated using age, gender and number of criteria according to Diamond and Forrester. **Subjects who were smokers were more likely to have CAD on angiogram as well as on the sestamibi scan.*

DISCUSSION

In this study the prevalence of atypical chest pain symptoms in low to intermediate risk subjects referred for evaluation of suspected myocardial ischaemia was 10% (531/5378). Amongst these subjects obstructive CAD (≥50% diameter stenosis in ≥1 vessel on catheter-based coronary angiography) was detected in 18.6% (99/531). Other studies that have examined the lifetime prevalence of chest pain[2,12,13,14] have reported much lower prevalences of CAD of about 9% - 12%. The high prevalence of CAD at catheterisation angiography 57% (99/173) is very similar to that reported in the South African national ACROSS registry[15] in which 1 892 subjects with chest pain underwent angiography after non-invasive stress testing, and in whom a positive test and conventional risk factors were found to be independent predictors of obstructive CAD. In the TOPIC study which evaluated chest pain symptoms in Switzerland in a general practice setting, CAD accounted for 12% of cases of chest pain.[2] The high prevalence of CAD in our study is due to the fact that our patients comprised a select group of subjects referred from secondary level hospitals to our tertiary clinic, often with medical co-morbidities, resulting in a much higher yield of a positive outcome for CAD.

Several factors might have contributed to the atypicality of pain in our subjects found to have obstructive CAD. Firstly, almost two thirds of our subjects with CAD had multivessel disease,

TABLE III: Predictors of coronary artery disease.

Risk factor variables	ANOVA p-value	Univariate p-value	Multivariate p-value
Age*	<0.001	<0.001	<0.001
Gender*	<0.001	0.021	<0.001
Race	0.851	0.571	0.764
Diabetes	0.230	0.241	0.154
Hypertension	0.599	0.859	0.620
Dyslipidaemia	0.133	0.339	0.104
Family History	0.245	0.331	0.280
Smoking*	<0.001	0.070	0.001
Waist Circumference increased > M102cm/F88cm	0.051	0.029	0.036
BMI increased >30Kg/m2	0.029	0.043	0.409

**Multiple analysis of variance showed that age, smoking and gender were associated with angiographic outcomes. The positive association of increased BMI with CAD on univariate analysis fell away after adjustment in the multivariable analysis.*

which might explain symptoms occurring at rest in addition to exertional chest pain. Secondly, the presence of other comorbidities could be a confounding factor. The autonomic neuropathy and microvascular disease in diabetes and the relative ischaemia in hypertension with left ventricular hypertrophy and arterial rarefaction may be associated with altered thresholds in pain perception and symptoms occurring at rest. When there is more than one underlying aetiology for chest pain the subject might perceive pain symptoms as arising from a single organ (and be interpreted by the clinician as such). For instance, smoking-related cough and chest pain may have contributed to the atypicality of symptoms in chronic bronchitis / chronic obstructive pulmonary disease,[16] conditions which are common accompaniments with CAD. Concomitant gastro-intestinal reflux disease may have contributed to the atypicality of chest pain with retrosternal chest symptoms occurring at rest, particularly in many of our subjects who were obese.[17] These considerations have clinical implications in the assessment of stable patients who present with atypical chest pain symptoms.

Several studies have reported that female patients complain more frequently of atypical chest pain symptoms[18,19,20,21,22] that are often unassociated with CAD. In a study performed in the primary care setting, Desiree Lie, et al.[23] examined gender differences and chest pain characteristics in 1 212 patients with chest pain in an attempt to define clinical markers associated with CHD. They found that women were diagnosed more frequently with psychogenic disorders (11.2% vs. 7.3%; p=.02), while men were more likely to have CAD (17.2% vs. 13.0%; p=.04). Although CAD was more common in males in our study, concomitant psychiatric illness was present in 15 subjects, of whom 6 had normal angiographic and nuclear imaging studies; of these 2 were women with anxiety and depression. There is evidence that women could experience chest pain from disease of the coronary arterioles, even in the absence of angiographically evident coronary disease.[24] The finding of myocardial ischaemia on sestamibi scans in subjects without obstructive CAD at angiography suggest the possibility of underlying microvascular disease in these subjects.[25] The constant demand - supply mismatch may account for symptoms occurring at rest, and lend support to the clinician's perception of the atypicality of symptoms in these subjects.[26] Recognition and treatment of microvascular angina are important in addressing the high cost burden associated with persistent symptoms and return visits, and potential for cardiac events associated with this condition.

Unlike previous reports[21,22] we did not show any gender differences in chest pain symptomatology, nor did we show any differences in symptoms between subjects with and without CAD. Using only the type pain, it has been suggested that the more criteria are met, the greater the likelihood of CAD.[27] In contrast, our findings reaffirm the limited ability of atypical symptoms to predict obstructive CAD in subjects with a low–intermediate pretest probability.[10] Indeed we found that many subjects with CAD satisfied none of the criteria for the diagnosis of angina. Older subjects, male gender, and smoking increased the odds of atypical symptoms being due to coronary disease. Our findings are similar to those of Rovai, et al.[27] who showed that age and gender had better predictive ability and this was increased further by the demonstrate on of inducible myocardial ischaemia on the sestamibi scan. Even In studies of subjects who presented in an acute setting[28,29,30] chest pain symptoms alone had limited predictive ability. Swap, et al.[30] found that no single element of the chest pain history increased or decreased the likelihood of an acute coronary syndrome alone or in com-

bination. In that study chest pain characteristics that were stabbing, pleuritic, positional, or reproducible by palpation decrease the likelihood of ACS or AMI (LR 0.2-0.3). Chest pain that radiated to one or both shoulders or arms or is precipitated by exertion was associated with higher likelihood of ACS (LR 2.3-4.7).

All the subjects in our study were of Indian ethnicity. There is evidence that atypical chest pain symptoms are more frequent in South Asians and people of Indian origin.[21,22] Recognising that the Diamond and Forrester model is not adaptable across different populations, and the limitations of chest pain symptoms in risk assessment Genders, et al.[31] developed and validated a new prediction model, based on clinical presentation and cardiovascular risk factors, to improve the estimate for the probability of obstructive coronary artery disease (CAD) in patients with new onset chest pain and guide further diagnostic testing. In an analysis of over 5 000 patients they found that the clinical model using risk factors improved prediction compared to the basic model using the Diamond and Forrester pretest likelihood assessment. We did not apply risk scoring systems such as the HEART score which uses the pain characteristics, age, number of risk factors, electrocardiographic findings, and troponin levels in acute settings of chest pain presenting to the emergency room.[32,33] We determined the pretest likelihood of CAD using the Diamond and Forrester scores[6,7] which have been used in stable subjects with chest pain. The baseline electrocardiograms and exercise stress test were either inconclusive or negative and these subjects underwent sestamibi scanning which was the only non-invasive test available at the hospital during the study period. Many of these subjects were unable to attain their target heart rate because of impaired mobility arising from morbid obesity, highlighting the importance proper pharmacological testing with achievement of target heart rates during sestamibi nuclear testing.

An important finding in our study was that although the major risk factors such as diabetes, hypertension and dyslipidemia were individually not associated with obstructive CAD, we found that clustering of these risk factors was more likely to be associated with myocardial perfusion defects indicative of obstructive coronary disease.[34,35] In the Botnia[34] study of 4 483 subjects the risk for coronary heart disease was increased threefold in subjects with risk factor clustering in the form of the metabolic syndrome ($p<0.001$) and associated with increased cardiovascular mortality (12.0% vs. 2.2%, $p<0.001$). In that study subjects with the metabolic syndrome were more likely to have macrovascular, or even microvascular disease. Detection of CAD in subjects with atypical chest pain has implications for the risk of undetected disease; likewise early exclusion of CAD in the majority of these subjects has health service implications on the cost burden of repeated admissions associated with ongoing symptoms.[36] In subjects with low to intermediate probability chest pain coronary calcium scoring has now been shown to have a better predictive value than the basic clinical model (age and gender plus risk factors) in subjects with stable chest pain.[37,38] Current international guidelines recommend using the CT-based coronary calcium score in patients calculated to be at low to intermediate pretest probability of CAD.

Limitations of our study include its retrospective design and the consequent lack of complete datasets for each patient. Being performed in a tertiary setting introduced a selection bias leaning towards a diagnosis of CAD in a select group of subjects referred to a tertiary centre which probably accounts for the higher prevalence of CAD in our subjects. Subjects with symptoms clearly attributable to non-ischaemic causes e.g. musculoskeletal or respiratory chest symptoms, would have been appropriately triaged, which probably accounts for the higher prevalence of CAD in subjects without typical again. These factors, (together with the fact that we chose subjects who underwent both sestamibi scans and coronary angiography) resulted in a smaller sample size for study. Also, we studied the pain characteristics in low-risk patients presenting with chest pain but did not analyse the effects of associated symptoms such as dyspepsia, dyspnoea and fatigue that have recently been shown to have additive value in the estimation of cardiovascular disease risk in the primary care setting.[39]

CONCLUSION

This study shows that subjects referred for suspected ischaemia without typical anginal symptoms have a wide differential diagnosis which includes CAD in about 10% of cases. It also highlights the limitations of chest pain characteristics in assessing the probability of CAD.[6] The atypicality of chest pain symptoms should alert the clinician to the possibility that existing comorbidities may influence the manifestations of chest pain and may account for the low to intermediate pretest likelihood for CAD. Chest pain characteristics alone were not a powerful enough predictive tool to determine the need for diagnostic testing. In addition to age and gender, smoking history and risk factor clustering influenced the likelihood of CAD and should help triage subjects with a low to intermediate risk of coronary artery disease. These subjects should best undergo non-invasive testing using calcium scoring / CT angiography which has a very high negative predictive value and obviates the need for invasive testing when the calcium score is zero.[40]

Conflict of interest: none declared.

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