

# Evaluation of Chest Pain in Premenopausal Indian Women

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## Abstract

**Introduction:** Chest pain is a major source of concern for patients and physicians alike as it may harbingers acute life-threatening cardiac events, yet many patients who describe chest pain typical of significant cardiac disease can actually be free of such disease.

**Purpose:** The purpose of the study is to study the clinical profile, assessment of risk factors and incidence of coronary artery disease (CAD) in premenopausal females presenting with typical and atypical chest pain.

**Material and Methods:** This cross-sectional study included 50 premenopausal females presenting with chest pain; all etiologies for the chest pain were considered. Patients were categorized into two groups, (1) those having chest pain considered typical for CAD and (2) those having atypical chest pain; and were subjected to various cardiological investigations, upper gastrointestinal (GI) endoscopies and psychiatric evaluation.

**Results:** About 72% patients had atypical chest pain; when characteristics of atypical and typical pain were compared, there was no statistically significant difference with regards to rapidity of onset, duration, intensity, and aggravating or relieving factors. Apprehension was more commonly associated with atypical; palpitation was more commonly associated with typical chest pain. When risk factors for CAD were compared, only body mass index (BMI)  $\geq 23$  kg/m<sup>2</sup> was more common with atypical chest pain. Diagnosis of CAD was made in overall 10% females; the most common etiologies were painful musculoskeletal conditions (34%), functional (30%), and GI pain (18%). All the females with atypical chest pain had normal electrocardiogram, cardiac enzymes, and resting echocardiography (barring one who had rheumatic heart disease); only treadmill test was suggestive of CAD in 1 female. Thus, only 2.7% females having atypical non-cardiac chest pain (NCCP) had CAD; on the other hand, 28.5% females having typical cardiac chest had CAD. Atypical chest pain was associated with musculoskeletal pain, GI disease and psychiatric disorder in almost all females.

**Conclusion:** Atypical chest pain is common in premenopausal females, common causes being non-cardiac ones; yet CAD is still a remote possibility. Characteristics of chest pain and absence of risk factors cannot reliably predict NCCP a detailed evaluation is warranted.

**Key words:** Age, Chest pain, Indian, Women

## INTRODUCTION

Chest pain is a major source of concern for patients and physicians alike as it may harbingers acute life-threatening

cardiac events, yet many patients who describe chest pain typical of significant cardiac disease can actually be free of such disease. Chest pain is the chief complaint in about 1-2% of outpatient practice and in 20-30% of all emergency medical admissions, surprisingly <50% patients are given a final diagnosis of acute myocardial infarction and an organic etiology is demonstrable in only about 16% of such patients.<sup>1-3</sup> About 50% of patients with non-cardiac chest pain (NCCP) and normal coronary anatomy had esophageal reflux or motility disorders,<sup>4</sup> and 60% had evidence of breathing disorders.<sup>5</sup> Patients with NCCP and no upper gastrointestinal (GI) disease has a higher

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proportion of panic disorder (15%), obsessive-compulsive disorder (21%), and major depressive episodes (28%).<sup>6</sup>

Premenopausal women are largely protected from heart disease. These women are more likely to have nonspecific chest pain symptoms than men and only half of women who had typical chest pain suggesting ischemia had stenotic coronary lesions (50% lumen diameter narrowing).<sup>7</sup> The probability of having coronary artery disease (CAD) in a cohort of young patients (2/3<sup>rd</sup> of them being females) with atypical chest pain is low; patients with no typical features had only 2% chance of an abnormal coronary angiogram if aged <55 years.<sup>5</sup> On the other hand, even women with proven CAD are more likely to present with atypical symptoms and have worse prognosis than men.<sup>8,9</sup>

As is true with cardiac chest pain, both peripheral stimuli (as from the esophagus) and psychological factors interact in producing the final report of pain. In clinical practice, the presentation determines the order of cardiac and noncardiac investigations. Only recently American Heart Association had given a consensus on noninvasive testing in symptomatic females. It states that young women with low pretest probability of CAD should not be subjected to noninvasive test including exercise tread mill testing (TMT).<sup>10</sup> AHA (2014) A more meticulous approach is needed for the assessment and management of female patients with chest pain. This can be done in many cases by the general practitioner, sometimes with the help of emergency chest pain clinics and easy referrals to a rheumatologist, a gastroenterologist or a psychiatrist. In our clinical experience, number of young premenopausal female patients present with symptoms of atypical chest pain, which brings a lot of apprehension, repeated consultations and expenses to leading to poor quality of lives for the patients and family. Still, long-term prognosis is relatively good.

Thus, we thought that it would be prudent to analyze chest pain in premenopausal females in a resource constrained setting. We aimed to study the clinical profile, assessment of risk factors and incidence of CAD in such population presenting with typical and atypical chest pain.

## MATERIALS AND METHODS

This cross-sectional study included 56 premenopausal female patients aged 15-55 years attending the medicine outpatient department (OPD), cardiology OPD and the emergency department of Netaji Subhash Chandra Bose Medical College and Hospital (NSBMCH), Jabalpur, India, with complaints of chest pain. The spectrum of chest pain included all descriptions; including typical angina or chest

pain characteristics considered atypical for ischemic heart disease. All etiologies for the chest pain were considered. Of these 6 patients were excluded due to noncompliance and lack of follow-up; thus a total of 50 subjects were studied. Patients with known CAD, diagnosed structural heart disease, acute coronary event, and pregnant women were not included in the study. The ethics committee of the institute approved the study. Each subject gave written informed consent before being included in the study. The guidelines lay down by ICMR (1994) and Helsinki declarations (modified 1989) were adhered to in all patients in the study.

The details of chest pain: Type, onset, duration, site, nature, intensity, radiation to other sites, aggravating and relieving factors, associated symptoms; and other coexisting diseases were analyzed. Patients were mainly categorized into those having chest pain considered typical for CAD and those having atypical chest pain. "Typical chest pain" was defined as pain felt under the sternum and characterized by a heavy or squeezing feeling often caused by exertion or emotions. It included pain experienced as discomfort or tightness, or pressure in the chest or in the back, neck, jaw, shoulders and arms (especially the left arm). Other types of chest pain were considered as "atypical chest pain." Atypical pain included those at sites other than substernal location, and with other characters such as pricking, shooting, piercing, and burning.

Character of chest pain was recorded in the patient's own language. It was found to fit into the burning, compression, crushing, dull aching, heaviness, pricking, sharp, and stabbing varieties. The intensity of chest pain was graded into mild (pain not interfering with daily activities), moderate (pain interrupting the daily activities), and severe (pain needing urgent medical attention). The site of pain was categorized into central, left sided, right sided, bilateral, and diffuse. The onset was divided into sudden (pain appearing and progressing over a period of <1 week) and insidious (slow onset pain progressing over a period of >1 week). The precipitating and relieving factors if any were noted. The associated symptoms of apprehension (nervousness and anxiety), palpitation, sweating, syncope, dyspnea, regurgitation, belching, nausea, vomiting, loss of consciousness, and abnormal behavior were noted. The family history and personal history including lifestyle, addictions, and oral contraceptive (OCP) usage were assessed. Detailed clinical examination which included vital signs, general and systemic examination was done.

Each patient was subjected to routine investigations including complete blood counts, fasting blood sugar, blood urea, serum creatinine, fasting lipid profile, electrocardiogram, creatine phosphokinase-MB (CPK-

MB), and chest X-ray. According to the history and relevant investigations, the patients were categorized into high risk and low risk groups for CAD. These patients were further investigated with echocardiography/Doppler study, cardiac enzymes, TMT, upper GI endoscopy and pulmonary function test. The subjects were also subjected to a psychiatric and orthopedic evaluation.

After detailed investigation the subjects were prescribed with multi-disciplinary measures based on the diagnosis ascertained. These patients were followed up for a period of 1 month and the response to the treatment was assessed. The response was graded subjectively into good (patient has no symptoms), average (patient has symptoms but of lower grade than initial), and poor (no notable difference in symptoms after treatment).

The various observations of the study were cross tabulated among each other and Chi-square test was applied to find out the statistical significance of the data.

## RESULTS

Between June 2011 and May 2012 premenopausal female patients aged 15-55 years attending the medicine OPD, cardiology OPD and the emergency departments of NSBMCH, Jabalpur, India, with new onset of chest pain were screened. Patients were excluded if they had a history of CAD, structural heart disease, bronchial asthma, chronic obstructive airway disease, trauma, and inability to perform TMT. Pregnant women were also excluded from the study. 56 thus screened were included in the study. Six patients were non compliant and/or did not follow; thus, the data from 50 subjects were analyzed.

Results showed that the majority presented with atypical chest pain, accounting for 72% of the patients. The mean age of patients with atypical chest pain and typical chest pain was  $26.64 \pm 6.49$  and  $29.10 \pm 7.6$  years; this difference was not statistically different. 68% of patients had chest pain for <1 month duration, 12% had chest pain of more than 6 months duration. Half of the patients had sudden onset of pain, another half had insidious onset. Majority of patients had dull aching (28%) and stabbing (24%) type of chest pain which predominantly was in central location (60%). Chest pain was most commonly associated with apprehension (74%) and palpitations (42%); patients commonly had more than one associated symptoms. In 56% of patients there no aggravating factors, in 30% exertion was the precipitating cause. In 54% patients, the pain was relieved spontaneously.

When characteristics of atypical and typical pain were compared, there was no statistically significant difference in regards to rapidity of onset, duration, and intensity of

chest pain. 75% of patients with atypical chest pain had the duration of <1 month, only 5.6% patients had duration more than 6 months; majority (69.5%) had chest pain of mild to moderate intensity. Apprehension was statistically more commonly associated with atypical; palpitation was more commonly associated with typical chest pain. There was no significant difference between atypical and typical chest pain in terms of other accompaniments of chest pain and aggravating or relieving factors.

When risk factors, namely, age, diabetes mellitus, hypertension, high BMI, low high density lipoprotein, cigarette smoking, family history of premature CAD, and OCP use were assessed in patients with atypical and typical chest pain; only BMI  $\geq 23$  kg/m<sup>2</sup> was statistically more common with atypical chest pain.

Overall, only in 5 (10%) females having chest pain, diagnosis of CAD was made; most common etiologies were painful musculo-skeletal conditions (34%), functional (30%), GI pain (reflux esophagitis 10%; gastritis 8%), pneumonia (4%), and mitral stenosis (4%). When the patients were subjected to resting electrocardiogram and cardiac enzymes estimation (CPK-MB and/or Troponin-I), none of the patients having atypical chest pain had a positive results; however, 2 (14.30%) patients of typical chest pain had both abnormal electrocardiogram and elevated cardiac enzymes to suggest acute coronary syndrome (ACS). ACS patients were then hospitalized and treated as per protocol. On resting echocardiography, among 14 patients with typical chest pain, 2 (14.3%) had regional wall motion abnormalities (those with ACS), 2 (14.3%) had left ventricular hypertrophy, and 1 (7.1%) had evidence of rheumatic heart disease (RHD). In total among them, 5 (35.7%) had abnormal echocardiography findings. This was in contrast to patients with atypical chest pain in whom only 1 (2.8%) had abnormal echocardiography finding of RHD; the difference being statistically significant. On subjecting the patients to TMT, 2 females having typical chest pain had evidence of CAD when compared to those with atypical chest pain in whom only 1 patient had evidence of CAD. When an overall diagnosis of CAD was entertained, 1 out of 36 females having atypical NCCP (2.7%) had CAD; on the other hand, 4 out of 14 (28.5%) female having typical cardiac chest had CAD ( $P < 0.05$ ). When other diagnoses were compared between the two groups, atypical chest pain was significantly more associated with a psychiatric diagnosis, GI disease and musculoskeletal pain (Table 1).

## DISCUSSION

This study is unique in the sense that evaluation of atypical chest pain in premenstrual females <55 years is seldom studied, although it is known than young females with

**Table 1: Final diagnosis in premenopausal females presenting with typical and atypical chest pain (n=50)**

Diagnosis	Atypical chest pain n=36 (%)	Typical chest pain n=14 (%)
CAD	1 (2.7)	4 (28.5)
Functional	13 (36.1)	2 (14.2)
Gastritis/reflux esophagitis	6 (16.6)	3 (21.4)
Mitral stenosis	1 (2.7)	1 (7.1)
Musculoskeletal pain	14 (38.8)	3 (21.4)
Pneumonia	1 (2.7)	1 (7.1)

Data are expressed as number (%),  $P < 0.05$ . CAD: Coronary artery disease

ACS are less likely to present with pain when compared to men.<sup>11</sup> Our study has shown that most of the females in this age group had atypical NCCP. In those having atypical chest pain, the probability of an underlying CAD is remote, yet possible.

Our study showed that 72% of premenstrual females presented with atypical chest pain, 50% of them had sudden onset and 66% of them had chest pain of <1 month duration. Mean age of patients with atypical and typical chest pain groups was similar ( $26.64 \pm 6.49$  and  $29.10 \pm 7.6$  years, respectively). Majority in each group had centrally located pain (60%). When both groups were compared, patients with atypical chest pain had significantly more apprehension, on the other hand those with typical chest pain complained more of palpitations. Otherwise, there was no difference in both groups in terms of aggravating and relieving factors. Cormier *et al.* estimated the relationship of chest pain with negative cardiac diagnostic studies to psychiatric illness. A total of 98 patients with chest pain and no prior history of organic heart disease underwent a structured psychiatric interview at the time of cardiac diagnostic testing, either coronary arteriography or TMT. Patients with negative cardiac test results were significantly younger and more likely to be female, endorsed a greater number of autonomic symptoms with their chest pain, and were more likely to report atypical chest pain.<sup>12</sup> In another study on 307 patients with NCCP from China, the prevalence of NCCP was 13.9% (95% CI 13-15) and was higher in men than in women (16.6% vs. 11.9%,  $P = 0.002$ ). The median duration of NCCP was 24 months (range 0.1-360 months). Most (96%) subjects with NCCP had mild to moderate chest pain over the central chest area (50%). The frequency of chest pain was less than once per month in three quarters of the subjects.<sup>13</sup> Cooke *et al.* studied 65 consecutive patients with chest pain and completely normal coronary angiograms recruited over a period of 1 year, and 65 sex matched patients with significant stenoses at angiography. Females constituted 2/3<sup>rd</sup> of patient population. The median duration of symptoms was

24 months (range 2-216) in patients with normal coronary angiography and 18 months (range 2-720) in patients with abnormal coronary angiography they showed that there were no important differences in the site, quality, radiation of pain and associated symptoms; but three symptoms were considered to be typical and had discriminatory value in differentiating CAD from non CAD; (1) the consistency with which pain was reproduced by exercise, (2) the duration of pain episodes (typical, 5 min), and (3) the frequency of pain at rest (typical, up to 10% of all pain episodes). All three symptoms were atypical in 21 (32%) patients with normal coronary angiograms, but only one patient with an abnormal coronary angiogram. Patients with no typical features had a 2% chance of an abnormal coronary angiogram if aged <55 years or 12% if aged 55 years or more.<sup>5</sup> In a recent meta analysis of 18 studies pooled prevalence of NCCP was 13% (95% confidence interval 9-16). The prevalence of NCCP was higher in Australian studies and in studies using a questionnaire to define its presence, compared with those using Rome I or II criteria. The prevalence was no different in women versus men (odds ratio 0.99; 95% confidence intervals 0.82-1.20).<sup>14</sup>

Even in patients who have CAD, atypical chest pain is not so uncommon. Summers *et al.* conducted a retrospective study of patients presenting to the emergency department of a southern United States urban hospital with enzyme-documented myocardial infarction to determine the prevalence of atypical chest pain descriptions. A multivariate analysis of those patients with atypical pain descriptions was conducted to determine the independent demographic factors associated with these descriptions. In a total of 77 subjects (56% black; 44% white, 49% male and 51% female) meeting the study criteria, 43% were found to have atypical elements in the character of their chest pain descriptions. African Americans and women had the highest rates of atypical pain (56% and 46%, respectively); the use of the descriptive term "sharp" accounted for nearly half of the atypical presentations.<sup>15</sup>

None of the risk factors for CAD were more commonly associated with females having typical chest pain; on the contrary, a BMI value of  $\geq 23$  kg/m<sup>2</sup> was significantly more commonly with atypical chest pain patients. This finding is seemingly odd, needs to be validated in larger population based studies. When other risk factors for CAD were evaluated by Sullivan *et al.*, only diabetes was significantly more common in females with chest pain and abnormal coronary angiography when compared with those having chest pain and normal coronary angiography. Rest of the risk factors like history of premature CAD in family members, hypertension, dyslipidemia, and smoking did not differ in females with or without obstructive coronary

arteries.<sup>16</sup> In patients of CAD, females when compared with males, the risk factors usually do not differ from those in males; diabetes and dyslipidemia were probably an exception. Sullivan *et al.* demonstrated that diabetes imposes a greater risk of heart disease in women than in men; in another study high triglycerides level was an important risk factor in women.<sup>16,17</sup>

Overall, only in 5 (10%) females having chest pain, diagnosis of CAD was made; most common etiologies were painful musculo-skeletal conditions (34%), functional (30%), GI pain (reflux esophagitis 10%; gastritis 8%), pneumonia (4%) and mitral stenosis (4%). Ortiz-Olvera *et al.* assessed 31 patients (22 females) with NCCP after excluding CAD using upper GI endoscopy, ambulatory pH monitoring, stationary esophageal manometry and psychiatric evaluation. They showed that 14 (64%) and 8 females (36%) had gastroesophageal reflux disease (GERD) and functional pain disorder, respectively.<sup>18</sup> In United States and Europe; musculoskeletal pain, GERD and nonspecific or functional pain disorders were among the most common causes of chest pain in patients visiting primary health-care centers; however in patients visiting emergency care centers, cardiac chest pain was the most common diagnoses entertained.<sup>19</sup> In a study of 250 patients presenting in emergency department in an UK center, on non invasive testing 142 had cardiac pain (mean age 79 years, 58% male) and 108 atypical chest pain (mean age 60 years, 55% male). Of those with atypical pain, 40 were discharged without a diagnosis; in the remaining 68 the pain was thought to be musculoskeletal (25), cardiac (21), GI (12) or respiratory (10) in origin. On 1 year follow-up half of the patients with atypical pain had undergone further investigations and 14% had been readmitted. As a result the proportion of positive diagnoses had increased in each of the subgroups, with the commonest categories being musculoskeletal (27), cardiac (25), GI (14), and respiratory (12). The yield of investigative procedures was generally low (20%) but at the end of the year only 27 patients remained undiagnosed. The mortality rate was 2.9% (3 patients) compared with 18.3% in those with an original cardiac event, none of the patient who had a non cardiac diagnosis died.<sup>20</sup>

In our study, when an overall diagnosis of CAD was entertained, only 2.7% females having atypical NCCP had CAD in contrast to 28.5% females having typical cardiac chest pain and CAD. This suggests that in young females presenting with atypical chest pain, the chances of CAD in them is remote. Bhardwaj studied patients with typical and atypical chest pain with dynamic electrocardiogram changes who were subjected to coronary angiography. 33 patients had atypical chest pain out of which 22 were females and 11 were males. Mean age of the patients was

45.15 ± 10.18 years. Only 2 (6%) of these patients had CAD. This was in contrast to 39 patients who had typical chest pain, among them 92% had CAD.<sup>21</sup>

Studies in late 19<sup>th</sup> century suggested that the prognosis of angina or angina like pain was good, with mortality rates close to zero.<sup>22,23</sup> An earlier study of 100 women with unexplained chest pain having some or all of the features of angina pectoris and normal selective coronary angiography. Atypical chest pain was seen in 76%; 46% gained relief of pain from nitroglycerin, and 40% had anxiety neurosis. Follow-up of remaining 86 patients for 6-30 months revealed that 50% had a decrease or disappearance of pain, and there was no adverse cardiac event or mortality.<sup>4</sup>

Recent studies have shown that prognosis of patients with NCCP is not benign as it was previously thought. Jespersen *et al.* conducted a retrospective study of cohort of 11223 patients with stable chest pain in 10 years referred for coronary angiography. They compared the results with 5705 participants from the Copenhagen City Heart Study. Results showed that significantly more women (65%) than men (32%) had normal coronary angiography. In the pooled analysis, the risk of major adverse cardiovascular event was higher with multivariable adjusted hazard ratios (HRs) of 1.52 (95% confidence intervals 1.27-1.83) for patients with normal coronary arteries; and 1.85 (95% confidence intervals 1.51-2.28) for patients with diffuse non-obstructive CAD when compared with the reference population. For all-cause mortality, normal coronary arteries and diffuse non-obstructive CAD were associated with HRs of 1.29 (95% confidence intervals 1.07-1.56) and 1.52 (95% confidence intervals 1.24-1.88), respectively.<sup>24</sup>

In Women's Ischemia Syndrome Evaluation (WISE) study, the cardiovascular events were most frequent in women with 4 or more cardiac risk factors, with the 5-years annualized cardiovascular event rate being 25.3% in women with non-obstructive CAD, 13.9% in WISE women with normal coronary arteries, and 6.5% in asymptomatic women.<sup>25</sup>

Being conducted in a resource constrained settings and unavailability of coronary angiography; we could not subject our patients for coronary angiography for confirmation of CAD. We think premenopausal women with low risk of CAD should not be subjected to invasive tests, neither is it indicated. However in patients with intermediate and high risks, it is warranted accordingly to guidelines of the American Heart Association. The sample size was small; moreover, ours was not a follow-up study to ascertain long-term prognosis of chest pain in premenopausal Indian females as well as to come up with some strategy for management of this selected subgroup. Despite these

shortcomings, we could draw some conclusion from this study. However, we suggest a long-term study with larger sample size to answer these questions in Indian scenario.

## CONCLUSION

Atypical chest pain is common in premenopausal females, common causes being musculoskeletal, psychiatric and GI disorders; incidence of CAD in them is very low. As characteristics of chest pain and absence of risk factors cannot reliably predict NCCP, and there is a remote possibility of CAD in these females, a cautious approach and detailed evaluation which may include a coronary angiography is warranted.

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