

## RESEARCH PAPER

# Association of Interatrial Septal Thickness with Severity of Coronary Artery Diseases

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## Abstract

**Background:** Epicardial adipose tissue is the main determinant of interatrial septum thickness (IST) and it is also a true marker of cardiac adiposity. The relationship of interatrial septal thickness as a marker cardiac adiposity with severity of coronary artery disease (CAD) is not thoroughly investigated in our population

**Objectives:** This study was conducted to evaluate the association of interatrial septal thickness (IST) with severity of coronary artery disease.

**Methods:** This cross-sectional study was conducted in the National Institute of Cardiovascular Disease (NICVD), Dhaka from April 2016 to March 2017. A total of 100 patients with coronary artery disease (CAD) who agreed to undergo coronary angiography were selected by non probability sampling. Interatrial septal thickness (IST) was measured using bidimensional echocardiography. On the basis of IST, study subjects were divided into two groups: 50 patients of CAD with IST  $\geq 14.2$  mm were designated as Group I (Thick) and 50 patients of CAD with IST  $< 14.2$  mm were designated as Group II (Thin). During angiogram coronary artery disease severity was assessed by Gensini score. Then the collected data were analysed. Categorical variables were analyzed by chi-square test. Quantitative variables were analyzed by unpaired t-test. Correlation between IST and angiographic severity (gensini score) was measured by Spearman's rank correlation coefficient test. Odds ratio (OR) and logistic regression test were done to identify the factors associate with CAD severity.  $P < 0.05$  was considered as significant. Statistical analyses were performed with SPSS, version 16.0 (SPSS Inc).

**Results:** Severe CAD patients were found significantly more in Group I (thick) than in Group II (thin) [78% vs 14%,  $p < 0.001$ ]. IST showed a moderate positive correlation with Gensini score ( $r = 0.58$ ). Univariate and multivariate analysis revealed that dyslipidemia, diabetes mellitus, high waist circumference and increased IST were independently significant predictors of severe CAD. Out of them increased IST was found be the strongest independent predictor of the severity of CAD with odd ratio 9.8 (95% CI 2.17 – 44.4).

**Conclusion:** The study concludes that increased interatrial septal thickness (IST) is associated with severe coronary artery disease (CAD). So, severe CAD may be predicted by measuring the interatrial septal thickness.

**Key words:** Interatrial septal thickness, severity of coronary artery disease, gensini score

## Introduction

Coronary heart disease (CHD) is a worldwide health epidemic. Globally, 30% of all deaths can be attributed to cardiovascular disease, of which more than half are caused by CHD. Those who die from cardiovascular diseases globally, 80% are in developing countries.<sup>1</sup>

Ischemic Heart Disease (IHD) is a major and increasing healthcare issue in Bangladesh.<sup>2</sup> Only a limited

number of small-scale epidemiological studies are available. Ischemic heart disease (IHD) prevalence was between 2.7% and 3.4% in two studies with a rural sample and 19.6% with an urban sample of working professionals. Despite the marked disparity in values, there seems to be a rising prevalence of coronary artery disease (CAD) in Bangladesh.<sup>3</sup>

Obesity is recognized as a major modifiable and independent risk factor for excess cardiovascular morbidity and mortality. After 44 years of follow-up of the Framingham Heart Study, it was found that cardiovascular risk (including angina, myocardial infarction, CHD or stroke) was higher among overweight men (RR 1.24; 95% CI: 1.07–1.44), and obese men

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(RR 1.38; 95% CI: 1.12–1.69) and obese women (RR 1.38; 95% CI: 1.14–1.68) after adjustment for age, smoking, high blood pressure, high cholesterol and diabetes<sup>4</sup>. Overweight and obesity are established risk factors for major debilitating chronic diseases including hypertension, type II diabetes mellitus, dyslipidemia, stroke, and CAD.<sup>5-8</sup>

Adipose tissue is anatomically distributed in different proportions throughout the human body, and the pattern of distribution is dependent upon many factors including sex, age, race, ethnicity, genotype, diet, physical activity, hormone levels and medication. The percentage of adipose tissue is higher in women, the elderly and overweight individuals<sup>9,10</sup>. Body fat tissue is traditionally distributed into two main compartments with different metabolic characteristics: subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). While both of these tissue types are important, particular attention has been directed to visceral adiposity owing to its association with various medical pathologies<sup>11</sup>.

Visceral adiposity has been distinctly linked to several pathological conditions including impaired glucose tolerance and lipid metabolism, insulin resistance<sup>12,13</sup>, increased predisposition to cancers of the colon<sup>14</sup>, breast<sup>15</sup> and prostate<sup>12-16</sup>. It is associated with prolonged hospital stays, increased incidence of infections and non-infectious complications, and increased mortality in hospital<sup>17</sup>. Visceral obesity itself is an independent component of metabolic syndrome and the magnitude of obesity directly relates to the prognosis of this condition<sup>13,18</sup>. VAT accumulation also determines a comprehensive cardiovascular risk profile and increases the susceptibility to ischemic heart disease and arterial hypertension<sup>12,18</sup>. Such difference in the risk may attributable to the depot specific difference in the expression and secretion of adipocytokines. As a hormonally active tissue, VAT releases different bioactive molecules and hormones, such as adiponectin, leptin, tumour necrosis factor, resistin and interleukin 6 (IL-6). Among these hormones, adiponectin is of particular significance owing to its protective antiangiogenic activity. Circulating adiponectin is inversely correlated with the amount of VAT<sup>19</sup>, while decreased concentrations of adiponectin are associated with Type 2 diabetes, elevated glucose levels, hypertension, cardiovascular disease and certain malignancies<sup>13,19</sup>.

So visceral adipose tissue, the fat that surrounds the internal organs in the cavities of the body seems to predict unfavorable cardiovascular and metabolic risk profile more than total adiposity. Some studies emphasized the potential importance of the anatomical closeness of some visceral adipose tissues depots to target organs, as well as the heart<sup>20</sup>. The concept of cardiac adiposity, as new cardiovascular risk factor and marker is rapidly emerging<sup>21</sup>. Recent evidences suggest that cardiac adiposity could locally modulate the morphology and function of the heart and work as easy and reliable biomarker and therapeutic target<sup>20,21</sup>.

The echocardiographic measurement of epicardial fat is a noninvasive and objective quantification method with high availability that has shown clear advantages as a marker of cardiometabolic risk, even superior to subcutaneous fat and total body adiposity<sup>22</sup>. Recently, some studies have shown the association between epicardial fat and subclinical atherosclerosis<sup>23</sup>, the presence, extension and severity of significant coronary artery disease (CAD)<sup>23,24</sup> and coronary flow reserve in women<sup>25</sup>.

In comparison with epicardial fat, other manifestations of cardiac fat deposition have received less attention in the literature. Epicardial fat is also the main determinant of the lipomatous infiltration of the atrial septum, which occasionally has been reported as lipomatous hypertrophy in several case reports<sup>26</sup>, a benign entity (defined as an atrial septum thickness > 20 mm) in association with supraventricular arrhythmias and sudden death. Regarding this subject, Chaowalit, et al. (2007) recently reported its association with the presence of significant coronary artery disease.<sup>27</sup>

Subepicardial fat is also the main determinant of atrial septum thickness. Postmortem studies have suggested that the posterior portion of the atrial septum is essentially an extracardiac structure, produced by the infolding of the atrial roof and containing subepicardial adipose tissue<sup>28</sup>. Pathologic data demonstrated that the adipose tissue of the atrial septum merged with the overlying subepicardial adipose tissue, which was also usually prominent<sup>28</sup>. The fossa ovalis is always free of adipose tissue<sup>29</sup>. Furthermore, the atrial septum thickness, representing mostly the adipose tissue, can be accurately determined by transthoracic echocardiography.

The clinical significance of a thick atrial septum has been increasingly recognized since the initial description of lipomatous hypertrophy of the atrial septum in 1964<sup>30</sup>. Since then, a possible association between a thick atrial septum and obesity<sup>26,29,31</sup>, advanced age<sup>26</sup>, atrial arrhythmias<sup>26,29</sup>, obstructive symptoms,<sup>32</sup> and sudden death have been reported<sup>33</sup>.

An autopsy study showed more atherosclerotic CAD in patients with fatty deposition in the atrial septum<sup>29</sup>. Chaowalit, et al. found a significant correlation between atrial septum thickness and any CAD, which persisted after controlling for age, gender, and body mass index. Patients in the lowest quartile of atrial septum thickness had a lower proportion of subjects with any CAD.<sup>27</sup> In 2011 Mustelie, et al. in a study among two hundred and fifty Hispanic patients showed all the cardiac fat deposition parameters including interatrial septal thickness (IST) showed a significant association with the presence of significant CAD<sup>34</sup>. Then Amin et al showed there was statistically significant increase in atrial septum and epicardial fat thickness in patients with significant CAD compared to patients with nonsignificant CAD on angiography. Patients with predominant visceral fat accumulation showed higher epicardial fat and atrial septum thickness than patients with average body weight respectively<sup>35</sup>.

So interatrial septal thickness being a marker of cardiac adiposity is gaining more importance worldwide as a new marker of presence and severity of coronary artery disease as it can be easily assessed by transthoracic echocardiography. There is no such study in our population who are facing an increasing prevalence of atherosclerotic coronary artery disease. Therefore, aim of our study is to find out the association of atrial septal thickness with the severity of coronary artery disease in our population.

## Materials & Methods

This cross-sectional study was conducted in the National Institute of Cardiovascular Disease (NICVD), Dhaka over a period of 12 months starting from April 2016 to March 2017. Patients were selected by non-probability sampling from those who were admitted in NICVD & agreed to do coronary angiography. Total 100 patients were included in this study. Echocardiographic findings of every patient were done by Siemens Acuson X700 ultrasound with simultaneous ECG tracing. Atrial septal thickness was

measured by two-dimensional echocardiography perpendicular in subcostal view at the thickest part at end diastole. Patients were grouped into two groups, Group I (thick) with interatrial septal thickness ( $\geq 14.2$ mm) and Group II (thin) with interatrial septal thickness ( $< 14.2$  cm). Patients with valvular heart disease, congenital heart disease and cardiomyopathy, atrial fibrillation, previous history of revascularization (PCI or CABG) and patients undergoing primary PCI or patients in whom subcostal echocardiographic view was not optimal for the measurement of atrial septum thickness were excluded from the study. Informed consent was obtained in accordance with the study protocol approved by the local ethical committee of NICVD. Coronary angiography was performed by percutaneous femoral or radial approach using standard angiographic techniques. Interpretation of coronary angiogram was done by visual estimation by two cardiologists. Severity of coronary stenosis was assessed by Gensini score. After calculation of Gensini score, 36 points was chosen as an appropriate cut-off value. Patients with Gensini score  $< 36$  points considered as absent or mild coronary artery disease and those with Gensini score  $\geq 36$  points considered as moderate to severe coronary artery disease. The numerical data obtained from the study was analyzed and significant differences was estimated by using statistical methods. Data were presented as frequency and precent for categorical variables and as mean with standard deviation for quantitative variables. Categorical variables were analyzed by chi-square test. Quantitative variables were analyzed by unpaired t-test. Correlation between IST and angiographic severity (gensini score) was measured by Spearman's rank correlation coefficient test. Odds ratio (OR) and logistic regression test were done to identify the factors associate with CAD severity.  $P < 0.05$  was considered as significant. Statistical analyses were performed with SPSS, version 16.0 (SPSS Inc).

## Results

Among 100 patients CAD, mean age was  $52.4 \pm 9.0$  years ranging from 28 to 75 years and there was no statistical difference between two groups ( $p = 0.76$ ). Majority of the study patients belonged to 51-60 years in both groups. There was no significant difference with respect to age, gender, smoking, family history of CAD, hypertension, DM and dyslipidaemia. between two groups. Mean body mass index (BMI) of group I

was  $23.9 \pm 2.1$  (kg/m<sup>2</sup>) and that of group II was  $22.7 \pm 1.1$  (kg/m<sup>2</sup>). Waist circumference (WC) was found in group I and group II  $89.3 \pm 4.4$  vs  $83.1 \pm 2.7$  cm respectively. BMI and WC were significantly ( $p < 0.001$ ) higher in group I than group II (table I).

It was found that moderate to severe form of CAD (Gensini score  $\geq 36$  points) was 72% and 28% in group I and group II respectively. No disease to mild form of CAD (Gensini score  $< 36$ ) was found 28% and 72% in group I and group II respectively. Moderate to severe

form of CAD patients were significantly more in group I than group II ( $p < 0.001$ ) and no disease to mild form of CAD patients were significantly more in group II than group I ( $p < 0.001$ ). There is a strong positive association between increased IST thickness and disease severity [table II].

Moderate positive correlation ( $r = 0.58$ ) was found between interatrial septal thickness (IST) and Gensini score (figure 1).

**Table I:** Demographic profile of study population (N=100)

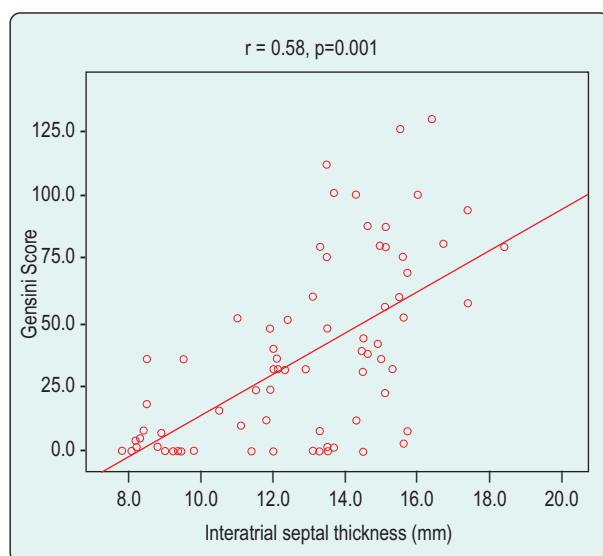
Risk Factors	Group I (Thick) [IST $\geq 14.2$ mm] (n= 50)		Group II (Thin) [IST $< 14.2$ mm] (n=50)		Total (n=100)	p value	
	Number	%	Number	%	Number	%	
Age in years Mean $\pm$ SD(Range)	52.6 $\pm$ 9.5 (28-70)		52.1 $\pm$ 8.6 (28-75)		52.4 $\pm$ 9.0		0.76 <sup>ns</sup>
Gender							0.33 <sup>ns</sup>
Male	41	37					
Female	09	13					
Smoking							
Smoker	35	70.0	32	64.0	67	67.0	0.52 <sup>ns</sup>
Non smoker	15	30.0	18	36.0	33	33.0	
Hypertension							
Hypertensive	28	56.0	25	50.0	53	53.0	0.55 <sup>ns</sup>
Normotensive	22	44.0	25	25.0	47	47.0	
Diabetes mellitus							
Diabetic	25	50.0	21	42.0	46	46.0	0.42 <sup>ns</sup>
Non diabetic	25	50.0	29	58.0	54	54.0	
Dyslipidaemia							
Dyslipidaemic	23	46.0	15	30.0	38	38.0	0.09 <sup>ns</sup>
Non dyslipidaemic	27	54.0	35	70.0	62	62.0	
Family H/O of CAD							
Present	7	14.0	14	28.0	21	21.0	0.09 <sup>ns</sup>
Absent	43	86.0	36	72.0	79	79.0	
Body Mass Index (kg/m <sup>2</sup> )	23.9 $\pm$ 2.1		22.7 $\pm$ 1.1				0.001 <sup>s</sup>
Waist circumference (cm)	89.3 $\pm$ 4.4		83.1 $\pm$ 2.7				$< 0.001$ <sup>s</sup>

ns= Not Significant ( $p > 0.05$ ); p value reached from Chi Square test and unpaired t-test.

**Table II:** Comparison of CAD severity between two groups (N=100)

IST	Moderate to Severe ( $\geq 36$ points) Number	No disease to mild ( $< 36$ points) Number	p-value
Group I (IST $\geq 14.2$ mm)	36 (72%)	14 (28%)	
Group II (IST $< 14.2$ mm)	14 (28%)	36 (72%)	

Chi-square test was done



**Figure 1:** Scatter plot diagram showing correlation between Interatrial septal thickness (IST) and Gensini score.

OR 6.61 suggests that thicker IST is a significant risk factor for disease severity in CAD patients. CAD

patients with thick IST ( $\geq 14.2$ mm) are at 6.61 times more risk to have severe disease compared to the CAD patients with thin IST ( $< 14.2$ mm) (table III).

Univariate and multivariate analysis revealed that dyslipidemia, diabetes mellitus, high waist circumference and increased IST were independently significant predictors of severe CAD. Out of them increased IST was found to be the strongest independent predictor of the severity of CAD with OR 9.8 (table IV).

**Table III:** Risk ratio of severe CAD for Thick IST

IST	Moderate to Severe ( $\geq 36$ points) Number	No disease to mild ( $< 36$ points) Number	OR
Group I (IST $\geq 14.2$ mm)	36	14	6.61
Group II (IST $< 14.2$ mm)	14	36	

?

**Table IV:** Univariate and multivariate binary logistic regression analysis of the determinants of CAD severity.

Variables of interest	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Advance age ( $> 50$ yrs)	2.45 (1.095 – 5.468)	0.02 <sup>s</sup>	2.37 (0.807 – 7.009)	0.12 <sup>ns</sup>
Smoking	1.43 (0.193 – 4.979)	0.34 <sup>ns</sup>	1.20 (0.134 – 3.167)	0.30 <sup>ns</sup>
Hypertension	1.64 (0.281 – 2.472)	0.24 <sup>ns</sup>	1.44 (0.286 – 2.709)	0.20 <sup>ns</sup>
Dyslipidemia	2.53 (1.112 – 5.744)	0.03 <sup>s</sup>	2.51 (1.800 – 7.915)	0.02 <sup>s</sup>
Diabetes mellitus	1.56 (1.236 – 5.338)	0.02 <sup>s</sup>	1.41 (1.127 – 3.388)	0.03 <sup>s</sup>
Waist Circumference (WC)	1.51 (1.116 – 3.204)	0.03 <sup>s</sup>	1.21 (1.015 – 4.083)	0.04 <sup>s</sup>
Increased BMI	0.99 (0.794 – 1.243)	0.45 <sup>ns</sup>	1.26 (0.928 – 1.713)	0.14 <sup>ns</sup>
Increased IST	6.61 (2.762 – 15.831)	0.001 <sup>s</sup>	9.82 (2.170–44.425)	0.003 <sup>s</sup>

s = Significant ( $p < 0.05$ ), ns = Not significant ( $p > 0.05$ )



## Discussion

The mean age of the study population was  $52.4 \pm 9.0$  years ranging from 28 to 75 years. The mean age of two groups was almost similar and the age difference between two groups was statistically not significant ( $p=0.76$ ). This finding was very close to the other relevant studies in our country<sup>36</sup>. Studies done by Chaowalit, et al.(2007) and Mustelir, et al.(2011) found that mean age was respectively  $68 \pm 13$  years and  $61.5 \pm 8$  which was higher than present study probably due to longer life expectancy, geographical and racial difference.<sup>27,34</sup>

This study was enrolled in 100 patients. In group I, 41 (82%) patients were male and 9 (18%) patients were female. In group II, 37 (74%) patients were male and 13 (26%) were female. Male female ratio was 3.5:1. Male patients were predominant in both groups. In almost all studies related to coronary artery disease (CAD) similar male preponderance was found<sup>3,37,38</sup>. As females were given less attention and access for them to the health care facilities was limited particularly in, low socioeconomic population like our country may contribute for this male predominance. No significant association ( $p=0.33$ ) was found between the groups in terms of sex distribution.

Among the study population, highest percentage had history of smoking (67%) followed by hypertension (53%), diabetes mellitus (46%), dyslipidemia (38%) and family history of CAD 21%. Rafiquzzaman K.(2015) found smoking was the most prevalent (86%) risk factor among the patients of coronary artery disease of the Bangladeshi population. Islam, et al.(2013) reported high prevalence of hypertension in elderly Bangladeshi population (40-65%) to contribute the CAD<sup>37</sup>. In this study, there was no significant difference in prevalence of CVD risk factors like hypertension, DM, dyslipidaemia etc. between two groups. Chaowalit, et al.(2007) also found the same in his study.<sup>27</sup> This may be because cardiac adiposity has more local effect in paracrine fashion than systemic effects caused by total adiposity<sup>39</sup>.

In this study, the mean triglyceride (TG) was  $143.1 \pm 19.3$  mg/dl in thick group and  $131.6 \pm 16.6$  mg/dl in thin group & the mean difference of TG level was statistically significant among the two groups ( $p=0.002$ ). Difference of other parameters of fasting lipid profile between the two groups was statistically nonsignificant & it was similar to the study of Chaowalit, et al., 2007<sup>27</sup>. The mean RBS level was  $8.5 \pm 1.8$  mmol/l in group I and  $6.6 \pm 1.4$  mmol/l in group II and the mean difference was statistically significant

between the two groups ( $p=0.001$ ). Study done by Chaowalit, et al.(2007) found that the mean difference of blood glucose was statistically nonsignificant ( $p=0.38$ ).<sup>27</sup>

Mean BMI of group I was  $23.9 \pm 2.1$  (kg/m<sup>2</sup>) and that of group II was  $22.7 \pm 1.1$  (kg/m<sup>2</sup>). Waist circumference was found in group I and group II  $89.3 \pm 4.4$  vs  $83.1 \pm 2.7$  cm.. Above two characteristics were significantly ( $p<0.001$ ) higher in group I than group II. Study done by Amr Salah Amin, 2013) also showed statistically significant increase in atrial septal thickness in obese patients with central obesity when compared to obese patients with peripheral obesity and average body weight, ( $p=0.000$  and  $p=0.06$ ) but Chaowalit, et al.(2007) showed no significant difference in two groups ( $p=0.98$  and  $p=0.71$ ).<sup>27,35</sup>

The mean percent of ejection fraction was  $51.9 \pm 10.1$ . It was  $47.4 \pm 9.7\%$  for the patients with group I and  $56.5 \pm 8.4\%$  for the patients of group II and the mean difference between the two groups was not statistically significant ( $p<0.001$ ).

Coronary artery disease (CAD) severity of the study patients were assessed by Gensini score and it was found that moderate to severe form of CAD (Gensini score  $\geq 36$  points) was 72% and 28% in group I and group II respectively. No to mild form of CAD (Gensini score  $<36$ ) was found 28% and 72% in group I and group II respectively. Moderate to severe form of CAD patients were significantly more in thick group than thin ( $p<0.001$ ) and no to moderate form of CAD patients were significantly more in thin group than thick ( $p<0.001$ ). Study done by Chaowalit, et al.(2007) also found that the proportion of patients with any CAD was significantly higher in patients with highest quartile of IST ( $p=0.02$ ).<sup>27</sup>

The mean level of interatrial septal thickness (IST) was observed  $14.6 \pm 2.0$  and  $12.1 \pm 2.5$  in significant CAD and insignificant CAD respectively. The difference of mean IST between the significant and insignificant CAD groups were statistically significant ( $p<0.001$ ) and it was compatible with the study of Amr Salah Amin(2013) but Chaowalit, et al.(2007) showed no significant difference between these two groups ( $p=.55$ ).<sup>27,35</sup>

In our study higher the number of vessels involved, the greater is the IST with mean score in none, single, double and triple vessel disease being 11.45, 12.71, 13.66 and 15.23 respectively and this difference was statistically significant ( $<0.001$ ). Other studies using bidimensional echocardiography fail to establish any

relationship between cardiac adiposity and extent of coronary artery disease<sup>27,34</sup>, but more recent investigations by cardiac computed tomography scan significant association between cardiac adiposity and extent of coronary artery disease been identified<sup>40</sup>. This supports our finding.

Regarding correlation coefficient of different anthropometric measurement with the severity of CAD as assessed by Gensini score, it was found that IST( $r=0.58$ ) had highest positive correlation followed by WC ( $r=0.44$ ).

This study demonstrated the binary logistic regression analysis of odds ratio (OR) for characteristics of the subjects likely to cause coronary artery disease. Univariate and multivariate analysis revealed that dyslipidemia, diabetes mellitus, high waist circumference and increased IST were found to be the independently significant predictors of severe CAD with ORs being 2.53 vs. 2.51, 1.56 vs. 1.41, 1.51 vs 1.21, 6.61 vs. 9.82 respectively. Advanced age >50 years was found to be significant predictors by univariate logistic regression analysis but not in multivariate analysis. Thus, the IST was found to be the strongest predictor of severe CAD with respect to the OR. An important study was done by Chaowalit, et al.(2007) in 75 patients & showed that IST was associated with the presence of CAD independent of age, sex and BMI by multivariate logistic regression analysis(  $p=0.05$ )<sup>27</sup> and another study by Amr Salah Amin (2013) also showed a significant association in univariate analysis. These two studies support our study findings<sup>35</sup>.

## Conclusion

Increased interatrial septal thickness (IST) is significantly associated with the increased severity of coronary artery disease. So, echocardiographic assessment of interatrial septal thickness may be considered as an emerging parameter to predict severe form of coronary artery disease.

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