Differentials and Determinants of Syndrome 'X' and its Role as Coronary Risk among Healthy Middle Aged Indian Army Personnel

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Abstract

Background : Syndrome 'X', a clustering of impaired glucose tolerance (IGT), raised blood pressure, raised serum triglycerides and low HDL-cholesterol, occurring under the influence of insulin resistance and resultant hyperinsulinaemia, has been hypothesised to be a major risk factor for ischaemic heart disease (IHD). However, there is a lack of research based evidence in this field, in our country.

Methods : The study was a cross-sectional analytical epidemiological design of 614 healthy Indian Army personnel, aged 35 years and above, selected by random sampling.

Results : The study indicated that there is a statistically significant ($p < 0.001$) clustering between fasting hyperinsulinaemia, raised blood pressure, IGT, raised triglycerides and low HDL. The prevalence of syndrome 'X' was 8.47% (95% CI 6.27% to 10.47%). Initial univariate and subsequent multivariate analysis using multiple logistic regression method, indicated that predictors of syndrome 'X' were increasing age, overweight, increasing central (abdominal) obesity, lack of adequate physical exercise and low level of physical fitness. Presence of syndrome 'X' increased the risk of resting ECG changes suggestive of coronary insufficiency (OR = 6.29, $p < 0.001$).

Conclusion : Based on the findings, recommendations for prevention of this syndrome have been submitted.

MJAFI 2006; 62 : 146-152

Key Words : Syndrome 'X'; Insulin resistance syndrome; Ischaemic heart disease; Coronary Risk factors; Military personnel.

Introduction

In 1988, the eminent diabetologist, Gerald Reaven, first put forward the concept of syndrome X. He hypothesized that central feature in many chronic diseases, especially Ischaemic Heart Disease (IHD) and diabetes mellitus is development of resistance to insulin action. As a compensatory mechanism hyperinsulinaemia results. Factors which cluster under the influence of insulin resistance are hyperinsulinaemia, impaired glucose tolerance, rise in blood pressure, and a specific dyslipidaemia, which includes increase in triglycerides and lowering of HDL. It was hypothesized that this syndrome is a major risk factor for IHD and diabetes mellitus [1].

Studies by McKeigue [2] and reviews by experts like Vardan [3] indicate that the frequency of IHD among migrant Indians was higher than the frequency of IHD among the local populations of affluent countries to which these Indians had migrated. The second observation was that while these migrant Indians had higher frequency of IHD, "conventional coronary risk

factors" (raised total cholesterol, high body weight and smoking) among these migrant Indians were not raised. On the other hand, certain "non conventional" factors like higher levels of triglycerides and lower HDL (in the face of normal total cholesterol levels), higher levels of central (abdominal) obesity (in the face of normal body weight) and impairment of glucose tolerance were noted. In addition, these subjects showed higher insulin resistance manifested by fasting hyperinsulinaemia. The hypothesis is that Indians are susceptible to develop syndrome X and the consequent adverse affects, notably IHD, as brought out in reviews [2-4].

Indian Army lays much stress on keeping physically fit, with regular exercises and prevention of obesity. It is paradoxical that in Indian Army, chronic diseases, especially IHD, hypertension and diabetes are leading causes of morbidity, next only to injuries. The reasons for this paradox needs to be evaluated. All the reviews and studies have been undertaken on Indian subjects who have migrated to affluent countries. However, there is a lack of population based epidemiological studies in our country. The present study was undertaken to study

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Received : 24.2.2004; Accepted : 15.9.2004

the significance of clustering of factors hypothesized in syndrome X, estimate the prevalence of this syndrome in the study population, study the role of certain epidemiological determinants as risk factors for syndrome X and study the risk that syndrome X carries for ECG changes suggestive of coronary insufficiency.

Material and Method

The present study was a community based, cross sectional analytical epidemiological design. The reference population were serving male personnel of Indian army, aged 35 years and above without any evidence of prevalent disease. Sample size was worked out to 614 subjects. This sample was selected using "multi-stage random sampling" procedure. A list of army units in the study area obtained from the military administrative authorities formed the "sampling frame" for the first stage. In the first stage, a 1 in 3 sample of the military units was drawn randomly using random number tables. In the second stage, the detailed list of "sub-units" of the military units selected in the first stage formed the sampling frame and a 1 in 3 sample of these sub-units was drawn using random number tables. In the third stage, a list of all army persons aged 35 years and above, in the selected sub-units formed the sampling frame. In this stage consecutive sample was taken up till the sample size of 614 was studied.

Measurements included orally recorded measurements (personal details, clinical history, and lifestyle factors like exercise, diet, alcohol and tobacco use), clinical measurements (clinical examination and anthropometry including height, weight, waist and hip circumferences and skin fold measurement), biochemical measurements (fasting insulin, fasting and 2 hours PP blood sugar and lipid profile) and resting ECG measurement. The procedures of epidemiological survey, laboratory and biochemical methods, anthropometric measurement, ECG recording and assessment, clinical measurement and assessment of physical exercise / energy expenditure levels were as per the standard guidelines given by WHO and other eminent bodies [5-9]. The entire methodology, including the proforma, was pretested and validated / standardized by a pilot study on 25 subjects. Subjects of the pilot study were not included in the main results.

Diagnostic criteria and cut off points, by workers in large scale epidemiological studies on Syndrome X, as also criteria suggested by WHO were used [7-20]. The following defining criteria were :-

- Insulin resistance was defined as subjects who had evidence of fasting hyperinsulinaemia [10-13].
- Fasting hyperinsulinaemia was defined as subjects in the uppermost (fifth) quintile of fasting insulin in the data set [13-17]. In the present study this corresponded to 124 subjects who had fasting insulin of 11.93 micro units / ml and above.
- Impaired glucose tolerance was as per WHO criteria [18] a venous plasma fasting level < 140 mg/dl with 2-hour level between 140 to < 200 mg / dl. NIDDM was fasting

>140 or 2 hours level $\geq$ 200 mg / dl.

- Raised blood pressure was defined as per WHO criteria [19] as Right arm sitting BP (mean of two consecutive readings) level of systolic $\geq$ 140 mm Hg and / or diastolic $\geq$ 90 mm Hg.
- Dyslipidemia as per guidelines of Reaven (1) and others [10-12, 14, 20-23] was defined as HDL < 35 mg/dl or triglycerides >200 mg/dl or both.
- Based on guidelines of various authorities [1,10,12,24] syndrome X was defined as "subjects having fasting hyperinsulinaemia (in the upper most quintile) with any two of the other three factors (glucose tolerance / raised blood pressure / dyslipidaemia).
- ECG evidence of coronary insufficiency was "Minnesota Codes", recommended by WHO [5] and used in large-epidemiological studies [25].

Results

In the hyperinsulinaemic group of 124, observed independent frequencies for only raised BP were 50, only IGT 2, and only dyslipidaemia 16 and for 490 subjects in normoinsulinaemic group, these independent frequencies were 91, 11 and 93 respectively. Thereafter, the expected probability of conjoint occurrence of combination of these variables was calculated on the basis of "multiplicative law of probability" and from these expected probabilities, the expected frequencies in the two groups were worked out. The differences between observed and expected frequencies were then compared using chi - square method, at one degree of freedom for each combination.

It was observed (Table 1) that in the group with fasting hyperinsulinaemia there was very highly significant ($p < 0.001$) clustering of dyslipidaemia, raised blood pressure and impaired glucose tolerance, either among each other, and among all three variables. The second part of the analyses was whether the clustering between dyslipidaemia, raised blood pressure and impaired glucose tolerance occurs only in presence of hyperinsulinaemia or can occur among the normoinsulinaemics. The results indicated that with normal insulin levels, there is no significant clustering ($p > 0.05$) between dyslipidaemia, raised BP and IGT.

The next issue was to evaluate whether raised total serum cholesterol ($\geq$ 200 mg / dl) or raised LDL - cholesterol ($\geq$ 160 mg / dl) also cluster significantly with hyperinsulinaemia. It was seen that raised total cholesterol or raised LDL cholesterol do not cluster significantly with hyperinsulinaemia (Table 2). The above results bring out that a very significant clustering, occurs between raised blood pressure, dyslipidaemia (raised triglycerides or lowered HDL) and impaired glucose tolerance, only when hyperinsulinaemia is present. Secondly, this risk factor clustering includes only raised blood pressure, IGT and dyslipidaemia (raised triglycerides or low HDL) but does not include raised total cholesterol or raised LDL.

Based on the criteria, as defined above in material and method, a total of 52 subjects (out of 614) qualified for the definition of syndrome X. The prevalence of syndrome X

Table 1

Comparison between observed and expected frequencies of conjoint occurrence of Impaired Glucose Tolerance (IGT), Raised Blood Pressure (HTN) and defined Dyslipidaemia (DYS) in the presence of and in the absence of Hyperinsulinaemia

Parameter	Observed		Expected (**)		X ² (Yates) (O – E – ½) ² E	D f	P value
	Frequency	Probability	Frequency	Probability			
Group – I : Having Hyperinsulinaemia (n = 124)							
HTN + IGT (no DYS)	6	0.0484	0.81	0.00645	27.16	1	< 0.0001
HTN = DYS (no IGT)	37	0.2984	6.45	0.052	140.00	1	< 0.0001
IGT + DYS (no HTN)	4	0.0323	0.26	0.0021	13.81	1	< 0.0001
IGT + HTN + DYS (all three)	5	0.040	0.10	0.00083	193.60	1	< 0.0001
Group – II : Normo-insulinaemic Group (N = 490)							
HTN + IGT (no DYS)	4	0.0082	2.06	0.0042	1.01	1	> 0.05
HTN + DYS (no IGT)	18	0.0367	17.25	0.0352	0.004	1	> 0.05
IGT + DYS (no HTN)	4	0.0082	2.11	0.0043	0.92	1	> 0.05
IGT + HTN + DYS (all three)	2	0.0041	0.39	0.0008	3.16	1	> 0.05

Table 2

Analysis of clustering of Hyperinsulinaemia with either raised serum total cholesterol (≥ 200 mg / dl) or with raised serum LDL - cholesterol

Parameter	Observed		Expected (**)		X ² (Yates) (O – E – ½) ² E	D f	P value
	Frequency	Probability	Frequency	Probability			
Part – I : Analysis of clustering of raised total cholesterol with hyperinsulinaemia (n = 614) (only hyperinsulinaemia & total cholesterol not raised = 111, only total cholesterol raised & no hyperinsulinaemia = 31)							
Both hyperinsulinaemia and raised total cholesterol	10	0.0163	5.61	0.0091	2.70	1	> 0.05(N S)
Part – II : Analysis of clustering of raised LDL - cholesterol with hyperinsulinaemia (n = 614)(only hyperinsulinaemia & LDL cholesterol not raised = 122, only LDL cholesterol raised & no hyperinsulinaemia = 9)							
Both hyperinsulinaemia and raised LDL cholesterol	2	0.00323	1.78	0.0029	0.04	1	> 0.05(N S)

thus worked out to 8.47 %, with a 95 % Confidence Interval of 6.27% to 10.47 %. The results indicate that, one out of every dozen, apparently healthy middle aged men of the Indian Army are likely to have syndrome X.

The risk factors for syndrome 'X' were

- Age : The risk of this syndrome was more than five times higher among subjects aged 45 years and above, compared to subjects 35-44 years old (OR= 5.67). This difference was statistically very highly significant ($p < 0.0001$).
- Physical exercise and syndrome X : It was observed (Table 3), that energy spent per week in leisure time and organized physical exercise showed a linearly increasing and highly significant protective effect against syndrome X. As compared to subjects who were not spending any energy in organized / leisure time exercise, there was hardly any protective effect among subjects who were spending less than 1400 kilocalories per week (OR = 0.97). Significant protective effect was observed among subjects who were spending 1400 to upto 2800 kcal per week, among whom there was 40 % reduction in risk (OR = 0.62). The best protection was among subjects who were spending more than 2800 Kcalories per week, the risk being one-fifth (OR=0.19). The overall trend of decreasing risk with increasing energy expenditure in

physical exercise was very highly significant ($p < 0.001$). Similarly (Table 4), there was linearly increasing protective effect against syndrome X, with increasing intensity of physical exercise. As compared to subjects who were not exercising, there was a slight reduction of risk by 15 % (OR=0.85) among subjects who were undertaking mild intensity exercises of less than 6 metabolic equivalents (METs). However, optimum level for protection was moderate intensity exercises at 6 to 9 METs level, among whom reduction in risk was almost 50 % (OR=0.54). Some additional protection occurred among subjects undertaking high intensity exercises (> 9 METs), in whom the risk was just two-fifth (OR=0.40). The overall trend of declining risk with increasing intensity of exercise was significant ($p < 0.05$).

- Generalised and centralised obesity: (Tables 5 & 6). The risk of syndrome X was more than 4 times higher (OR = 4.67) among those having BMI of ≥ 25 as compared to normal weight persons, and this difference was highly significant ($p < 0.001$). Increasing Waist-Hip Ratio (WHR) was associated with increasing risk of syndrome X. As compared to subjects who had WHR < 0.9 , the risk was two-fold among subjects having WHR between 0.9 and 0.949 and risk increased to as high as seven times among subjects having WHR ≥ 0.95 . This trend of increasing risk with increasing WHR was highly significant ($p <$

Table 3**Association between various levels of weekly energy expenditure and syndrome X**

Energy (kcal) spent in leisure time physical exercise in a week	Syndrome X		Total No (%)	Stratum OR
	Present No (%)	Absent No (%)		
No energy spent	17 (12.59)	118 (87.41)	135 (100)	1.00
Spend < 1400 kcal	12 (12.24)	86 (87.76)	98 (100)	0.97
1400 to < 2800 kcal	19 (8.19)	213 (91.81)	232 (100)	0.62
2800 kcal and above	4 (2.68)	145 (97.32)	149 (100)	0.19
Total	52	562	614	

Chi square for linear trend test = 9.99, df = 1, p < 0.001 (very highly significant)

Table 4**Association between severity of exercise and syndrome X**

Severity of physical exercise	Syndrome X		Total No (%)	Stratum OR
	Present No (%)	Absent No (%)		
No exercise	17 (12.59)	118 (87.41)	135 (100%)	1.00
Mild exercise (less than)	11 (10.89)	90 (89.11)	101 (100%)	0.85
Moderate exercise	14 (7.25)	179 (92.75)	193 (100%)	0.54
Strenuous exercise	10 (5.41)	175 (94.59)	185 (100%)	0.40
Total	52	562	614	

Chi-square for linear trend = 6.2, df = 1, p<0.05 (significant)

Table 5**Association between overweight and syndrome X**

Category of body mass index (BMI)	Syndrome X		Total No (%)
	Present No (%)	Absent No (%)	
Overweight (BMI ≥ 25)	31 (18.67)	135 (81.33)	166 (100%)
Normal weight (BMI < 25)	21 (4.69)	427 (95.31)	448 (100%)
Total	52	562	614

OR=4.67, 95% CI of OR = 2.49 to 8.80; X² = 30.57, df = 1, p<0.001 (v. highly significant)**Table 6****Association between central obesity (as measured in terms of raised WHR) and syndrome X**

Waist : Hip ratio (WHR)	Syndrome X		Total No (%)	Stratum OR
	Present No (%)	Absent No (%)		
< 0.9	5 (2.62)	186 (97.38)	191 (100)	1.00
0.9 to 0.949	11 (5.45)	191 (94.55)	202 (100)	2.14
> 0.95	36 (16.29)	185 (83.71)	221 (100)	7.24
Total	52	562	614	

Chi square for linear trend = 25.41, df = 1, p < 0.001 (very highly significant)

0.001).

- (iv) Resting Heart Rate: (Table 7). Subjects with resting heart rate (RHR) of >72 beats per minute had more than two times risk of syndrome X (OR=2.14) as compared to

Table 7**Association of resting heart rate and syndrome X**

Resting heart rate (beat per minute)	Syndrome X		Total No (%)
	Present No (%)	Absent No (%)	
>72	25 (12.82)	170 (87.18)	195 (100%)
≤ 72	27 (6.44)	392 (93.56)	419 (100)
Total	52	562	614

OR = 2.14 (95% CI = 1.15 to 3.95); X² = 6.98, p < 0.01 (highly significant)

subjects with RHR of ≤72. This difference was highly significant (p < 0.001).

The population based “non-conventional” coronary risk factors in the face of normal distribution of “conventional” risk factors:

- Central obesity in the face of “normal BMI” : It was observed that out of the 614 subjects, 448 (73%) had “normal” body weight (BMI <25). However, out of these 448, 274 (61%) had WHR ≥0.9, thus indicating that central obesity occurs with apparently normal weight. The results of stratified analysis using Mantel-Haenszel technique indicated that central obesity among those normal weight with greatly increased the risk of syndrome X.
- Low HDL and raised triglycerides in the face of “normal” total cholesterol levels: - The results indicated that 93% subjects had “normal” total cholesterol levels of ≤200 mg/dl. However, among these 21% had low HDL (< 35 mg / dl) while 11% had raised triglycerides (>200 mg/dl)
- Prevalence of impairment of glucose tolerance :- All 614

subjects were apparently healthy. However, 50 subjects (8.14%) had either impaired glucose tolerance (38 subjects) or NIDDM (12 subjects).

Syndrome X/ Raised fasting insulin levels as risk factors for resting ECG changes of coronary insufficiency : It was seen that the mean fasting insulin level was higher (10.93 mu / ml) among 34 subjects who had resting ECG changes suggestive of coronary insufficiency. On the other hand the mean level was 8.90 mu / ml among those who did not show ECG changes. This difference in mean fasting insulin levels was highly significant ($p < 0.01$). It was further observed (Table 8) that presence of syndrome X significantly increased the risk of having an ECG change suggestive of coronary insufficiency, this risk being 6 times ($OR = 6.29$, $p < 0.001$).

Other socio demographic variables: No significant association was observed between syndrome X and educational status, army rank, Arms/Services difference, religion, place of origin, family history of IHD, hypertension and diabetes, veg / non vegetarian diet, alcohol use and tobacco use (Table 9).

Multivariate analysis of the risk factors of syndrome X: Multiple logistic regression analysis with syndrome X as binary outcome variable was undertaken to study

Table 8
Association between syndrome X and Resting ECG changes suggestive of coronary insufficiency

Syndrome X	ECG changes		Total No (%)
	Present No (%)	Absent No (%)	
Present	11 (21.15)	41 (78.85)	52 (100)
Absent	23 (4.09)	539 95.91	562 (100)
Total	34 (5.54)	580 (94.46)	614 (100)

$OR = 6.29$, 95% CI = 2.64 to 14.78, Chi square = 26.49, df = 1, $p < 0.001$ (very highly significant)

Table 9
Association between major socio-demographic variables and syndrome 'X'

Variable	Categories	Syndrome 'X'		Statistical details
		Present (No)	Absent (No)	
Socio- economic status (Rank)	Officers	2	23	$X^2 = 5.55$ Df = 2P > 0.05 (N S)
	JCOs	15	90	
	Other Ranks	35	449	
	Total	52	562	
Occupation (Arms / services)	Arms	33	409	$X^2 = 2.05$ df = 1p > 0.05 (N S)
	Services	19	153	
	Total	52	562	
Educational status	Less than metric	28	356	$X^2 = 3.50$ Df = 3P > 0.05 (N S)
	Metric pass	17	126	
	Intermediate pass	3	47	
	Graduate & above	4	33	
	Total	52	562	
Religion	Hindus	29	398	$X^2 = 6.13$ Df = 2P > 0.05 (N S)
	Muslims	18	131	
	Sikhs	4	31	
	Christians / Parsis	1	2	
	Total	52	562	

independent adjusted effect of putative risk factors. Statistically significant and independent (adjusted) risk predictors of syndrome X were BMI ($OR = 1.34$ for each unit increase in BMI), RHR ($OR = 3.22$ for $RHR > 72/mt$), Age ($OR = 1.07$ for each year increase in age), physical exercise ($OR = 0.65$ for those spending > 2800 kcal per week in physical exercise and WHR ($OR = 2.32$ for those with $WHR \geq 0.95$). On the other hand, use of tobacco and alcohol, hypercholesterolemia and raised LDL-cholesterol did not show significant risk effect (Table 10).

Discussion

In the present study the level of upper most quintile corresponded to ≥ 11.93 mu / ml. In the Kupio Ischaemic Heart Disease study this level corresponded to 12.0 mu / ml [10] while in the San Antonio Study this level corresponded to 11.5 mu / ml [12], both being in close agreement to the level of 11.93 mu / ml in the present study.

The present study demonstrated that a statistically significant clustering of IGT, raised BP, low HDL and raised triglycerides (but not of raised total or LDL-cholesterol) occur in the presence of hyperinsulinemia. This is in agreement with postulates of Reaven [1] as well as Haffner et al [12]. With a prevalence of 8.47%, this syndrome is an important health problem for our middle aged soldiers.

The present study indicated that at least 1400 kcal per week (200 kcal per day) or more should be spent to achieve at least some protective effect. This is in agreement with recommendations of CDC Atlanta and American College of Sports Medicine for adult Americans, that at least 200 kcal per day should be spent in physical exercise [8]. However, the best protective

Table 10**Multiple logistic regression analysis of syndrome X as outcome variable**

Predictor variable	Scale of measurement	Beta coefficient	OR	SE	Zvalue	pvalue
Age	Continuous variable in years	0.065	1.07	0.026	2.47	< 0.05 (signif)
Alcohol intake	Dichotomous. 1= users 0 = non users	- 0.75	0.47	0.40	-1.92	> 0.05 (N S)
Tobacco use	Dichotomous. 1= users 0 = non users	0.29	1.34	0.38	0.76	> 0.05 (N S)
Energy spent/week in exercise	Dichotomous. 1= spend >2800 Kcal per week otherwise zero	-0.43	0.65	0.21	1.99	< 0.05 (signif)
Body mass index	Continuous variable	0.296	1.34	0.06	4.9	< 0.001 (signif)
Waist : Hip ratio	Dichotomous. 1 = WHR >= 0.95 otherwise zero	0.84	0.32	0.38	2.19	< 0.05 (signif)
Heart rate	Dichotomous. 1=Heart rate >72/mt otherwise zero	1.26	3.53	0.39	3.22	< 0.01(signif)
Serum Cholesterol	Dichotomous. 1=Serum cholesterol >200mg/dl otherwise zero	- 0.44	0.64	1.46	- 0.3	> 0.05 (N S)
Serum LDL	Dichotomous. 1=LDL >160 mg / dl, otherwise zero	0.88	2.41	0.96	0.93	> 0.05 (N S)
Constant		-12.7	-	2.03	-6.27	< 0.001

effect was observed when 2800 kcal or more were being spent per week. This level is in agreement with two large scale epidemiological studies by Paffenbanger et al on Harvard alumni [26] and by Morris et al on British civil servants [27], both having observed that the best level is 2500 kcal per week on physical exercise. The most optimum effect of physical exercise comes at intensity level of 6 to 9 METs. Very brisk walking / combined walking and jogging 7 to 8 kilometers in one hour a day to 5 days a week amounts to 2800 kcal in a week at 7 to 8 METs. The present study indicated that the protective effects of physical exercise are independent as seen in multivariate analysis. The beneficial effects of physical exercise are not simply by reducing the body weight but due to other pathways, like increased insulin sensitivity, improved peripheral glucose uptake and increased cardiovascular fitness and so on.

The risk increased as WHR crossed 0.9 and became substantial when it crossed 0.95. This level of 0.95 is in close agreement with the level of 0.95 observed by Rimm et al in a large-scale epidemiological study [28]. The independent risk of WHR in the face of normal body weight has been documented among migrant Indians [2-4].

The results of the present study have practical implications. Measurement of WHR even in persons with normal weight holds importance. Secondly physical exercise habits need to be evaluated since one may be having normal body weight without exercising optimally.

In the present study, increasing resting heart rate (RHR) showed strong, significant and independent risk for syndrome X. The results are in agreement with the San Antonio heart study [14] and Palatini [29]. The results indicate that it is not expenditure of calories through exercise, but the resulting "fitness" that is

actually protective.

Finally, the results of the present study indicates a risk of increasing fasting insulin levels on resting ECG evidence of coronary insufficiency and syndrome X is a definite, significant and strong risk factor for coronary insufficiency. These results are in line with the Paris prospective study [13], the Helsinki Policemen study [16], meta-analysis by Ruige et al [17], and Perry et al on British civil servants [30].

The present study, thus, being most probably the first ever community based epidemiological study to address the issue to syndrome X among middle aged Indian Army personnel, convincingly demonstrates that the typical and unique risk factor clustering of syndrome X is a reality and that the prevalence of this syndrome in our reference population is substantial enough to identify it as a public health problem, especially in view of the demonstrated association of this syndrome with coronary insufficiency as well as the potential preventability of this syndrome by addressing its risk factors.

Conflicts of Interest

None identified

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