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ORIGINAL ARTICLE

Syndrome 'Z': A Predictor of Angiographic Severity of Coronary Artery Disease in Patients of Acute Coronary Syndrome

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Background Owing to the growing evidence that the pathophysiology of obstructive sleep apnoea (OSA) and metabolic syndrome (MS) overlap considerably and both adversely impact cardiovascular health, we hypothesised that the presence of OSA with MS additively and adversely affect the severity of coronary artery disease (CAD). Exploration and understanding of this may have direct implications for the development of targeted, preventive strategies for CAD. Thus, this prospective study was aimed to determine the prevalence of 'Syndrome Z' in patients of MS who present with an acute coronary event and to correlate it with the angiographic severity of CAD in these patients.

Methods The present study was a single centre, cross sectional study conducted in a university teaching hospital. In a span of 6 months, 922 patients with acute coronary syndromes (ACS) were screened for the study. Among these, 861 patients had no evidence of MS. The remaining 61 patients who were diagnosed to have MS were then subjected to an overnight sleep study. Only 58 had good sleep data so were included for further analysis. Angiographic parameters in terms of number of vessels involved and culprit lesions were noted and correlated with presence and absence of OSA and also with its severity based on the Apnoea/Hypopnoea Index (AHI).

Results The prevalence of OSA positivity in patients with MS who presented with ACS was 34.5% (n = 20). Most of the patients in the OSA negative group (78.9%, n = 30) had disease limited to only one vessel while in the OSA positive group only a minority (15%, n = 3) of patients had their disease limited to a single vessel (p = 0.001). The number of lesions in the culprit vessel was also significantly less in the OSA negative group compared to the OSA positive group. While in the OSA negative group 68.4% (n = 26) patients had a solitary lesion, followed by two and three lesions in 15.8% (n = 6) of the patients each, multiple lesions were more common in OSA positive patients, involving 80% of cases (45.0%, n = 9 with two lesions; 35.0%, n = 7 with three lesions; only 20%, n = 4 had a solitary lesion).

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Conclusions Prevalence of 'Syndrome Z' is high in patients having MS presenting with ACS and it correlates with the angiographic severity of CAD.

Keywords Coronary artery disease • Syndrome Z • Metabolic syndrome • Obstructive sleep apnoea

Introduction

'Syndrome Z' is referred to as a combination of obstructive sleep apnoea (OSA) and metabolic syndrome (MS). The possible risk factor association of OSA for cardio-vascular consequences was first hypothesised in the late 1990's [1]. Understanding of risk factor clustering is of immense clinical significance in order to avoid underestimation of the severity of the situation and risk stratification. Metabolic syndrome is one such cluster quartet of systemic hypertension, insulin resistance, hyperlipidaemia, and central obesity identified by the epidemiologist for cardiovascular risk prediction [2,3]. On the other hand OSA, which is defined as sleep disorder characterised by recurrent episodes of narrowing or collapse of pharyngeal airway during sleep despite ongoing breathing efforts [4], is also demonstrated to be a risk factor for cardiovascular consequences [5–7], and is usually found in association with various components of MS [8].

There is growing evidence that the pathophysiology of OSA and MS overlap considerably and both of them adversely impact cardiovascular health. In this study, we hypothesised that the presence of OSA with MS additively and adversely affects the severity of coronary artery disease (CAD). Exploration and understanding of this fact may have direct implications for the development of targeted preventive strategies for CAD. Thus, this prospective study was aimed to determine the prevalence of 'Syndrome Z' in patients of MS who present with an acute coronary event and to correlate it with the angiographic severity of CAD in these patients.

Material and Methods

The present study was a single centre, cross sectional study conducted over 6 months in a university teaching hospital of North India. The study followed ethical guidelines of the Institutional Review Board. Patients who presented to the hospital with acute coronary syndrome (ACS) were screened for MS using a detailed history (elicited through a pre-tested questionnaire) and meticulous physical and biochemical examination with particular reference to conventional coronary risk factors. Comprehensive cardiovascular system assessment was made in all patients and systematically recorded in a predesigned proforma. Those patients with ACS, who were found to have MS and were planned for coronary angiography and/or angioplasty, were recruited for the study. Patients with diabetes, on mechanical ventilation, with cardiogenic shock and those at high risk for malignant ventricular arrhythmias were excluded. Metabolic syndrome was defined according to the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII) criteria [9].

Written informed consent was obtained from all patients. Further, all patients were then subjected to an overnight sleep study using a level III portable polysomnography diagnostic device (Embletta Gold, ResMED, Abingdon, Oxfordshire, UK). The sleep study was done during hospital stay and only those patients with good sleep study data of at least 3 hours were finally included in the study. Manual scoring of sleep tracing was done and events were scored in accordance with principles laid down by American Academy of Sleep Medicine in 2007 and updated in 2012. For OSA severity, classification according to the Apnoea/Hypopnoea Index (AHI) was used; wherein AHI <5 events/hour were taken as non OSA, and mild, moderate and severe OSA were classified as AHI 5–15, 15–30 and ≥ 30 events/hour respectively [4]. Overnight oxygen saturation (SaO2) was recorded separately for each patient from the overall sleep data. Lowest SaO2 during sleep as well as total time SaO2 remained lower than 90% which was noted in all patients.

'Syndrome Z' was defined as presence of both OSA (AHI ≥ 5) and MS in the same patient. Angiographic results obtained from OSA positive patients (i.e. Syndrome Z) were compared with OSA negative ones. Angiographic severity of CAD was expressed not only by the number of major epicardial vessels involved but also by the number of lesions per vessel involved. In calculating the number of lesions in the culprit artery, the lesions were considered separate if they were separated by a distance greater than three times the vessel diameter. In different coronary artery lesions, severity greater than 50% diameter stenosis was considered to be significant to qualify as angiographically involved vessels.

Statistical Analysis

Multivariate logistic regression was used to assess the impact of the presence of OSA on the extent and severity of CAD by angiography. P-values less than 0.05 were considered to be statistically significant. All the hypotheses were formulated using two-tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data was statistically analysed using Statistical Package for Social Sciences (SPSS ver. 20.0, IBM Corporation, Armonk, NY, USA) for MS Windows. The data on categorical variables was shown as percentage (%). The inter-group comparison of categorical variables was done using the chi-square test or Fisher's exact probability test for 2×2 contingency table.

Results

A total of 922 patients admitted with a diagnosis of ACS and planned for coronary angiography and/or revascularisation were screened for the study. Among them, in 861 (93.4%) patients, there was no evidence of MS. Thus, the prevalence of MS in our cohort of patients presenting with ACS was 6.6% (n = 61). Out of those with MS, three patients had to be excluded because of inconclusive sleep study data. After an overnight sleep study data of at least 3 hours, 34.5% (n = 20) had OSA and the rest 65.5% (n = 38) were found to be OSA negative. Thus rendering an overall prevalence of 'Syndrome Z', in patients with ACS as 2.17% (Figure 1).

Of all the demographic parameters, AHI correlated positively in a statistically significant fashion only with weight (Coefficient of correlation r = 0.271, p = 0.038) and body mass index (BMI) (Coefficient of correlation r = 0.30, p = 0.02; Figure 2a & 2b).

The multivariate logistic regression analysis of independent variables showed that Syndrome 'Z' (as compared to MS alone), was not additionally correlated to any of the conventional risk factors of CAD (Table 1).

In our study cohort, non-ST elevated myocardial infarction (NSTEMI) was the most common indication for angiography in both OSA positive (n = 11; 55%) as well as OSA negative group (n = 22; 56.4%), followed by ST-elevated myocardial infarction (STEMI) and unstable angina. With all the indications being statistically comparable in the two groups ($p < 0.59$), on angiography, the most commonly involved vessel was left anterior descending artery (OSA positive: 70%, n = 14; OSA negative: 21%, n = 53.8%) followed by right coronary artery followed by left circumflex artery in both the groups. Only one patient presented with a re-stenotic lesion, in the OSA negative groups. The rest all were de-novo lesions.

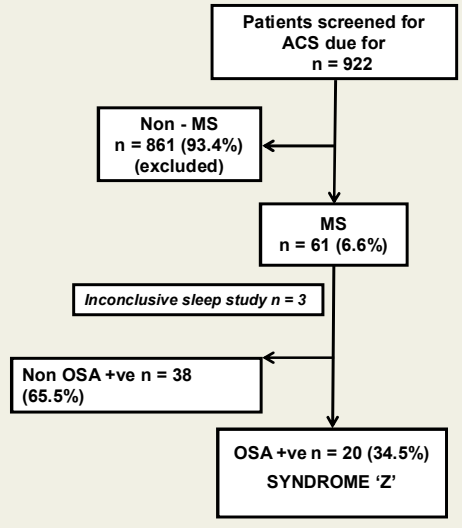

Figure 1 Distribution of patients recruited for the study. Abbreviations: ACS, acute coronary syndrome; OSA, obstructive sleep apnoea; MS, metabolic syndrome.

A positive diagnosis of OSA correlated with severity of underlying CAD expressed as the number of epicardial vessels afflicted. Most of the patients with OSA negative status (78.9%, n = 30) had disease limited to only one vessel while in OSA positive group only a minority (15%, n = 3) of patients had their disease limited to a single vessel (p = 0.001). Obstructive sleep apnoea positive patients or patients having 'Syndrome Z' were more likely to have multiple vessel involvement at the time of first diagnosis. Nearly half of these patients (45%, n = 9) had disease in two vessels and in 40% (n = 8) of cases the disease had involved all the three vessels (Table 2a).

A high severity of disease burden expressed as vessels with multiple versus single lesions was typical of patients with coexistent OSA. While in the OSA negative group 68.4% (n = 26) of patients had a solitary lesion, followed by two and three lesions in 15.4% (n = 6) of the patients each, multiple lesions were a more or less universal phenomenon in OSA positive cases involving 80% of cases (45%, n = 9 with two lesions; 35%, n = 7 with three lesions). Only a minority of four patients had disease limited to one lesion with OSA positive status (Table 2b).

The distribution of angiographic severity of CAD in relation to the number of vessels involved and the number of culprit lesions and severity of OSA (mild, moderate, and severe) is depicted in Tables 3a and 3b. There was a dose response relationship between OSA severity and the presence of CAD. Interestingly, all patients with moderate and severe OSA had either multivessel disease or multiple lesions in their coronary arteries.

The patients in whom the SaO2 remained below 90% for a longer period of time during sleep study had more propensity for having triple vessel disease (32.7 vs 46.2 minutes in 1 vs. 3 vessel disease; p-value = 0.007) (Table 4).

Discussion

In the present study, the prevalence of 'Syndrome Z' among patients presenting with ACS was found to be 2.17%. The prevalence of 'Syndrome Z' or OSA positive status among patients diagnosed to have MS was higher as compared to its prevalence in population cited in the literature. In a population based study from India, the prevalence of 'Syndrome Z' among the general population was found to be 4.5% [10]. Among four different socioeconomic zones from the capital city of India the prevalence was estimated to be 19.9% [11]. Obstructive sleep apnoea independently has been shown to be present in 46–66% of patients presenting with ACS [12,13]. In our study, we have included only those patients who presented with ACS and had MS and then tried to estimate the prevalence of 'Syndrome Z' in this subset of the population and found it to be 34.5%. A pilot study conducted in a teaching hospital in Singapore found an extremely high association of OSA with MS conferring a prevalence of 95.8% to Syndrome Z [14]. However, this study had many confounding factors, like small sample

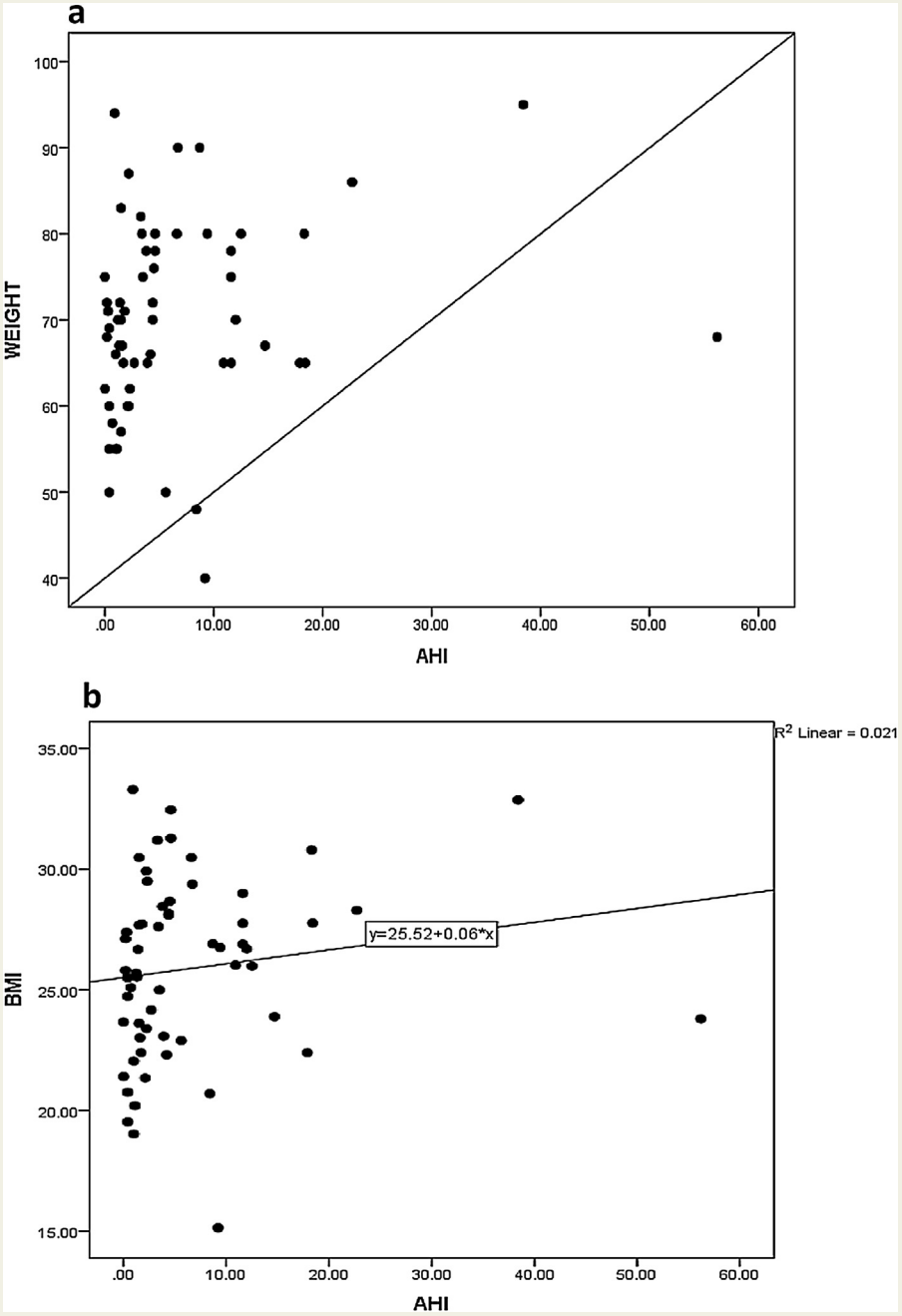

Figure 2 (a) Correlation of weight with AHI (Apnoea/Hypopnoea Index). (b) Correlation of BMI (body mass index) with AHI.

size, and a high dropout rate, thus these results must be interpreted with caution. Though there have not been many studies in India or elsewhere to determine the prevalence of Syndrome Z, we still feel that the prevalence in our subset of the population is much higher owing to the fact that all our patients already had cardiovascular pathology and we also had male preponderance (90%). The lower incidence of 'Syndrome Z' or OSA in women [15] can be explained by the lack of testosterone, which mediates aggravation of sleep disordered breathing, coupled with a protective effect of female hormones. Smoking and alcoholism, two important risk factors, are also, on an average, presumably less common among women.

The analysis of variables revealed only one statistically significant correlation, as the BMI increased so did the AHI and subsequently the incidence of OSA or 'Syndrome Z'. Similar results have been reported in earlier studies too [10,13].

According to the recent ''European Guidelines on Cardiovascular Disease Prevention in Clinical Practice'', OSA is considered a new cardiovascular risk factor [16]. Many studies have shown a positive correlation between OSA and CAD

Table 1 The independent determinants of prevalence of OSA positivity (multivariate logistic regression analysis).

Risk factors (variables included in the model)		Odds Ratio (OR)	95% CI for Odds Ratio	P-value
Age Group (years)	<50	1.000	–	–
	>50	2.245	0.473–10.643	0.309^{NS}
Sex	Female	1.000	–	–
	Male	1.079	0.119–9.758	0.946^{NS}
Hypertension	Absent	1.000	–	–
	Present	2.146	0.620–7.433	0.228^{NS}
Neck Circumference (cm)	<43.0	1.000	–	–
	>43.0	2.422	0.676–8.675	0.174^{NS}
Smoking Status	No	1.000	–	–
	Yes	2.461	0.543–11.159	0.243^{NS}
Waist Circumference (cm)	<102 (M), <90 (F)	1.000	–	–
	≥102 (M), <90 (F)	1.197	0.226–6.349	0.832^{NS}
S. Creatinine	<1.2 mg/dL	1.000	–	–
	≥1.2 mg/dL	1.600	0.255–10.055	0.616^{NS}

Odds Ratio = 1: Reference Category. Dependent variable: OSA Positivity. NS: Statistically Non-Significant.
Abbreviation: OSA, obstructive sleep apnoea.

Table 2a The distribution of angiographic severity coronary artery disease according to OSA positivity.

	OSA Negative (n = 38)		OSA Positive (n = 21)		P-value
No. of Vessels	n	%	n	%	
1	30	78.9	3	14.3	0.001***
2	5	13.2	10	47.6	
3	3	7.9	8	38.1	
Total	38	100.0	21	100.0	

Abbreviation: OSA, obstructive sleep apnoea.
*P-value by chi-Square test. P-value <0.05 is considered to be statistically significant.
***P-value <0.001 (Statistically Highly Significant).

Table 2b The distribution of angiographic severity coronary artery disease according to OSA positivity.

	OSA Negative (n = 38)		OSA Positive (n = 21)		P-value
No. of Lesions	n	%	n	%	
1	26	68.4	4	19.0	0.001***
2	6	15.8	9	42.9	
3	6	15.8	8	38.1	
Total	38	100.0	21	100.0	

Abbreviation: OSA, obstructive sleep apnoea.
P-value by Chi-Square test. P-value < 0.05 is considered to be statistically significant.
***P-value <0.001 (Statistically Highly Significant).

Table 3a The distribution of angiographic severity coronary artery disease according to severity of OSA positivity.

	OSA Negative (n = 38)		Mild OSA (n = 13)		Moderate OSA (n = 5)		Severe OSA (n = 2)		P-value
No. of Vessels	n	%	n	%	n	%	n	%	
1	30	78.9	3	21.4	0	0.0	0	0.0	0.001**
2	5	13.2	6	42.9	4	80.0	0	0.0	
3	3	7.9	5	35.7	1	20.0	2	100.0	
Total	38	100.0	14	100.0	5	100.0	2	100.0	

Abbreviations: OSA, obstructive sleep apnoea.
P-value by Chi-Square test. P-value <0.05 is considered to be statistically significant.
**P-value <0.01 (Statistically Significant).

Table 3b The distribution of angiographic severity coronary artery disease according to severity of OSA positivity.

	OSA Negative (n = 38)		Mild OSA (n = 13)		Moderate OSA (n = 5)		Severe OSA (n = 2)		P-value
No. of Lesions	n	%	n	%	n	%	n	%	
1	26	68.4	4	28.6	0	0.0	0	0.0	0.002**
2	6	15.8	7	50.0	1	20.0	1	50.0	
3	6	15.8	3	21.4	4	80.0	1	50.0	
Total	38	100.0	14	100.0	5	100.0	2	100.0	

Abbreviations: OSA, obstructive sleep apnoea.
P-value by Chi-Square test. P-value <0.05 is considered to be statistically significant.
**P-value <0.01 (Statistically Significant).

Table 4 The distribution of average time of SaO2 <90% according to angiographic severity of CAD (No. of vessels).

	Time SaO2 < 90% (Mins)**				
No. of Vessels	N	Mean	SD	Median	Min–Max
1	32	32.71	90.33	0.00	0.0–440.4
2	14	13.46	19.15	5.10	0.0–69.4
3	11	46.21	98.97	2.40	0.0–275.2

Abbreviations: CAD, coronary artery disease; SaO2, oxygen saturation.
P-value = 0.007**. P-value by Kruskal Wallis H test, p-value <0.05 is considered to be statistically significant.
**P-value <0.01 (xtatistically xignificant).

[17–20]. The novelty of the present study lies not only in the fact that we have demonstrated an association of OSA with MS (Syndrome Z) and CAD, but also in the observation that angiographic severity of CAD was related to presence or absence of OSA in cases with MS.

Baseline thrombolysis in myocardial infarction (TIMI) flow did not show a significant correlation with AHI. Most cases in the present study had a single vessel involved. The baseline TIMI flow was good (i.e. 3) in most subjects. Only 25.4% cases had a baseline TIMI 0. We were able to reperfuse successfully in all cases and achieve a TIMI of 3 post procedure in all of them.

The majority of patients in our cohort had NSTEMI and the most common vessel involved was the LAD artery in both OSA positive and OSA negative groups followed by the RCA though there was no statistically significant difference between the two groups of subjects. There is no similar study in the literature to compare our angiographic findings. Lee et al. have studied the angiographic profile in patients with OSA admitted for acute myocardial infarction and found the left anterior descending artery as the most common culprit lesion [13]. The relationship between MS and angiographic severity of CAD has already been established [21–23]. However, to the best of our knowledge this is the first study which prospectively evaluated the association of 'Syndrome Z' with ACS and angiographic severity of CAD. These results definitely create a platform for large population-based studies to link the association of 'Syndrome Z' and CAD in the general population to direct implications for the development of targeted preventive strategies for ACS. A study from Spain that established OSA to be an independent risk factor for the development of left ventricular diastolic abnormalities, also demonstrated the role of nasal Continuous Positive Airway Pressure (nCPAP) in improving these alterations by eliminating apnoeic events. Thus, it is proposed that the chronic

application of CPAP could avoid the progression of diastolic abnormalities, and indeed, it might reverse these alterations, at least in the initial stages before severe structural changes can be developed [24]. A meta-analysis of 10 randomised controlled trials also supports the notion that CPAP may improve the LVEF among patients with OSA [25].

The results of this study seem to render a new direction for the development of prevention and management strategies for patients with ACS in the presence of MS. However, these need to be interpreted with caution as the study was conducted in a focussed group of patients presenting at a tertiary care referral centre setting with a mostly high-risk case population. The other limitations of our study were small sample size, preponderance of male subjects in the study cohort, and short duration of study.

Conclusion

Prevalence of syndrome 'Z' is much higher in patients having MS presenting with ACS and the presence of Syndrome 'Z' correlates with the angiographic severity of CAD in this clinical setting. Clinicians should keep a high index of suspicion for Syndrome 'Z' while managing patients with ACS.

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