

## “Syndrome Z”: the interaction of sleep apnoea, vascular risk factors and heart disease

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Obstructive sleep apnoea (OSA) has been linked to increased cardiovascular morbidity and mortality from both coronary heart disease and stroke,<sup>1-3</sup> but whether this risk is due to coexistent known cardiovascular risk factors or specific effects of OSA remains to be established.

In populations at risk of vascular disease, many patients who experience a cardiovascular event either do not have identifiable risk factors or have disease severity which appears to be out of proportion to their known risk factors. A lot of the variance in the incidence of vascular disease is therefore not explained by known risk factors. It is possible that OSA is a cardiovascular risk factor, previously largely unrecognised, which may account for some of the apparently unexplained variance in vascular risk.

Data from the Framingham and other studies have clearly shown that at any level of systolic blood pressure there is a substantial increase in cardiovascular risk with increasing levels of plasma cholesterol, and the presence of glucose intolerance (insulin resistance) further increases this risk.<sup>4</sup> Although obesity is a well recognised cardiovascular risk factor, the distribution of body fat is an independent risk factor with central or visceral obesity increasing cardiovascular risk. In the study by Larsen and co-workers<sup>5</sup> increasing waist circumference (an index of central obesity) increased the risk of both coronary heart disease and stroke at all tertiles of body mass index.

Since these risk factors have been shown to be independent predictors of adverse events, they will show at least additive effects in combination and possibly potentiate each other. Epidemiological and other studies have identified clustering of multiple vascular risk factors. One such cluster is a quartet of risk factors which includes systemic hypertension, insulin resistance, hyperlipidaemia, and central obesity which has been defined as “syndrome X”.<sup>6</sup> In this cluster there are positive adverse interactions between factors which further increase the risk to the patient.

An important clinical significance of risk factor clustering is that, in individual patients with several risk factors, the independent risk associated with one factor is substantially underestimated when the other risk factors are not taken into account. For example, the ideal systolic blood pressure may depend on the patient's cholesterol level and waist circumference.

Obstructive sleep apnoea affects approximately 10% of middle aged men and 5% of women and is therefore a common condition.<sup>7</sup> Patients with OSA have many features in common with those with syndrome X, including

systemic hypertension which is commonly reported,<sup>8-12</sup> patients are typically overweight (usually with a central pattern<sup>13 14</sup>), and insulin resistance based on clinical diabetes or measured insulin resistance is well documented.<sup>13 15-17</sup> Dyslipidaemia (mixed elevation of cholesterol and triglycerides) has not been extensively studied in OSA<sup>13</sup> but, since this pattern of lipid abnormality reflects resistance to lipoprotein lipase which is partly dependent on insulin, it too is likely to be present.

Aside from the possibility that OSA identifies a group of patients with a cluster of vascular risk factors, there may be specific effects of OSA which further increase the cardiovascular consequences of this possible risk factor association. Thus, “syndrome X” may actually include OSA and could be better considered as “syndrome Z” (table 1).

### Sleep apnoea and hypertension

In examining the relationship between OSA and systemic hypertension it is important to consider a number of blood pressure variables including not only daytime systolic and diastolic pressure but also circadian patterns (dipping versus non-dipping), and blood pressure variability, all of which have been shown to be important prognostic factors in patients with systemic hypertension (table 2).<sup>4 19 20</sup> The presence of cardiac<sup>21</sup> and possibly vascular hypertrophy identifies patients with hypertension who are at increased risk of cardiovascular events.

Systemic hypertension during daytime measurements of blood pressure is common in patients with OSA<sup>8-14</sup> but a causal link between these two conditions has been disputed.<sup>22 23</sup> Sleep apnoea has been shown to be common in patients with hypertension<sup>8-11</sup> and, conversely, patients with OSA have a high prevalence of hypertension.<sup>13-15</sup> The frequency with which risk factors for hypertension such as increasing age and obesity coexist in patients with OSA has confounded identification of a causal relationship between OSA and hypertension.

In a cross sectional study of men referred for diagnostic polysomnography, most of whom were subsequently shown to have OSA, Grunstein *et al*<sup>14</sup> showed that the severity of sleep disordered breathing (expressed as respiratory disturbance index, RDI) was an independent predictor of both morning systolic and

Table 1 Features of “syndrome Z”?

Hypertension
Central obesity
Insulin resistance
Hyperlipidaemia
Obstructive sleep apnoea

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Table 2 Factors influencing the relationship between blood pressure and cardiovascular risk

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- (1) Systolic blood pressure
  - (2) Diastolic blood pressure
  - (3) Circadian blood pressure patterns ("dippers" versus "non-dippers")
  - (4) Blood pressure variability
  - (5) Cardiac and vascular hypertrophy
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diastolic blood pressure. Predictors of systolic blood pressure were age, RDI, and waist circumference and for diastolic blood pressure were RDI, waist, and age. The effect was not present for evening blood pressure, which suggests that the effect of OSA on blood pressure may be maximal in the morning. The strength of the relationship between sleep apnoea and blood pressure was examined in a smaller cohort of women and shown to be similar and possibly stronger.<sup>24</sup>

There are a number of studies in both animals and humans which favour more than a casual relationship between these two conditions. Repetitive hypoxia in certain rat strains is associated with the development of hypertension and left ventricular hypertrophy.<sup>25</sup> In some but not all studies in human subjects treatment of OSA with tracheostomy or nasal continuous positive airway pressure (nasal CPAP) has led to falls in office,<sup>12 26</sup> intra-arterial<sup>26 27</sup> and ambulatory blood pressure.<sup>28</sup>

Acute haemodynamic responses to obstructive apnoeas include an initial fall in blood pressure followed by a steady rise with a sudden surge in systolic blood pressure of 20–40 mm Hg which coincides with arousal from sleep and resumption of respiration.<sup>29</sup> These changes in blood pressure are paralleled by increased muscle sympathetic nerve activity which is abruptly inhibited by resumption of breathing.<sup>30</sup> Untreated sleep apnoea is therefore associated with cyclical surges in peripheral sympathetic nerve activity and blood pressure.

In patients with hypertension increased variability in blood pressure is recognised to be an important additional risk factor for cardiovascular events<sup>20</sup>; this effect is probably more important at lower blood pressures. Untreated OSA is associated with markedly increased variability in blood pressure during sleep<sup>26 27 29</sup> which, in normal subjects, is a period of lower blood pressure levels and less variable blood pressure.

Left ventricular hypertrophy, documented echocardiographically, has been shown to be one of the most powerful independent predictors of outcome in both men and women with hypertension.<sup>21</sup> Factors which lead to hypertrophy include blood pressure (table 2), growth factors (for example, angiotensin II), and sympathetic nerve activity.

There are relatively few data on the prevalence of left ventricular hypertrophy in men with OSA but in one study left ventricular mass was increased in normotensive men with OSA compared with matched normotensive control subjects.<sup>31</sup> Given the haemodynamic stresses and activation of the sympathetic nervous system in untreated OSA, it would be expected

that the prevalence of left ventricular hypertrophy would be increased in OSA and may be reduced by effective therapy.

The pathophysiological mechanisms by which OSA increases blood pressure are poorly understood but abnormalities of peripheral sympathetic nerve activity, chemoreflex sensitivity, and endothelial function have been reported and may be important.

Microneurographic studies have demonstrated a number of abnormalities in patients with OSA. Recurrent apnoeic events are paralleled by surges in peripheral sympathetic nerve activity<sup>30</sup> and associated blood pressure changes during sleep. Increased sympathetic nerve activity persists during wakefulness and is reduced by treatment with nasal CPAP.<sup>32</sup>

Central control of blood pressure may be affected by OSA. We demonstrated markedly abnormal blood pressure responses to hypoxia during the day in patients with OSA.<sup>33 34</sup> These patients developed a marked pressor response to this stimulus which, in normal subjects, has little effect on blood pressure. The magnitude of this pressor response increased with increasing OSA severity. Ventilatory responses to hypoxia were also increased and correlated with the magnitude of this pressor response, suggesting that abnormal control of blood pressure may be linked with increased chemosensitivity, presumably at a central level.<sup>34</sup>

Abnormal vascular endothelial function has been reported in hypertension, diabetes and hyperlipidaemia; evidence of abnormal function typically precedes the onset of symptoms of vascular disease by many years. There are some preliminary data that report abnormal endothelial function in patients with OSA and hypertension,<sup>35</sup> but whether OSA affects this process independently of co-factors such as hypertension and insulin resistance remains to be determined.

### Sleep apnoea and obesity

Obesity is a well recognised cardiovascular risk factor with a J-shaped relationship between body mass index and cardiovascular morbidity and mortality. The distribution of body fat is important with a central or visceral fat distribution being significantly worse than peripheral (generalised) obesity.<sup>5</sup>

Obesity is common in OSA<sup>13–15 17</sup> and the reverse is also true—that is, as body mass increases the incidence of OSA also increases—and approximately 50% of morbidly obese subjects have OSA. The distribution of fat is typically central or truncal and this includes not only an increase in relative waist circumference (waist:hip ratio) but also in neck circumference. The notion that OSA may actually be due to fat deposition around the upper airway has been examined previously and, although there is evidence which links increasing absolute or relative neck circumference with severity of OSA,<sup>36</sup> these studies are potentially confounded by the strong relationship between neck and waist circumference.

In a study of a sleep laboratory population<sup>14</sup> we noted that waist circumference and severity of OSA (respiratory disturbance index) were

independent predictors of both morning systolic and diastolic blood pressure in multivariate analysis. In this study neck and waist circumference were strongly correlated ( $r = 0.73$ ) and could not be examined simultaneously in the regression model because of colinearity. Thus, an additional independent effect of neck circumference could not be excluded.

Central obesity is common in patients with insulin resistant diabetes and clinical diabetes substantially underestimates the true prevalence of insulin resistance. The observation of central obesity in OSA is possibly more important because of its links with insulin resistance and both macrovascular and microvascular disease than mechanical or reflex mediated effects on the upper airway due to its association with similar fat deposits in the neck.

### Insulin resistance

The pattern of obesity associated with OSA is central rather than peripheral and this increase in visceral fat is associated with insulin resistance. On this basis insulin resistant (type II) diabetes would be expected to occur more commonly in patients with OSA. Insulin resistance occurs much more frequently than clinical diabetes mellitus, affecting most patients with type II diabetes, and is common in hypertensive and obese subjects. Abnormal glucose tolerance or increased plasma insulin levels have been reported in a number of studies in patients with OSA.<sup>13 15-18</sup>

Stoohs<sup>18</sup> examined insulin resistance in 50 healthy normotensive subjects and showed that patients with >10 hypoxic respiratory events/h were more insulin resistant but that this relationship was completely explained by differences in body mass after adjusting for confounding variables.

In a subset of patients in the Swedish Obese Subjects Study with a high likelihood of OSA, based on questionnaire data, Grunstein *et al*<sup>17</sup> reported that plasma insulin levels were increased in both men and women when weight and other variables were adjusted for using multivariable analysis.

Brooks *et al*<sup>16</sup> showed, in a carefully controlled study of a group of patients with type II diabetes and OSA treated with nasal CPAP, that there was an improvement in insulin sensitivity in most patients. The subjects' weight and treatment was unchanged during the course of CPAP therapy. The one patient who did not have a reduction in insulin resistance was suspected to be poorly compliant with CPAP although the lack of accurate measurement of compliance was a limiting factor in the interpretation of the study results.

These data suggest that there is an effect of OSA on insulin resistance apart from the effects of co-existent central obesity. Possible mechanisms include increased sympathetic nerve activity which is present during sleep and wakefulness and which has been reported to occur in OSA. This has been strongly linked to increased insulin resistance in a large number of studies on the relationship between the development of hypertension and insulin

resistance<sup>37</sup> and the interaction of these factors with obesity.

### Circadian variation in the onset of cardiovascular events

A series of studies has shown that the risk of experiencing angina or an acute coronary syndrome (unstable angina, acute myocardial infarction, or sudden cardiac death) varies with the time of day.<sup>38</sup> In the overall population this risk is particularly increased in the hours after awakening from sleep. This circadian variation in risk of cardiovascular events is paralleled by changes in heart rate, blood pressure, and autonomic balance. In normal subjects there is a preponderance of vagal influences during sleep, although the relative balance between sympathetic and parasympathetic nerve activity varies between non-REM and REM sleep with relatively greater and more variable sympathetic nerve activity in REM. Awakening from sleep is associated with a rapid increase in sympathetic nerve activity and a relative reduction in vagal nerve activity. Increased platelet aggregability has been shown to occur in the morning and is believed to be due to increased sympathetic nerve activity.<sup>39</sup>

The pathological substrate for all these unstable coronary syndromes is rupture of an atheromatous, typically lipid rich, plaque.<sup>40</sup> Factors which promote plaque rupture include: plaque morphology, haemodynamic factors, endothelial function, dynamic changes in vessel tone, platelets and the coagulation cascade and inflammatory cells (neutrophils, monocytes/macrophages, lymphocytes and mast cells). The commonest site of rupture of a plaque is at the shoulder of the plaque and the next commonest site is the apex. The mechanical stresses on the plaque are greatest at these sites and it is generally believed that, although these plaques rupture throughout the day and night, the early morning increase in the incidence of the clinical manifestations of plaque rupture is due in part to the mechanical stress placed on vulnerable plaques by the sudden increase in heart rate and blood pressure which occurs on awakening from sleep.

In OSA the cyclical variations in heart rate and blood pressure are dramatic<sup>27 29</sup>—more so than many haemodynamic stresses in daily life—and occur during sleep, a time when in normal subjects blood pressure and heart rate are lowest and least variable. It is possible that the circadian distribution of acute coronary events is different in patients with OSA with, for example, a disproportionate proportion of events occurring during sleep. The influence of obstructed breathing during sleep may also carry over into the early hours after awakening. Increased peripheral sympathetic nerve activity during sleep<sup>30</sup> persists during wakefulness at approximately twice normal levels<sup>32</sup> and may affect acute coronary events in the early hours of the day.

The median age at presentation of men with coronary artery disease is approximately 55 years and from epidemiological studies at least 10% would be expected to have OSA. However, because of risk factor clustering this is

likely to be a substantial underestimate with the real figure probably being nearer to 30%. Thus, studies of patients with coronary heart disease are likely to include a significant minority of patients with OSA whose pathophysiology has potentially been substantially affected by concurrent OSA.

### Conclusion

Obstructive sleep apnoea is closely linked to the cluster of cardiovascular risk factors known as "syndrome X" and the converse is also likely but has not yet been proved ("syndrome Z"). These relationships should lead physicians to consider that patients with OSA may have co-existent modifiable cardiovascular risk factors and, conversely, that OSA should be suspected in patients with hypertension, central obesity, insulin resistant diabetes, or dyslipidaemia.

Aside from these co-existent risk factors there is some evidence that untreated OSA is associated with an additional independent cardiovascular risk which is reduced by effective treatment of OSA. While treatment of OSA eliminates recurrent episodes of hypoxaemia, reduces overall blood pressure levels and variability, may reduce insulin resistance and therefore reduce triglycerides, it has little effect on weight or fat distribution. Thus, the relative contributions of improvements in associated risk factors versus elimination of the haemodynamic and respiratory stresses, which occur during sleep in untreated OSA, remain to be fully elucidated.

Currently, the majority of patients with OSA are treated because of symptoms such as daytime tiredness or sleepiness. If OSA can be convincingly linked to an increased risk of heart disease or stroke then, in the future, treatment of OSA may be indicated for prognostic reasons.

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