

# Sleep apnoea and autonomic function

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Broad interest has evolved in the interaction between sleep apnoea and autonomic function. Much of this interest has resulted from a suspicion that cardiovascular morbidity and mortality<sup>1-6</sup> is increased in individuals with untreated apnoea. Further interest has recently been generated by evidence that sleep-disordered breathing is common among asymptomatic middle aged adults<sup>6</sup> and that systemic hypertension is far more common in such individuals.<sup>5</sup>

Soon after the initial description of the sleep apnoea syndrome, polysomnographic recordings coupled with cardiac catheterisation findings during apnoeic events demonstrated cardiovascular instability. For example, transient but striking increases in systemic blood pressure at apnoea termination, along with significant decrements in heart rate during periods of apnoea, were found to be characteristic of apnoeic events associated with arterial hypoxaemia. These alterations in cardiovascular homeostasis, along with the understanding that untreated apnoea is associated with cardiovascular morbidity and mortality, has stimulated investigational activity in the association between sleep apnoea and autonomic nervous system control and this subject has recently been reviewed.<sup>7</sup>

This paper will describe only two of the important interactions between apnoea and autonomic function. Since bradycardia appears to be a common feature of prolonged apnoeic events associated with hypoxaemia, its mechanism will be discussed. The influence of apnoea on the development of transient and fixed sympathetic nervous system excitation will also be reviewed because of the recent evidence that untreated apnoea, even if mild, may be associated with sustained hypertension.

## Apnoea and bradycardia

Clearly the autonomic nervous system plays an important role in modulating cardiac rhythm. Increased sympathetic neural activity accelerates heart rate, shortens the ventricular refractory period, and decreases the threshold for ventricular fibrillation. Parasympathetic excitation slows heart rate, decreases atrial-ventricular nodal conduction, while increasing ventricular refractory and fibrillation thresholds. During sleep, sympathetic neural activity decreases in association with an increase in parasympathetic activation. These alterations in neural output, probably in association with a decrease in metabolic rate, result in a reduction in heart rate during sleep. In healthy young individuals sinus bradycardia and even second degree heart block may occur.<sup>8,9</sup> Arousals from sleep are associated with transient sympathetic hyperexcitation and cardioacceleration. These

events appear to be linked because cardiac sympathetic blockade in dogs prevents arousal induced increases in heart rate.<sup>10</sup> Some evidence links sudden arousal from sleep with cardiac arrhythmias<sup>11</sup> and even coronary artery vasoconstriction.<sup>12</sup>

Bradycardia during apnoea was reported in some of the earliest series of patients studied.<sup>13</sup> Interestingly, almost every patient studied had significant bradyarrhythmias with heart rates transiently dropping below 30/min while asystoles of 2.5-13 s were found in approximately one third of the patients. Subsequent reports have demonstrated the common finding of progressive bradycardia during apnoea.<sup>14-16</sup> However, some recent studies found the decrease in heart rate during apnoea to vary, in part depending on sleep stage or the time in the apnoea/hyperpnoea cycle at which the heart rate was recorded.<sup>17</sup> Occasionally, individuals with well characterised obstructive apnoea do not demonstrate apnoea related decreases in heart rate.<sup>18</sup> The fact that both tracheostomy and nasal CPAP eliminate both apnoea and apnoea-related bradyarrhythmias suggests a further cause and effect relationship.<sup>16</sup>

## Mechanism

The mechanism whereby apnoea, with associated hypoxaemia, results in bradycardia has been reasonably well established. More than 30 years ago deBurg Daly *et al*<sup>19</sup> showed that hypoxaemia resulted in tachycardia in spontaneously breathing anaesthetised animals but, if hypoxia-induced hyperpnoea was limited by fixed mechanical ventilation or neuromuscular blockade, tachycardia would not occur. They also showed that if the hypoxia was severe and if apnoea was present, bradycardia would invariably result. Pretreatment with intravenous atropine sulphate prevented the bradycardia induced by apnoea with hypoxaemia in this dog model.<sup>20</sup> In order to determine whether a primary carotid body mediated reflex stimulated by hypoxia caused cardiac deceleration, experiments were repeated following section of the carotid body nerves. This intervention demonstrated that carotid body neurostimulation as a result of arterial hypoxaemia caused bradycardia when lung inflation (hyperpnoea) was inhibited. The authors hypothesised that carotid body stimulation without lung inflation results in a high degree of vagal tone with resultant bradycardia. However, in the natural state tachycardia is the usual response to arterial hypoxaemia resulting from the combined influence of carotid body stimulation (vagotonic and sympathetic), in consort with carotid body neural stimulation of respiration which results in hyperpnoea (lung stretch). In the intact animal hyperpnoea

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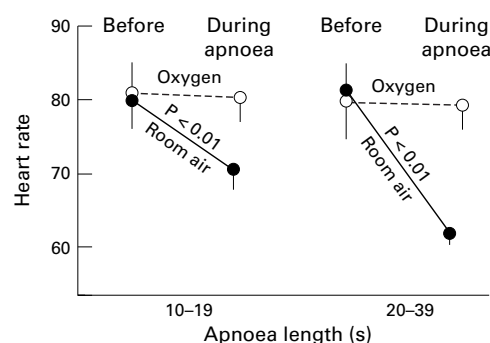


Figure 1 Impact of oxygen administration on the heart rate response to brief apnoeas (10–19 seconds) and more prolonged apnoeas (20–39 seconds). During both short and longer apnoeas, oxygen administration prevented oxyhaemoglobin desaturation (not shown) and the decrease in heart rate seen during apnoea when the subjects were breathing room air. During room air breathing apnoea is associated with oxyhaemoglobin desaturation and a significant decrease in heart rate.

results in the Herring-Brauer reflex where lung stretch has a prominent vagolytic influence. Accordingly, hypoxaemia results in hyperpnoea and tachycardia.<sup>19 20</sup>

### Studies in man

Observations in normal subjects and in patients with obstructive apnoea have produced similar findings. Although apnoea and hypoxaemia routinely result in bradycardia, the administration of supplemental oxygen during sleep in apnoeic patients often results in prolongation of apnoea but cardiac deceleration is either eliminated or attenuated (fig 1).<sup>21</sup>

The fact that apnoeic hypoxaemia associated bradycardia occurs during sleep raises the question about the impact of hypoxaemia on heart rate in non-apnoeic sleeping individuals. Since the tachycardia associated with hypoxaemia depends upon the degree of hyperpnoea, it is anticipated that the heart rate response to hypoxaemia during sleep might also be attenuated since hypoxaemia stimulates breathing less during sleep than it does during wakefulness in normal individuals,<sup>22</sup> but that bradycardia would not occur as long as ventilation was present. This is exactly what is found.<sup>21</sup> Normal individuals rendered hypoxaemic during sleep exhibit an acceleration in heart rate but this increase is significantly less ( $p < 0.05$ ) than that found during wakefulness (fig 2). The increase in heart rate is least during REM sleep where the ventilatory response to hypoxia is less than during wakefulness or other sleep stages.<sup>22</sup> Accordingly, bradycardia is not typical during sleep when hypoxaemia is present as long as hyperpnoea is occurring. The bradycardiac response to hypoxaemia during wakefulness can be easily demonstrated in normals during breath holding. Under these circumstances breath holding associated with hypoxaemia routinely results in cardiac rhythm deceleration, a physiological response that does not occur during breath holding following the inhalation of high concentrations of oxygen. Pretreatment with atropine blocks the decrease in heart rate (fig 3). A fascinating recent study

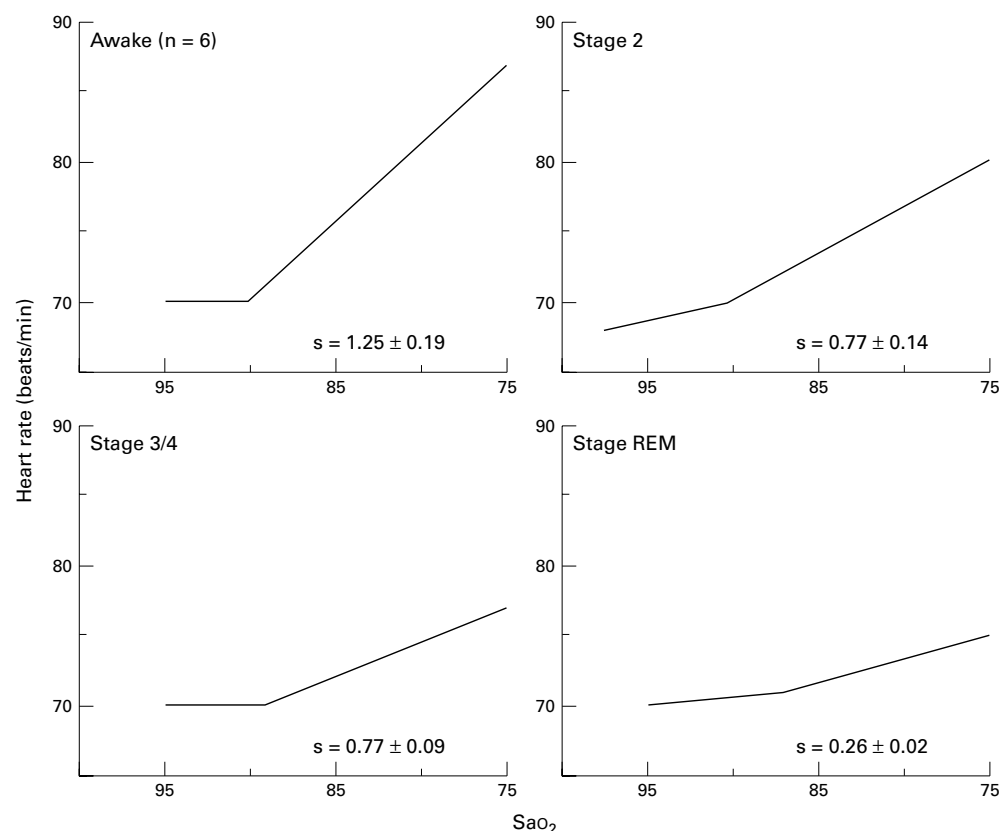
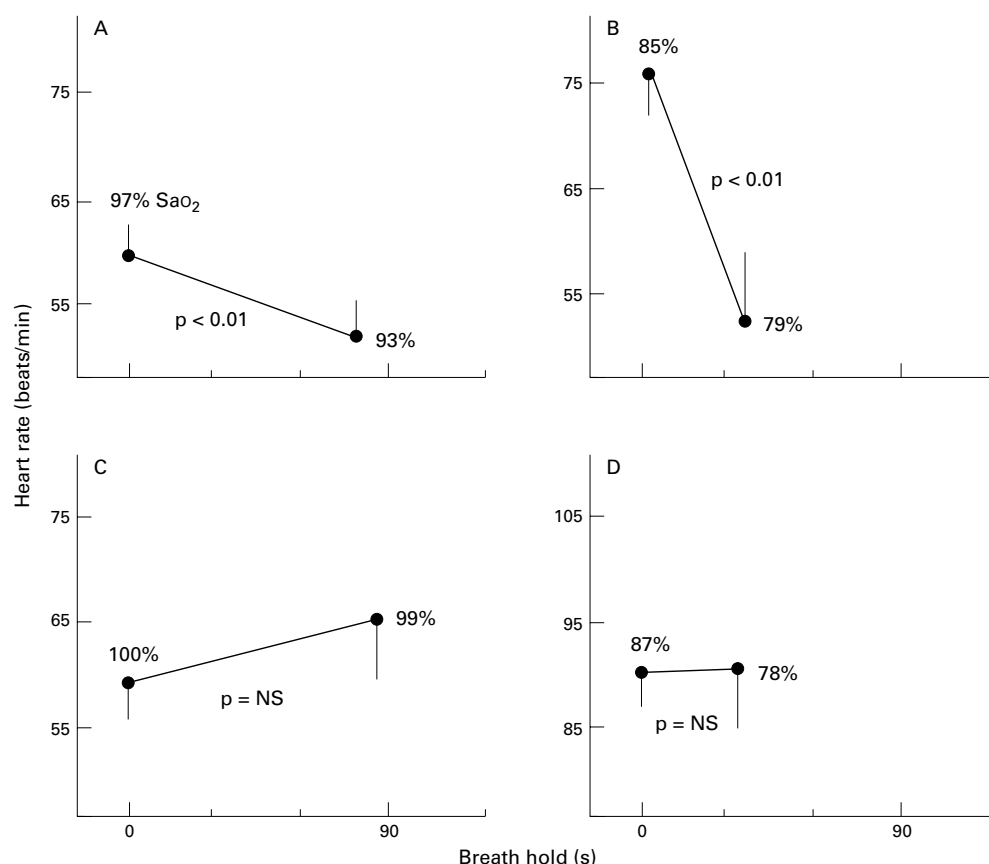


Figure 2 Influence of laboratory induced oxyhaemoglobin desaturation in normal subjects during wakefulness and during different sleep stages. Apnoea was absent in all subjects during hypoxaemia. During wakefulness and during all sleep stages the heart rate increased during progressive hypoxaemia although the increase was significantly less ( $p < 0.05$ ) during REM sleep.



**Figure 3** Heart rate response to voluntary breath holding in normal subjects during (A) room air breath holding, (B) hypoxia breath holding, (C) 100% oxygen breath holding, and (D) hypoxia breath holding after atropine. Room air breath holding (A) resulted in a small but significant fall in oxyhaemoglobin saturation and a small but consistent ( $p < 0.01$ ) decrease in heart rate. During hypoxia breath holding (B) the subjects held their breath following nitrogen breathing resulting in oxyhaemoglobin desaturation from 85% to 79% over a 15 second period. Heart rate decelerated rapidly and significantly ( $p < 0.01$ ). Breathing 100% oxygen prior to breath holding (C) eliminated oxyhaemoglobin desaturation and the decrease in heart rate found under previous conditions. Pretreatment with atropine (D) blocked any decrement in heart rate during hypoxic breath holding even though oxyhaemoglobin saturation fell to 78%.

in man showed that the decrease in heart rate in patients during obstructive apnoea was correlated with their hypoxic ventilatory response during wakefulness.<sup>23</sup> This further suggests the importance of carotid chemosensitivity in the pathogenesis of bradycardia during apnoea.

It has therefore been clearly established that bradycardia is the expected rhythm during apnoeas. Short apnoeas without hypoxaemia or prolonged apnoeas during which time hypoxaemia is prevented by breathing enriched oxygen gases do not result in bradycardia. Accordingly, apnoea combined with hypoxaemia appears to be required to produce significant bradycardia.

### Sympathetic excitation and apnoea

Interest in sympathetic excitation as an important feature of obstructive apnoea results from several observations. The increase in heart rate typically occurs following the transition from apnoea to hyperpnoea and there is usually a transient increase in blood pressure at apnoea termination. In addition, systemic hypertension during wakefulness is more common in untreated apnoeic populations.<sup>3</sup> These findings suggest the possible role of adrenergic discharge. Twenty four hour urinary catecholamine concentrations are increased in subjects

with untreated obstructive sleep apnoea<sup>24, 25</sup> and the expected decrement in sympathetic activation during sleep, measured as overnight urinary catecholamine excretion, does not occur in untreated apnoeic subjects, a phenomenon which reverses towards normal during treatment.<sup>26</sup> These findings raise the possibility that sympathetic activation might explain the systemic hypertension, surges in blood pressure at apnoea termination, and possibly some of the previously reported cardiovascular morbidity and mortality found with untreated apnoea.

Hedner *et al*<sup>27</sup> used microneurography to record muscle sympathetic nerve activity during wakefulness in six patients with untreated apnoea and compared these findings with sex matched controls. Resting muscle sympathetic nerve activity was twice as high in the apnoeic patients than in the control subjects and there was no overlap in the range of sympathetic hyperexcitation in apnoeic subjects (65.0–86.0 units/minute) compared with controls (24.0–47.7 units). The authors reasoned that the high resting sympathetic nerve activity may be important in the development of systemic hypertension commonly seen in these patients. Sympathetic neural recordings were also completed in some of their patients during sleep at

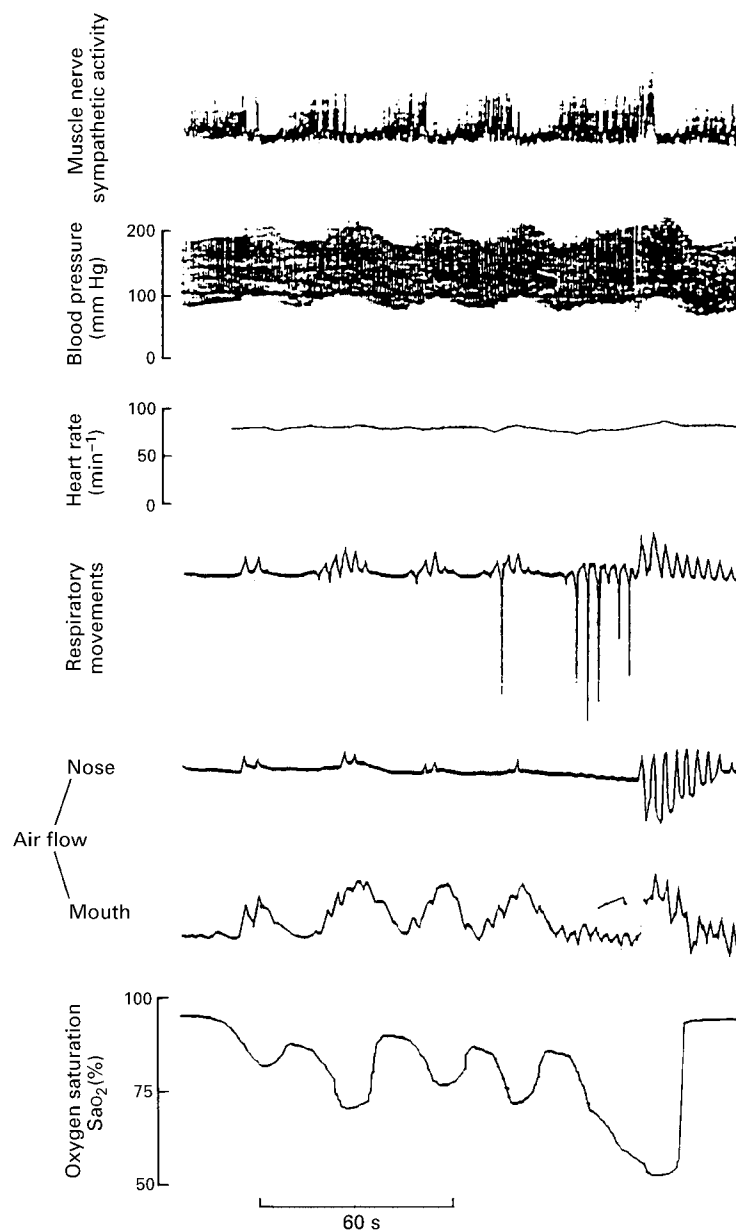


Figure 4 Influence of apnoea on muscle sympathetic nerve activity and blood pressure. Sympathetic activity rose during apnoea and peaked during the transition period between apnoea and hyperpnoea. Blood pressure rose late in apnoea and also peaked during the transition between apnoea and hyperpnoea when arousal from sleep typically occurs.

which time intra-arterial pressure was measured. They found a striking relationship between apnoea, oxyhaemoglobin desaturation, surges in interarterial pressure, and sympathetic activation (fig 4).

These initial observations have stimulated increasing investigational interest into the mechanisms of sympathetic excitation and the possible role it may play in the pathophysiology of obstructive sleep apnoea. Earlier experiments<sup>20</sup> showed that artificially induced apnoea in animals resulted in peripheral vasoconstriction when hypoxaemia was present. A carotid body mediated response was thought to be important. In an interesting group of experiments Fletcher *et al* demonstrated in rats that repetitive episodes of hypoxaemia causes sustained hypertension.<sup>28</sup> He later showed that

carotid chemodenervation<sup>29</sup> abolished the development of hypertension in a second group of rats exposed to episodic hypoxia. These experiments suggest the importance of a carotid body mediated response in the development of sustained hypertension following intermittent hypoxaemia.

Do these observations in animals impact upon our understanding of the interaction between apnoea, hypoxaemia, sympathetic activation and arterial vasoconstriction? A recent array of published reports strongly supports a similar association between apnoea and sympathetic excitation in man. From earlier experiments one would expect that hypoxaemia during breath holding would accentuate the sympathetic discharge and blood pressure response to voluntary apnoea in humans. This has recently been shown in normal subjects where breath holding after breathing a low oxygen mixture ( $\text{SaO}_2$  71%) resulted in a greater muscle sympathetic nerve discharge frequency and blood pressure response than breath holding following breathing room air ( $\text{SaO}_2$  93%).<sup>30</sup> Somers *et al*<sup>31</sup> reported a rise in sympathetic nerve activation during sleep in a group of individuals with obstructive apnoea and found that apnoea induced sleep arousals were associated with striking sympathetic excitation and an increase in blood pressure. They demonstrated an attenuation in sympathetic excitation and blood pressure surges during CPAP administration which effectively eliminated apnoeas and frequent arousals (fig 5). Longer term experiments<sup>32</sup> have evaluated the impact of apnoea treatment on sympathetic hyperexcitation in apnoeic patients. A remarkable decrement in sympathetic activity while awake occurred only in those apnoeic individuals undergoing effective treatment. Specifically, apnoeic patients did not exhibit a decrement in increased adrenergic drive if they were on CPAP therapy for less than four hours per night. Those individuals in whom objective monitoring demonstrated higher levels of CPAP use on a nightly basis had a significant decrement in sympathetic excitation while awake. Interestingly, sustained CPAP treatment lowers systemic blood pressure in patients with apnoea.<sup>33</sup>

Additional evidence that autonomic dysfunction may be present during wakefulness in those with obstructive apnoea is suggested by the systemic hypertensive response to laboratory induced hypoxaemia in those patients compared with normal subjects.<sup>34</sup>

In conclusion, parasympathetic and sympathetic excitation appear to be important during obstructive sleep apnoea. Bradycardia appears to be parasympathetically driven and is the result of the combined influence of apnoea associated with arterial hypoxaemia. The frequency and degree of bradycardia occurring in this population is correlated with the frequency and severity of apnoeic events during sleep. Sympathetic excitation is typical of the untreated apnoeic population during wakefulness with further excitation during sleep apnoea. Although unproved, the high frequency of fixed arterial hypertension during



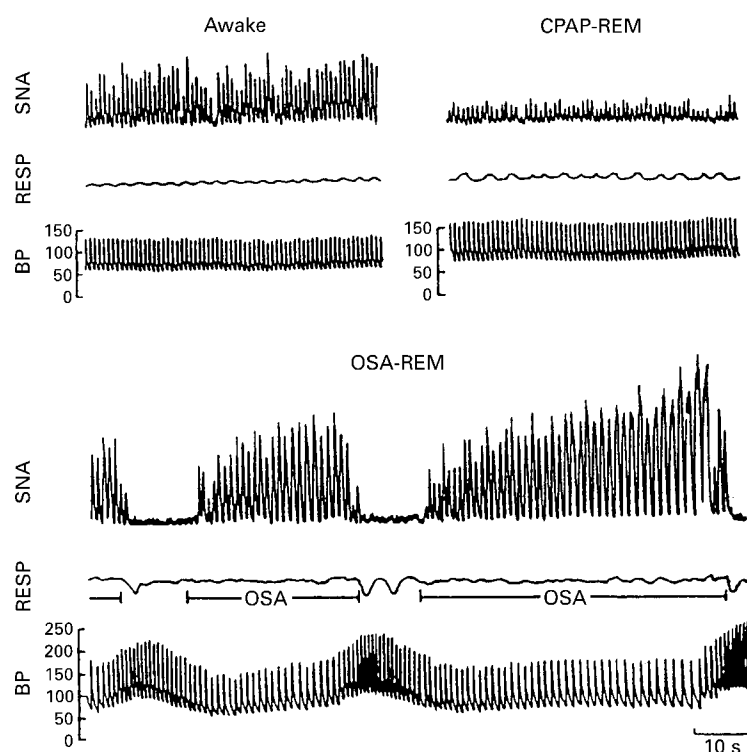


Figure 5 Sympathetic nerve activity (SNA) and blood pressure (BP) in an untreated sleep apnoea patient while awake showing a high spiking SNA; following resumption of breathing (OSA-REM) showing increased sympathetic activity and blood pressure followed by a decrease in sympathetic activity and blood pressure (both abnormalities recurred during the subsequent apnoea); in an apnoeic patient during CPAP therapy (CPAP-REM) where apnoea and hypoxaemia are no longer occurring showing low sympathetic nerve activity and non-oscillating blood pressure.

wakefulness in this population may be the result of sympathetic excitation. During sleep, increments in muscle sympathetic nerve activity is associated with rising systemic pressure which usually peaks following apnoea associated arousal and the resumption of breathing. These responses are associated with arterial oxygen desaturation and are attenuated by hyperoxia, suggesting the pivotal role of carotid body stimulation in the pathogenesis of both the bradycardia and sympathetic hyperexcitation found in patients with untreated OSA. Whether these autonomic responses explain an important portion of the morbidity and mortality of untreated apnoea remains to be determined.

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