A dog model to investigate the relationship between obstructive sleep apnoea and blood pressure regulation

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SUMMARY Patients exhibiting obstructive sleep apnoea (OSA) do not display a normal circadian pattern of blood pressure. It is not clear whether this disruption of the circadian blood pressure pattern is a result of the intermittent airway obstruction during sleep or is the result of confounding factors, such as obesity and age, which are common in OSA and may independently affect blood pressure. To determine if a cause and effect relationship exists between repetitive airway obstruction during sleep and blood pressure regulation a chronically instrumented canine model of OSA has been developed. This canine model has been shown to reproduce the characteristic apnoea and hypersomnolence of human OSA. Furthermore, in this model a 12-h nocturnal period of repetitive airway obstruction during sleep caused an increase in baseline blood pressure of more than 10 mmHg that was sustained for at least two hours following the restoration of normal airway patency. These results imply that there is a cause and effect relationship between intermittent airway obstruction during sleep and elevated blood pressure.

KEYWORDS apnoea, arousal, circadian rhythm, MAP, oxyhaemoglobin saturation.

INTRODUCTION

The regulation of human blood pressure follows a circadian pattern, and in its simplest form can be characterized by a 5–10% decrease in blood pressure between daytime and night-time (Khatri and Freis 1967). There can be a disruption in this 'nocturnal dip' in blood pressure in patients suffering from obstructive sleep apnoea (OSA) (Hoffstein and Mateika 1992). Each period of apnoea is accompanied by haemoglobin desaturation, large intrathoracic pressure swings and arousal, which produce an acute increase in blood pressure (Shepard 1986; Ringler et al. 1990; Levinson and Millman 1991). Thus, in patients with high disordered breathing rates, the accumulated effect of repetitive acute increases in blood pressure is to abolish the nocturnal dip in blood pressure.

It has been more difficult to determine if OSA can also disrupt the daytime circadian pattern of blood pressure control. There is an increasing amount of evidence suggesting an association between OSA and daytime hypertension (Kales et al. 1984; Lavie et al. 1984; Fletcher et al. 1985; Williams et al. 1985; Jeong and Dimsdale 1989; Hoffstein et al. 1991; Milman et al. 1991). Despite the strength of this association, it is still unknown whether the disturbances in sleep and breathing that occur at night-time in OSA can propagate into daytime hypertension. It is possible that confounding factors, such as obesity and age, which are common to both OSA and hypertension may be responsible for the relationship (Fletcher et al. 1985; Jeong and Dimsdale 1989; Kiselak et al. 1993). A potential method to directly examine the causality between OSA and hypertension would be to develop an animal model of OSA.

ANIMAL MODELS OF OSA

There are a number of animal models that have been developed to reproduce the disordered breathing of OSA. Attempts have been made to model OSA by obstructing the upper airway of anaesthetized dogs (Iwase et al. 1992; Scharf et al. 1992; Tarasiuk and Scharf 1993). Although this approach may be useful in studies focusing on mechanical heart–lung interactions, the model is limited by the absence...
of an arousal response and in the study of circadian blood pressure regulation. Another approach has been to study the English bulldog which spontaneously exhibits collapse of the upper airway during sleep, predominantly REM sleep, in a manner that may be analogous to human OSA (Hendricks et al. 1987). A potential limitation of the bulldog model may be that blood pressure changes that occur as a result of airway obstruction may, in fact, produce further changes in airway collapsibility (Wasicko et al. 1993) as part of a positive feedback loop. This may complicate the interpretation of studies which focus on the relationship between upper airway obstruction during sleep and regulation of blood pressure. Recently, a model was developed to obstruct the upper airway of chronically instrumented, tracheostomized pigs during sleep (Pinto et al. 1993). A potential drawback of this model is that the periods of obstruction were very brief (<10 s) and unlikely to produce hypoxaemia. Thus, no single model described above is able to simultaneously produce the hypoxaemia and arousal responses representative of clinical OSA, independent of changes in upper airway collapsibility.

Recent evidence suggests that the chronically instrumented, tracheostomized dog may accurately reproduce the disturbances in sleep and breathing that occur in OSA (Kimoff et al. 1994; O'Donnell et al. 1994a, b). Apnoea could be experimentally induced at rates in excess of 30 per hour throughout a 12-h nocturnal period (O'Donnell et al. 1994b). These experimentally induced apnoeas in NREM sleep were in excess of 20 s in duration, resulted in arterial haemoglobin desaturation to approximately 90% and caused intrathoracic pressure swings in excess of 25 mmHg during the last occluded breath (O'Donnell et al. 1994b). There was also evidence that the dogs exhibited hypersomnolence following a single night of repetitive airway obstruction during sleep (O'Donnell et al. 1994b). Thus, these studies demonstrate that the chronically instrumented sleeping dog can model the characteristic apnoea and increased somnolence exhibited in OSA.

Acute Changes in Blood Pressure in Response to Airway Obstruction

In clinical OSA, blood pressure has been shown to fluctuate at night with a rhythm corresponding to the periodic apnoea (Levinson and Milman 1991; Shepard 1986). The mean arterial pressure (MAP) has been reported to increase approximately 20 mmHg between unobstructed NREM sleep and arousal in response to period of apnoea (Ringler et al. 1990). This is almost identical to the 18 mmHg increase in MAP between the preobstruction and arousal period during NREM sleep reported in the chronically instrumented dog (O'Donnell et al. 1994a). Thus, not only does experimentally induced airway obstruction in the sleeping dog model the sleep and breathing disturbances of OSA, but it also reproduces the corresponding acute blood pressure responses.

The Effect of Repetitive Airway Obstruction on Baseline Blood Pressure Over Time

It has been argued above that the chronically instrumented dog can model the acute blood pressure responses that occur with apnoea and arousal during sleep. An obvious application of this model would be to determine what happens to blood pressure regulation during, and following, an extended period of repetitive airway obstruction. In particular, is there an increase in the baseline blood pressure over time in addition to the acute fluctuations in blood pressure with each period of apnoea and arousal? There is now evidence that a single 12-h period of repetitive airway obstruction in the sleeping dog can increase baseline blood pressure in excess of 10 mmHg (Fig. 1; O'Donnell et al. 1994a). Furthermore, this increase in baseline blood pressure was sustained for at least two hours following the restoration of normal airway patency (O'Donnell et al. 1994a).

Figure 1. The mean ± SEM MAP (mmHg) over time in response to repetitive airway obstruction during NREM sleep (n = 4). These data are independent of whether MAP was measured in the pre-obstruction or arousal period, and the presence or absence of sleep deprivation. A star represents an increase (P < 0.05) from the first 3-h time period (18.00–21.00 hours), and a cross represents an increase (P < 0.05) from the second 3-h time period (21.00–24.00 hours). The MAP data collected at one minute intervals during NREM sleep in the time control experiment were averaged in 3-h blocks and are shown for visual, but not statistical, comparison with the airway obstruction experiments. Reprinted with permission (O'Donnell et al. 1994a).
These changes in blood pressure during repetitive airway obstruction developed over a number of hours which suggests the mechanism may be of humoral or neural origin. The rise in baseline blood pressure did not appear to be a humorally mediated response from vasoactive peptides, since plasma levels of renin and atrial natriuretic peptide remained basal before, during, and after the period of repetitive airway obstruction (O'Donnell et al. 1994a). There was, however, evidence that the elevated blood pressure may be associated with an alteration in neural baroreflex control of blood pressure. A comparison of the blood pressure–heart rate data following the period of repetitive airway obstruction revealed that the elevated blood pressure was not accompanied by a corresponding reduction in heart rate (O'Donnell et al. 1994a). This suggests, that in the absence of a change in baroreflex sensitivity, the set point of the baroreflex has been reset upwards by 10 mmHg in response to a 12-h nocturnal period of repetitive airway obstruction (Fig. 2).

In summary, the development of a dog model has enabled new insights into the control of blood pressure in OSA. It is evident that cyclical periods of apnoea, hypoxaemia and arousal will cause both (i) a corresponding pattern of acute perturbations in blood pressure, and (ii) a significant upward drift in baseline blood pressure. Furthermore, the presence of a sustained elevation in blood pressure following the restoration of normal airway patency suggests that some component(s) of the night-time disturbances in sleep and breathing may propagate into the daytime to produce hypertension.

IMPLICATIONS FOR AN ANIMAL MODEL OF OSA

There is evidence that a positive feedback loop (Fig. 3) may exist between obstructive sleep apnoea, blood pressure and upper airway collapsibility (Gleadhill et al. 1991; Schwartz et al. 1991; Schwartz et al. 1992; Wasicko et al. 1993). Furthermore, a number of factors such as obesity, age, hormones, alcohol and medications may also act to modulate upper airway collapsibility and blood pressure regulation. This suggests that any attempt to study the relationship between OSA and blood pressure in the clinical setting will be subject to a large number of interacting variables that will be difficult to control.

The implication of the work reported here is that a model now exists to determine independently the relationship between OSA and blood pressure regulation. The model uses healthy adult dogs, thereby eliminating confounding variables such as obesity, ages etc., and allows paired, within animal, experimental designs. In addition, the tracheostomy provides a method to obstruct the airway independent of any effect of blood pressure on upper airway collapsibility. It is anticipated that this model will enhance understanding of how OSA affects blood pressure and provide a useful tool to systematically evaluate putative mechanisms.

REFERENCES


Hoffstein, V. and Mateika, J. Evening-to-morning blood pressure

Figure 2. The heart rate (beats/min) and MAP (mmHg) data in a two hour recovery period following a time control and an airway obstruction experiment (O'Donnell et al. 1994a) plotted on a hypothetical cardiac baroreflex curve with a constant baroreflex sensitivity.

Figure 3. A theoretical positive feedback loop between obstructive sleep apnoea, blood pressure and upper airway collapsibility. $P_{cr}$ is the critical closing pressure of the collapsible site in the upper airway (Schwartz et al. 1988; Smith et al. 1988; Gleadhill et al. 1991).


