In this issue of *Thorax*, Edwards *et al*[10] confirm the reproducibility of two recently described prognostic scoring systems. The authors retrospectively analysed a large group of patients with mesothelioma treated within a single institution in Leicester between 1988 and 1999. Prognostic variables were analysed by univariate and multivariate models and were then incorporated into groups as described by two established scoring systems. The prognostic scoring systems used were the European Organization for Research and Treatment of Cancer (EORTC) system[11] and the US Cancer and Leukemia Group B (CALGB) system.[12] The EORTC system defines a high risk group of patients according to several factors: poor performance status, high white blood cell count at diagnosis, probable or possible (uncertain) histology, male sex, and sarcomatous cell type. The CALGB system defines six distinct prognostic subgroups with two year survival times ranging from 1.4 months to 13.9 months. The subgroup with best survival included patients with normal performance status and younger age (<49 years). Another indicator of better prognosis was a haemoglobin level at diagnosis of 14.6 g/dl or more. The worst survival was associated with patients with poorer performance status and baseline white blood cell count of more than 15.5 $\times 10^9$/l. Both scoring systems correctly identified patients with a poor prognosis in the Leicester series. Poor prognosis factors by multivariate analysis of the Leicester patients were sarcomatous cell type, low haemoglobin, high white blood cell count, poor performance status, and male sex. One year and two year survival rates were 21.3% and 3.5%, respectively. Survival rates for Leicester patients within prognostic groups were equivalent to patients in the EORTC and CALGB series.

The EORTC and CALGB prognostic scoring systems have thus been validated in a retrospective cohort. These systems could be considered for use prospectively in forthcoming phase II and III trials in malignant mesothelioma. Variation in prognostic factors may at least partially explain variation in survival between different phase II trials and information about such factors could be useful in interpreting the results. The British Thoracic Society and Medical Research Council are initiating a three arm phase III trial this year. Patients will receive single agent vinorelbine chemotherapy or combination chemotherapy with mitomycin, vinblastine and cisplatin ("MVP") or best supportive care. This important trial should help to define the role of chemotherapy in terms of effects on quality of life and survival in malignant mesothelioma.

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Hypertension in patients with sleep apnoea, a combined effect?

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Studies in both humans and animal show beyond doubt that obstructive apnoea produces an acute rise in systemic blood pressure. Such increases are well characterised with regard to timing and peripheral events such as changes in oxyhaemoglobin saturation, pulse rate, and autonomic activity. However, following early reports of sustained hypertension in patients with sleep apnoea, it has been argued that this long term haemodynamic abnormality is related to obesity rather than to nightly repetitive apnoeas. Since obesity is so common in obstructive sleep apnoea, it is nearly impossible to accumulate chronic blood pressure data on non-obese apnoeic individuals. In the past few months, including the current issue of *Thorax*, four fairly definitive studies have been published. The authors of these studies conclude that there is an independent relationship between the presence of obstructive sleep apnoea and chronic hypertension, considering other risk factors including obesity.[1–4]

Obesity associated hypertension[5] is believed to result from a combination of mechanisms mainly centering around insulin resistance. Obesity and high caloric intake are associated with activation of the sympathetic nervous system (as evidenced by high rates of muscle sympathetic nerve activity) through hyperinsulinaemia. High insulin levels are associated with increased tubular sodium reabsorption resulting in sodium retention. Hyperinsulinaemia is further implicated in vascular hypertrophy, as well as attenuated vasodilation in skeletal muscle of obese patients. That all of these mechanisms can exist in obese patients with sleep apnoea goes without saying. Thus, in part there can be no argument that obesity, in and of itself, can contribute to hypertension in some or even many

patients with sleep apnoea. The question is whether obesity and hyperinsulinaemia account for all of the blood pressure changes in these patients.

Several early publications examining this question attempted to control for weight as a variable, but were probably less than accurate because of relatively small numbers of subjects.[6 7] Indeed, some studies failed to find differences in the apnoea index between normotensive and hypertensive groups when matched for age and body mass index.[8] Many factors contributed to these conflicting data, including sample size, concurrent medications, variability in blood pressure and apnoea index by random sampling, and disregard of body fat distribution. Failure to delineate a mechanism accounting for the translation of nightly recurrent episodes of apnoea, hypoxaemia, and arousal into sustained daytime hypertension has also cast some doubt upon the apnoea-hypertension relationship.

Larger epidemiological studies have helped to clarify some of these issues. One study of 377 consecutive patients referred for full polysomnographic sleep study showed that age, body mass index, and degree of sleep apnoea were all independent predictors of hypertension.[9] The relative risk of hypertension associated with age was 4.3, associated with obesity was 2.7, and associated with a diagnosis of sleep apnoea was 2.1. Among 1464 consecutive men referred for sleep studies Gruenstein *et al* showed that the degree of sleep apnoea was independently related to morning blood pressure while both obesity and apnoea severity were independent risk factors for hypertension.[10]

Observational, prospective studies of active working populations using ambulatory blood pressure monitoring have attempted to resolve the small numbers, medication effect, and blood pressure sampling errors that have plagued previous studies. Using ambulatory blood pressure recording while controlling for age and weight, Hla *et al* found a graduated increase in blood pressure associated with an increase in the frequency of apnoeas in 147 asymptomatic working subjects.[11] Among 1060 working subjects studied overnight in the sleep laboratory Young *et al* found that sitting cuff blood pressure increased linearly with increasing apnoea hypopnoea index (AHI).[12] The odds ratio for hypertension associated with an AHI of 15 events/hour was 1.8. The 4–8 year follow up to this Wisconsin Sleep Cohort Study has just been published in the *New England Journal of Medicine*.[2] A total of 709 participants were followed for a minimum of four years with 184 being followed for eight years. Adjustment was made for baseline hypertension status, body mass index, neck and waist circumference, age, sex, and alcohol and cigarette use. The odds ratio for hypertension at follow up was 1.42, 2.03, and 2.89, respectively, for AHI values of <4.9/h, 5.0–14.9/h, and >15/h at baseline.

Probably the largest multicentre prospective study to date on the relationship of chronic hypertension and sleep apnoea was published in a recent issue of *JAMA* as part of the ongoing Sleep Heart Health Study.[2] The study measured seated cuff blood pressure and applied unattended home polysomnography to 6132 subjects. Hypertension was defined as a blood pressure of more than 140/90 mm Hg or the use of antihypertensive medication. After adjusting for body mass index, neck circumference, waist-to-hip ratio, alcohol intake, and smoking, the odds ratio for hypertension comparing the highest AHI (>30 events/h) with the lowest (<1.5/h) was 1.37. Similarly, the percentage of time during sleep spent below 90% saturation showed an odds ratio of 1.46.

Lavie *et al* recently reported findings in 2677 adults who underwent polysomnographic sleep studies.[3] Multiple regression analysis of blood pressure in subjects not on medication showed that the apnoea index predicted both systolic and diastolic blood pressure following adjustment for age, body mass index, and sex. Indeed, multiple logistic regression showed that, for every 1 event/h apnoea index, the odds ratio of hypertension increased by 1%. Furthermore, episodic hypoxia as an aetiological mechanism in the apnoea-hypertension relationship gained further support since a 10% decrease in apnoea related saturation increased the odds of hypertension by 13%.

In the current issue of *Thorax* Davies *et al* have carefully matched 45 patients with symptomatic apnoea with 45 non-apnoeic controls taken from a primary care setting with regard to age, body mass index, alcohol and cigarette consumption, hypertension treatment, and the presence of ischaemic heart disease.[4] They examined their 24 hour ambulatory blood pressure and found that daytime and night time diastolic as well as night time systolic blood pressure was significantly higher in patients with obstructive sleep apnoea than in the controls. Body fat distribution was not different between the groups, minimising the possibility that upper versus central body fat distribution played a role in determining differences in blood pressure.

Where do these observational studies leave us with regard to the relationship between obstructive sleep apnoea and chronic systemic hypertension? I believe that they irrefutably show the association, independent of obesity, and challenge us to investigate the mechanisms further. Such mechanisms include at least the following: (1) direct effects of episodic hypoxemia and hypercapnia on chemoreceptors and sympathetic activity; (2) resetting of baroreflex function; (3) modification of the cardiovascular system (for example, fluid balance-atrial natriuretic peptide) in response to the intrathoracic pressure fluctuations of obstructed breathing; (4) generalised stress from arousal and disruption of sleep acting upon the sympathetic nervous system; and (5) endothelial cell changes and vascular remodelling in response to the recurrent hypoxia, heightened sympathetic activity, and cyclic blood pressure fluctuations.

Prospective studies examining these mechanisms are few in number because the evolution of chronic hypertension in the setting of sleep apnoea is likely to be very slow, making it difficult to study. Certainly, heightened sympathetic activity plays a part in this early sustained hypertension, whether it results from hypoxia, arousal, or intrathoracic pressure variation. Numerous studies have shown an increase in sympathetic output during acute apnoea[13 14] and in the immediate (20 minute) post-apnoeic period.[15] Sympathetic activity may also be increased by arousal from sleep, and may contribute to the acute sympathetic cardiovascular response to apnoea. Of more importance to dissecting the mechanisms of chronic increased blood pressure is the recent demonstration of raised resting daytime sympathetic activity in patients with chronic apnoea.[16 17]

Chemoreceptors which respond to episodic hypoxia stimulate the sympathetic nervous system. They may undergo adaptation in response to long term hypoxia and hypercarbia, thus altering basal blood pressure. One study has shown that hypertensive apnoea patients show an augmented ventilatory response to brief hyperoxic inactivation of chemoreceptors compared with normotensive apnoea patients.[18] Also, patients with hypertension and sleep apnoea show a greater pressor response to hypoxia than hypertensive patients without apnoea.[19]

Baroreflexes seek to maintain blood pressure at a given level, but may be reset. It is possible that the raised blood pressure seen with each acute apnoea during the night could reset or "desensitise" the baroreflex so that daytime awake pressure is maintained at a slightly higher level. As apnoea patients have been shown to have raised

catecholamine levels as well as increased sympathetic activity, baroreceptor sensitivity may well be impaired. A recent study in dogs, however, suggests that the baroreceptor slope is not reset but is simply shifted to the right.[20] Rightward shift of the baroreflex is often seen in most forms of hypertension and thus may not be specific to apnoea induced increases in blood pressure.

Atrial stretch during the repeated Mueller maneouvres of apnoea in humans may cause a twofold increase in atrial natriuretic peptide which significantly decreases when the apnoea is treated with nasal CPAP. However, increased excretion of atrial natriuretic peptide with increased urine and sodium excretion (as has been shown in patients with apnoea)[21 22] seemingly opposes the development of chronic fluid retention and systemic hypertension in these patients. Plasma renin activity can be extremely difficult to measure accurately in the setting of sleep apnoea, but two studies in humans suggest that plasma renin is not increased, suggesting that the systemic renin-angiotensin system is not upregulated in sleep apnoea.[22 23] There is no information available on local (tissue) renin-angiotensin activity.

A most promising area for future research regarding a link between long term recurrent apnoea-hypoxaemia and systemic hypertension is the cellular effect of hypoxia, especially upon the vascular endothelial cell. New studies are published nearly every week about the effects of hyperoxia, hypoxia, and oxygen free radicals on endothelial and vascular smooth muscle cells, which can directly and indirectly alter hormones, enzymes, and growth factors that affect vascular remodelling, reactivity and tone in resistance vessels. One important example is the interaction between the superoxide anion and nitric oxide. Because the superoxide anion and nitric oxide are both free radicals, they undergo extremely rapid diffusion-limited radical/radical reaction which markedly alters biological availability of nitric oxide for many cell functions.[24 25] For example, a major product of this reaction is peroxynitrite anion ($OONO^-$) which is only a weak vasodilator compared with $NO^{\cdot}$, markedly impairing vasodilator function. In normal vessels the balance between superoxide anion and nitric oxide favours net production of nitric oxide, permitting a basal state of vasorelaxation and normal blood pressure. Disease states such as atherosclerosis, hypertension, and diabetes may alter this balance.

Although purely conjectural, another disease state that might alter this balance by creating excess oxygen free radicals is the cyclic episodic hypoxia of sleep apnoea, analogous to induction of reactive oxygen species in hypoxia-reperfusion injury. One group has shown that acetylcholine (nitric oxide dependent) as well as nitroprusside (non-nitric oxide dependent) induced vasodilation is impaired in hypertensive sleep apnoea patients.[26] Another group has demonstrated an impaired venodilator response to bradykinin (non-nitric oxide dependent) in awake, normotensive patients with obstructive sleep apnoea which normalised after 60 days of nasal CPAP treatment.[27] These preliminary data indicate that there are abnormalities of endothelial cell function in patients with obstructive sleep apnoea which are unrelated to obesity and are potentially correctable with effective apnoea treatment.

In summary, the search for a connection between obstructive sleep apnoea and hypertension continues. The Wisconsin Cohort, the Sleep Heart Health Study, and the findings of Davies *et al* and Lavie *et al*, while not surprising, add to the long line of epidemiological studies which show that recurrent apnoeas lead to systemic hypertension, independent of obesity. Hopefully, these most recent findings will put the final nail in the coffin of the myth that hypertension in obstructive sleep is only related to obesity. It is likely that raised blood pressure in many obese patients with sleep apnoea has several aetiologies and that work up and treatment must be adjusted appropriately. It is hoped that further research in this area of sleep medicine will move on to mechanisms involved in the relationship between apnoea and hypertension.

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