Thorax

Editorials

Journal Impact Factors for 1999

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The Journal Impact Factors for 1999 have recently been released[1] and indicate that *Thorax* has again increased its impact factor, from 2.861 in 1998 to 3.437 in 1999. *Thorax* has thus further consolidated its position as the highest ranking specialist respiratory journal after the two American Thoracic Society publications. The position of *Thorax* in terms of impact factor relative to other selected specialist journals of similar or complementary interest is shown in the table. We are pleased to see this continued improvement in the international status of the journal, and thank all who have helped to achieve it.

American Journal of Respiratory and Critical Care Medicine	5.491
American Journal of Respiratory Cell and Molecular Biology	4.541
Thorax	**3.437**
American Journal of Physiology—Lung Cellular and Molecular Physiology	3.147
Journal of Thoracic and Cardiovascular Surgery	2.986
Clinical and Experimental Allergy	2.702
Journal of Heart and Lung Transplantation	2.438
Chest	2.410
European Respiratory Journal	2.334

The ultimate determinant of the impact factor of the journal is the standard of the papers submitted to us. Thank you to all who have sent us their work. Please send us more!

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Executive Editors

1 Institute for Scientific Information Journal Citation Reports 1999. http://jcrweb.com

Thorax 2000;**55**:725–726

Malignant mesothelioma: predictors of prognosis and clinical trials

J P C Steele, R M Rudd

The incidence of malignant mesothelioma is increasing in the UK and continental Europe.[1] In 1995 Peto *et al* predicted a progressive rise in the number of new cases recorded until the year 2020.[2] Specialist units are seeing more patients than ever and some general practitioners are seeing patients with mesothelioma for the first time. Effective treatment remains elusive. Radical surgery is rarely performed in the UK. The reasons for this are unclear but probably relate to the lack of randomised data to support its use and a perception that the mortality and morbidity of the preferred operation (extrapleural pneumonectomy) is excessive. Radiotherapy can be useful for relief of pain and shrinkage of chest wall masses[3] but there is no evidence that it improves survival. Chemotherapy, however, is showing some promise: three recent phase II trials have reported tumour response rates exceeding 20% and in each of these studies symptoms were improved by treatment.[4–6] In view of these encouraging data it is now an appropriate time to perform randomised clinical trials for patients with malignant mesothelioma. To increase confidence that treatment effects are real, clinical trials should stratify patients according to prognostic group.

There is no single accepted way in which to stage or predict prognosis for mesothelioma patients. The simple Butchart staging system has been widely used in the UK.[7] Several systems based on TNM staging have been proposed but have been largely superseded by a new staging system proposed by the International Mesothelioma Interest Group (IMIG).[8] The IMIG system has the advantage that resectable disease is described in a practical and more detailed fashion. A similar system has been described by Sugarbaker *et al*[9] and is known as the Brigham staging. The disadvantage of these latter two systems is that full staging information—for example, about resection margin and lymph node involvement—can only be obtained after pleural debulking surgery, either by total pleurectomy or extrapleural pneumonectomy, with lymph node sampling. This limits the usefulness of the systems, particularly in the UK where these operations are rarely performed. Computed tomography with magnetic resonance imaging in selected cases often allows a fair approximation of clinical stage and PET scanning may prove to be of additional value. Detailed staging by imaging is certainly required for identification of patients who may be suitable for multimodality therapy (radical surgery followed by chemotherapy and/or radiotherapy). However, prognostic scoring systems are the most readily available and practical method for assessing prognosis for most patients and may be valuable in stratification for clinical trials.

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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Thorax 2000;**55**:726–728

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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Smoking, lung function, and mortality

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In this issue of *Thorax* Pelkonen *et al*[1] make another contribution to the substantial body of literature relating smoking habit, lung function, and long term mortality. In this paper the effects of smoking cessation are emphasised, describing 30 years of follow up of a Finnish cohort recruited in 1959 for the Seven Countries study of coronary artery disease. It is somewhat unusual in that the study enrolled essentially all the age eligible (40–59 years) men in two localities and had extremely high rates of follow up. Lung function was measured at baseline, as were other risk factors for coronary disease such as smoking habit, blood pressure, cholesterol, and body mass index. About half of the 1600 men were smoking on entry to the study and about 37% of them quit during follow up. Baseline lung function was reasonable, with two thirds of the men having forced expiratory volume in one second in 0.75 of a second ($FEV_{0.75}$) of more than 88% of predicted normal. One third, the lowest tertile, had values below this, and presumably some were in the range of clinical obstructive disease.

Lung function predicted overall mortality after adjustment for coronary risk factors; men in the lowest tertile of lung function were significantly more likely to die than the rest, and men in the middle tertile with expiratory flows of 88–102% of predicted had a slightly higher death rate than those with better lung function. The fact that poor lung function predicts mortality has been well known for decades[2]; reduced lung function predicts death due to lung cancer, chronic obstructive pulmonary disease (COPD), and cardiovascular disease, particularly coronary artery disease. The mechanisms involved probably differ. Poor lung function—that is, reduction in expiratory flow rates—is virtually synonymous with COPD so that an association of the former with death from the latter amounts to tautology. Lung cancer has been shown repeatedly to be more common in smokers with airways obstruction than without, and the lung function effect persists after statistical consideration of the smoking habit.[3 4] On the other hand, lung function appears not to predict lung cancer in non-smokers,[5] although lung cancer in non-smokers is uncommon enough to make this kind of estimation tricky. Nevertheless it appears that, for lung cancer, the level of lung function reflects either host factors that influence cancer development in response to smoking or a particularly sensitive measure of smoking exposure. The mechanism of the lung function effect in cardiovascular mortality is even more mysterious. It appears not to be closely related to smoking in that lung function predicts cardiovascular death in non-smokers.[6] One explanation—that lung function causes cardiovascular disease by virtue of causing hypoxaemia—does not seem credible as the effect is evident at levels of lung function not associated with abnormalities of pulmonary gas exchange. There is an interesting unsolved problem here.

Pelkonen *et al* found that smoking cessation improved mortality and that this effect was not confined to men with the worst lung function at study entry. The decrease in all cause mortality was largely the result of a decrease in deaths from cardiovascular disease. A prompt decline in cardiovascular mortality and morbidity, significant within five years or less after smoking cessation, has been observed before.[7] The best estimates are that, after cessation, mortality from coronary artery disease and stroke approach those of lifetime non-smokers in some 15 years.[8] This probably relates to reductions in thromboses and in the progression of atherosclerosis, which should have nothing to do with lung function, so it is not surprising that the benefit of smoking cessation was evident at all levels of airways obstruction. However, there was some evidence to suggest a positive interaction between smoking cessation and lung function in that those with the worst lung function appeared to benefit the most. If this is true, its cause is not apparent and it re-emphasises the fact that we do not understand why poor lung function predisposes to cardiovascular disease.

Pelkonen *et al* did not observe significant decreases in mortality from lung cancer or respiratory disease after smoking cessation. This failure is consistent with other data. While there is good evidence that the incidence of lung cancer decreases after smoking cessation, it has been derived from very large cohorts studied for a very long time.[9] After cessation the incidence of lung cancer does not begin to decline for some five years and then falls gradually, not stabilising until 20 years after cessation. Even then, ex-smokers have a roughly twofold increase in lung cancer mortality compared with lifetime non-smokers.[8] The men studied by Pelkonen *et al* had been followed for 20 years after smoking cessation and lung cancer mortality in those who quit was 62% of the rate in those who did not, which is consistent with these results but not statistically significant because of the relatively small size of the Finnish cohort. The smoking induced tissue damage that produces lung cancer is not easily or quickly reversed by cessation. This probably accounts for the finding of an insignificant negative interdependence between cessation and lung function in lung cancer; those who quit with low levels of lung function were less likely to avoid lung cancer than those with better lung function.

The effects of smoking cessation in COPD have been well studied. Smoking cessation results in a very small improvement in lung function which is probably clinically insignificant. The chief benefit of cessation is that it reduces the subsequent rate of decline in lung function, at least in people with mild or moderate airways obstruction. In such individuals, who have largely preclinical disease, the benefits of cessation are clear and almost certainly lifesaving[10]; these people simply will not get symptomatic COPD. However, in patients with established symptomatic COPD the situation is less clear. Many severely ill patients with COPD spontaneously quit smoking, probably in response to their symptoms and disability, and it is hardly surprising that these patients do not do well afterwards. For this reason studies of patients with well established disease have often not shown a reduction in mortality with smoking cessation.[11 12] As the authors indicate, this probably explains their finding that deaths from respiratory diseases were more common in those who quit than in those who continued to smoke.

For the clinician the message of the Finnish paper is clear and, one hopes, consonant with routine practice. Stopping smoking is always a good thing. The 37% spontaneous quit rate observed in the cohort of Pelkonen *et al* may be

regarded as a background phenomenon; this is what middle aged Finnish men did in response to a non-smoking climate. It is our job to improve on this.

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