Ten more years of CPAP: tribulations and trials

In 1997, 16 years after Sullivan’s original publication [1] on the application of continuous positive airway pressure (CPAP) in obstructive sleep apnoea, a report [2] in the British Medical Journal from the National Health Service Centre for Reviews Dissemination (University of York, UK) argued the following:

- Obstructive sleep apnoea (OSA) is claimed to be an important cause of premature death and disability.
- There is increasing pressure to provide sleep services for the treatment of patients with sleep apnoea.
- Epidemiological evidence suggests that sleep apnoea causes daytime sleepiness and possibly vehicle accidents.
- Evidence of a causal association between sleep apnoea and other adverse health outcomes is weak.
- There is a paucity of robust evidence for the clinical and cost-effectiveness of CPAP in the treatment of most patients with sleep apnoea.

The authors concluded that “the relevance of sleep apnoea to public health has been exaggerated”.

Several consequences flowed from this report. It was used by some healthcare providers to curtail sleep services and make it impossible in some regions in the UK to provide CPAP therapy. In countries where health technology reviews came to the opposite conclusion (e.g. Australia), there was no such impact on the development of sleep services. Trends in provision of sleep studies and CPAP for OSA across Europe in the past decade are difficult to discern accurately and are affected by healthcare funding systems, but where there is comprehensive data capture (e.g. in France) rapid and consistent growth in CPAP provision has been seen from 1992 to the present. Subsequent surveys have shown large disparities in CPAP provision within countries, and more widely [3]. Lack of awareness of the problem and poor education also play a part.

To pile on the irony, the majority of CPAP provision has always been based on the presence of troublesome sleepiness, not on cardiovascular outcome considerations. Respiratory physicians were castigated for not working harder at encouraging weight loss in patients before starting CPAP [2], yet even a 6-month delay in providing CPAP deprives individuals with severe OSA of a significant improvement in sleepiness and quality of life [4]. Cognitive and health costs did not differ between a group provided with CPAP immediately compared with those in whom polysomnography diagnosis was delayed by 6 months, in a French randomised trial [4], although the authors reported that incremental cost-effectiveness may also improve in those treated immediately.

So what have we learned over the past decade? First, early debate on the effectiveness of CPAP at controlling sleepiness in moderate and severe OSA has been settled by a series of randomised trials [5, 6], some of which were already in train in the mid-1990s; furthermore, CPAP leads to an improvement in health-related quality of life. Two large US longitudinal studies, the Wisconsin Sleep cohort and the Sleep Heart Health Study, have produced important prevalence and associated outcome data. In the Wisconsin cohort, there was an association between untreated OSA and new-onset hypertension, even in individuals with mild OSA. In the Sleep Heart Health cohort, there was an increased risk of insulin resistance even after controlling for body mass index and visceral obesity. The latter study has also shown an association between OSA, stroke and myocardial infarction. Plainly, a causative role for OSA cannot be inferred from cross-sectional, non-interventional studies and interpretation is always confounded.
by the fact that obesity is a risk factor not only for OSA but also for cardiovascular disease. To clarify matters, in the past year three European publications have summarised the current state of play – Professor W. McNicholas and colleagues [7] from the European Scientific and Technical research COST action on obstructive sleep apnoea syndrome have provided an analysis of sleep apnoea as an independent risk factor for cardiovascular disease; and the European Respiratory Review on Respiratory Somnology [8] has provided an international update for clinicians across the whole field of respiratory sleep disorders. In addition, the National Institute of Health and Clinical Excellence (NICE) in the UK has just produced a Health Technology Appraisal of CPAP in obstructive sleep apnoea-hypopnoea syndrome in the form of a systematic review and economic analysis [9]. This is due to be published at the end of March 2008, but a representative Final Appraisal Determination is available on the NICE website (www.nice.org.uk).

The NICE report confirms unequivocally that:
- CPAP is effective treatment for OSA compared with conservative/usual care in populations with moderate-to-severe daytime sleepiness and that there may be benefits when the disease is mild; and
- the incremental cost per quality adjusted life year (QALY) gained of CPAP is <€28,000 and there was a high probability of CPAP being more cost-effective than dental devices and conservative management for a cost-effectiveness threshold of €28,000 per QALY gained.

What remains

It should be noted that the NICE health technology appraisal considered only the health consequences of road traffic accidents and did not take into account full costs to society. Dental devices were considered to be a treatment option in moderate disease, but the difficulty for practitioners in interpreting this advice is that a variety of devices was used. These devices have evolved and will continue to develop over time, making it problematic to predict efficacy on an individual basis. Similarly, although the process of delivery of care should not be confused with the efficacy of the therapy itself, in practice, care pathways matter as these inevitably contribute to overall health costs. Ideal follow-up of the increasing numbers of patients on CPAP is unclear. How often should CPAP users be seen? Can telephone consultations and smartcard downloads substitute satisfactorily for clinic visits? The importance of these pragmatic simplifications to care have not been lost on the US system, where the Centers for Medicare and Medicaid have recently begun to consider expanding provision of CPAP to patients diagnosed by unattended home monitoring. Which brings us to the impact of manufacturers. Credit is due as huge strides have been made by manufacturers in improving equipment portability and mask design, while smartcard downloads and compliance reports have helped us understand how patients use (or fail to comply with) therapy. On the other hand, autotitrating CPAP devices have been promoted strongly despite the fact that there is little evidence to suggest that they are superior to fixed-level CPAP other than for particular subgroups, and it is difficult for the clinician to understand the intricacies of the underlying algorithms. There may, however, be a role for these devices in first-line ambulatory management of cases with a high probability of CPAP, when compared to polysomnography and manual titration of CPAP in the sleep laboratory [10].

And while we are in murky waters, what physician does not sit in the clinic and see patients with significant co-pathology that is likely to impact on decisionmaking? These cases are unlikely to appear in metaanalyses, e.g. the chronic obstructive pulmonary disease patient with baseline hypoxaemia and OSA; the elderly patient with recent transient ischaemic attacks, poor memory and mild OSA; or the obese female patient with mild obstructive hypoventilation who is due to undergo hip replacement. At best,
when considering treatment one juggles the evidence available, the best interests of the patient and the cost and the risk of not treating. Such subtleties may be lost on health care planners.

**Something lost and something gained**

Paradoxically, over the long term the York review [2] cited at the beginning of this article has acted as a stimulus to high-quality research and respiratory support (CPAP and noninvasive ventilation) is now one of the most evidence-based areas of respiratory medicine.

So, what are the current research priorities? The report from the European COST action [7] outlines possible trials in three areas: cellular and molecular; animal studies; and human cohort studies. For the latter, large studies with carefully defined cohorts are required to explore the interactions of OSA, diabetes and hyperlipidaemia in the genesis of cardiovascular disease. CPAP interventional trials hitherto have tended not to be short-term and ethically patients with symptomatic moderate or severe sleep apnoea cannot be deprived of CPAP. However, asymptomatic patients with mild-to-moderate OSA can reasonably be randomised to CPAP or control groups [11] and trials such as the well-designed Oxford Mosaic study will evaluate the impact of CPAP on cardiovascular risk (Framingham index), 

|HbA1c, obesity, blood pressure, cardiovascular events, health status and health service utilisation in this group.|

There are important question marks over the impact of sleep apnoea, and the effects of CPAP, in the elderly. Sleep-disordered breathing appears more common in older individuals, but what are the cognitive effects, and are these reversible with CPAP? Similarly, in children, the long-term consequences of sleep-disordered breathing are not clear. As McNICHOLAS et al. [7] point out, the prevalence of obesity, metabolic syndrome and type 2 diabetes in children is rising and this may be a productive group to investigate as confounders associated with OSA in adults may be absent.

Finally, sleep-disordered breathing, predominantly central in nature, has been shown to occur in >50% of patients with mild-to-moderate heart failure [12, 13]. While the evidence for treating OSA in heart failure patients is relatively secure [14], the CANPAP study of CPAP in heart failure patients with central sleep apnoea did not produce survival benefit [15]. There is little gain in screening heart failure patients for sleep-disordered breathing if no effective treatment is available, not least as this patient group does not appear to be sleepy like typical OSA patients. However, modified approaches such as servo ventilation might be a way forward and a large multicentre randomised trial (SERVE-HF) of adaptive servo ventilation in predominant central sleep-disordered breathing is now recruiting. Plenty then to keep the respiratory sleep community busy for the next decade.

### References