Never too old: beneficial neurobehavioural effects of continuous positive airway pressure in the elderly

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Clinicians should be no less aggressive in treating OSA in the elderly compared with middle-aged and younger groups <http://ow.ly/MGC4n>

This month's issue of the *European Respiratory Journal* contains a report of a randomised controlled clinical trial for the treatment of obstructive sleep apnoea (OSA) using continuous positive airway pressure (CPAP) [1]. What makes this trial unique and distinguishes it from dozens of other such studies in the published literature is that all of the participants were elderly (≥ 70 years of age).

Sleep disordered breathing in the elderly has long been thought to be different, both mechanistically, in terms of predisposing pathophysiology, and functionally, in terms of its consequences, when compared with the sleep apnoea of middle age. The origin of this perspective may hark back to the very old retrospective study of OSA patients by HE *et al.* [2], which showed that, relative to those untreated, individuals who underwent tracheostomy or other surgical treatments for sleep apnoea (including 25 cases using the at-the-time novel treatment of CPAP) showed clear benefits for survival only if younger than 50 years of age. Several years after that study, LAVIE *et al.* [3], also reporting retrospectively on a sleep clinic population, noted that older patients with sleep apnoea had lower mortality rates than middle-aged patients with the condition, an observation later incorporated into the ischaemic preconditioning hypothesis [4] (discussed later in this editorial). Since that time, a large number of descriptive epidemiological studies, many derived from the Sleep Heart Health Study, repeatedly showed that the effect sizes for adverse cardiovascular outcomes and mortality associated with sleep apnoea were diminished in magnitude with increasing chronological age [5–8].

There is now good evidence that the mechanisms of upper airway collapse may indeed differ among the elderly [9]; however, the outcomes side of the equation has remained very much in doubt. Specifically in older populations, composite indices of cardiovascular disease [10], clinically defined hypertension [11], a nocturnal non-dipping blood pressure pattern [12], cerebrovascular events [13], reduced renal clearance [14] and poorer physical function [15] have all been associated with sleep disordered breathing (see [16] for a more complete review). These findings continue to reinforce the notion that age-dependent (compared with age-related [17, 18]) sleep disordered breathing may have just as many morbidities associated with it in old age as in younger and middle-aged populations, although they may also be somewhat different and more specifically problematic for the aged population (*e.g.* frailty [19], nocturia [20] or impaired cognition [21, 22]). Given this situation, it certainly would seem that clinical trials of treatments for sleep apnoea should focus on such individuals.

The current study is one of the few recent randomised trials (see also [23]) devoted specifically to treatment of OSA in aged patients. This is not to deny that many recent, well-performed clinical trials for OSA have included some elderly persons. For example, a recent trial comparing nocturnal supplementary

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oxygen *versus* CPAP included at least some patients over the age of 65 years (mean 63 years, range 45–75 years) [24]. Other studies have examined OSA treatment in elderly patients subsequent to stroke, findings which have often shown contradictory results [25–27]. A previous, relatively large observational study from the researchers of the current study comparing mortality rates in older individuals with OSA using CPAP *versus* those not using CPAP demonstrated significantly lower cardiovascular mortality associated with use of CPAP [28], but that study, although described as prospective, was not randomised. Only very recently have randomised trials (e.g. the PREDICT trial) suggested a benefit of CPAP use in elderly patients with sleep apnoea on healthcare costs and daytime sleepiness [23]. The current study by MARTÍNEZ-GARCÍA *et al.* [1] essentially expands these findings by demonstrating that a large array of quality of life, behavioural and cognitive measures showed improvement with CPAP use, and the magnitude of these effects could be quite substantial in older persons.

And how do these results jibe with ischaemic preconditioning? The concept of hormesis is important for geriatrics, since it contends that physiological stressors (such as sleep apnoea) might confer protective benefits for the organism. In the case of sleep apnoea, upregulation of vascularly mediated gene products affecting angiogenesis have been shown in both animal models and humans [4]. However, unless one assumes that the original hypothesis [4] was intended only to refer to the myocardium and systemic (as opposed to cerebral) vasculature, the results of the current [1] and other recent [23] clinical trials would imply that very real, but potentially reversible, deficits in neurobehavioural function occur in older adults with OSA. This might call into question some evidence for ischaemic preconditioning, at least as it applies to OSA in the elderly. The linchpin study supporting the hypothesis showed that untreated sleep apnoea conferred benefit (*i.e.* actual survival advantage) in older patients [29]. That study compared standardised mortality ratios (SMRs) between an Israeli sleep clinic population with OSA and the general Israeli population matched for age, sex and ethnicity. SMRs were lower among older OSA patients. Overlooked in these data were the body mass index (BMI) values of the elderly OSA patients studied (means 30–31 kg·m⁻²; these levels of obesity were comparable to BMIs in the current [1] and other newer [23] trials). Unlike what is seen in middle-aged subjects, moderate levels of BMI in elderly persons may not always portend adverse health outcomes [30]. Modestly high levels of BMI (30–32 kg·m⁻²) in the aged have been shown to be *protective* for some diseases and are associated with *lower* mortality rates [31, 32], and these findings have extended to even higher levels of BMI in elderly nonsmokers [33]. Of note is that the BMIs reported by LAVIE *et al.* [29] for their aged patients were greater than five standard errors higher than those from a population from the USA of comparable age and sex, regardless of ethnicity, sampled in the National Health and Nutrition Examination Survey (NHANES) III from 1999–2002 [34], although, interestingly, such values were also comparable to the BMIs of both the overall Arab and Jewish Israeli populations in that age range over the period of 1999–2000 [35]. The apparent survival advantage of sleep apnoea in overweight elderly populations may be a proxy for robust nutritional reserves, which can contribute to survivorship in old age [36]. A corollary of this is that mortality may be a misleading end-point when discussing outcomes of sleep apnoea in the aged.

In summary, the take-home message from the valuable clinical trial of MARTÍNEZ-GARCÍA *et al.* [1] is that clinicians should be no less (or more) aggressive in treating OSA in the elderly compared with middle-aged and younger groups. From the perspective of usage, age appears most assuredly not to be a risk for lower adherence to CPAP [37] and some evidence suggests that elderly persons may demonstrate enhanced adherence to CPAP [38]. Undoubtedly, implementing CPAP in the elderly may have its own particular challenges, particularly for mild [39, 40] or advanced dementia [41, 42], but providing care for millions of aged patients with sleep apnoea who may be ready and willing to accept treatment cannot and should not be dismissed outright either on a theoretical or an empirical basis.

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