Sleep apnoea and risk of post-operative infection: beyond cardiovascular impact

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Recent decades have seen the publication of numerous studies on the association between excessive sleep disordered breathing (SDB), particularly sleep apnoea, and an increase in cardiovascular morbidity and mortality. These studies have used a wide range of methodologies and criteria for patient inclusion. The results have been diverse, depending on the type of cardiovascular event or risk factor investigated, the patients' cardiovascular risk, the severity or type of the SDB, and the analysis of the primary and secondary prevention of cardiovascular events [1].

Sleep apnoea is a disease capable of activating (mainly *via* intermittent hypoxaemia and sleep fragmentation and their consequences) several pathophysiological mechanisms not exclusive to cardiovascular disease, such as sympathetic hyperactivity, pro-inflammatory state, hypercoagulability, oxidative stress, endothelial dysfunction and immune dysfunction [1]. It therefore seems logical to suppose that excessive SDB could also be associated with the incidence, severity and prognosis of other noncardiovascular diseases, even in patients with a high cardiovascular risk. Along these lines, some studies in recent years have examined the association between sleep apnoea and other less investigated diseases, such as autoimmune diseases [2], cancer [3] and various infectious diseases [4].

In the current issue of the *European Respiratory Journal*, Rupprecht *et al.* [5] publish the results of a study that examined a group of patients with high cardiovascular risk who had recently undergone elective coronary bypass graft surgery (CABG), to analyse the impact of pre-operative excessive SDB on parameters, such as the incidence of respiratory infections and complications, which are not exclusively cardiovascular but are extremely important in the immediate post-operative period. Although the study's main outcome (a broad composite of variables associated with post-operative mortality and a range of post-operative complications) showed no discrepancy between the group with excessive SDB and the group with a normal or near-normal SDB, this was not true of the incidence of sepsis and pneumonia, which were higher, particularly in the untreated forms of moderate to severe sleep apnoea. This association between sleep apnoea and various infections, already demonstrated by other previous studies [4, 6, 7], emphasises the importance of moving beyond an exclusive focus on the analysis of the cardiovascular impact of sleep apnoea (even in patients with a high cardiovascular risk, as in the study in question) and exploring other possibilities in which SDB could have potentially preventable or treatable consequences.

There is a sufficiently plausible biological explanation for an increase in the number of post-operative infectious complications in patients with sleep apnoea. The coordination between respiration and swallowing

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as a defence mechanism against aspiration is impaired during sleep, even in healthy adult individuals [8]. Furthermore, some studies have shown that sleep apnoea is associated with an increased risk of silent aspiration, due to changes in intra-thoracic pressure during apnoea or gastroesophageal reflux disease, and due to a weak or nonexistent cough reflex during REM sleep [9, 10]. All these mechanisms may not only intensify the passage of potentially pathogenic microorganisms towards the lower airways but also enhance their growth, with the subsequent appearance of pneumonia, particularly in post-operative and hospitalised patients.

Moreover, sleep apnoea has been associated with a low degree of systemic inflammation and an increased concentration of various pro-inflammatory molecules such as tumour necrosis factor-α, C-reactive protein, interleukin (IL)-1b, IL-6, IL-8 and IL-17, and adhesion molecules. This, combined with impairment to immunity (caused by sleep arousals and impaired neutrophil and macrophage function due to hypercapnia), could lead to poor progression of sepsis [11, 12]. The aforementioned increase in the concentration of IL-17 (mainly due to T-helper type 17 lymphocytes) and the activation of the sympathetic system, which are both associated with SA [1, 11], seem to have acquired a particular pathophysiological relevance in recent years in connection with the origin and prolongation of sepsis [12], and they could both be interesting targets for future research. Finally, the normal inflammatory response to acute infections follows a robust circadian pattern. Disruption of normal circadian rhythm at the molecular level affects the severity of inflammation in sepsis, contributing to inflammatory response and affecting the duration of obstructive sleep apnoeas and an increase in mortality from sepsis [13].

One of the most intriguing aspects of the study, however, is the authors' suggestion that the risk of pneumonia or sepsis is more than doubled in patients with a predominance of central, rather than obstructive, respiratory events. There seems to be no easy explanation for this finding. Central events, like their obstructive counterparts, have been shown to cause intermittent hypoxaemia and sleep fragmentation, but there has been no clear evidence to date supporting any greater impact from central (as opposed to obstructive) events on these pathophysiological routes. It is also true, however, that some studies have suggested that central events can produce a poorer vital prognosis in community-dwelling elderly people [14] and in patients with underlying cardiovascular disease (heart failure or acute ischaemic heart disease) [15, 16]. One other possibility is that some of these central events could be linked to the administration of certain narcotic analgesics or sedative drugs, which can increase the probability of micro-aspirations [17], or it could be that many of these events are in fact obstructive, as in the case of very obese patients with reduced impedance resulting from a severe alteration to thoracic and pulmonary compliance that is aggravated in a supine position. In any case, it is important to take into account that this was not the main objective of the study but rather a *post hoc* analysis, which weakens the results in this respect as there was no calculation of the sample size required to obtain the necessary statistical power. Lastly, the authors did not provide any data on the validation of the device used to diagnose central respiratory events.

Another question of great clinical interest is whether treatment with continuous positive airway pressure (CPAP) in the subgroup of patients with excessive SDB prior to surgery (in this case CABG) would help protect them against post-operative infections, as posited by the authors of the present study (although they did not carry out such analysis) [5]. Although it is true that CPAP has been shown to decrease some systemic inflammatory markers [18] and could be an effective treatment in the perioperative period [19], its protective capacity is likely to be less than expected if the results of Rupprecht *et al.* [5] are confirmed. This is because, on the one hand, the significant number of patients with central SA would theoretically limit the action of CPAP (an evaluation of the effect of adaptive servoventilation in this subgroup of patients would be an interesting research topic), while on the other hand, as has already been made evident by other studies, CPAP or noninvasive ventilation treatments in patients under sedation with a higher risk of infections (*i.e.* post-operative or hospitalised) may be more susceptible to adverse effects, particularly reduction of sputum expectoration and subsequent increase in the chance of pulmonary aspiration or upper airway infection [20–22]. Moreover, the addition of a humidifier also provides a potential source of bacterial contamination, which could trigger pneumonia. Further studies are therefore needed before we can confirm a positive effect of CPAP or noninvasive ventilation for these patients.

All this means that studies such as the one reported by Rupprecht *et al.* [5] cannot be considered definitive, although they do highlight the need to identify patients susceptible to obstructive sleep apnoea in the pre-operative period, as well as providing interesting working hypotheses that allow us to broaden our vision of the possible impact of sleep apnoea on clinically relevant outcomes beyond the cardiovascular sphere, even in patients with a high cardiovascular risk. There is an obvious need for sufficiently large-scale multicentre studies to assess the impact of sleep apnoea and CPAP treatment on a specific outcome of clinical interest, thereby avoiding the use of composites made up of variables with different origin, clinical relevance and management, which would probably not have an analogous relationship with sleep apnoea as they would activate very different pathophysiological routes.

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