May continuous positive airway pressure (CPAP) treatment be detrimental in obstructive sleep apnea?

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In the last few years, several common beliefs on obstructive sleep apnea (OSA) have been challenged by new data. Recognition of different pathophysiological features of OSA has changed the attitude towards alternative treatments targeted to correct specific functional abnormalities.[1] Such treatments may be more acceptable for patients compared to life-long continuous positive airway pressure (CPAP) treatment. Similarly, the diagnostic criteria for OSA have been critically reviewed, since the apnea hypopnea index (AHI) is a poor marker of OSA severity. New markers, such as OSA-associated hypoxic burden[2] or autonomic responses,[3] were shown to predict prognosis better than AHI.

Cardiovascular risk is an important issue in the management of OSA patients, since OSA is associated with increased cardiovascular mortality. CPAP treatment would reduce this risk by correcting the hypoxic burden and sleep fragmentation. However, randomized controlled trials failed to prove that positive airway pressure (PAP) therapy reduces cardiovascular risk in non-sleepy patients with coronary artery disease (CAD). Rather, the recently identified markers of OSA severity do allow to distinguish subgroups of patients in which CPAP treatment may be effective, as opposed to subgroups in which prognosis is unaffected by CPAP.

The role of biological mechanisms in the complex effects of OSA and CPAP treatment on cardiovascular risk has been insufficiently explored to date, and that CPAP may exert pro-inflammatory effects represents the most recent challenge in field of the OSA. In this issue, Peker and coworkers hypothesized that in non-sleepy patients with revascularized CAD and OSA from the Randomized Intervention with CPAP in CAD and OSA (RICCADSA) randomized clinical trial, CPAP treatment could exert a proinflammatory effect, thus counteracting possible beneficial effects of OSA treatment on cardiovascular risk.[4] In plasma samples collected in patients from the RICCADSA study, they examined the time course of Vascular Endothelial Growth Factor A (VEGF-A) and Angiopoietin-2 (Ang-2), a proangiogenic factor which amplifies endothelial inflammation and disturbs junctional integrity, in relation to occurrence of cardiovascular events during follow-up.

In patients without OSA and in the standard-care arm of the study, Ang-2 levels decreased over 12 months after revascularization, while levels of VEGF-A increased. Conversely, in the group treated with CPAP, Ang-2 levels remained elevated, and VEGF-A levels were low. Interestingly, patients treated with median CPAP levels >7 cmH_2O showed worse cardiovascular outcomes, compared to patients treated with lower therapeutic pressures. The proposed explanation is that CPAP pressure, by increasing functional residual capacity by over a liter per 10 cmH_2O, could perpetuate inflammation by increasing lung volume and alveolar distension, with a mechanism similar to that seen in ventilator-induced lung injury.[4]

These results confirm previous results from the same group showing increased circulating levels of Ang-2 in OSA patients compared to controls.[5] Moreover, elevated Ang-2 levels were found in patients with moderate-severe OSA after 3–6 months of CPAP treatment.[6] A clinically important finding was that statin treatment blunted the increase in the levels of markers of endothelial damage in CPAP-treated OSA patients.[7]

The study by Peker and coworkers opens new perspectives for future clinical and basic research, for example on whether pulmonary stretch or the applied pressure causes endothelial inflammation. From the clinical point of view, PAP treatment is used not only for OSA but also in patients with chronic respiratory failure treated with home noninvasive ventilation (NIV). Safety of PAP treatment should be verified in patients with chronic obstructive pulmonary disease who are known to be at increased cardiovascular risk.[8] Cancer patient with OSA may represent another population at potential risk, since PAP treatment may have, besides palliative effects with major impact on quality of life, positive effects on cancer progression, as suggested by recent studies on CPAP treatment in patients with melanoma.[9] The Ang-2 level is often elevated in cancer patients and correlates with poor prognosis.[10] Therefore, it will be crucial to obtain additional data on the potentially detrimental effects of PAP treatment, by confirming the current data in OSA patients, and by extending the studies to patients on home NIV. The protective effect of statins also deserves attention in future studies.

In summary, the study on potentially negative effects of CPAP on cardiovascular risk opens the way to

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new challenges in the respiratory field, given the widespread use of PAP treatment. Based on the new findings, it is wise to be cautious with using high therapeutic pressures.

Contributors

Conceptualisation AC and MRB; writing—original draft AC; and writing—review & editing MRB.

Declaration of interests

MRB is on the advisory board of Bioprojet.

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