Editorial

The ANDANTE Project: A Worldwide Individual Data Meta-Analysis of the Effect of Sleep Apnea Treatment on Blood Pressure

El proyecto ANDANTE: un metanálisis a nivel mundial de datos individuales sobre el efecto del tratamiento de la apnea del sueño en la presión arterial

Obstructive sleep apnea (OSA) is the most prevalent type of sleep-disordered breathing which has increasingly caused multiple health problems, particularly in the last decades due to the worsening of the obesity epidemic.[1] OSA has repeatedly been associated with a number of cardiovascular conditions and is thus considered a potential risk factor for cardiovascular disease.[2] Furthermore, treatment with continuous positive airway pressure (CPAP) has been shown to reduce cardiovascular disease burden in large observational studies.[3]

Nevertheless, a recent randomised controlled trial (RCT) failed to demonstrate that treatment of OSA, by means of continuous positive airway pressure (CPAP), is associated with a reduction of cardiovascular events and mortality.[4]

These results were somehow unexpected, as CPAP is known to mitigate sympathetic activation caused by OSA, and to reduce, not only awake blood pressure (BP), but also the BP swings due to the intermittent apneic and hypopneic cycles, one of the hallmarks of the disease.[5,6]

A number of possible explanations for this finding have been proposed.

Adherence to CPAP is often suboptimal in RCTs, as was the case in the largest RCT in the field, where average duration of nightly CPAP usage was 3.3 h.[4] This is below what is commonly considered to be the minimum average daily usage that favours a beneficial treatment effect and is below the threshold for coverage of PAP devices by many third party payers.[7,8] However, there was no significant effect on cardiovascular events even in the more adherent CPAP users.[4]

In addition to this, CPAP treatment can sometimes disturb the patient's sleep by causing awakenings, particularly if the air pressure titration is not conducted appropriately: studies have shown that excessively high CPAP pressures can not only lead to increased neural respiratory drive and subjective discomfort while awake, but can also cause rises in BP and contribute to increased BP variability.[9,10]

Conversely, setting sub-therapeutic CPAP pressures may fail to abolish apneas and hypopneas, thus leaving the patient undertreated and with residual OSA.

Finally, patient selection may be another limitation, with many RCTs excluding highly symptomatic or sleepy patients who may be more likely to adhere to CPAP. Additionally, patients with excessive daytime sleepiness are more likely to have hypertension, metabolic dysfunction, and cardiovascular morbidity compared to those without.[3]

With regard to the effect of CPAP on cardiovascular outcomes, BP has often been studied as a surrogate marker for cardiovascular risk for several reasons: it is relatively easy to measure, it is cost effective, and it is widely available. Most importantly, in other situations, BP is linearly associated with the risk of cardiovascular events and many studies have shown that OSA treatment results in a modest but significant BP reduction.[11]

All studies looking at the effects of CPAP on BP have shown a large interindividual variation in the response, with some subjects experiencing rises in BP rather than falls. A recent systematic review and meta-analysis on the BP effects of OSA treatment, mostly focusing on CPAP use, showed that some subgroups of patients exhibited a greater BP response to treatment, i.e. those who were younger (aged < 60 years), with uncontrolled BP at baseline and with severe oxygen desaturations were more likely to benefit from treatment.[12] It is important to note that such variables were not available in all RCTs highlighting the need for a thorough patient characterisation prior to initiating OSA treatment.

Such aggregate data meta-analysis can help to detect specific subgroups and phenotypes which respond better to OSA treatment. Data obtained in this manner, however, might suffer from limitations such as publication bias, heterogeneity between the various study designs, model selections, different analysis approaches, and variable categorisations of the original studies.

One way to reduce such limitations is to conduct an individual patient data (IPD) meta-analysis which is considered the "gold standard" for exploring the effectiveness of a given intervention in different patient cohorts.[13]

It was indeed with the aim to run an IPD meta-analysis in patients with OSA that the ANDANTE (effect of treatment for obstructive sleep apnea on blood pressure: an individual patient data meta-analysis) project was conceived and implemented, by building a worldwide collaboration among the principal investigators of most available RCTs on BP effects of OSA treatment (Fig. 1). These researchers were invited to share the individual data of their previously published RCTs in order to merge them in a single

Fig. 1. World map showing ANDANTE centres.

database, thereby allowing for a refined meta-analysis with sensitivity analyses on a large scale, to better understand predictors of BP response in different patient groups.

The primary objective of the ANDANTE collaboration is to confirm the results of our previously published meta-analysis of aggregate data.[12] The secondary objective is to refine the cutoffs for age, BP at baseline and oxygen saturation at which OSA treatment achieves the best BP reduction. Tertiary objectives are to explore other predictors of BP reduction with OSA treatment and to separately investigate changes in 24 h, daytime and nighttime BP, as well as in nocturnal BP dipping and in BP variability indices induced by OSA treatment.

Potential limitations of such an approach to explore the BP effects of OSA treatment include the number of RCTs where the individual data are no longer available, thus preventing their inclusion in the meta-analysis, and the relative paucity of studies investigating the role of non-CPAP therapies on BP.

Nevertheless, the ANDANTE project will include data from more than 60% of the available studies (see list of Andante investigators in the acknowledgments), thus likely enabling us to satisfactorily characterise patient phenotypes associated with greater or smaller BP reduction. Another important point to be addressed is the characteristics of patients who are likely to benefit from OSA treatment in preventing cardiovascular diseases. Interestingly, in the Sleep Apnea Cardiovascular Endpoints (SAVE) trial the mean age of the included subjects was 61.3 years and the mean BP was within normal limits at baseline (131/79 mmHg).[4] In our previously published meta-analysis, this phenotype was associated with a reduced BP response whilst on CPAP treatment and this might, at least in part, explain the negative results on the primary outcome of the trial. The ANDANTE study is designed to further clarify this issue by allowing us to consider individual data and thus to identify possible confounders of the protective effect of OSA treatment vs cardiovascular outcome on an individual basis.

We thus expect the ANDANTE collaboration to shed some further light on predictors of greater BP reduction among OSA patients treated with CPAP. Despite the large number of RCTs conducted, current guidelines and recommendations support the treatment of OSA with the aim of reducing BP, but do not define clear BP thresholds nor identify phenotypes of hypertensive patients in whom this approach could be most useful and successful, or indeed potentially harmful.[14]

The task force of the American Academy of Sleep Medicine (AASM) suggested in their clinical practice guidelines to use positive airway pressure (PAP) therapy to treat OSA in adult patients with co-morbid hypertension, but again, without defining specific BP cut-offs.[15]

The task force noted that the overall quality of evidence, based on the critical outcome of mean arterial BP, was moderate due to imprecision. They concluded that in adult patients with OSA and co-morbid hypertension, the benefits of CPAP therapy compared to no CPAP therapy likely outweighed its potential harms and burdens, and that the majority of well-informed patients would choose the intervention over no treatment.[15]

This view is understandable however, there remain various views as to whether asymptomatic patients with hypertension would accept CPAP. We believe that the field of sleep-disordered breathing is now in the position to endorse a precision medicine approach. On one side this will avoid over-delivery of treatment in asymptomatic patients with OSA, with the sole aim of preventing possible cardiovascular complications. On the other side it will avoid OSA treatment in those patients with individual features requiring a therapeutic intervention and associated with the possibility of greater BP reduction with treatment. In the latter case, a personalised approach will also be particularly useful to tailor optimal therapeutic options in individual patients and to improve their adherence to CPAP treatment as much as possible.

To conclude, in the present and future era of precision medicine, collaboration of all actors involved in healthcare delivery is an essential requirement for the provision of best possible care, aimed at improving diagnostic criteria, primary and secondary prevention implementation, and treatment efficacy, based on a holistic, individually tailored approach.

The ANDANTE project will contribute to a greater precision in managing OSA by identifying individual predictors of BP response to treatment and by providing information about the effect of OSA treatment in the less studied patients' phenotypes such as women and asymptomatic or non-obese patients. This will help clinicians identify patients who benefit the most from OSA treatment and provide individually tailored treatments that may better impact on cardiovascular outcomes. It will also provide valuable data on which to base future intervention trials that aim to demonstrate the benefit of OSA treatment on these same outcomes.

Appendix. Researchers Collaborating in the ANDANTE PROJECT

The authors gratefully acknowledge the support of the ANDANTE investigators, patients and collaborators. In particular, ANDANTE collaboration include the following researchers (listed in alphabetical order): **Najib T. 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