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The search for optimal blood pressure control in type 2 diabetes mellitus: have we found the holy grail?

Our current insights into the relationship between sleep disordered breathing and arterial hypertension/higher systolic blood pressure arose from general population studies [1,2]; specifically cases with obstructive sleep apnea (OSA). Later, such observations were confirmed in a sample of type 2 diabetes mellitus (DM2) patients [3,4]. Moreover, treatment of OSA with positive airway pressure (PAP) led to a significant reduction of blood pressure, particularly in patients that demonstrate good adherence to the device [5,6]. However, data on a relationship between periodic breathing and blood pressure are scarce [7]. So far, only acute night time effects of periodic breathing were reported [8]. Blood pressure fluctuations during periodic breathing were shown to occur in line with oscillations in ventilation during periodic breathing in patients with chronic heart failure [8,9]. Additionally, evidence has shown that intermittent hypoxia (not repetitive arousals) appears to be the dominant cause of daytime increases in blood pressure [10]. Notably, Sin et al., found no alterations in daytime blood pressure in chronic heart failure with central sleep apnea, in contrast to those presenting with obstructive events [11]. Moreover, in the same context, according to Yumino et al., obstructive and central respiratory events have opposite hemodynamic effects: whereas OSA appears to have an adverse effect on stroke volume (SV), central sleep apnea appears to have little or slightly positive effects on SV [12]. Currently, no studies have looked at an association between periodic breathing and control of blood pressure in DM2, although arterial hypertension is common and strongly associated with DM2. Therefore, epidemiological studies exploring this area are warranted.

In this issue of Sleep Medicine, Schreib et al. [13], were the first to perform a cross-sectional study researching the association between periodic breathing and DM2. The work is both relevant and timely to this need. In their study, the authors tried to get new insights in the contribution of periodic breathing to hypertension, and to identify the driving factor(s), using data from 679 patients. Despite the use of more antihypertensive drugs in these patients, periodic breathing was independently associated with higher systolic blood pressure and blood pressure above the target range in patients with DM2, after correction for gender, age, high-density lipoproteins, renal function, coronary artery disease and antihypertensive treatment (OR 2.1; $p = 0.03$). Notably, 68% of the study population did not meet the currently recommended blood pressure target, with 11% presenting with periodic breathing (between 2 and 72% of recording time). However, in this small group of periodic breathing, 83% of the cases had blood pressure above target and 44% was using at least 3 antihypertensives (vs 33% without periodic breathing). It is noteworthy that 33% also had sleep-disordered breathing (SDB) (AHI$\geq$15), but SDB was not independently associated with blood pressure (OR 1.2; $p = 0.3$), while neither SaO_2<90% nor self-reported sleeping time were found to contribute [13].

So, what are the clinical relevance of these findings? We can only speculate, since the study was cross-sectional, without longitudinal follow-up and lacking intervention with PAP. From indirect observations, we know that effective blood pressure control in DM can significantly reduce the cardiovascular risk [14]. Furthermore, the same systolic blood pressure reduction translates into a higher risk reduction for cardiovascular events in patients with DM2, compared to those without [15]. Assuming that at least part of the blood pressure increase is reversible, the authors suggested that PAP therapy could contribute to reach the target blood pressure in 0–25% of DM2 patients with blood pressure above the target. There is also recent evidence from a recent metanalysis that sufficient control of blood pressure in this population accounts for a significant risk reduction of major cardiovascular events to 0.82, but strictly spoken, the prognostic significance in the study of Schreib et al., remains unproven [16]. In either case, the study provides important data which might impact care. However, advantages have to be weighed against the added costs of performing sleep studies and treating these patients on a large scale. Alternately, in general, assessment of sleep apnea is cost-effective based on Markov models [17].

Future studies in this field will need to focus on evaluating in some detail the longitudinal impact of periodic breathing in DM2 patients, in order to better elucidate causality, and prioritize treatment in managing DM2 patients with periodic breathing.

The paper of Schreib et al., also raises a number of unresolved questions. First, how robust are these data? The authors themselves noted a number of significant limitations to their investigations, including the use of a type 4 polygraphy (automatic analysis of breathing pattern, lack of objective sleep data, arousals not measured, 6% measurement failure) and a lack of nocturnal blood pressure measurement. Nonetheless, the authors rigorously utilized an automated blood pressure device according to the guidelines and included a huge number of patients.

To conclude, the paper discussed emphasizes the importance of continuous investigation of the interaction among diabetes, SDB, periodic breathing, obesity and blood pressure, and sheds light on the association between periodic breathing and blood pressure values above the currently recommended target for diabetes patients. This study represents a new horizon, but many questions remain. Altogether, we are one step further in the battle to optimize blood pressure control in DM2, and hence still in the quest to find the holy grail.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleepx.2020.100015.

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Johan Verbraecken

Department of Pulmonary Medicine and Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Wilrijkstraat 10, 2650 Edegem, Antwerp, Belgium

E-mail address: johan.verbraecken@uza.be.

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