



EDITORIAL

Arrhythmias and conduction disturbances in obstructive sleep apnoea: the heart of the problem?

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Hear rhythm disorders temporally associated with obstructive apnoeic events have been highlighted for more than 30 years. An ECG from polysomnographic recordings enables both sleep medicine specialists and cardiologists to address occasional very impressive paroxysmal atrioventricular conduction blocks or sinus pauses (of up to 10 s during rapid eye movement (REM) sleep) [1]. The pathophysiology of these disorders induced by respiratory events is obviously complex and represents an exciting challenge in the context of integrative human physiology. The role of acute and chronic imbalances in the autonomic nervous system (ANS) associated with obstructive sleep apnoeas or hypopnoeas (OSA) has been clearly demonstrated in many cellular mechanisms of myocardial adaptation to such repeated stresses [2–4]. In addition, these autonomic disorders are now recognised as independent risk factors or triggers of sudden cardiac death not only in heart failure patients [5] but also in people with preserved systolic/diastolic left ventricular function [6, 7]. Although sleep is normally a time when the parasympathetic modulation of the heart predominates and myocardial electrical stability is enhanced, OSA disturbs this quiescence, creating an autonomic profile in which both profound vagal activity leading to bradycardia and sympathetic overactivity favouring ventricular ectopy are commonly observed [8].

The authors of a review paper published in the current issue of the *European Respiratory Journal* [9] must be congratulated for successfully detailing of the mechanisms present during apnoea/hypopnoea that can lead to heart rhythm disturbances. This paper is, for me, a remarkable teaching tool that I will use again in the future due to its clarity and its “updated” literature review.

In a second part of their paper, Rossi *et al.* [9] discuss the clinical level of evidence that is currently recognised in routine practice to ensure a statistically strong relationship between cardiac arrhythmias and conduction disturbances and sleep-related breathing disorders. Although all sleep clinicians in their daily practice would bet on a deleterious effect of sleep

apnoea, the authors show that high-quality studies are few and, more importantly, studies testing the therapeutic effect of continuous positive airway pressure (CPAP) on these cardiac abnormalities are rare or have insufficient statistical power to demonstrate the role played by sleep-related respiratory diseases in the field. Controlled trials have demonstrated that OSA causes hypertension, and prospective epidemiological studies have indicated that OSA might be an independent risk factor for stroke [10] and myocardial infarction [11].

Studies showing the same relationship between OSA and cardiac arrhythmias are still missing. Here, all sleep laboratory clinicians in their daily practice would bet on a deleterious effect of sleep apnoea with a resulting tendency toward cardiac arrhythmia that may directly contribute to sudden cardiac death and premature mortality in patients with sleep apnoea. However, the authors showed that studies on this topic suffer from poor methodological quality and, more importantly, that studies testing the therapeutic effects of CPAP on these cardiac abnormalities are rare or have insufficient statistical power to demonstrate the role of the “risk factor” that could be represented by OSA for cardiac arrhythmias.

As often occurs in medical science, the most impressive disorders are not the greatest danger. Thus, long sinus pauses contemporary with apnoea that appear worrisome are generally promptly controlled by efficient CPAP treatment. A high-grade atrioventricular block often poses the question of a degenerative conduction defect even if the functional “vagal-dependent” origin is understood in the clinical context of sleep apnoea. However, confirming that the cardiac conduction disorder will not reappear later under CPAP is often difficult. Evaluating the associated risk of noncompliant patients is even more difficult. For ventricular arrhythmia, the problem of sudden death is so complex that respiratory events may represent only part of a more deleterious process. I believe that the ANS imbalance severity (cardiac and vascular sympathetic overactivity and loss of daytime parasympathetic control) caused by apnoeas/hypopnoeas on myocardial depolarisation (QRS duration) [12] and repolarisation (QT duration and QT/RR slope adaptation) are significant markers in terms of the ventricular arrhythmic risk in OSA patients [13]. However, survival studies are lacking.

Myocardial ischaemic events during the night carefully analysed by ECG Holter monitoring are rare even in severe apnoea events, regardless of the presence of coronary artery disease. The trigger mechanisms of acute coronary events are

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very complex and intricate. Some degree of myocardial preconditioning associated with chronic intermittent hypoxia may explain this phenomenon [14]. Hypoxia and increased sympathetic activity should also be associated with abnormalities in platelet function that can eventually lead to coronary thrombosis. The relationship between ventilatory control during sleep and cardiovascular functional status after myocardial infarction is probably more complex than we previously understood. Indeed, a recent study showed that an improvement of cardiac function early after myocardial infarction is associated with an alleviation of sleep apnoea [15].

From my point of view, more attention must be paid to atrial rhythm disorders (isolated atrial ectopic beats or paroxysmal atrial fibrillation episodes) that may occur in apnoeic patients, especially during the night and even with a “normal” heart. In addition, the particular susceptibility in terms of atrial rhythm disorders of older subjects and females must lead to large observational cohort studies on the impact of OSA. A recent Spanish study [16, 17] demonstrated that it is probably premature to affirm that these populations of patients benefit less from the CPAP treatment than others in terms of cardiovascular morbidity and mortality.

The issue of whether conducting a randomised trial with a primary end-point such as reducing the incidence of paroxysmal atrial fibrillation episodes in patients with known sleep apnoea and documented atrial rhythm disturbances would be ethical in 2013 arises at this stage. The answer is certainly not easy. This type of study would lead to very important medico-economic responses to support a pathology involved in many ischaemic strokes. In addition, the current interventional attitude to management of such patients (pulmonary vein isolation) is particularly expensive, and although this management is undoubtedly effective, no randomised double-blind study has provided a convincing formal argument in terms of the cardiovascular morbidity and mortality. In addition, CPAP may indeed represent an interesting, cost-effective therapy to control such atrial arrhythmias and potentially prevent many strokes with dramatic human consequences [18, 19]. This item must be considered, since it has been highlighted that the presence of moderate-to-severe OSA is associated with an increased long-term incidence of nonfatal cardiovascular events in stroke patients and that CPAP reduces the excess of incidence seen in these patients [20].

The usual problem of clinical studies in OSA is, of course, represented by the inclusion of patients at high cardiovascular risk, seen for secondary prevention after myocardial infarction or in heart failure. Hypertension associated with left ventricular hypertrophy is a possible cause of ventricular hyperexcitability, intraventricular conduction defects, dilated left atrium and thus sustained atrial arrhythmias. The link between hypertension and OSA is so strong that whether improvement in rhythm disorders is related to the control of the apnoea, to the better control of blood pressure (under CPAP) or to both mechanisms is often unclear.

Progress on the pharmacological and interventional planes obtained in heart disease populations makes it a very risky challenge for sponsors to complete a new, well-designed (randomised/controlled) study against sham CPAP. However,

sleep medicine needs this type of challenge in order to achieve better recognition by the health authorities of the effectiveness of nocturnal ventilatory support with CPAP [21].

At this point, the possibility that up to 30% of the adult population in Western countries may be affected by asymptomatic OSA should be kept in mind. Miniaturised and validated diagnostic tools to assess the impact of CPAP on the reduction of heart rhythm disorders are numerous and should be used widely in cohort studies [22, 23]. Regarding the impact of therapy on reducing the risk of sudden death, the information provided by registries of the OSA population monitored by teams of independent statisticians is essential. Organisations of national and international epidemiological registers, even if they do not replace randomised controlled studies, are also needed to advance the field of “evidence-based sleep medicine”.

STATEMENT OF INTEREST

Conflict of interest information can be found alongside the online version of this article at www.erj.ersjournals.com

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