Altered ventricular repolarisation dynamic: the missing link between obstructive sleep apnoea and sudden death?

Karim Benali[1,2], Kanchan Kulkarni[2] and Frederic Roche[3]

[1]Cardiology Department, Saint-Étienne University Hospital, INSERM, SAINBIOSE U1059, Jean Monnet University, Saint-Étienne, France. [2]IHU LIRYC, Electrophysiology and Heart Modeling Institute, Bordeaux, France. [3]Clinical Physiology Department, Saint-Étienne University Hospital, INSERM, SAINBIOSE U1059, Jean Monnet University, Saint-Étienne, France.

Corresponding author: Frederic Roche (frederic.roche@univ-st-etienne.fr)

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Research is needed to explore the broader links between oxygen desaturation episodes, ventricular repolarisation instability and genesis of malignant arrhythmic events https://bit.ly/3WeQNHy

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Obstructive sleep apnoea (OSA) has a major negative health impact, affecting an estimated 1 billion adults worldwide and being the most common sleep-related breathing disorder [1]. While epidemiological data support the association between OSA and a wide range of cardiovascular outcomes, the magnitude of the association is distinctly stronger with regard to cardiac arrhythmias [2–5]. Behind the widely recognised association between OSA and atrial fibrillation, the more subtle relationship between OSA and sudden cardiac death has also been emphasised for several decades [6–8].

A strong argument in favour of a causal relationship between sleep disordered breathing and sudden cardiac death is the identification of a temporal association between these two phenomena. In 2005, Gami *et al*. [9] reported that patients with OSA present a peak in sudden death from cardiac causes during the sleeping hours, sudden death occurring during sleep in 46% of patients suffering from OSA, compared to only 23% of control patients. Multiple studies subsequently reported that malignant ventricular arrhythmias mainly occur during sleep in patients with OSA, and could be attenuated by effective treatment of the sleep disorder [3, 10–13].

While numerous preclinical, pathophysiological and clinical data have provided insights into the underlying mechanisms by which OSA contributes to atrial arrhythmogenesis, the understanding of its influence on ventricular arrhythmogenesis remains unclear. Notably, data regarding the direct impact of OSA on the electrophysiological properties of the ventricles are sparse [14–16]. One point to note is that the incidence of arrhythmogenic triggers (*e.g.* premature ventricular complexes) seems to be higher in individuals with OSA. In addition to the more frequent triggers, the chronic effects of OSA on cardiac substrate merit consideration. Prolonged exposure to OSA-related stressors may lead to the development of a substrate prone to sustained re-entry, further predisposing individuals to malignant arrhythmias. Similarly, it has been shown that patients with OSA also tend to have an increase in left ventricular mass (*e.g.* eccentric hypertrophy), independently of the presence of hypertension, a ventricular remodelling that may contribute to the development of ventricular arrhythmias [17–19]. However, a prominent pathophysiological hypothesis centres on the existence of substantial instability in the ventricular repolarisation phase of OSA patients, setting the stage for the occurrence of malignant arrhythmias [3, 4, 8, 12].

During the early years of ECG development and the pioneering work of Willem Einthoven, the impact of respiratory phases on repolarisation changes was already noted [20]. While the classic influence of the respiratory cycle on cardiac depolarisation, mainly represented by respiratory sinus arrhythmia, has been extensively documented, ventricular repolarisation changes have also been observed in healthy individuals under various respiratory conditions [21–23].

Numerous studies have investigated abnormalities of repolarisation parameters in patients with sleep-related breathing disorders. The majority have focused on classical parameters of ventricular repolarisation, such as the corrected QT interval (QTc), the interval from the peak to the end of the T-wave (Tp–Te), or the QT dispersion (defined as the difference between the longest and the shortest QT intervals within a 12-lead ECG recording). Several authors have reported that abnormal repolarisation parameters are more frequent in patients with OSA compared to individuals without OSA, such as a longer QT interval, a greater QT dispersion, and an extended Tp–Te interval (figure 1) [23–27]. Correction of the sleep disorder has been associated with the restoration of normal repolarisation parameters [28–30].

However, while data regarding disturbances in baseline repolarisation parameters in patients with OSA are accumulating, data examining these parameters during apnoeic episodes are limited. Specifically, the impact of desaturation periods on the repolarisation phase has not been well documented. Understanding the nuances of how desaturation events influence ventricular repolarisation instability is crucial, as these periods could temporarily exacerbate the risk of malignant arrhythmic events in patients with OSA.

In this issue of *ERJ Open Research*, Sillanmäki *et al*. [31] investigated the link between hypoxaemic load in patients with OSA and the occurrence of acute changes in T-wave amplitude. The authors retrospectively analysed ECGs from polysomnography of 492 patients with suspected OSA. ECG analyses were conducted before, during and after 9137 episodes of oxyhaemoglobin desaturation related to nocturnal apnoea or hypopnoea, using the modified lead II of the polysomnography recordings. The mean T-wave amplitude changes from the baseline level to the levels during and after desaturations were calculated (ΔT_{amp_mean}), with subgroup analyses based on the duration and magnitude of blood oxygen saturation drops. The authors reported that desaturation episodes caused significant changes in the ΔT_{amp_mean} during and after desaturation phases. In men, the median ΔT_{amp_mean} values during and after deep desaturations (change in peripheral oxygen saturation (ΔS_{pO_2}) ⩾7.5%) were 21 µV and 24 µV, respectively. In women, the median ΔT_{amp_mean} values during and after deep desaturations were 15 µV and

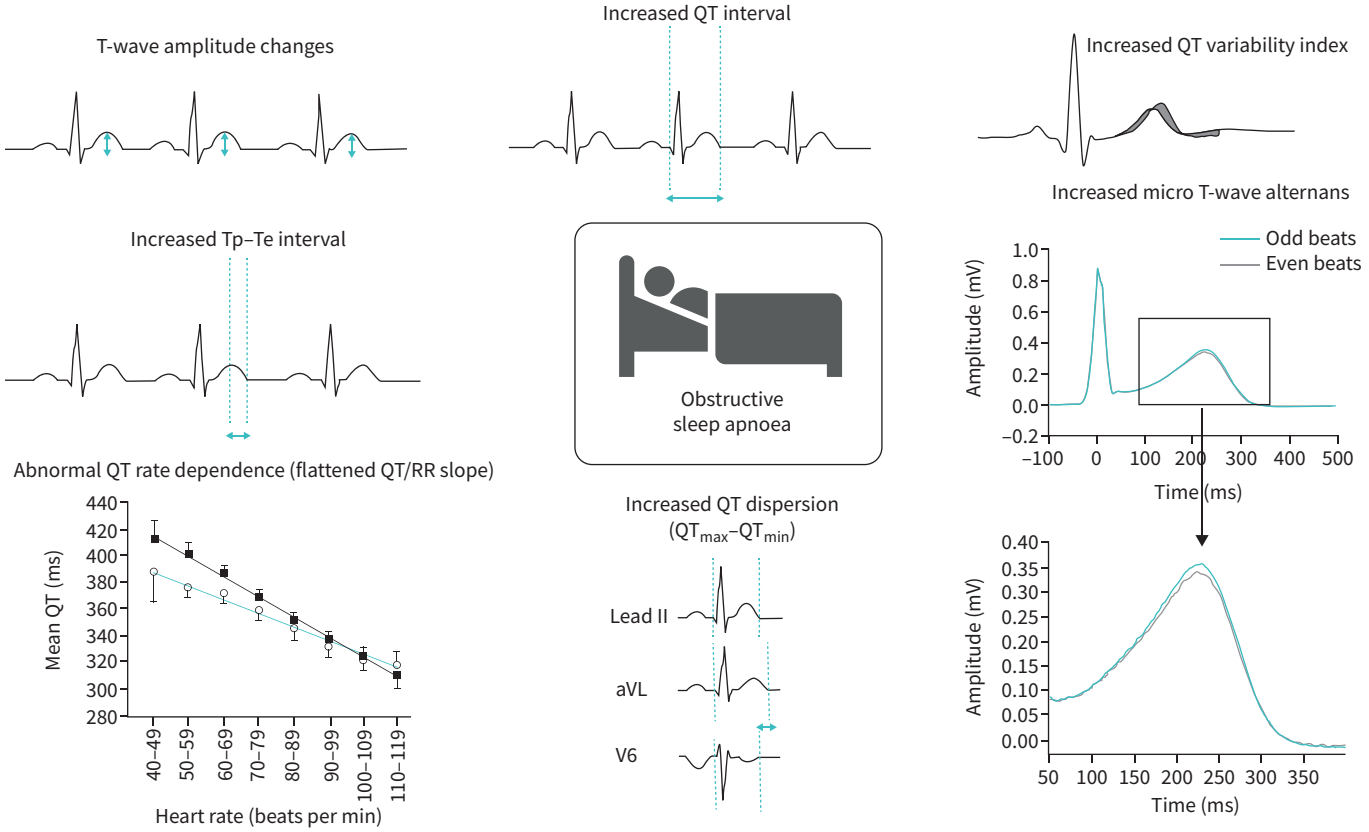

FIGURE 1 Methods for assessing ventricular repolarisation abnormalities in patients with obstructive sleep apnoea. Tp–Te interval: interval from the peak to the end of the T-wave.

21 μV, respectively. The authors also observed an independent association between the severity of nocturnal desaturation and the magnitude of changes in T-wave amplitude.

Although the results from Sillanmäki *et al*. [31] represent important findings, several aspects warrant further discussion. First, a significant number of patients were excluded from the analysis, potentially limiting the generalisability of the results. Hence, patients with heart failure, atrial fibrillation, pacemaker/defibrillator or "abnormal T-waves" were all excluded from the current study. Unfortunately, this may reduce the extrapolability of the authors' results, as these cardiac conditions are common comorbidities in patients with OSA. Furthermore, this subgroup of patients frequently presents with baseline repolarisation instability (*i.e.* linked to heart failure status, prescription of antiarrhythmic drugs, *etc*.) and represents a subgroup of patients at significantly higher risk of ventricular arrhythmias in the context of an associated sleep-related breathing disorder. Therefore, including patients with common cardiac conditions and those with abnormal T-wave morphology could have provided significant insights into the relationship between episodes of desaturation during OSA and ventricular repolarisation instability in patients with different underlying cardiac pathologies.

Secondly, the approach used to assess repolarisation instability may also be a source of limitation in the results. Specifically, in this study, Sillanmäki *et al*. [31] examined the changes in the amplitude of the T-wave as recorded using a single-lead ECG (modified lead II). However, such analysis may result in substantial overlooking of the overall instability in the repolarisation phase. Indeed, it is now established that the T-wave loop (*i.e.* the writing of the T-wave vector in an orthogonal three-dimensional space) is a major determinant of the T-wave morphology in the standard 12-lead ECG [32]. Depending on the patient's cardiac orientation in the torso, the presence of pulmonary diseases or the three-dimensional dynamic of the T-wave vector during respiration, this single-lead analysis is unlikely to capture the full range of information related to changes in the repolarisation process. Thus, the more T-loop projections are used in different ECG leads, the more sensitive the measurement of T-wave changes becomes. It would therefore be interesting to potentiate the authors' already valuable results by including an analysis of T-wave changes occurring over 12 (or more) ECG leads (which we acknowledge is not common practice in polysomnography studies).

With regard to the effect of different disturbances associated with sleep-related breathing disorders, there may be other important modulators of ventricular repolarisation besides desaturation episodes. For example, arousals and/or micro-arousals, which are known to cause significant autonomic disturbances, could also significantly influence the stability of cardiac repolarisation. It is therefore regrettable that the authors did not investigate the effect of arousals on these T-wave changes in combination with episodes of desaturation, despite having recently described their impact on another repolarisation parameter (QT variability index) [33]. A combined description might have been useful to appreciate the complex interplay between these different manifestations of the sleep disorder spectrum, and their respective impact on T-wave instability.

Finally, in the absence of arrhythmic events in the cohort, it is still impossible to establish a direct link between these intermittent hypoxaemic-related ventricular repolarisation abnormalities and the occurrence of malignant arrhythmias in patients with OSA. For the time being, this link remains somewhat speculative, although evidence continues to accumulate to support this causal relationship. Addressing the complex relationship between OSA and cardiac arrhythmias requires interdisciplinary collaboration and innovative research efforts. By delving deeper into the underlying mechanisms and conducting longitudinal studies, these elusive links can be further elucidated, potentially paving the way for targeted interventions to reduce arrhythmic burden in OSA patients.

Regarding pathophysiology, several hypotheses may explain the ventricular instability observed in patients with OSA. Direct mechanisms may include the effects of sympathetic activation on the ventricular repolarisation phase or the effects of forced inspirations against closed upper airways, leading to significant negative intrathoracic pressures, ventricular walls stress and changes in cardiac afterload. Additionally, cardiomyocyte repolarisation is a highly complex cellular process, involving several types of ion channels through a complex interplay, in which potassium and calcium pathways play a critical role. It has been shown that both potassium channels (which are notably involved in the pathophysiology of long QT syndrome) and calcium channels exhibit abnormal functioning in patients with OSA [34, 35].

In terms of the future perspective, static repolarisation parameters (*e.g.* QTc, Tp–Te, T-wave amplitude, *etc*.) have long been used to analyse the influence of sleep disordered breathing on cardiac repolarisation. However, recent years have seen the emergence of novel periodic parameters for the analysis of abnormal

repolarisation dynamics, which have demonstrated a stronger association with arrhythmic events in different populations. The most extreme form of periodic instability observable on an ECG is the macro T-wave alternans, a rare and striking dynamic T-wave abnormality, highly predictive of short-term occurrence of malignant ventricular arrhythmia (*e.g.* torsade de pointe in patients with long QT syndrome). However, more subtle periodic changes in T-wave morphology, on the order of microvolts, have also been established as strong markers of repolarisation abnormalities. In 1994, Rosenbaum *et al*. [36] reported the existence of a 0.5-Hz alternans in the QRS and T-wave of patients with a history of malignant ventricular arrhythmias, using frequency domain analyses. Since then, accumulating evidence has shown that micro T-wave alternans is a valuable short- and long-term predictor of lethal ventricular arrhythmias [37]. In addition, T-wave alternans has been shown to be associated with increased sympathetic activity and directly modulated by interventions that alter autonomic tone [38]. Hence, there is a distinct possibility that T-wave alternans may be indicative of sympathetic discharges that occur during episodes of apnoea and may serve as a biomarker of the susceptibility to cardiac arrhythmias. Recently, other markers of micro-oscillations in the T-wave morphology, with lower periodicity (~0.1 Hz), have also been described, demonstrating a strong association with the occurrence of arrhythmic cardiac death in different subsets of patients [39, 40]. Such markers of periodic abnormalities could be valuable to investigate in patients with OSA, in order to better elucidate the full spectrum of abnormalities of the ventricular repolarisation phase in this population.

In conclusion, the study by Sillanmäki *et al*. [31] provides valuable insights into the relationship between OSA and cardiac repolarisation instability during sleep, highlighting that repolarisation changes occur during desaturation episodes, with more severe desaturation causing higher levels of change in the T-wave amplitude. The authors are to be congratulated on this work, which paves the way for a better understanding of ventricular arrhythmogenesis in patients with OSA. Further research is needed to explore the broader implications of these findings and to establish more definitive links between desaturation episodes, ventricular repolarisation instability, and genesis of malignant arrhythmic events.

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