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Editorial

Beyond phrenic nerve stimulation to reduce the hypoxemic burden in central apneas: Targeting chemoreflex?

Central "sleep" apneas (CA) are characterized by a reduction in or cessation of airflow due to the absence of respiratory effort, in contrast to obstructive sleep apneas (OSA), where breathing is impaired due to upper airways obstruction [1]. Differently from OSA, often found in the general population, CA are particularly observed in patients with heart failure (HF), not only during nighttime, but also at daytime in the awake patient, even in the upright position [2,3]. CA are mainly due to circulatory time delay, altered plant gain and chemoreflex function [4,5], all conditions independent from the state of consciousness (wakefulness and sleep). CA are associated with autonomic imbalance, increased risk of arrhythmias and HF progression, and, eventually, to cardiovascular mortality, because related to a significant desaturation burden [6], especially when present across the 24-h period [2,3].

In the past, the treatment of CA has been uncritically derived from that of OSA, hence applying positive pressure to already opened upper airways [1]. While effective in decreasing by variable amount the apnea-hypopnea index (AHI) at night (or at least during the part of the night in which the patient was using the device), continuous positive airway pressure and adaptive servo-ventilation (ASV), have notwithstanding shown neutral or even detrimental prognostic effects in HF patients [1]. Therefore, alternative treatment options based on neural control of a neurally-mediated phenomenon have been developed. Phrenic nerve stimulation (PNS) is a novel technique specifically designed to improve the breathing pattern in patients with CA [7]. The device sends electrical impulses to the phrenic nerve to prompts the diaphragm to contract, restoring a normal breathing pattern in case of neurologically generated loss of muscle activity, as in patients with HF and CA or with neurological conditions, such as spinal cord injuries or neurodegenerative disorders [7].

The main trial on PNS was conducted by Costanzo et al. in 2016 and aimed to assess the safety and efficacy of the Remedé system (Respicardia Inc., Minnetonka, MN, USA), a transvenous implantable PNS device for the treatment of CA [8]. The study included 151 patients (64% with HF) with moderate-to-severe CA, randomized 1:1 to receive either the stimulation or no stimulation. The study showed that patients who received the active treatment had a significant reduction in CA burden (AHI reduction of 50.8 vs. 11.5 events/h, $p < 0.001$), as well as improvements in quality of life, exercise capacity, and cardiac function compared to controls at 6 months [8]. Adverse events were mostly related to the implantation procedure and were generally mild and manageable [8]. Long term results of the original trial have been published thereafter, confirming positive effects on CA severity and sleep quality [9].

In this issue of the IJC, Baumert and coworkers reported the effect of PNS on the composition of the nocturnal hypoxemic in patients with CA [10]. Authors analyzed by automatic algorithms several metrics from oximetry data derived from the Remedé Pivotal Trial [8], including the oxygen desaturation index (ODI), the relative sleep time spent with an oxygen saturation (SpO2) <90% (T90) due to either acute episodic desaturations (T90desat) or non-specific and noncyclic SpO2 drifts (T90non-specific). The main finding of the study was that PNS was mainly able to ameliorate the CA-related oxygen desaturations (T90desat), rather than acting on non-specific SpO2 drifts (T90non-specific) [10]. Considering the action of PNS, this finding seems not surprising. Nonetheless, the fact that a "considerable nocturnal hypoxemic burden remains" despite PNS is of potential clinical interest [10].

The importance of SpO2 in patients with CA has been provided by Oldenburg with a seminal publication a few years ago [7]. In a large cohort of HF patients ($n = 963$) undergoing a multi-channel sleep study, the desaturation burden, as expressed by the T90, was the strongest predictor of all-cause mortality, independently of the severity, as expressed by the AHI, of either CA or OSA [7]. Different mechanisms may explain this finding. First, in HF patients, due to worse systolic function and longer circulatory delay, the hyperpnea phase and the total cycle duration (including hyperpnea and apnea) may be longer, with a paradoxically lower AHI [4]. Similar findings may occur in patients with mixed apneas. Second, oxygen desaturation may per se amplify respiratory instability and sympathetic surges by stimulating peripheral chemoreceptors, often hyperactive in HF [5]. Last, intermittent desaturations may be linked to the ischemia-reperfusion/re-oxygenation cascade, contributing together with chemoreflex-dependent sympathetic surges to the adverse outcomes observed in some patients with CA and/or OSA [1,6].

The persistence of non-specific SpO2 drifts reported by Baumert et al. [10] may hence raise some concern regarding the prognostic benefits of PNS. Indeed, residual desaturations were also observed with the use of ASV and may have contributed to the negative findings of the SERVE-HF trial [1]. While the precise determinants of the T90non-specific remains unclear, obesity and increased neck circumference seem to play some role [10]. Targeting such conditions may hence be required to optimize PNS efficacy. On the other hand, low-flow oxygen nocturnal supplementation has been specifically proposed to target oxygen desaturations in HF patients with CA. However, despite the encouraging pathophysiological premises, the phase 3 randomized controlled trial LOFT-HF has been prematurely terminated due to slow participant accrual during the COVID-19 pandemic (NCT03745898).

Parallelly to oxygen desaturation, CA are also associated to carbon dioxide oscillations, which contribute to breathing instability and

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sympathetic surges by stimulating peripheral and, most notably, central chemoreceptors, increasing the risk of HF hospitalization and death [5]. Novel therapeutic approaches have been proposed to target the central chemoreflex system. In the BREATH study, the oral administration of the serotoninergic 5-HT1A agonist buspirone, acting on a presynaptic autoceptor and thus decreasing the serotoninergic firing, was associated with a significant reduction of the central chemosensitivity, favoring ventilation stability with decrease of AHI, central apnea index and ODI both at nighttime and daytime in 16 patients with systolic HF [11].

Integrating PNS with these therapies to target the residual desaturation burden and chemoreflex hyperactivation may be an ideal strategy for improving ventilation stability and autonomic balance not only during the night but also throughout the 24-h period, even in the awake and active patients, to eventually improve hard outcomes, especially in patients with HF and CA.

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Declaration of Competing Interest

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