Novel Drug Targets for Central Apneas in Heart Failure: On the Road

To the Editor:

In the official American Thoracic Research Statement, Orr and colleagues highlight the research priorities in the field of central apneas (CA) in heart failure (HF) (1). The authors underscore that the pathophysiological mechanisms of CA have only been partially addressed and that a deeper understanding of the neurobiology of respiration both during sleep and wakefulness in health and disease is needed. In particular, unraveling the daytime and nighttime physiology and pathology of the respiratory controllers and their interactions with downstream effectors is essential to test and validate novel therapeutic strategies.

The loop gain mathematical hypothesis has helped researchers to model the pathophysiology of CA in HF: Increased controller (chemoreflex) gain together with increased (lung) plant gain and prolonged circulatory time are known predictors of respiratory instability and CA occurrence (1). Those mechanisms are state independent so that CA can be observed not only during sleep but also during wakefulness and even in the upright position in patients with HF (2, 3).

Nonetheless, the majority of treatments so far investigated have not specifically targeted its pathophysiological determinants, nor were they designed to cover 24 hours. In fact, noninvasive ventilation, which did not impact favorably on prognosis, or phrenic nerve stimulation, still under evaluation, are so far applied at nighttime and in the supine position only, leaving uncovered a large portion of daily life.

A pharmacological approach should therefore be considered a valid strategy to overcome those issues.

Among the pathophysiological determinants of CA, several attempts were made to target the chemoreflex, especially given its prognostic significance (4). Although surgical denervation of the carotid bodies is risky, some less hazardous pharmacological strategies with acetazolamide or xanthines have been proposed (1). However, given the crucial role of peripheral chemoreceptors in oxygen sensing, a safer approach might be to target central chemoreceptors.

Among the possible targets, the serotonergic system is very promising (5); indeed, serotonergic chemoreceptors are responsible for most of the response to carbon dioxide in physiologic conditions and may be targeted by drugs that are already available, though marketed with different indications, with a safe profile.

In particular, the 5-HT1a presynaptic receptor agonist buspirone is mentioned by the authors as a suitable drug based on previous works in neurological patients and in animal models of CA (1). Very recently, a randomized placebo-controlled crossover phase II trial has investigated its efficacy on CA in patients with systolic HF (6).

Buspirone (15 mg three times daily) decreased by 41% carbon dioxide chemosensitivity, reducing the apnea–hypopnea index by around 50%, the central apnea index by around 80%, and the oxygen desaturation index by around 80%, both at nighttime and at daytime (6). No major adverse reactions were described, making this drug a possible option for the treatment of CA in HF over the whole 24-hour period. Multicenter, larger phase III trials are needed to confirm those preliminary findings.

Increased chemosensitivity is a crucial pathophysiological determinant of CA in HF both at nighttime and daytime and independently from the patient's position. Pharmacological strategies directed on this target have shown very promising preliminary results. The development and validation of drugs aiming at different receptors, modulating chemoreflex hyperactivity while preserving its physiologic functions, undoubtedly represents a major research focus in this field. ■

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Reply to Borrelli *et al.*

From the Authors:

We thank the authors for calling attention to an important recent study on examining the use of pharmacotherapy with buspirone in patients with central sleep apnea related to heart failure with reduced ejection fraction (1) in our recent statement (2). As noted, the study found important decreases in chemoreflex sensitivity to carbon dioxide without changes in sensitivity to oxygen. These findings lend support to emerging evidence that central chemoreceptors play an important role in the pathogenesis of central sleep apnea in those with heart failure and stand in contrast to the traditional view that peripheral chemoreceptors are the sole important drivers in this context (3). Although the reductions in the apnea–hypopnea index in this study were modest, this work provides a foundation for much needed novel clinical investigations in addition to clarifying relevant underlying neurobiology. ■

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The 4DPRR Index and Mechanical Power: A Step Ahead or Four Steps Backward?

To the Editor:

We read with interest the manuscript by Costa and colleagues (1) showing that the combination of driving pressure and respiratory rate is significantly associated with mortality in patients with acute respiratory distress syndrome. Their analysis suggests that a simplified composite variable (driving pressure multiplied by four plus respiratory rate [4DPRR]) is as informative as the more comprehensive equation of mechanical power. Although we are delighted to see that respiratory rate, long neglected, has finally been considered (better late than never) as an essential determinant of ventilator-induced lung injury (VILI), we believe that some conceptual and methodological considerations need to be highlighted.

First, it is essential to make a clear distinction between a parsimonious epidemiological model that includes ventilatory variables associated with mortality and the more VILI-relevant *physical* concept of total energy transferred during mechanical ventilation—expressed as mechanical power (2). Regarding the latter, all elements of the ventilator's settings, including positive end-expiratory pressure (PEEP), should be included because all contribute to the total mechanical energy (3). Mechanical power is not intended to be the "unifying theoretical explanation" of VILI, but it is a more physiological way to summarize the physical contributions of the ventilator settings expressed in meaningful and understandable physical units (J/min) (2).

Although 4DPRR may help estimate the average trade-off between driving pressure and respiratory rate under purely theoretical isocapnic conditions, it is a population-associated statistical measure based entirely on the effect size derived from a mediation analysis; it does not describe a physical quantity or encapsulate total mechanical energy. Indeed, its 4:1 ratio may not apply under all conditions (e.g., when PEEP achieves lung

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