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PRO/CON DEBATE

Rebuttal to Javaheri, Brown and Khayat

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Drs. Javaheri, Brown, and Khayat highlight the controversy about the pathophysiological concepts associated with Hunter-Cheyne-Stokes breathing (HCSB) in the setting of heart failure (HF) with reduced ejection fraction.[1] Debate over such matters is healthy and should lead to further research in what is a fascinating overlap between cardiology, pulmonary, sleep, and autonomic function.

Simply put, it is my view that HF-related HCSB (1) is simply a reflection of HF severity, (2) may recede if cardiac function improves, and (3) has physiological advantages when the failing heart is leading to dyspnea.[2,3] If identified, HCSB should not be ignored! Indeed, a search for reversible causes should be undertaken. Note that HF is not always reversible: it can be malignant. In this context, a plethora of therapies (including continuous positive airway pressure [CPAP]) may assist cardiac function in some patients and attenuate HCSB. Whereas other treatments directed solely at controlling the ventilatory pattern of HCSB, without regard for cardiac function, may disguise rather than treat the cause of HCSB and in my opinion require carefully performed clinical trials before becoming mainstream treatments.

Four physiological effects were raised for debate by Javaheri et al.[1]

The first issue they highlighted was that "hyperventilation-related increase in end-expiratory lung volume and associated rise in end-expiratory pressure may be detrimental." I concur that changes in intrathoracic pressure (ITP) and lung volume may have differing effects on right and left ventricular function dependent on filling pressure (preload) and upstream resistance (afterload). In cases of acute heart failure (AHF), the Forrester plot is a helpful clinical guide, based on filling pressure and cardiac index, to guide treatments.[4] Patients presenting with AHF can be either "wet" or "dry" (ie, high or low filling pressures). Patients with HCSB are generally "wet"[5] and usually increase their stroke volume acutely with CPAP.[6] Such patients with HCSB also have a restrictive ventilatory defect that predisposes to greater oscillations in ventilatory drive and reduced oxygen stores (half the body's oxygen stores are kept in a gaseous mixture within the lungs). Thereby reversal of this restriction with large tidal volumes during the hyperventilation phase with HCSB (or more continuously with CPAP) should increase oxygen stores and reduce HCSB. Episodic rises in SpO_2 during sleep in patients with HCSB is caused by the increase in tidal volume and increase in end-expiratory lung volume. Lung inflation with CPAP is best illustrated when applied in AHF with a virtually immediate rise in SpO_2 and a slowing of respiratory rate.

In contrast to prolonged elevations of ITP (> 10 seconds as with the Valsalva maneuver) which reduce preload and stroke volume in healthy normal individuals, short swings in ITP related to periodic hyperventilation during sleep (< 5 seconds) increase stroke volume as measured by echocardiography[7] and digital photoplethysmography[8] techniques. Criley et al. showed that intermittent swings in ITP caused by voluntary coughing could maintain cardiac output in asystolic humans,[9] supporting the concept that the chest wall can in some circumstances augment stroke volume (ie, similar to a second heart). Moreover, the elevations in end-expiratory ITP proposed with HCSB (~ 5 $mmHg^3$) are similar to that seen with intrinsic positive end-expiratory pressure, which might prevent alveolar collapse.

The second issue is related to the relationship between disturbed HF, autonomic dysregulation, and HCSB. It is correct that we observed muscle sympathetic nerve activity (MSNA) inversely correlated with tidal volume in a group of patients with HF during wakefulness.[10] This was a correlation and does not confirm causation. The beauty of MSNA activity is that it accurately follows short-term changes in sympathetic activity (SNA). If one carefully examines Figure 1 of our paper[10] it can be seen that the large tidal breaths were associated with a more cyclic pattern of MSNA compared with rapid shallow breaths. As with the study by van de Borne,[11] MSNA during HCSB was decreased during the periods of hyperventilation compared with the central apneic period. As with a yawn, sympathetic activity is attenuated by inspiration.

Based on our group's observation that HF severity explained most of the variance of elevated SNA (measured by tritiated norepinephrine spillover), the contribution from HCSB was minimal.[12] Limitations of this study were that the tritiated norepinephrine spillover was measured while awake and HCSB occurred during sleep. However, HCSB can occur during wakefulness (eg, at rest or during exercise) when there is an absence of hypoxemia and arousals. Moreover, we have observed that markers of SNA do not increase across the night in patients with HCSB,[13] which would support the concept that HCSB is not "adding" to SNA. My hypothesis is that HF leads to increased SNA, which leads to hyperventilation (not the other way around): this is supported by the observation that

venous norepinephrine infusions result in hyperventilation, which can be blocked by propranolol.[14]

I agree with Javaheri et al.[1] that "treatment of HCSB reduces sympathetic tone"; however, the mechanism by which this occurs is by attenuating HF rather than turning off HCSB. Turning off (ie, disguising) HCSB, without improving cardiac function, such as via phrenic nerve stimulation, respiratory stimulant pharmacotherapy, dead space, or CO_2 inhalation are speculative and potentially dangerous as the studies to date have shown.[2,3]

I disagree with the proposition by Javaheri et al.[1] that "there has developed overwhelming evidence that in patients with HF with reduced ejection fraction, HCSB induces a hyperadrenergic state that is reversed when sleep-disordered breathing is suppressed regardless of the therapeutic modality." Treatment of HF is beneficial in terms of SNA and would suppress HCSB if present. However disguising HCSB without augmenting cardiac function (eg, with stimulatory drugs, dead space, CO_2 inhalation, and phrenic nerve pacing) has no proven benefit nor effect on improving autonomic dysregulation.

The third issue related to the implications of respiratory alkalosis is associated with HCSB. I deny making the statement that "treatment of HCSB leads to respiratory acidosis." What has been shown is that successful CPAP treatment of HF in the setting of HCSB leads to a reduction in minute volume of ventilation and thereby normalization of CO_2 and pH. This may sound counterintuitive; however, when CPAP augments cardiac function, SNA falls, minute ventilation falls, and CO_2 rises back to normal levels. Simply put, treatment of HCSB will return the pH toward normality (7.35–7.45).

Whether "respiratory alkalosis is cardioprotective" (Javaheri et al.[1] statement, not mine!) is speculative. My hypothesis is that in terms of cardiac function, (1) acidosis has a far more detrimental effect than alkalosis and (2) if AHF develops, it is better to have come from a state of mild alkalosis than a neutral pH. Accordingly, patients with AHF rarely present with hypercapnic respiratory failure. Javaheri et al. state they could find "virtually" no data regarding arterial blood gases in AHF. We too found a paucity of data[15]; however, we did estimate the development of hypercapnia in 25% to 50% of patients with isolated AHF (ie, free of other organ disease).

The effects of acidosis or alkalosis on cardiac contractility are of great interest. The paper by Bing et al.[16] is extremely important and I recommend all to read to make their personal opinion and not be guided by the paper's speculative (misleading?) title. This group clearly and categorically demonstrated an increased cardiac tensile strength (ie, a marker of cardiac contractility) in isolated hypoxic rat myocardium when in an alkaline environment (pH = 7.8) compared with an acidic (pH = 7.1) environment. The group showed that during acidosis, cardiac contractility was nonexistent. Supportive data are provided by Wixels et al.[17] who demonstrated using intact dogs with ischemic cardiomyopathy that hypercapnia (83 mmHg) reduced cardiac output and increased pulmonary capillary wedge pressure. Hypocapnia had no effect on cardiac function, and indeed increased myocardial oxygen extraction (another benefit of HCSB).

Javaheri et al.[1] refer to a paper by Nakao et al.[18] with an interesting and contrasting view that hyperventilation is a trigger for coronary artery spasm. In this study, 389 humans who were undergoing a coronary angiogram for chest pain were asked to perform continuous hyperventilation for 6 minutes with the primary outcome of electrocardiographic change or chest pain. Electrocardiographic changes developed in only 28%, and the number developing chest pain was not reported. Cardiac arrhythmias were not commented on. Only a third of the group had arterial blood gas samples taken and their results were not reported. Minute ventilation was not measured. Hyperventilation is not recommended in contemporary guidelines for the investigation of chest pain. Six minutes of uninterrupted hyperventilation is not equivalent to the periodic hyperventilation seen with HCSB. However, I do acknowledge that large changes in arterial blood gases may possibly adversely affect coronary flow. Moreover, I remind readers of the adverse effect of hyperoxia on coronary arterial flow[19] and survival after myocardial infarct.[20]

The fourth issue that Javaheri et al. criticize relates to the benefit of periodic rest. This is possibly the most important effect of HCSB. I appreciate the attention paid to our abstract, which attempted to differentiate work of breathing (pressure volume product) from efficiency of breathing (pressure time product).[21] What became evident in this study was that during the obstructive events, the intrathoracic pressures observed in heart failure (~ −25 mmHg) were significantly less compared with OSA without HF (~ −100 mmHg).[22] Our group's observation, yet to be confirmed, is that if HF develops in patients with OSA, the negative ITP become less negative (ie, less detrimental) and eventually similar to that observed with HCSB. Clearly more work with measuring ITP is needed and I would encourage all readers of this manuscript to attempt this difficult physiological measurement.

In the words of historian and philosopher Yuval Noah Harari, "modern science is based on the Latin injunction "ignoramus" – "we do not know." It assumes that we do not know everything. Even more critically, it accepts that the things that we think we know could be proven wrong as we gain more knowledge. No concept, idea, or theory is sacred and beyond challenge.[23] Like Javaheri et al.,[1] I also thought HCSB was a "bad bedfellow" in 1998[24]; however, as more clinical research was undertaken, by 2000 I had changed my view.[25]

CITATION

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DISCLOSURE STATEMENT

The author reports no conflicts of interest.