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Cheyne-Stokes Respiration in Heart Failure Is Not a Therapeutic Target: A Lesson from *CANPAP*, *SERVE-HF* and *ADVENT-HF* Trials (Letter to the Editor)

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Dear Editor,

Chyene-Stokes respiration (CSR) in heart failure has long been a topic of debate among cardiologists, respiratory physicians, and sleep specialists. Recently, a randomized controlled trial (RCT) on the effects of positive airway pressure (PAP) in heart failure with reduced ejection fraction ≤ 45% (HF-REF) with CSR was published in The Lancet Respir Med [1]. Letter to the editor addresses the trial, named *ADVENT-HF*, challenging the hypothesis that "CSR in HF-REF is a therapeutic target", which is based on high-quality RCTs over the past two decades, including *CANPAP* [2], and *SERVE-HF* [3].

In *CANPAP* [2], Bradley *et al.* aimed to alleviate CSR in HF-REF with central sleep apnea identified by apnea-hypopnea index (AHI) ≥ 15 through six months of PAP. However, the trial was prematurely terminated due to worsened outcomes in the PAP-treated group compared to the untreated cohort. Subsequent post-hoc analysis revealed improved outcomes in responders with AHI < 15 after three months of PAP compared to non-responders with AHI ≥ 15, recommending continued PAP if AHI < 15 and a switch to alternative treatments otherwise [4].

Inspired by *CANPAP*, many researchers conducted trials with adaptive servo-ventilation (ASV) to effectively eliminate CSR, assuming that "CSR is a therapeutic target". In one such trial, *SERVE-HF* [3], Cowie *et al.* revealed worsened outcomes in HF-REF patients with CSR treated with ASV, causing considerable confusion. In *ADVENT-HF*, Bradley *et al.* demonstrated that ASV, while eliminating CSR in HF-REF, had no impact on prognosis [1].

The authors posit that Bradley *et al.*'s hypothesis is flawed and propose that "CSR is not a therapeutic target; rather, cardio-respiratory coupling (CRC)

compensating for HF-REF". In a respiratory cycle, heartbeats fluctuate, increasing during inspiration and decreasing during expiration, a phenomenon known as respiratory sinus arrhythmia (RSA). The authors have shown in model experiments that RSA's physiological significance lies in enhancing cardio-respiratory efficacy through the CRC [5]. CSR frequently coexists with HF-REF, where heartbeats in CSR increase during hyperpnea and decrease during hypopnea/apnea. The CRC with different time constants from RSA may also improve the efficacy of respiratory and circulatory functions. As a consequence, the concern arises that "removing CSR may lead to a disappearance of the CRC compensating for HF-REF, thereby worsening patient outcomes".

Since the author published one of the earliest prevalence studies of CSR in congestive heart failure [6], CSR has been known as a clinical sign of poor prognosis in heart failure [7]. For example, Hanly and Zuberi-Khokhar showed higher mortality rates in patients with CSR compared to those without CSR [8], suggesting that CSR is a phenomenon that is more likely to occur in heart failure patients with poor prognosis. However, this does not necessarily imply that CSR itself is a factor that worsens prognosis.

CSR might be a simple byproduct of heart failure, which could compensate the impaired cardiac function from the physiological standpoint [9] [10]. The existence of CSR may indicate that the heart failure condition is so poor that CSR must be mobilized as a "protective response". If so, neutral or even negative effect on prognosis due to removal of CSR by ASV is a predictable outcome.

The author reported that a surgical valve replacement for mitral regurgitation enhanced cardiac output to eliminate CSR [11] and that continuous PAP of 5 - 8 cmH_2O (Low-CPAP) improved cardiac function to decrease CSR substantially in five representative cases with HF-REF [12]. In another case of acute mitral prolapse and regurgitation with distinct CSR, the author utilized Low-CPAP, not ASV, to control intractable heart failure. Thereby, the author aimed to reduce mitral regurgitation through its hydrostatic benefits, ameliorate obstructive apnea and hypopnea, and improve oxygenation, while CSR was well preserved [13].

The authors implore a reassessment of CSR's role in HF-REF and exploration of alternative perspectives for therapeutic approaches. The results on PAP, either worsening or not affecting mortality [1] [2] [3], may stem from the flawed idea that "CSR in HF-REF is a therapeutic target". A lesson from *CANPAP, SERVE-HF,* and *ADVENT-HF* emphasizes the imperative of scrutinizing hypotheses in the high-quality RCTs, by which we should address the fundamental question "why does the heartbeat synchronize with respiratory rhythm [14]?"

Sincerely.

Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this paper.

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