International Journal of Cardiology 289 (2019) 99–100

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Cheyne-Stokes respiration in heart failure: Only provocative pathophysiology will provide new insights!

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ARTICLE INFO

Article history:
Received 26 April 2019
Accepted 29 April 2019
Available online 3 May 2019

Cheyne-Stokes respiration (CSR) - a type of periodic breathing characterised by periods of hyperventilation (crescendo-decrescendo pattern) that alternate with central apneas - is highly prevalent in patients with systolic heart failure (HF) [1–3]. CSR has been hypothesised to further increase sympathetic drive and stroke volume, thus exerting detrimental effects if left untreated [4]. At least, this is what most people thought prior to publication of the SERVE-HF trial in 2015 [5]. This trial enrolled more than 1300 patients with systolic HF and central sleep apnea who were randomly assigned to adaptive servo-ventilation (ASV) added to guideline-based medical therapy compared with guideline-based medical therapy alone (control) [5]. ASV significantly reduced the number of respiratory events compared to both baseline values and control subjects, but unexpectedly, both all-cause and cardiovascular mortality rates were significantly increased in the ASV versus control group (by 28% and 34%, respectively) [5]. These results were in sharp contrast to data from previous cohort studies, small randomized trials and meta-analyses which preceded the SERVE-HF trial and suggested that CSR is detrimental in systolic HF and deserves to be treated [3,6].

However, the results of this trial challenged this hypothesis and revitalised two provocative thoughts that (as most people think) may help explain the unexpected results of the SERVE-HF trial [7,8]:

1) *ASV is toxic in HF.* While ASV obviously corrects CSR from a mere respiratory perspective its long-term effects on cardiac hemodynamics and/or sympathetic drive may be different in patients with systolic HF [9]. It was undoubtedly a logical next step to conduct the SERVE-HF trial. However, basic (and more importantly) multidisciplinary respiratory physiological data on the long term effects of ASV on sympathetic drive (that our pathophysiological understanding of systolic HF spins around) were scarce at best.
2) *CSR is a compensatory mechanism of the failing heart.* This is a hypothesis now commonly referred to as the Naughton hypothesis since it was elegantly brought up by Matthew Naughton against the mainstream opinion even before the SERVE-HF study was published [8]. Therein, the point was made that, physiologically, CSR may exert beneficial rather than detrimental effects in systolic HF. Beneficial effects are believed to derive from the hyperventilation phase, due to increased venous return and cardiac output, and from the presumed positive effects of hypocapnia on sympathetic drive [8]. Plus, the point was elegantly made that CSR may not further increase sympathetic drive if underlying HF severity is properly adjusted for [8]. Although this hypothesis is intriguing, there is only little and unsatisfactory evidence from basic pathophysiological research supporting it to date. In fact, to the best of these authors knowledge, there is not a single study investigating the effects of spontaneously occurring CSR on sympathetic drive (as invasively assessed by muscle sympathetic nerve activity) in systolic HF. This is the case despite the fact that our pathophysiological understanding of systolic HF spins around sympathetic drive. Nor are there many studies critically investigating the effects of CSR on cardiopulmonary hemodynamics.

In this context, it is highly commendable that *Giannoni et al. now present a study which investigates the impact on daytime CSR on hemodynamics and surrogates of sympathetic drive in patients with HF.* Using an innovative approach by combining respiratory monitoring and echocardiography, the authors were able to comprehensively analyze hemodynamic changes throughout the CSR cycle. Central apneas increased pulmonary vascular resistance supporting possible detrimental effects on cardiac function in the long run. In addition, chemoreflex evaluation was performed and elegantly revealed that CSR and chemosensitivity to hypercapnia -that underlies CSR- are related to adrenergic overactivity. These findings were overdue from a basic respiratory physiological standpoint and justify to further explore whether and how CSR and central apneas should be treated in patients with HF. Notably, the present study also shows that the net effect of a CSR breathing pattern is likely to be detrimental. This is a crucial puzzle finding since it has been previously suggested that whatever negative (may it be hemodynamics or sympathetic drive) effects may originate from central apneas may be reversed during the subsequent hyperventilation phase [10]. Obviously, the negative effects (i.e. in the present elegant work: the increase in

DOI of original article: https://doi.org/10.1016/j.ijcard.2019.03.033.
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https://doi.org/10.1016/j.ijcard.2019.04.094

pulmonary vascular resistances) seen during the apnea phase are not fully reversed in the subsequent hyperventilation phase hence speaking out against the Naughton hypothesis that CSR exerts beneficial effects in systolic HF.

But why have people become sceptical about treatment of CSR in systolic HF in general after the SERVE-HF trial was published? Is this really related to unsolved pathophysiological issues only or does it teach the scientific community something else, too?

Undoubtedly, the SERVE-HF trial was a milestone in terms of applied respiratory pathophysiology. It clearly showed that our understanding of CSR and its prognostic relevance is still limited. However, beyond the unexpected study result it is even more surprising how fast pathophysiological beliefs appear to have changed and how fast the interest in CSR in systolic HF has decreased thereafter [7].

It is a given fact that CSR affects approximately every third patient with systolic HF, and central apneas are present not only during nighttime but also during daytime in many patients [1–3]. It is therefore now more than ever mandatory to explore its pathophysiological nature, and it is the innovative effort of basic respiratory physiologists from which new insights will arise. *Giannoni et al*'s report is therefore undoubtedly a crucial step towards this avenue. It will stimulate additional research on CSR and central apneas in HF that may offer novel approaches to help improve treatment strategies and prognosis for patients with systolic HF.

Conflict of interest

The author reports no relationships that could be construed as a conflict of interest. However, Dr. Jens Spiesshoefer is supported by Else-Kröner-Fresenius Stiftung (Grant A109) and by Kommission für Innovative Medizinische Forschung an der Medizinischen Fakultät Münster (IMF Grant SP 11 18 15) for basic respiratory physiology work related to heart failure.

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