EDITORIAL

Bigger numbers needed!

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In this issue of the *European Respiratory Journal*, ROEBUCK *et al.* [1] assess the effect of Cheyne-Stokes respiration (CSR) on mortality in patients with heart failure. Of the 78 patients, the largest patient group studied so far, CSR was present in 33 (42%). After 500 days of follow-up, mortality was increased in patients with CSR, but after a median of 52 months of follow-up, this difference was no longer present.

Congestive heart failure is one of the leading causes of morbidity and mortality in developed countries and, despite advances in pharmacological therapy, incidence rates are still rising. Ever since the description of apnoeas followed by a waxing and waning breathing pattern (Cheyne 1818 and Stokes 1854), the occurrence of breathing disturbances in chronic congestive heart failure has been recognised in the medical community. However, until a couple of years ago, many may have thought that CSR was a rare condition occurring in a few patients with end-stage heart failure or severe stroke. In fact, several studies published in recent years uniformly demonstrate that CSR is a very common problem in patients with stable congestive heart failure, with prevalence rates ranging 33–40% [2, 3]. CSR leads to several unfavourable consequences: hypoxia, arousal from sleep, sympathetic activation, blood pressure surges and susceptibility to cardiac arrhythmia [4–6]. Pulmonary capillary wedge pressure (PCWP), as a likely cause of CSR [7], and right heart load, as a consequence of CSR [8], are increased in heart failure patients with CSR, as compared to those without CSR, despite a comparable reduction of left ventricular ejection fraction in both groups.

The pathophysiological concept to explain CSR in heart failure that has received most attention suggests that hyperventilation due to pulmonary congestion leads to a drop of CO₂ pressure below the apnoeic threshold, especially during nonrapid eye movement sleep [9, 10]. Prolonged circulation time and increased ventilatory response to CO₂ cause sustained oscillations of breathing [11]. An important finding to support this concept is the almost complete elimination of CSR with supplemental CO₂ [12, 13].

Given all the above-mentioned negative consequences of CSR, one would expect that mortality in heart failure patients with CSR is higher than in those without CSR. However, studies addressing this hypothesis have shown conflicting results. Out of the six studies with a follow-up period of ≥ 2 yrs that have been published so far, three have reported increased mortality in chronic stable heart failure patients with CSR as compared to those without CSR [14–16]. In contrast, the other three studies [1, 17, 18], including the one by ROEBUCK *et al.* [1] published in this issue of the *ERJ*, observed no increased mortality in patients with CSR.

Which factors contribute to these discrepant results? First of all, the cut-off point for the apnoea/hypopnoea index differed in all studies, mainly because there is no accepted

"normal value" for CSR. One might speculate that by choosing more severely affected patients, like in the two positive studies by LANFRANCHI *et al.* [15] and SIN *et al.* [16], the chances of demonstrating an effect of CSR on mortality increase.

Secondly, statistical methods and end-point definitions varied.

A third contributing factor could be the varying drug treatment throughout the studies. Optimisation of heart failure therapy after the initial sleep study influences the results, because, almost certainly, improved medical treatment reduces CSR [19]. This causes a bias towards a negative result.

The follow-up time is another crucial point. Whereas after 500 days there was a significant difference in mortality in patients with CSR as compared to those without CSR, this effect was no longer present at the end of the study after 52 months. One might argue that severe CSR exerts its negative effects on mortality early on during the follow-up phase, leaving patients without CSR in both groups and thus lead to a similar mortality rate in a sufficiently long follow-up period.

Only the studies by ROEBUCK *et al.* [1] and by TRAVERSI *et al.* [18] provide right heart catheter data. Increased PCWP is clearly linked to the occurrence of CSR and is also a known risk factor for mortality in heart failure patients. Thus, even if CSR is a mere consequence of increased PCWP, in sufficiently large studies, CSR should turn out to be related to increased mortality due to the increased PCWP in CSR patients. However, in the study by ROEBUCK *et al.* [1] this was not demonstrated. This fact emphasises the lack of statistical power despite the largest patient group studied so far.

Finally, let us take a closer look at the number of patients analysed to date. All six studies included a total of only 318 patients, 139 of them with CSR. In the three studies that did suggest an effect of CSR on mortality, a total of 56 patients with CSR were included. Additionally, statistical power calculation has not been reported in any of the studies published so far. Even in the absence of CSR, heart failure patients have a poor prognosis. Multiple complications arising from heart failure itself and possible underlying diseases like coronary heart disease, myocardial infarction, arrhythmia, *etc.*, may lead to death independent of breathing disorders during sleep. Patients on the transplant list will be transplanted if an organ is available and not necessarily because of deterioration of heart failure. Therefore, many confounding factors are present in these patients, making it difficult to detect the effect of a single additional factor like CSR on mortality.

Indeed, the study by ROEBUCK *et al.* [1] deals with a clinically important question: does CSR increase mortality in chronic heart failure patients? ROEBUCK *et al.* [1] do not come to the conclusion that this is not the case, but that they did not find a mortality increase after a median follow-up period of >4 yrs. They, therefore, conclude that mortality increase has not been proven!

The consequence of their paper should not be diagnostic

and therapeutic nihilism. We have to admit that the currently available clinical studies are only a drop in the ocean. As a consequence, additional large multicentre trials with sufficient statistical power and optimal design should be initiated to address the gaps in our knowledge. Bigger numbers are indeed needed!

References

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