Heart rate recovery in obstructive sleep apnea: scientific toy or clinical tool?

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Autonomic dysfunction is a hallmark of the obstructive sleep apnea syndrome (OSA). Intermittent hypoxia and sleep fragmentation are thought to represent the key mechanisms promoting sympathetic overactivity and blunted vagal tone even during wakefulness in OSA. Muscle sympathetic activity (MSNA) is increased in OSA compared to controls [1] and treatment with continuous positive airway pressure (CPAP) can reverse this [2]. However, the measurement of MSNA is a demanding technique. In recent years, a simpler measure of autonomic tone has become very popular in a variety of settings including OSA: heart rate recovery (HRR), which simply measures how quickly heart rate is reduced after exercise. The seminal study by Cole et al. [3] promoting an intense interest in HRR showed that among subjects undergoing a maximal treadmill test for the evaluation of possible coronary artery disease, those with a reduction in heart rate within the first minute after exercise termination (HRR-1) of 12 beats or less had a substantially worse outcome than those with HRR-1 >12 bpm. The theoretical background for the application of HRR as a measure of autonomic tone comes from a study by Imai et al. [4] showing that the time constant of the decrease in heart rate during the first 30 s after exercise was influenced by atropine but not propranolol administration, whereas the time constant of the decrease in heart rate during the first 120 s after exercise was influenced by both atropine and propranolol. This led to the paradigm that HRR-1 is mainly a marker of vagal reactivation after exercise, whereas HRR during the first

2 min after exercise also reflects sympathetic withdrawal. In the present issue of the journal, Chien and colleagues [5] present a novel analysis of HRR-1 in OSA. It is therefore appropriate to quickly review the context of this research and to discuss its implications.

In the first study looking at the association between HRR-1 and OSA severity [6], we had shown that in a population with a large range of apnea–hypopnea index (AHI), HRR-1 was slower in patients with severe OSA compared to those with mild or moderate OSA, and HRR-1 was independently associated with AHI. In a cohort of morbidly obese patients, Vanhecke et al. [7] found that those with OSA had slower HRR than those without. Similarly, Hargens et al. [8] demonstrated that overweight young men with OSA had significantly slower HRR than men with similar body mass index but without OSA and men with normal weight and without OSA. Thus, the results of these studies were overall consistent. However, the average body mass index was more than 30 kg/m² in all three studies, and it remained somewhat unclear whether the reduction in HRR was mediated by OSA per se or rather by obesity or the interaction between obesity and OSA. The paper by Chien et al. [5] in this issue of the journal further improves our understanding on HRR in OSA for two reasons. First, the authors were able to recruit two age- and gender-matched (men only) OSA and non-OSA populations with similar and relatively low body mass index, which is a remarkable achievement. Although the average body mass index of approximately 26 kg/m² is within the overweight range, particularly in Asians, this study best demonstrates that HRR-1 is indeed reduced in OSA because the confounding impact of obesity has been minimized.

Second, the authors demonstrated elevated plasma concentration of high-sensitivity C-reactive protein (hs-CRP) and

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an association between elevated hs-CRP and blunted HRR-1. The association between OSA and elevated hs-CRP is not novel [9], but again, it is remarkable to see this even in a non-obese population of subjects with and without OSA. The nature underlying the association between elevated hs-CRP and blunted HRR-1 remains unclear however. On one hand, both hs-CRP and HRR-1 are markers of OSA and OSA severity, and there may be no causal relationship. On the other hand, it is possible that a blunted vagal tone leads to a blunted inhibition of the inflammatory response (“inflammatory reflex”), or the inflammatory state leads to autonomic dysfunction. We had previously shown that in OSA patients (mean age 53 years versus 51 years in the present study), higher insulin resistance and higher total cholesterol (not measured in the present study) were independently associated with slower HRR-1 [10]. It is possible that by an association with the metabolic changes hs-CRP was related to HRR-1 in the present study. However, in an uncontrolled study we had also shown that in patients with severe OSA, HRR is improved by CPAP [11], while recent studies on the effects of CPAP on hs-CRP and insulin resistance have been neutral [12, 13]. Thus, the relationship between HRR-1 and hs-CRP seems to be more complicated and remains to be elucidated.

A key question now is whether HRR in OSA is of any clinical value. Would HRR help to identify those with the strongest inflammatory response or the worst metabolic profile or those who will benefit most from CPAP? At the moment, the answer is no because the associations between HRR and measures of interest are not strong enough, studies evaluating to the use of HRR as a tool to guide decisions in patients with OSA are not available, and importantly because the methodology of HRR assessment is an issue. Heart rate recovery depends on the mode of exercise (treadmill versus cycle exercise), the type of exercise (maximal versus submaximal), and the mode (active cool down versus passive) and position (sitting versus supine) of recovery [14]. Unfortunately, studies have been heterogeneous with respect to all these aspects. Thus, at the moment, HRR is not a clinical tool yet. To change this, we would first need a rigorous standardization of its assessment. This would be the basis for further and larger studies on the role of HRR in OSA. Why should then HRR not become a simple global risk marker in OSA?

Conflicts of interest The author has no conflicts of interest to declare.

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