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Heart rate recovery: what now?

Physicians have known for hundreds, perhaps thousands, of years that the pulse and its rate are simple, yet powerful, measures of human health [1]. In the early 17th century, Santorio Sanctorius (1561–1636) invented the 'pulsilogy', a clever pendulum-like device by which physicians could quantitatively assess pulse rate. About 100 years later, John Floyer (1649–1734) became the first physician to formerly measure pulse as number of beats per minute. His work stimulated others to correlate pulse with other measures like age and fever [1]. In 1843, a physician correspondent to the *Lancet* commented on changes in pulse with stress, writing 'The pulse in rising and falling from accidental and temporary excitement, rises and falls through a series of duodecimal degrees; when within the first few minutes of an interview the pulse of a patient rapidly subsides from 120 to 108, 96, 84, a knowledge is at once afforded of the highly excitable and therefore susceptible constitution of the patient' [2]. This may be one of the earliest recordings of the clinical implications of heart rate changes occurring during and after stress.

Over the past 50 years, scientists have come to better appreciate links between heart rate and health, links that may reflect fundamental pathophysiological processes [3]. Amongst vertebrates, there is a strong inverse association between resting heart rate and life expectancy. In 1971, Coburn *et al.* [4] showed that low-dose digoxin, a parasympathomimetic agent that slows heart rate, could prolong life in mice. In 2008, Custodis *et al.* [5] used a knockout mouse model to show that ivabradine, an agent that slows heart rate at the level of the sinus node, can slow development and progression of atherosclerosis. In humans, there are extensive epidemiological data showing that higher resting heart rates predict greater mortality [3, 6]. Amongst patients randomized to beta-blockers in postmyocardial infarction trials, the magnitude of survival benefit correlates most strongly with the drug-induced reduction in heart rate [7]. And just last year, Swedberg *et al.* [8] showed in a randomized trial of over 6500 patients that ivabradine reduces the risk of heart failure hospitalization and death, particularly amongst patients with higher heart rates at baseline [9]. Although there is still much to learn, resting heart rate has evolved as a measure going from a pathophysiological phenomenon to an independent epidemiological risk factor all the way to a viable treatment target.

Now there is increasing interest in heart rate changes with stress [3]. With the onset of physical or mental stress, there is an abrupt withdrawal of central nervous system vagal output, along with a gradual increase in sympathetic tone. During stress, heart rate is largely driven by increasing sympathetic tone, which is modulated by both central and hormonal factors. The increase in heart rate is known as the 'chronotropic response' [3]. Investigators studying healthy adults in the Framingham Heart Study showed that an impaired chronotropic response, or 'chronotropic incompetence', predicts a higher risk of death or major cardiac events [10]. These findings were later confirmed in clinical cohorts [11].

In 1994, Imai *et al.* [12] showed that vagal tone is reactivated rapidly within the first 30–40 s following exercise, but this reactivation is blunted in heart failure. Cole *et al.* [13] took advantage of these observations to evaluate the link between the decline in heart rate in the first few minutes after exercise, or 'heart rate recovery', and mortality. In a cohort of 2428 patients who were candidates for first-time coronary angiography and who were referred for treadmill myocardial perfusion imaging, heart rate recovery emerged as an independent predictor of death, even after accounting for exercise capacity, chronotropic response and evidence of myocardial ischaemia.

Since Cole *et al.*'s report, other groups have confirmed the association between heart rate recovery, its link to parasympathetic reactivation [6, 14] and adverse cardiovascular outcomes. An impaired heart rate recovery predicts in men and women all-cause mortality [15], cardiovascular mortality [16], sudden cardiac death [17], heart failure mortality [18] and even risk of developing atrial fibrillation [19]. Heart rate recovery has also been linked to other disease pathways, in particular insulin resistance [20]. In an animal model, heart rate recovery predicts susceptibility

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to developing ventricular fibrillation during the first few minutes of an experimental myocardial infarction [21]; this observation reflects a finding in humans that heart rate recovery is a better predictor of sudden death than other modes of cardiac death [17]. It is conceivable that heart rate recovery reflects the ability of the parasympathetic nervous system to protect the heart from ischaemia-induced arrhythmias.

In the current issue of the *Journal of Internal Medicine,* Savonen *et al.* [22] followed the outcomes of 1102 healthy middle-aged men who underwent cycle ergometry as part of a standard evaluation within a population-based East Finland cohort study. During 18 years of follow-up, 238 men died. In their carefully performed study, the investigators found that heart rate recovery predicted death, even after accounting for standard risk factors. However, the association was markedly attenuated by chronotropic response and exercise capacity. It is not clear why the authors' findings are at odds with previously published reports. One likely reason is the absence of a uniform recovery protocol. Admittedly, the absence of internationally accepted and adopted exercise recovery protocols represents a major limitation in comparing reports and in implementing clinical recommendations. The authors used cycle ergometry; some investigators have found that cycle ergometry, as compared to treadmill exercise, may lead to altered measures of functional capacity and heart rate recovery (particularly during the first minute after exercise) [23].

What now for heart rate recovery? The time has come to redirect focus towards therapeutic implications. A number of tantalizing, though small, reports suggest that heart rate recovery can be modified with exercise training [24], weight loss [25], bariatric surgery [26], angiotensin-converting enzyme inhibitors [27], pyridostigmine (a cholinesterase inhibitor) [28] and even statins [29]. One group found that heart rate recovery may predict which heart failure patients are most likely to respond to biventricular pacing [30]. Should otherwise healthy adults with abnormal heart rate recovery be targeted for primary prevention interventions, including rigorous exercise programs? Should heart rate recovery be used to identify patients who might be most likely to benefit from heart rate modulating and other therapies? Could heart rate recovery itself function as a viable treatable biomarker, similar to resting heart rate in patients with established disease? Should our new insights into the central role of heart rate and autonomic dysfunction stimulate us to develop and test new wholly new approaches, including modulators like ivabradine and pyridostigmine? By thinking about questions like these, the scientific community can further leverage medicine's longstanding fascination with heart rate into new paradigms for improving health.

Conflict of interest

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