Commentary: Heart rate and blood pressure: risk factors or risk markers?

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In this issue of the Journal, Nagaya and colleagues\(^1\) tested whether resting blood pressure and heart rate are each associated with the development of type 2 diabetes in middle-aged adults. The novelty of their study is the hypothesis that elevated blood pressure and heart rate are involved in the development of type 2 diabetes. Having failed to reject the null hypothesis of no association, the authors conclude that ‘resting heart rate and BP [blood pressure] ... proportionately raise the risk for development of DM [diabetes mellitus] in middle-aged healthy men and women’.\(^1\) However, it is not clear whether such strong causal language is justified without first considering what heart rate and blood pressure really represent.

One of Sir Bradford-Hill’s (1897–1991) criteria for determining causality is **consistency**—namely that the association is more likely to be causal if it can be observed in different settings and using different methods.\(^2\) Thus, the present study strengthens the argument that there is an association between heart rate and incident diabetes since, as the authors point out, most of the prior research was carried out by a small group of investigators in collaboration with numerous research teams.\(^3\)–\(^7\) Consequently, it is refreshing to observe similar findings by an entirely separate set of investigators. Despite the strengths of the present study and the meaningful contribution to the field of study, the authors seem not to have met another one of the Bradford-Hill’s criteria for causality: ‘biological plausibility’. In their Introduction and Discussion, the authors assert that heart rate and blood pressure *per se* influence glucose tolerance and the development of diabetes when it is far more likely that these haemodynamic processes represent some underlying pathophysiological mechanism associated with glucose homeostasis.

Nearly all definitions of the metabolic syndrome include diabetes and elevated blood pressure (alongside abdominal adiposity and dyslipidaemia),\(^8\) as the two are considered correlates that have developed secondary to excess adiposity or insulin resistance. The authors note that heart rate is typically not included in metabolic syndrome definitions despite the direct correlation of heart rate with blood pressure and fasting glucose. The even stronger association of heart rate variability with blood pressure and fasting glucose in cross-sectional studies,\(^9\) provides a hint that autonomic nervous system dysfunction may be a common mechanism underlying all three factors.

A healthy heart rate is characterized by high beat-to-beat variability, which reflects inputs from the autonomic nervous system and the endocrine system. The autonomic nervous system is responsible for automated body functions including heart rate, blood pressure, digestion and metabolism. The parasympathetic division of the autonomic nervous system slows heart rate and blood pressure to promote digestion, whereas the sympathetic division enacts antagonistic actions on those same systems. In a physically and psychologically healthy person, the sympathetic response arises in the presence of physical or psychological stimuli requiring glucose in the blood stream that can be used for immediate energy (i.e. ‘fight or flight’). At the same time, autonomic nerve fibres on the walls of the blood vessels constrict in response to sympathetic input and parasympathetic withdrawal to raise blood pressure in preparation for postural changes or other major skeletal muscle movement.

Whereas autonomic nervous system dysfunction is an established complication of diabetes expressed as diabetic autonomic neuropathy, glucose and insulin are regulated by a feedback cycle that is controlled in part by autonomic inputs. Parasympathetic and sympathetic nerve fibres are present in each of the major organs and body systems that control metabolism including the pancreas and liver. If systems were awry, autonomic nervous system imbalance could result in the underproduction of insulin in the pancreas or the slowing of glucose uptake by the liver, resulting in steadily rising glucose unabated by insulin release. Similarly, chronic sympathetic overactivity minus the counterbalancing influence of the
parasympathetic division could lead to higher blood pressure.

Our understanding of these biomechanical relationships provides evidence in support of the observed associations among heart rate, blood pressure and diabetes that are presented in Nagaya’s report. However, they do not support the argument that blood pressure and heart rate per se are ‘risk factors’ for the development of diabetes. In the precise language of the epidemiologist, blood pressure and heart rate can most appropriately be considered ‘risk markers’ that reflect a common process underlying blood pressure, heart rate and diabetes. To describe it otherwise is to apply the fallacy that correlation is equal to causation, which is not biologically plausible in the present argument.

There is a considerable benefit in identifying risk markers for diabetes that can be easily measured in clinical practice. Blood pressure and heart rate are routinely collected during health provider encounters in the US medical system. Because such measurements are not standardized in clinical practice as they are in research (e.g. required resting time of at least 5 min, repeated measurements), a single measure is only conditionally informative. However, extremely high (or low) values or repeated measures over time in heart rate and blood pressure that indicate marked worsening (i.e. individual temporal trends), should be flagged for follow-up and close observation.

In conclusion, elevated blood pressure and heart rate reflect a high-risk state for metabolic disorders. That autonomic nervous system dysfunction may underlie elevated blood pressure and heart rate is important given the growing body of research correlating autonomic nervous system function with physical inactivity, diet, psychological distress, sleep patterns and socio-economic status. Many of those same factors are associated with the development of diabetes, hypertension and clinical cardiovascular disease and are amenable to modification. When interpreted carefully, well-designed epidemiological studies such as those published by Nagaya and colleagues in this issue of the Journal, have the potential to positively influence the health of the population by identifying risk markers for important sources of morbidity and mortality.

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**References**


