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COMMENT

Resting heart rate as a possible biomarker and target to prevent future cardiovascular disease in type 2 diabetes patients (HTR-2023-0066.R2)

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Elevated resting heart rate has been associated with development of cardiovascular disease and mortality in patients with a variety of conditions such as diabetes, hypertension, cardiovascular disease, and COPD [1, 2]. Elevated resting heart rate has many causes, including hypoxemia, low circulating plasma volume, cardiac dysfunction, respiratory dysfunction, and anemia. These causes have a final pathway of imbalance between the sympathetic and parasympathetic nervous systems. In patients with diabetes, resting heart rate has been associated with all-cause mortality and cardiovascular events [3]. It is generally believed that the main cause of increased heart rate in diabetes is due to imbalance of the sympathetic nervous system and the parasympathetic nervous system from parasympathetic denervation.

Cardiovascular autonomic neuropathy (CAN) may contribute to elevated resting heart rate in patients with diabetes [4]. CAN is a complication of microangiopathy and is defined as a problem with cardiovascular autonomic regulation in patients with diabetes without other causes [4]. Despite its significant negative impact on survival and quality of life of people with diabetes, CAN remains a poorly recognized and understood disease. The prevalence of CAN in patients with diabetes has been reported to be as low as around 2% in newly diagnosed or well-controlled patients, while it has been reported to reach as high as 60% in people with long-standing type 2 diabetes [4]. Although the mechanisms of CAN have not been well clarified, the main cause is thought to be hyperglycemia in the long-term course of diabetes, resulting in the accumulation of advanced glycation end products (AGEs). Accumulation of AGEs inside and outside a cell leads to subsequent activation of intracellular signaling systems such as phosphatidylinositol-3 kinase (PI3-K) or mitogen-activated protein kinases (MAPK), and consequently activating nuclear factor kappa B (NF-kB) which leads to the provocation of positive feedback of AGE/RAGE signaling. These signaling cascades lead to increased production of reactive oxygen species and inflammation, and these may lead to parasympathetic denervation [4]. CAN is difficult to detect because it generally progresses asymptomatically in patients with chronic type 2 diabetes for years, even CAN is a significant risk for future cardiovascular disease. Because the presence of diabetic retinopathy is closely associated with diabetic neuropathy, it is likely that many patients with retinopathy have concurrent neuropathy, including CAN [5].

Ikeda et al. investigated the relationship between resting heart rate and the onset of cardiovascular disease in patients with diabetic retinopathy and no prior cardiovascular disease or renal dysfunction [6]. Resting heart rate ≥ 70 bpm was associated with risk of cardiovascular events in a dose-dependent manner compared with patients with resting heart rate 60-69 bpm [6]. As the authors state, there have been few studies to date that have examined the relationship between resting heart rate and cardiovascular events in people with type 2 diabetes without a previous history of cardiovascular disease. This study selected people with type 2 diabetes and retinopathy without previous cardiovascular disease. Although diabetic retinopathy itself is a risk factor for cardiovascular disease, resting heart rate may be a useful tool for risk stratification for the future cardiovascular events. Ikeda and colleagues observed that resting heart rate was associated with the incidence of cardiovascular disease even in those without overt cardiovascular disease at

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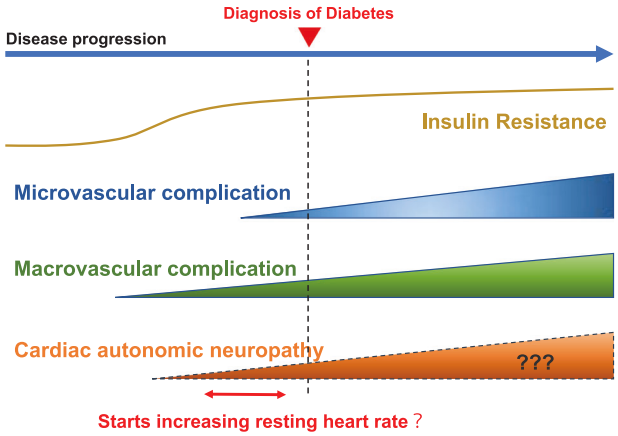

Fig. 1 Disease progression and timing of associated vascular complication and cardiac autonomic neuropathy in type 2 diabetes

baseline, suggesting increased resting heart rate may reflect latent progression of cardiovascular disease [6]. The Fig. 1 shows the time course of angiopathy during the progression of diabetes. Although the time course of CAN in patients with type 2 diabetes has not been elucidated, parasympathetic nerve damage, which is the initial stage of CAN, may begin in the pre-diabetic stage. Sympathetic nervous activity becomes dominant, and resting heart rate may be elevated by the time when overt type 2 diabetes is diagnosed (Fig. 1). Once cardiovascular disease develops in patients with diabetes, it could impact patients' lives considerably, so it's important to detect it at an early stage and prevent the progression of disease. Several clinical tests including heart rate variability and MIBG scintigraphy have been used to diagnose CAN, but the resting heart rate could be a part of a comprehensive evaluation in combination with these tests which can be used to detect CAN at an early stage. Thus, CAN may play a role as a marker for predicting cardiovascular disease in patients with diabetes.

As mentioned above, the increase in heart rate itself is highly likely to be a marker that suggests the latent progression of cardiovascular disease in diabetes. On the other hand, what about its potential as a therapeutic target? Previous studies showed that even in diseases other than diabetes, an elevated heart rate is associated with the onset of cardiovascular disease and death. As the authors described in the discussion, previous studies have also investigated the possibility that an elevated resting heart rate itself may adversely affect the cardiovascular system. In basic experiments, increased resting heart rate has been associated with coronary atherosclerosis, vascular endothelial dysfunction, arteriosclerosis, and increased arterial stiffness [7–9]. High resting heart rate is also associated with various serum biomarkers of arteriosclerosis [10]. In animal experiments, the decrease in heart rate by ivabradine, which is a heart-rate-lowering agent that acts by selectively and specifically inhibiting the cardiac pacemaker current (I_f), suppressed the decrease in endothelial function, arteriosclerosis, and arterial compliance [11]. Also, treatment with ivabradine appears to improve endothelial function, vascular stiffness, and symptoms in sinus tachycardia in humans [11]. In addition, it has been reported that high resting heart rate is related to the development and worsening of diabetes itself. These findings suggest that an increased resting heart rate itself may be a therapeutic target and randomized controlled trials to clarify whether suppressing increased resting heart rate is effective to prevent the development of cardiovascular disease are warranted.

In conclusion, resting heart rate may play a role as an early marker for latent progression of cardiovascular disease in patients with type 2 diabetes without cardiovascular disease. In addition, higher resting heart rate is a potential new therapeutic target for cardiovascular disease prevention, and further clinical trials in this field are warranted.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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