Clinical Implications of Baroreflex Sensitivity in Type 2 Diabetes
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Summary
The evaluation of baroreflex sensitivity (BRS), which maintains systemic circulatory homeostasis, is an established tool to assess cardiovascular autonomic neuropathy in type 2 diabetes mellitus (T2DM). As BRS plays an important function in blood pressure regulation, reduced BRS leads to an increase in blood pressure variability, which further leads to reduced BRS. This sequence of events becomes a vicious cycle. The major risk factors for reduced BRS are T2DM and essential hypertension, but many other risk factors have been reported to influence BRS. In recent years, reports have indicated that glycemic variability (GV), such as short- and long-term GV that are considered important risk factors for macrovascular and microvascular complications, is involved in reductions in BRS independently of blood glucose levels. In this review, we discuss reduced BRS in T2DM, its features, and the potential for its reversal.

Key words: Cardiovascular autonomic neuropathy, Short-term glycemic variability, Long-term glycemic variability, Visit-to-visit glycemic variability

Cardiovascular autonomic neuropathy (CAN), an early complication of type 2 diabetes mellitus (T2DM), is among the most common complications in T2DM and is associated with cardiovascular (CV) events.1-3) Evaluating baroreflex sensitivity (BRS), which, in particular, decreases in patients with T2DM accompanied by hypertension, is an established tool to assess CAN. In addition to the physiological role by which BRS maintains systemic circulatory homeostasis, accumulated evidence indicates that changes in BRS reflect alterations in autonomic control of the CV system. BRS is also associated with CV events,4,6) furthermore, BRS tests have higher sensitivity and specificity than classic laboratory autonomic function tests, such as those for heart rate variability.7,8) Therefore, the measurement of BRS is a source of valuable information in the clinical management of T2DM, particularly in risk stratification. In this review, we discuss reduced BRS in T2DM, its features, and the potential for its reversal.

Assessment of Baroreflex Sensitivity
When the baroreceptors located in the carotid sinus and the aortic arch stretch as blood pressure increases, information is transmitted through the glossopharyngeal and vagus nerves to the CV control center in the medulla oblongata, where the inputs are integrated and controlled. In the same region, efferent parasympathetic nerve activity is enhanced and sympathetic nerve activity is inhibited. Blood pressure is regulated not only by changes in the sympathetic nerve activity that affect the reflex regulation/control of vascular resistance and the heart rate, but also by changes in parasympathetic nerve activity that affect only the heart (Figure 1).

The measurement of BRS, which is a sensitive measure of CAN, is a source of valuable information in the clinical management of T2DM. Several methods are available to determine BRS in humans, such as the Oxford method, neck chamber method, and sequence method. In the Oxford method,9,10) vasoactive drugs, such as phenylephrine and nitroprusside that have relatively small effects on the sinus node, are used to increase or decrease blood pressure, followed by the evaluation of BRS after measuring the reflex changes in the R-R intervals; however, limitations exist in actual clinical practice because this method is highly invasive and can produce only one value from a single drug dose. When measuring BRS by the neck chamber method,9,10) a chamber is placed around the neck and the carotid sinus baroreceptors are stimulated by positive or negative pressure indirectly applied to the carotid arteries. However, as with the Oxford method, its use in daily clinical practice is limited because it is also highly invasive. Recently, the sequence method has been used to evaluate BRS noninvasively.9,10) First, in this method, only the sequences during which the blood pressure reading and R-R interval synchronously increase or decrease for more than three consecutive beats are extracted (up- or down-sequence); second, a gain in BRS is
calculated using the least-squares method after plotting the blood pressure and R-R interval for each sequence; and finally, the average of all gains is taken. This method has major advantages in that it is noninvasive, easy to use, and yields many values from a single test. In addition, estimates obtained from the sequence method were correlated significantly with BRS assessed with the Oxford method. Due to accumulated evidence on the relationships between BRS and CV events as assessed by the sequence method, BRS assessed in this way is an extremely useful indicator to predict CV events and prognosis in individuals with T2DM.

Clinical Features of Reduced Baroreflex Sensitivity

The major risk factors for the reduction of BRS are T2DM and essential hypertension, but many other risk factors that have been reported to influence BRS are shown in Figure 2.

Aging: Older age is a key factor in reduced BRS. Although the detailed mechanism responsible for the decrease in BRS with aging has not been elucidated, loss of arterial distensibility has been proposed as the major mechanism responsible for reduced BRS in elderly patients. On the other hand, a defect in central mediation of the baroreflex rather than loss of arterial distensibility has been reported as a factor involved in the decreased BRS in elderly patients.

Dyslipidemia: It was shown that BRS determined by the sequence method was correlated significantly and independently with levels of serum total cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglycerides in patients with hypertension and that patients with dyslipidemia on regular LDL apheresis treatment had significantly reduced BRS. In nonobese patients with T2DM and dyslipidemia, low doses of atorvastatin improved BRS; other studies also showed that statin increased BRS. As a large percentage of patients with T2DM develop dyslipidemia, proper control of both blood glucose levels and lipid metabolism variables is important to prevent a reduction in BRS.

Obesity, insulin resistance, hyperinsulinemia, and hypoadiponectinemia: BRS was reported to be decreased markedly in an obese group compared to a control group, indicating that obesity was a factor in sympathovagal imbalance (increased sympathetic nerve activity and decreased parasympathetic nerve activity). Furthermore, a report showed that males with increased total and abdominal visceral fat volumes experienced reduced BRS in contrast with those with lower volumes of total and abdominal visceral fat. The majority of patients with T2DM are obese, and exacerbation of obesity-related insulin resistance or obesity-related hyperinsulinemia is becoming known as an important cause of reductions in BRS. Insulin resistance was shown to be related to reduced BRS, and elevations in fasting plasma insulin were associated with reductions in BRS. In patients with T2DM, hypoadiponectinemia has been linked to a reduction in BRS. Weight loss caused by a hypocaloric diet improved BRS in obese normotensive individuals.

Atherosclerosis: Patients with T2DM are more likely to develop atherosclerosis due to a high co-occurrence of hypertension and dyslipidemia. According to pulse wave velocity assessments in normotensive and hypertensive patients, atherosclerosis was significantly independently associated with reduced BRS. Recently, we reported that the cardio-ankle vascular index, an indicator of atherosclerosis, was independently associated with BRS. In a carotid bulb containing highly concentrated baroreceptors, increased intima-media thickness was also reportedly associated with reduced BRS.
Baroreflex Sensitivity and Variability of Blood Pressure

BRS was shown to be damaged by multiple factors, but hypertension, in particular, is considered an important risk factor for reduced BRS. As BRS plays an important function in blood pressure regulation, reduced BRS leads to an increase in blood pressure variability (BPV), which further leads to reduced BRS. This sequence of events becomes a vicious cycle. A large percentage of patients with T2DM develop hypertension, further exacerbating their prognoses; BPV, as well as individual blood pressure readings, has been reported as an important risk factor for CV events. Compared to patients with T2DM alone, those with T2DM accompanied by hypertension experience a more severe disease condition, including the relative enhancement of sympathetic nerve activity caused by autonomic dysfunction, exacerbation of insulin resistance, and atherosclerosis, resulting in reduced BRS and subsequently increased BPV. Therefore, in T2DM with hypertension, blood pressure readings and BPV can be corrected by an early evaluation and effective preservation of BRS using antihypertensive drugs, which may have the potential to improve the prognosis. Recently, baroreflex activation therapy (BAT), which activates baroreceptors in the carotid sinus by electrostimulation induced by an implantable device (Rheos System, CVRx Inc., Minneapolis, MN, USA), inhibits sympathetic nerve activity, and eventually decreases blood pressure, has drawn attention as a nondrug treatment. BAT was shown to decrease blood pressure and BPV in patients with resistant hypertension. BAT also improved BRS and muscle sympathetic nerve activity in patients with chronic heart failure with elevated sympathetic nerve activity. In addition, BAT improved cardiac function, cardiac hypertrophy, N-terminal pro-brain natriuretic peptide, and exercise tolerability, and much evidence has accumulated showing its efficacy in the treatment of heart failure. A prospective multicenter randomized controlled clinical study of the use of BAT in treating heart failure is now in progress, and the inhibitory effects of CV events are anticipated. In terms of pharmacotherapy, calcium
channel blockers, β-blockers, and renin-angiotensin-aldosterone system inhibitors reportedly increase BRS. A calcium channel blocker, an antihypertensive agent, reportedly decreased BPV, therefore, such an agent may act through an as-yet unknown mechanism to improve BRS.

**BRS and Variability of Blood Glucose**

As T2DM is a major risk factor for reduced BRS, which further exacerbates the prognosis of T2DM, it is important to elucidate the mechanism of reductions in BRS to improve the prognosis of patients with these conditions. It is arguable whether pre-diabetes, which is described as impaired fasting glucose impaired plasma glucose (IFG) and impaired glucose tolerance (IGT), is related to BRS. Although BRS was reportedly reduced in patients with IGT in comparison with a control group, another study showed that no significant relationship existed between BRS and IGT. A further study also did not show a significant relationship between IFG and BRS. Blood glucose levels rise soon after meals, and short-term glycemic variability (GV) as assessed on a 24-hour basis is large, with the potential for inducing impaired BRS. In fact, we recently reported that in patients with T2DM, there was an association of increased short-term GV assessed by continuous glucose monitoring with reduced BRS, independently of blood glucose levels. Furthermore, we reported that long-term GV represented by visit-to-visit HbA1c variability over a 2-year period, which is an independent risk factor for CV events, was inversely related to BRS independently of mean HbA1c in patients with T2DM. Details of the mechanism for reduced BRS in patients with T2DM are not yet fully understood. However, as the principal mechanism, various disease conditions, such as those manifested by increased oxidative stress, chronic inflammation, and vascular endothelial dysfunction due to high blood glucose, and damage to nerve cells resulting in apoptosis, were noted according to a report. GV is known to induce oxidative stress and vascular endothelial dysfunction independently of blood glucose levels. Thus, GV may be considered as a mechanism by which BRS reduction occurs. BRS was reduced in patients with IGT diagnosed with pre-diabetes, but in patients with T2DM, it has not been clear when the reduction in BRS begins. We reported previously that the reduction in BRS starts at a relatively early stage of diabetes. Taken together, BRS reduction could potentially be an initial manifestation of the occurrence of diabetic complications. Atherosclerosis is known to cause reduced BRS, but as atherosclerosis occurs in patients with a relatively long duration of diabetes, an early reduction in BRS is not likely to be due to atherosclerosis. A reduction in BRS was reported to occur before the development of atherosclerosis. Therefore, reduced BRS can be both an early marker of CAN in T2DM and a predictive factor for prognosis.

However, only a few antidiabetic drugs show efficacy in altering BRS. Pioglitazone improved BRS in patients with T2DM with a history of myocardial infarction. An animal study showed that rosiglitazone improved BRS, and another study using an animal model demonstrated that metformin increased BRS. As thiazolidinedione and metformin, so-called representative antidiabetic drugs, improve insulin resistance, the increased BRS could be due to the improvement in insulin resistance. Recently, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) Study and the Canagliflozin Cardiovascular Assessment Study (CANVAS) showed that sodium-glucose cotransporter 2 (SGLT-2) inhibitors decreased the incidence of CV events in the early stage of T2DM. GLT-2 inhibitors comprise a new class of antidiabetic drugs that lower blood glucose levels by inhibiting SGLT-2 in the renal proximal tubule and increase urinary glucose excretion. Compensatory enhancement of sympathetic nerve activity was of concern due to a significant diuretic effect of SGLT-2 inhibitors. Loop diuretics used for heart failure are known to increase sympathetic nervous system activity by reducing plasma volume, thus adversely affecting the long-term outcome. Animal testing, however, showed that SGLT-2 inhibitors not only improved BRS but also reduced BPV. Recently, we reported that SGLT-2 inhibitors improved GV in a T2DM model, which may be one of the factors related to the improved BRS in animal studies. We also conducted a prospective study of the effects of 3 months of treatment with a SGLT-2 inhibitor on BRS in patients with T2DM and showed that SGLT-2 inhibitors do not worsen BRS despite their diuretic effect. A large percentage of patients with T2DM have complications of obesity, hypertension, dyslipidemia, and chronic kidney disease, which affect BRS, but as SGLT-2 inhibitors, unlike other antidiabetic drugs, have the effect of comprehensively ameliorating these complications, their efficacy in reducing BRS is expected. More large-scale clinical trials are required to study the effects of SGLT-2 inhibitors on BRS.

**Conclusion**

Reduced BRS is a risk factor for CV events in patients with T2DM. BRS measurement is also useful as a diagnostic test of arteriosclerotic diseases and BPV and GV, such as short- and long-term GV. Routine examinations are recommended in clinical practice, in addition to various coronary risk markers.

**Disclosures**

**Conflicts of interest:** The authors of this manuscript have the following competing interests: M.S. has participated in speaker’s bureaus/advisory panels for Sanofi, Daiichi-Sankyo, Astellas, and Tanabe-Mitsubishi.

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