

## Diabetes and cardiac autonomic neuropathy: Clinical manifestations, cardiovascular consequences, diagnosis and treatment

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dilatation. It causes a wide range of cardiac disorders, including resting tachycardia, arrhythmias, intraoperative cardiovascular instability, asymptomatic myocardial ischemia and infarction and increased rate of mortality after myocardial infarction. Etiological factors associated with autonomic neuropathy include insufficient glycemic control, a longer period since the onset of diabetes, increased age, female sex and greater body mass index. The most commonly used methods for the diagnosis of CAN are based upon the assessment of heart rate variability (the physiological variation in the time interval between heartbeats), as it is one of the first findings in both clinically asymptomatic and symptomatic patients. Clinical symptoms associated with CAN generally occur late in the disease process and include early fatigue and exhaustion during exercise, orthostatic hypotension, dizziness, presyncope and syncope. Treatment is based on early diagnosis, life style changes, optimization of glycemic control and management of cardiovascular risk factors. Medical therapies, including aldose reductase inhibitors, angiotensin-converting enzyme inhibitors, prostoglandin analogs and alpha-lipoic acid, have been found to be effective in randomized controlled trials. The following article includes the epidemiology, clinical findings and cardiovascular consequences, diagnosis, and approaches to prevention and treatment of CAN.

**Key words:** Diabetes mellitus; Autonomic neuropathy; Heart rate variability; Cardiac; Cardiovascular reflex tests

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**Core tip:** Although very frequent, cardiac autonomic neuropathy (CAN) is one of the most commonly overlooked complication of diabetes. Higher incidence of cardiovascular events is encountered with CAN due to its relation with silent myocardial ischemia, arrhythmias, intraoperative cardiovascular instability,

### Abstract

Cardiac autonomic neuropathy (CAN) is a frequent chronic complication of diabetes mellitus with potentially life-threatening outcomes. CAN is caused by the impairment of the autonomic nerve fibers regulating heart rate, cardiac output, myocardial contractility, cardiac electrophysiology and blood vessel constriction and

orthostatic hypotension and cardiomyopathy. Diabetic patients should be screened for CAN due to the possibility of reversal of cardiovascular denervation in the early stages of the disease. Cardiovascular reflex tests and Holter-derived time- and frequency-domain measurements are frequently used for the diagnosis. Therapeutic approaches are promising and may hinder or reverse the progression of the disease when initiated during the early stages.

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## INTRODUCTION

Cardiac autonomic neuropathy (CAN), a type of generalized symmetric polyneuropathy, is the most examined and clinically significant diabetic autonomic neuropathy<sup>[1]</sup>. The autonomic nervous system has 2 major components: the parasympathetic and the sympathetic nervous systems. These may operate independently of each other or interact cooperatively to control heart rate, cardiac output, myocardial contractility, cardiac electrophysiology, and the constriction and dilatation of blood vessels<sup>[2]</sup>. CAN is caused by damage to the autonomic nerve fibers that innervate the heart and blood vessels and leads to abnormalities in cardiovascular dynamics<sup>[2]</sup>. The earliest finding of CAN, even at the subclinical stage, is a decrease in heart rate variability (HRV)<sup>[3]</sup>.

## EPIDEMIOLOGY

Diabetes is estimated to affect approximately 350 million people globally<sup>[4]</sup>. Diabetic neuropathies, including CAN, are frequent chronic complications of type 1 and 2 diabetes that influence quality of life and have potentially fatal outcomes<sup>[2]</sup>. Prevalence rates between 1.6% to 90% have been reported, varying according to the diagnostic methods used, population studied and disease stage<sup>[1]</sup>. The Diabetes Control and Complications Trial (DCCT) showed abnormal HRV values of 1.65%, 6.2% and 12.2% in patients with diabetes for a duration of less than 5 years, 5 to 9 years and more than 9 years, respectively<sup>[5]</sup>. A study including 1171 patients with both type of diabetes mellitus reported impaired HRV tests in 25.3% of type 1 and 34.3% of type 2 patients<sup>[6]</sup>. The different methodology between various studies makes epidemiological comparison difficult. Risk factors of decreased HRV in patients with type 2 diabetes include age, duration of diabetes, obesity and smoking<sup>[2]</sup>. In type 1 diabetes, risk factors of CAN include higher levels of HbA1c, hypertension, distal symmetrical polyneuropathy, retinopathy and hyperglycemic exposure<sup>[7,8]</sup>.

## PATHOGENESIS

Diabetic CAN is eventually caused by complex interactions among a number of pathogenic pathways. Hyperglycemia is the leading cause of the initiation of this pathogenic process<sup>[9,10]</sup>. The pathogenesis of diabetic CAN is multifactorial, including increased mitochondrial production of free radicals due to hyperglycemia-induced oxidative stress. Neuronal activity, mitochondrial function, membrane permeability and endothelial function are impacted by advanced glycation end product formation, polyol aldose reductase signaling and poly(ADP ribose) polymerase activation and the alteration of the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump function. Neuronal apoptotic processes are precipitated by endoplasmic reticulum stress induced by hyperglycemia, along with impaired nerve perfusion, dyslipidemia, alterations in redox status, low-grade inflammation and disturbance in calcium balance<sup>[11]</sup>. The literature has described these mechanisms and their interactions but is beyond the scope of this article<sup>[9-11]</sup>.

## CLINICAL MANIFESTATIONS

Diabetes can lead to dysfunction in the autonomic nervous system, causing various cardiovascular disorders, including resting tachycardia, postural hypotension, higher intra/perioperative cardiovascular instability, more frequent asymptomatic myocardial ischemia and infarction, and greater mortality after myocardial infarction<sup>[2]</sup>. Clinical symptoms associated with CAN generally occur at later stages and include postural hypotension, dizziness, lightheadedness, presyncope, syncope, and early fatigue and exhaustion during exercise<sup>[1]</sup>. However, subclinical autonomic dysfunction, revealed as deterioration in HRV, can occur in the 1<sup>st</sup> year following diagnosis in patients with type 2 diabetes and within 2 years following diagnosis in type 1<sup>[12]</sup>. Low et al<sup>[13]</sup> reported a higher rate of autonomic symptoms in type 1 than in type 2 diabetes. A greater number of autonomic symptoms have been associated with an increased risk of CAN as measured by HRV<sup>[14]</sup>.

Because neuropathy first affects the longest nerve fibers, the first manifestation of diabetic CAN tends to be related with vagus nerve damage, which is responsible for nearly 75% of parasympathetic activity<sup>[9]</sup>. This damage causes resting tachycardia as the sympathetic tone becomes dominant<sup>[15]</sup>. Tachycardia eventually diminishes in a few years due to progressive sympathetic nerve fiber damage. However, increased heart rate persists in these patients<sup>[16]</sup>. The progressive damage of the autonomic balance is indicated by additional symptoms, including intolerance to exercise, orthostatic hypotension and a further HRV reduction<sup>[17]</sup>. Cardiac pain perception often deteriorates with the involvement of sensory nerve fibers, making patients prone to silent ischemia and myocardial infarction<sup>[18,19]</sup>.

Etiological factors associated with autonomic neuropathy include poor glycemic control, longer diabetes duration, increased age, female sex and greater body

mass index<sup>[20]</sup>. Mortality rates of 25% to 50% within 5 to 10 years of diagnosis have been found in patients with symptomatic autonomic dysfunction<sup>[21,22]</sup>. Among diabetic patients, the 5-year mortality rate is 3 times higher in those with autonomic involvement than in those without<sup>[23]</sup>.

## CARDIOVASCULAR CONSEQUENCES

### **Impaired heart rate variability**

HRV is a physiological variation in the interval between heartbeats and is regulated by the interaction of the sympathetic and parasympathetic tone<sup>[24]</sup>. The functional response to the instantaneous metabolic needs of the body is regulated by this beat-to-beat variation. As high variability reflects the cardiac ability to adapt and implies good health, damage or disturbances to this control system results in lower HRV values. Even in a normal heart rate, the first finding of CAN is a decrease in HRV, which is apparent at the subclinical stage and can be detected through deep respiration<sup>[25]</sup>.

### **Resting tachycardia**

Due to the dominant sympathetic tone, resting heart rates of 90 to 100 beats per minute with occasional increases to as many as 130 beats per minute are frequent findings in CAN with vagal impairment<sup>[16,26]</sup>. Highest resting heart rates have been shown in patients with lone parasympathetic impairment<sup>[16,26]</sup>. As the disease progresses and involves both parasympathetic and sympathetic nerves, the heart rate tends to return to the normal range but remains higher than in healthy individuals<sup>[16,26]</sup>. Tang *et al*<sup>[27]</sup> showed that resting heart rate is independently associated with CAN and has a high predictive value in predicting CAN in the general population<sup>[27]</sup>. A steady heart rate less responsive to exercise, stress or sleep is suggestive of almost total cardiac denervation, which indicates severe CAN<sup>[20]</sup>.

### **Exercise intolerance**

Exercise tolerance is worsened by CAN through the blunting of the increases in heart rate, blood pressure and cardiac output response to exertion<sup>[20]</sup>. The development of hypotension or hypertension following strenuous exercise is more likely in individuals with CAN, particularly in the onset of a new exercise program<sup>[11]</sup>. Therefore, patients with diabetes probably to have CAN should be checked for cardiac stress before beginning to exercise<sup>[11]</sup>. Due to poor thermoregulation, such patients should avoid exercising in environments that are too hot or cold and hydrate adequately<sup>[11]</sup>.

### **Intraoperative and perioperative cardiovascular instability**

The perioperative risk of cardiovascular morbidity and mortality are 2 to 3 times higher in diabetic individuals<sup>[28]</sup>. Since the normal autonomic response of vasoconstriction and the increase in heart rate cannot appropriately compensate for the vasodilatation and negative chronotropic

effects of anesthesia, diabetic patients with CAN are subject to more pronounced decreases in blood pressure and heart rate during induction of anesthesia and, to a lesser extent, after intubation and extubation<sup>[20,28]</sup>. In addition, more severe intraoperative hypothermia in patients with CAN resulting in decelerated metabolism of anesthetic drugs may cause deepening of anesthesia and/or delayed recovery<sup>[29]</sup>. Accordingly, screening for CAN is recommended during the preoperative evaluation of diabetic patients for anesthetic management planning.

### **Non-dipping blood pressure profile and orthostatic hypotension**

Blood pressure has diurnal variations. Decreases in nighttime and increases in daytime blood pressure show its circadian rhythm<sup>[30]</sup>. Declines in parasympathetic tone occur at night and nocturnal unopposed sympathetic activity leads to deterioration of the circadian rhythm of blood pressure and results in the lack of or a less than 10% reduction in nocturnal blood pressure in patients with CAN<sup>[31]</sup>. Such "non-dipper" CAN subjects experience more frequent left ventricular hypertrophy and are predisposed to cardiovascular events<sup>[32]</sup>. Another blood pressure regulation abnormality related to CAN is orthostatic hypotension, which is defined as a decrease in systolic blood pressure by a minimum of 20 mmHg (at least 30 mmHg in patients with hypertension) or diastolic blood pressure of 10 mmHg in response to postural shifts from the supine to the standing<sup>[2,20]</sup>. In diabetic individuals, orthostatic hypotension develops as a consequence of denervation of the efferent sympathetic vasomotor nerves, especially in the splanchnic vascular bed<sup>[33]</sup>. Additionally, pathogenesis of orthostatic hypotension includes lower cutaneous, splanchnic and total vascular resistance<sup>[10]</sup>. Impaired chronotropic and/or blood pressure response to exercise may accompany this condition<sup>[10]</sup>. Orthostatic hypotension can cause many symptoms that reduce quality of life or lead to serious injury due to falling, such as lightheadedness, dizziness, faintness, visual blurring, presyncope and syncope while standing<sup>[20]</sup>. However, an important number of patients are asymptomatic despite significant decreases in blood pressure<sup>[2]</sup>. Orthostatic hypotension can be provoked by several drugs, which may be used concurrently for treatment of diabetes or its complications, including, vasodilators, diuretics, phenothiazines, insulin (through endothelium-dependent vasodilation) and tricyclic antidepressants for symptomatic relief of pain associated with diabetic neuropathy<sup>[9]</sup>.

### **Silent myocardial ischemia**

Coronary artery disease has long been considered as a major complication of diabetes mellitus<sup>[34]</sup>. Numerous studies have reported more extensive atherosclerotic disease, particularly that of the coronary arteries, in diabetic individuals<sup>[35,36]</sup>. Silent myocardial ischemia is defined as the objective documentation of myocardial ischemia without angina or its equivalents<sup>[37]</sup>. Several

reports have shown the predictive role of silent ischemia during exercise testing<sup>[38]</sup> or ambulatory electrocardiography (ECG) monitoring<sup>[39]</sup> on poor clinical outcomes and survival. A threefold increase in cardiac deaths was witnessed over a 2-year follow-up in individuals with silent ischemia during ambulatory ECG monitoring<sup>[39]</sup>. Painless presentation of myocardial infarction in patients with CAN may include diaphoresis, dyspnea, fatigue, lightheadedness, palpitations, acute confusion, indigestion, nausea, and vomiting<sup>[20]</sup>. Several explanations are possible for the variety of symptom patterns in individuals with diabetes, such as various pain perception thresholds, sensorial denervation secondary to autonomic neuropathy and psychological disavowal<sup>[34]</sup>. Therefore, despite increasing ischemia, individuals with CAN and coronary artery disease may resume exercise as the longer threshold or subthreshold ischemia is not sufficient to induce pain, thus endangering the patient<sup>[40]</sup>. Likewise, the Framingham Heart Study reported higher incidences of painless myocardial infarction in patients with diabetes than without (39% vs 22%)<sup>[41,42]</sup>. Similarly, the National Registry of Myocardial Infarction 2 (NRMI-2) survey found that one-third of patients presented without angina<sup>[43]</sup>. In the NRMI-2, diabetes was present in 32% of subjects without chest pain and 25.4% with angina<sup>[43]</sup>. The Detection of Ischemia in Asymptomatic Diabetic Study, including 1123 patients with type 2 diabetes, reported that CAN is able to strongly predict silent ischemia and succeeding adverse cardiovascular events<sup>[44]</sup>. Vinik *et al*<sup>[10]</sup>, in their meta-analysis of 12 studies, reported the association between CAN and the existence of silent ischemia detected by exercise stress tests with prevalence rate ratios of 0.85 to 15.53<sup>[10]</sup>. Therefore, patients with CAN require more rigorous evaluation of the presence of coronary artery disease. The presence and extent of macrovascular coronary artery disease in such patients can be noninvasively tested by resting and stress thallium myocardial scintigraphy<sup>[11]</sup>. Moreover, cardiovascular autonomic function testing should be included in the coronary artery risk assessment of all diabetic patients.

#### **Myocardial infarction and increased risk of mortality**

Myocardial infarction tends to be more extensive and severe in patients with diabetes<sup>[42,45]</sup>. The timely diagnosis of myocardial ischemia or infarction is often delayed due to diminished angina perception and therefore the period before first medical contact is prolonged<sup>[46]</sup>. Long-term survival rates following acute myocardial infarction are lower in patients with diabetes<sup>[20]</sup>. In diabetic patients, 5-year survival rates of 38% have been reported following the first major coronary event, lowering to just 25% for those with subsequent events, while the rates are 75% and 50%, respectively, in non-diabetic patients<sup>[45,47]</sup>. HRV has been demonstrated to be a good predictor of post-myocardial infarction mortality<sup>[48-50]</sup>. For this reason, cardiovascular autonomic function testing is advisable for all diabetic patients after a myocardial infarction to identify the candidates who have a high risk of death<sup>[51]</sup>.

#### **Sudden death**

CAN is associated with a higher risk of malignant arrhythmias and sudden death<sup>[9]</sup>. Previous studies have found 5-year mortality rates between 16% and 50% in patients with both CAN and either type of diabetes, often attributed to sudden cardiac death<sup>[14,23]</sup>. Severe asymptomatic ischemia inducing fatal arrhythmias has been reported as the leading potential cause<sup>[22]</sup>. Additionally, life-threatening arrhythmias and sudden death may be predisposed by QT prolongation<sup>[52]</sup>. The European Diabetes Insulin-Dependent Diabetes Mellitus (EURODIAB IDDM) Complications Study established the association between impaired HRV and corrected QT prolongation<sup>[53]</sup>. In addition, unopposed increases in sympathetic activity and resultant norepinephrine signaling and metabolism<sup>[9]</sup>, along with increased mitochondrial oxidative stress<sup>[54]</sup> and calcium-dependent apoptosis<sup>[55]</sup>, is thought to contribute to myocardial injury<sup>[54,56]</sup> and clarify the higher risk of sudden cardiac events and deaths. The EURODIAB IDDM Prospective Cohort Study, including 2787 patients with type 1 diabetes, reported CAN to be the strongest predictor of mortality over the 7-year follow-up period, even greater than traditional cardiovascular risk factors<sup>[57]</sup>. A meta-analysis including 15 studies and 2900 diabetic patients showed CAN patients to have a pooled relative risk of mortality of 3.45 (95%CI: 2.66-4.47) and an increase in line with higher numbers of cardiovascular autonomic function abnormalities<sup>[58]</sup>. Similar results were confirmed in 2 other studies of patients with type 1 and type 2 diabetes, strengthening the role in predicting mortality of abnormalities in both HRV and the QT index independent of conventional risk factors<sup>[59,60]</sup>. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial<sup>[61]</sup> also confirmed the association between CAN and mortality in type 2 diabetic patients. In this trial, Pop-Busui *et al*<sup>[62]</sup> showed that mortality was between 1.55 and 2.14 times more likely in patients with baseline CAN than those without<sup>[62]</sup>. Three large studies (the ACCORD trial<sup>[61]</sup>, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial<sup>[63]</sup>, and the Veterans Affairs Diabetes Trial<sup>[64]</sup>) investigated the role of more intensive treatment and the frequency of cardiovascular events on individuals with long-term type 2 diabetes. In these trials, tight glycemic control was not shown to reduce cardiovascular adverse events<sup>[2]</sup> and the ACCORD trial was terminated early due to the increased mortality risk in the intensive therapy group<sup>[65]</sup>. Hypoglycemia is known to reduce the threshold for malignant ventricular arrhythmias that can result in sudden death<sup>[9,66]</sup>. In addition, hypoglycemic periods were reported to lead to impaired autonomic cardiovascular function even in healthy volunteers<sup>[67]</sup>. Hence, the cause of a lack of a decrease, or even an increase, in cardiovascular events in the intensive therapy arm may be linked to deterioration of cardiac autonomic function due to episodes of hypoglycemia.

#### **Cardiomyopathy**

Diabetic cardiomyopathy is defined as structural and

functional myocardial abnormalities without coronary artery disease, hypertension or valvular heart disease<sup>[68]</sup>. It is characterized by diastolic dysfunction<sup>[69]</sup>. The responsible mechanisms are left ventricular hypertrophy (increased left ventricular mass and concentric remodeling<sup>[70]</sup>), myocardial lipotoxicity, increased oxidative stress, cell death, interstitial and perivascular fibrosis, impaired contractile reserve, changes in myocardial substrate and energy metabolism, altered substrate utilization and mitochondrial dysfunction<sup>[69]</sup>. In patients with CAN, the initial augmentation in cardiac sympathetic activity stimulates the renin-angiotensin-aldosterone system and increases heart rate, stroke volume and peripheral vascular resistance<sup>[71]</sup>. In addition, the combination of sympathetic hyperactivity and regional myocardial sympathetic denervation cause reduced coronary blood flow and diastolic dysfunction, which may lead to impairment of systolic function<sup>[2]</sup>.

### **Stroke**

Previous studies have revealed the relationship between CAN and cerebrovascular events. Ko *et al*<sup>[72]</sup> reported that the presence of CAN, assessed by HRV testing, was significantly associated with the ischemic stroke in a study of 1458 patients with type 2 diabetes with a 7-year follow-up<sup>[72]</sup>. Another study of 133 subjects with type 2 diabetes showed that stroke could be predicted by parasympathetic and sympathetic autonomic function abnormalities<sup>[73]</sup>.

## **DIAGNOSTIC METHODS OF CARDIAC AUTONOMIC NEUROPATHY**

Variability in heart rate and blood pressure values can provide data regarding both parasympathetic and sympathetic autonomic function and is useful in clinical settings.

### **Heart rate variability**

The most commonly used methods for the diagnosis of CAN are based on HRV assessment. HRV testing is noninvasive and objective in the evaluation of cardiac autonomic function and can be performed by recording electrocardiograms during deep breathing, standing, and Valsalva maneuvers<sup>[74]</sup>. HRV analysis enables the independent measurement of the sympathetic and parasympathetic components of the autonomic nervous system and can be assessed with a number of simple clinical tests<sup>[75]</sup> or easier digital 24-h electrocardiographic recordings<sup>[24]</sup>. In the 1970s, Ewing *et al*<sup>[75]</sup> discovered 5 simple tests of short-term R-R alterations to identify CAN in patients with diabetes: (1) heart rate response to respiration, which measures beat to beat sinus arrhythmia (R-R variation) during paced deep expiration and inspiration (E:I ratio); (2) heart rate response to standing, known as the 30:15 ratio, which is the ratio of the longest R-R interval (between beats 20 to 40) to the shortest R-R interval (between beats 5 to 25); (3) the

Valsalva maneuver, measuring the heart rate response during and after a provoked increase in intra-thoracic and intra-abdominal pressures; (4) blood pressure response to orthostasis, which evaluates baroreflex mediated blood pressure fluctuations after changes in posture; and (5) blood pressure response to isometric exercise, as defined by the diastolic blood pressure increase due to continuous muscle contraction using a handgrip dynamometer<sup>[75]</sup>. Tests 1 and 2 reflect parasympathetic function, and 4 and 5, sympathetic function<sup>[76,77]</sup>. Although the Valsalva ratio primarily represents parasympathetic activity, the resultant autonomic changes are complicated and include both the sympathetic and parasympathetic components<sup>[78]</sup>. An American Diabetes Association statement describes these validated cardiac autonomic reflex tests (CART) in detail and recommends their use in the diagnosis of CAN (Table 1)<sup>[1]</sup>. HRV with deep breathing is the most commonly used autonomic function test and has a specificity of approximately 80%<sup>[79,80]</sup>.

The assessment of HRV has become easier and more detailed due to new, digital, high frequency, 24-h multi-channel electrocardiographic recorders and the use of statistical indexes in the time and frequency domains.

### **Time domain methods**

Time domain methods determine the heart rate at any point in time or the intervals between consecutive normal complexes<sup>[24]</sup>. Each QRS complex is detected and the normal-to-normal (NN) intervals (that is all intervals between adjacent QRS complexes resulting from sinus node depolarizations) or the instantaneous heart rate is determined through a continuous ECG record<sup>[24]</sup>. Simple time-domain variables that can be analyzed include mean NN interval, mean heart rate, the difference between the longest and the shortest NN interval and the variation between night and day heart rate<sup>[24]</sup>. More complex time-domain parameter calculations can be performed from a series of instantaneous heart rates or cycle intervals, particularly those recorded during 24-h periods<sup>[24]</sup>. The complex parameters can be divided into 2 classes: those derived from direct measurements of the NN intervals and those derived from the differences between NN intervals. The parameters calculated by direct measurements include: standard deviation of the NN interval (SDNN), reflecting all cyclic components responsible for variability in the recording period; standard deviation of the average NN interval (SDANN) calculated over periods (usually 5 min), estimating heart rate changes from cycles longer than 5 min; and the mean of the 5-min standard deviation of the NN interval (SDNN index) calculated over 24 h, measuring variability from cycles of less than 5 min. Secondly, the parameters calculated by the differences between NN intervals include the square root of the mean squared differences of successive NN intervals (RMSSD), the number of interval differences of successive NN intervals of more than 50 msec (NN50), and the division of NN50 by the total number of NN intervals (pNN50)<sup>[24]</sup>. Although influenced by several

**Table 1** Cardiovascular autonomic reflex tests<sup>[1]</sup>

Test	Technique	Normal response and values
Beat-to-beat HRV	With the patient at rest and supine, heart rate is monitored by ECG while the patient breathes in and out at 6 breaths per minute, paced by a metronome or similar device	A difference in heart rate of > 15 beats per minute is normal and < 10 beats per minute is abnormal. The lowest normal value for the expiration-to inspiration ratio of the R-R interval decreases with age: age 20-24 yr, 1.17; 25-29, 1.15; 30-34, 1.13; 35-39, 1.12; 40-44, 1.10; 45-49, 1.08; 50-54, 1.07; 55-59, 1.06; 60-64, 1.04; 65-69, 1.03; and 70-75, 1.02
Heart rate response to standing	During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing	Normally, a tachycardia is followed by reflex bradycardia. The 30:15 ratio should be > 1.03
Heart rate response to the Valsalva maneuver	The subject forcibly exhales into the mouthpiece of a manometer to 40 mmHg for 15 s during ECG monitoring	Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in blood pressure with release. The normal ratio of longest R-R to shortest R-R is > 1.2
Systolic blood pressure response to standing	Systolic blood pressure is measured in the supine subject. The patient stands and the systolic blood pressure is measured after 2 min	Normal response is a fall of < 10 mmHg, borderline fall is a fall of 10-29 mmHg and abnormal fall is a decrease of > 30 mmHg with symptoms
Diastolic blood pressure response to isometric exercise	The subject squeezes a handgrip dynamometer to establish a maximum. Grip is then squeezed at 30% maximum for 5 min	The normal response for diastolic blood pressure is a rise of > 16 mmHg in the other arm

HRV: Heart rate variability; ECG: Electrocardiogram.

arrhythmias and requiring normal sinus rhythm and atrioventricular nodal function, these short-term variation measurements estimate high frequency variations in heart rate and are therefore highly correlated<sup>[24]</sup>. SDNN represents both the sympathetic and parasympathetic modulation of HRV, and RMSSD and pNN50 the parasympathetic system<sup>[24]</sup>.

### Frequency domain methods

CAN may also be evaluated using spectral analysis of HRV, which divides the R-R signal into sine and cosine waves to estimate the amount of variability as a function of frequency<sup>[24]</sup>. Three main spectral components are distinguished in a spectrum calculated from short-term recordings of 2 to 5 min: very-low-frequency ( $\leq 0.04$  Hz) of fluctuations in vasomotor tone related to thermoregulation, low-frequency (0.04-0.15 Hz) associated with the baroreceptor reflex, and high-frequency (0.15-0.4 Hz) related to respiratory activity<sup>[24]</sup>. The sympathetic system is thought to modulate the 2 low-frequency components and the parasympathetic system the high-frequency component<sup>[20]</sup>. Accordingly, while decreases in very-low- and low-frequency peaks indicate sympathetic dysfunction, a decrease in the high-frequency peak is a sign of parasympathetic dysfunction<sup>[1]</sup>. A decrease in the ratio of low-frequency-to-high-frequency demonstrates sympathetic imbalance<sup>[1]</sup>. Various mathematical methods can be used to analyze the spectral components of HRV. Most common is the Fourier transform because of its simplicity and high processing speed<sup>[24]</sup>. A noise-free signal is necessary in order to correctly perform the spectral analysis. Because artefacts and extra beats must be removed, this correction leads to data loss and is associated with an underestimation in each case. Additionally, specific reference values must be obtained as each HRV-analysing device has different technical properties for spectral measurements.

It is not yet clear which of these 2 methods is preferable: time-domain methods including the standardized CART of Ewing or frequency-domain methods. However, many time- and frequency-domain variables obtained over the 24-h period are highly correlated with each other<sup>[24]</sup>. On the other hand, studies comparing Holter-based analysis and CART found a high (83%) correlation between the both techniques<sup>[81]</sup>. The advantages of Holter-based techniques include simpler, less stressful and faster implementation during daily routine use, independence of patient cooperation and greater sensitivity allowing for the identification of disorders in the early stages. However, CART can be applied quickly (less than 15 min) using stand-alone operator friendly devices during routine physical examination.

### Heart rate turbulence

Another Holter-based technique for evaluating CAN is the heart rate turbulence (HRT)<sup>[82]</sup>. HRT refers to sinus rhythm cycle length fluctuations following isolated premature ventricular beats. After an initial acceleration, the sinus rate decelerates after a premature ventricular beat. There are 2 components of HRT; turbulence onset and turbulence slope. A transient vagal inhibition triggers the mentioned initial acceleration in heart rate as a response to the missed baroreflex afferent input due to hemodynamically ineffective ventricular contraction. The successive deceleration in heart rate is caused by a sympathetically mediated overshoot of arterial pressure through vagal recruitment<sup>[82]</sup>. HRT evaluation can be used in the risk assessment after acute myocardial infarction and in the monitoring of disease progression in heart failure and CAN<sup>[82]</sup>. We previously demonstrated that among HRV and HRT indexes, turbulence slope has the greatest correlation with CAN severity<sup>[83]</sup>. A turbulence slope of below 3.32 msec/R-R is 97% sensitive and 71% specific for the diagnosis of CAN as detected by the

CART in patients with type 2 diabetes<sup>[83]</sup>.

### Other diagnostic tools

Other methods currently used in research settings are scintigraphic evaluation of sympathetic innervation of the heart, which can reveal cardiac sympathetic nerve population changes and early anatomical regional deficits of sympathetic denervation<sup>[84-86]</sup>; microneurography, which records electrical activity released by peroneal, tibial or radial sympathetic nerves and identifies sympathetic dysfunction<sup>[87]</sup>; neurovascular flow, using noninvasive laser Doppler measures of peripheral sympathetic reactions to nociception<sup>[88]</sup>; and baroreflex sensitivity, which evaluates the capability to reflexively increase vagal activity in response to a sudden increase in blood pressure<sup>[89]</sup>. As many of these tests assess the influence on sympathetic component, they do not provide information about early stage CAN. In a recent study, it was shown that altered cardiac autonomic balance can be detected through exercise stress testing in diabetic subjects even with minimal evidence of CAN<sup>[90]</sup>.

### Criteria for diagnosis and staging

CART are the gold standard clinical tests for cardiovascular autonomic neuropathy<sup>[91]</sup>. Following the 8<sup>th</sup> international symposium on diabetic neuropathy in 2010, criteria for diagnosis and staging of CAN are defined in the CAN Subcommittee of the Toronto Consensus Panel statement<sup>[92]</sup>. Accordingly, only 1 abnormal CART result is sufficient to diagnose possible or early CAN; among the 7 autonomic function analysis (5 CART, time-domain and frequency-domain HRV tests), 2 or 3 abnormal tests indicate definite or confirmed CAN; and severe/advanced CAN can be indicated by concurrent orthostatic hypotension<sup>[91]</sup>.

## SCREENING FOR CAN

By the time clinical signs occur, CAN has often reached to a late stage, making management more difficult. Therefore, patients should be screened for CAN at the time of diagnosis of type 2 diabetes and within 5 years of diagnosis of type 1 diabetes (except presence of symptoms suggesting autonomic neuropathy earlier)<sup>[1]</sup>. In addition, screening may be of benefit before undergoing an operation or beginning a new intense exercise program<sup>[93,94]</sup>. Screening should include a clinical history and an evaluation for evidence of autonomic dysfunction. Main HRV tests (E:I ratio, heart rate response to Valsalva maneuver, and heart rate response to standing) should also be performed. As an alternative to CART, easier screening methods have been attempted to develop. For instance, sudomotor function tests that assess the cholinergic innervation of sweat glands have been found to be useful for early screening of CAN<sup>[95]</sup>. Ge *et al*<sup>[96]</sup> offered a new risk score system not requiring specific tests for screening CAN, using clinical parameters including age, body mass index, hypertension and resting heart rate. The risk score can be between 0 and 15, and

a score of 6 can detect CAN in 72.87% of previously undiagnosed individuals<sup>[96]</sup>. Screening should be repeated annually in the presence of negative results<sup>[1]</sup>.

## THERAPEUTIC APPROACHES

Early determination of CAN is significant for the success of therapeutic strategies as cardiovascular denervation seems to be reversible at onset<sup>[97]</sup>. In less affected patients, lifestyle changes including graded supervised exercise associated with weight loss improve HRV<sup>[97]</sup>.

### Optimizing glycemic control

Blood glucose optimization is the essential treatment for CAN. The Framingham Heart Study showed the significant association between reduced HRV and increased fasting plasma glucose level<sup>[98]</sup>. This finding is present in diabetics as well as individuals with impaired glucose tolerance<sup>[99]</sup>. Additionally, the DCCT reported that intensive insulin therapy reduced the incidence of CAN in comparison to conventional insulin therapy after approximately 5 years (14% *vs* 7%;  $P < 0.004$ ) in type 1 diabetics<sup>[100]</sup>. The Epidemiology of Diabetes Intervention and Complication Study (EDIC) is a longitudinal cohort follow-up study for the DCCT<sup>[101]</sup>. Pop-Busui *et al*<sup>[102]</sup> demonstrated that during EDIC follow-up, CAN progressed in both the conventional and intensive insulin therapy groups, while its incidence and prevalence remained lower in the intensive therapy group despite similar glycemic control<sup>[102]</sup>. Accordingly, the early initiation of intensive glucose control in type 1 diabetics can help to minimize the development of CAN<sup>[102]</sup>. On the other hand, the benefit of glycemic control in type 2 diabetics is less certain<sup>[1,2]</sup>. The Veterans Affairs Cooperative Study reported a similar prevalence of autonomic neuropathy in type 2 diabetics after 2 years of intense glucose control in comparison with conventional glycemic control<sup>[103]</sup>. Similarly, in the Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen Detected Diabetes in Primary Care Danish arm, CAN was frequently found 6 years following diagnosis of type 2 diabetes and this prevalence was not significantly affected by intensive multifactorial treatment in comparison with routine care<sup>[104]</sup>. Conversely, in the Steno-2 Trial patients with type 2 diabetes were given intensive multifactorial treatment (*e.g.*, targeting hyperglycemia, hypertension and dyslipidemia, including acetylsalicylic acid for secondary prevention) and targeted strict glycemic control as well as other cardiovascular risk factor modification, which reduced the incidence of autonomic dysfunction by approximately 60%<sup>[105]</sup>. Briefly, the intensive blood glucose, HbA1c, blood pressure and lipid levels control using pharmacological therapy with lifestyle changes are recommended for all diabetic patients<sup>[1]</sup>.

### Other therapies

Functional disorders of the autonomic nervous system can be treated with a variety of medications. In a trial

including 73 type 2 diabetic subjects, a four-month period of treatment with alpha-lipoic acid, which reduces oxygen free radicals, improved HRV detected by standardized CART<sup>[1,106]</sup>. While the use of aldose reductase inhibitors (epalrestat, fidarestat and AS-3201), which reduce nerve sorbitol, had a positive influence on HRV in patients with mild abnormalities, they were ineffective in advanced CAN patients<sup>[1,107]</sup>. Total HRV has been shown to be increased and parasympathetic/sympathetic balance improved by angiotensin-converting enzyme (ACE) inhibition in patients with mild autonomic neuropathy through increases in nerve blood flow<sup>[1]</sup>. Prostaglandin analogs have been shown to be effective through the same mechanism<sup>[1]</sup>. Cardioselective beta-blockers are considered to have positive effects on autonomic dysfunction. For example, the addition of metoprolol to ramipril therapy in patients with type 1 diabetes resulted in recovery of HRV parameters<sup>[108]</sup>. Furthermore, bisoprolol improved HRV in heart failure<sup>[109]</sup>. In a study including individuals with long-term diabetes and diabetic neuropathy, the combination of ACE inhibition and angiotensin-receptor blockade improved autonomic neuropathy<sup>[110]</sup>. In addition, Ozdemir *et al*<sup>[111]</sup> showed that losartan therapy significantly improved HRV in patients with ischemic cardiomyopathy already receiving ACE inhibitors and beta-blockers. Similarly, sympathovagal imbalance in heart failure patients was improved following the administration of spironolactone along with enalapril, furosemide, and digoxin<sup>[112]</sup>. Such evidence reveals that combination therapies appear to provide better results than monotherapies.

### Orthostatic hypotension

Because orthostatic hypotension is a relatively late complication of CAN, the treatment is challenging due to advanced disease. Nonpharmacological treatments include: increased water consumption; the use of lower-extremity stockings; avoidance of sudden postural changes to standing up; avoidance of medicines such as vasodilators, diuretics, phenothiazines and tricyclic antidepressants that provoke hypotension; eating frequent, small meals to prevent postprandial hypotension; and avoidance of exercises and maneuvers that increase intra-abdominal and intra-thoracic pressure resulting in venous return decrease<sup>[20]</sup>. Some physical preventive maneuvers, such as crossing of the legs and squatting may counter decreases in blood pressure<sup>[9]</sup>. While pharmacological treatments, such as midodrine, clonidine, octreotide, fludrocortisone acetate, erythropoietin, nonselective beta-blockers and pyridostigmine bromide appear promising, all have mild to severe side effects, including hypertension<sup>[9]</sup>.

### CONCLUSION

Although very common and serious, CAN is a frequently overlooked complication of diabetes. Related with intraoperative and perioperative cardiovascular instability, abnormal blood pressure profile, orthostatic hypotension,

silent myocardial ischemia, arrhythmias, diabetic cardiomyopathy, and stroke, CAN is associated with significant increases in morbidity and mortality. Patients may have subclinical CAN for several years before it becomes clinically apparent. Because the progression of cardiovascular denervation is partly reversible or can be slowed down in the early stages of the disease, recent guidelines strongly recommend screening for CAN in patients with diabetes. Assessment of CAN is possible through a variety of methods, such as CART, HRV and imaging modalities. Operator friendly devices and use of Holter-based analysis has simplified CAN testing. Treatment principles include early diagnosis, optimization of glycemic control, life style changes and management of cardiovascular risk factors. Medical therapy, including aldose reductase inhibitors, ACE inhibitors, prostaglandin analogs and alpha-lipoic acid, have been found to be effective in randomized control trials for the treatment of autonomic neuropathies. Orthostatic hypotension, which may lead to life-threatening injuries, is an undesired manifestation and indicates severe or advanced CAN.

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