# Cardiac Autonomic Neuropathy in Diabetes Mellitus

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**ABSTRACT:** Cardiovascular autonomic neuropathy (CAN) is a severely debilitating yet underdiagnosed condition in patients with diabetes. The prevalence can range from 2.5% (based on the primary prevention cohort in the Diabetes Control and Complications Trial) to as high as 90% of patients with type 1 diabetes. Clinical manifestations range from orthostasis to myocardial infarction. The diagnosis is made using multiple autonomic function tests to assess both sympathetic and parasympathetic function. The pathophysiology of CAN is complex, likely multifactorial, and not completely understood. Treatment is limited to symptomatic control of orthostatic hypotension, which is a late complication, and current strategies to reverse CAN are limited. This review explores the epidemiology, pathophysiology, clinical manifestations, diagnosis, and complications of CAN as well as current treatment options.

## INTRODUCTION

Diabetes-associated cardiovascular autonomic neuropathy (CAN) damages autonomic nerve fibers that innervate the heart and blood vessels, in turn causing abnormalities in heart rate and vascular dynamics. It is known to affect multiple organ systems and is a major cause of morbidity and mortality in patients with diabetes.[1-3] The CAN Subcommittee of Toronto Consensus Panel on Diabetic Neuropathy defines CAN as an "impairment of cardiovascular autonomic control in patients with established diabetes after excluding other causes."[1,4] Significantly underdiagnosed, CAN exhibits multiple clinical manifestations, such as orthostasis, resting tachycardia, exercise intolerance, silent myocardial infarction, and intraoperative cardiovascular liability. It is a severely debilitating complication that often decreases survival in patients with diabetes.[1,5] This review discusses the latest evidence regarding the epidemiology, pathophysiology, clinical manifestations, diagnosis, and complications of CAN as well as current treatment options.

## EPIDEMIOLOGY AND SCREENING

The prevalence of CAN is variable based on published studies and ranges from 2% to 91% in type I diabetes mellitus (T1DM) and 25% to 75% in type 2 diabetes (T2DM).[1,6] This significant variability can likely be attributed to the lack of a uniform diagnostic criteria as well as underdiagnoses in the typical hospital setting.[1,7] Based on the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study, the prevalence of CAN in T1DM after 15 years was close to 60%.[1,2,5,8] Although CAN is associated with a longer duration of disease, some studies suggest that it may be present in patients with newly diagnosed diabetes as well, although the percentage is significantly lower.[1,2,5]

The CAN Subcommittee of Toronto Consensus Panel on Diabetic Neuropathy recommends that patients with T2DM be screened for CAN at the time of diagnosis and those with T1DM within 5 years of their diagnosis, especially in patients exhibiting multiple risk factors, such as poor glycemic control, smoking, hypertension, or dyslipidemia. The Panel also recommends that screening be part of a perioperative risk assessment in patients with coronary artery disease. Some studies suggest that CAN may be seen in prediabetes as well; however, the prevalence and association have not been well studied.[1,2,5,6] Similarly, guidelines from the American Diabetes Association (ADA) recommend that diabetic patients displaying common CAN symptoms—such as lightheadedness, weakness, palpitations, and syncope that occurs on standing—undergo further assessment to rule out causes other than CAN, especially if they have microvascular/neuropathic complications or hypoglycemia unawareness.[1,5,9,10]

## PATHOPHYSIOLOGY

According to Pop-Busui et al., diabetes-related CAN results from complex interactions between glycemic control, duration of disease, systolic and diastolic blood pressure, and aging-related neuronal death.[9] Hyperglycemia is thought to be a primary culprit, spurring a cascade of multiple complex mechanisms and pathways that induce oxidative stress and toxic glycosylation products—ultimately resulting in neuronal dysfunction and death (Figure 1).[1,2,9] Hyperglycemia increases mitochondrial production of free reactive oxygen species, thereby causing oxidative damage to the microvasculature supplying these peripheral nerves.[6,9,11]

However, the full pathogenesis of CAN is not clearly understood since the mechanisms involved in its development have only been studied in somatic models and extrapolated to the

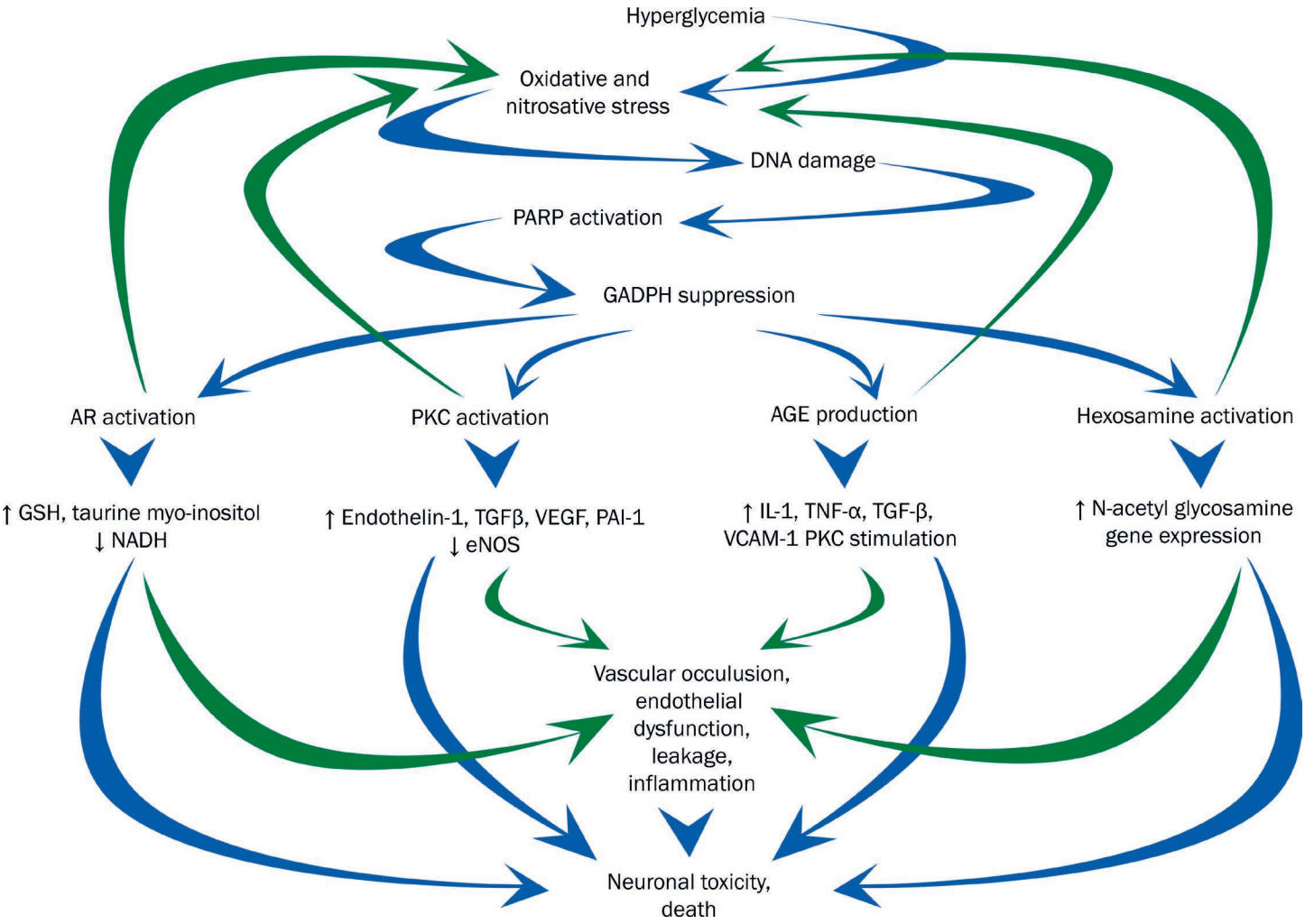


*Figure 1.*
Summary of the mechanisms that relate hyperglycemia to microvascular complications such as neuropathy in patients with diabetes.[1] PKC: protein kinase C; AGE: advanced glycation end-products; PARP: poly ADP-ribose polymerase; GAPDH: glyceraldehyde-3 phosphate dehydrogenase; GSH: glutathione; NADH: nicotinamide adenine dinucleotide; TGF-β: transforming growth factor beta; VEGF: vascular endothelial growth factor; PAI-1: plasminogen activator inhibitor-1; eNOS: endothelial nitric oxide synthase; IL-1: interleukin 1; TNF-α: tumor necrosis factor alpha; VCAM-1: vascular cell adhesion molecule 1

autonomic nervous system.[1] In the 2003 Steno-2 trial involving multifactorial intervention, strict glycemic control and lifestyle changes in T2DM reduced the development of autonomic neuropathy but did not significantly affect somatic neuropathy progression.[1,6] Diabetes triggers multiple reactions that promote neuropathic changes, such as advanced glycosylation end products from glycation of proteins, activation of poly(ADP ribose) polymerase reductase pathways, direct DNA damage, negative effects on neuronal regeneration and repair, reduced neurotransmitter release and synapse function, altered Na/K/ATPase pump, and damage to endoplasmic reticulum that activates apoptotic pathways.[1,5,9,11] Microvascular changes of diabetes, including retinopathy and albuminuria, are associated with progression of CAN based on the results from the EURODIAB study.[12] Increased production of cytokines such as interleukin 6, tumor necrosis factor alpha, and C-reactive protein, as well as inflammation in general, are known to be associated with CAN.[1,5,8] In addition, underlying genetic susceptibility, obstructive sleep apnea, lower C peptide levels, and autoimmune antibodies may also be associated with CAN.[1,13]

Just like the somatic neuropathies, diabetes affects autonomic nerves in a length-dependent fashion.[5,9] As a result, CAN often first manifests in the vagus nerve, the body's longest parasympathetic autonomic nerve and the one responsible

| 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/min, paced by a metronome or similar device. | A difference in heart rate of > 15 bpm is normal and < 10 bpm is abnormal. The lowest normal value for the expiration-inspiration ratio of the R-R interval is 1.17 in patients aged 20-24; this value decreases with age. |
| Heart rate response to standing | During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing. | Typically, a tachycardia is followed by reflex bradycardia. The 30:15 ratio should be > 1.03. |
| Heart rate response to Valsalva maneuver | The subject forcibly exhales into the mouthpiece of a manometer to 40 mm Hg 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 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 mm Hg; borderline is a fall of 10-29 mm Hg; abnormal is a fall of > 30 mm Hg 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. | A normal response for diastolic blood pressure is a rise of > 16 mm Hg in the opposite arm. |

*Table 1.*
Standard cardiovascular autonomic reflex tests (CARTS).[2] HRV: heart rate variability; ECG: electrocardiogram; bpm: beats per minute

for almost three-quarters of parasympathetic activity; damage to the vagus nerve causes resting tachycardia and an overall decrease in parasympathetic tone.[5] In the later stages of CAN, sympathetic denervation occurs, starting from the apex of the ventricles to the base of the heart.[9]

## DIAGNOSIS

Diagnostic assessment of CAN should involve testing of both sympathetic and vagal function. The gold standard of tests, known as cardiac autonomic reflex tests (CARTs), are based on heart rate, blood pressure, and sudomotor responses and were discovered by Ewing et al. in the 1970s (Table 1).[1,5,9,14] CARTs involve measuring autonomic responses through changes in heart rate (HR) variability and blood pressure (BP) with various maneuvers. Sympathetic function is assessed by BP response to postural changes, the Valsalva maneuver, and sustained isometric muscular strain (i.e., the sustained hand grip test).[1,5,14] Parasympathetic function is assessed by HR response to deep breathing, changes in posture (i.e., lying to standing), and the Valsalva maneuver.[1,5] These tests of cardiovagal and adrenergic function have higher supportive evidence than sudomotor testing.[1,5,14]

In the autonomic reflex tests, the HR response to respiration is measured as the expiration to inspiration (E:I) ratio, which measures beat to beat sinus arrhythmia (R-R variation) during paced deep expiration and inspiration. Heart rate is measured via electrocardiogram with the patient in the supine position and breathing at 6 breaths per minute (bpm); a difference of > 15 bpm is considered normal. Heart rate response to standing is known as the 30:15 ratio and usually consists of an initial increase and then decrease in HR.[5,14] In this test, the R-R interval is measured at 15 beats and 30 beats after standing, with the normal value > 1.03.[1,3,5] Heart rate response to Valsalva involves an initial increase in HR followed by an excessive decrease in HR, and the normal ratio of longest to shortest R-R interval is > 1.2.[5,6,14] These tests can be easier and more informative when the HR variability is tested using time or frequency domain measurements with digital modalities and statistical analysis.[1,5,15] Sympathetic function is assessed by noting changes in systolic BP in the supine position and again after standing for 2 minutes, with normal being a fall of < 10 mm Hg.[5,6] Sympathetic function can also be gauged by measuring diastolic BP response to isometric exercise using a handgrip dynamometer; BP normally increases on the contralateral side by > 16 mm Hg.[5,14]

In terms of other types of testing, positron emission tomography with either [$^{123}$I]meta-iodobenzylguanidine or [$^{11}$C]-meta-hydroxyephedrine can quantify the adrenergic innervation of the heart.[5,9] Holter monitoring can be used to estimate sinus cycle changes after premature ventricular complexes, and baroreflex sensitivity testing after intravenous phenylephrine bolus can assess both adrenergic and vagal responses.[1,5,6] Microneurography that identifies sympathetic burst activity primarily in the peroneal nerve is useful as a direct measure of peripheral sympathetic function.[16] Sudomotor dysfunction, one of the earliest signs of autonomic nervous system impairment, can be assessed with a variety of tests, including the thermoregulatory sweat test (TST), quantitative sudomotor axon reflex test (QSART), sympathetic skin response (SSR), and Silastic sweat imprint test.[1,15] It is important to note, however, that CARTs remain the gold standard, and these other tests are not routinely used except in more specialized centers.[1,5] Even so, the American Academy of Neurology guidelines on testing of autonomic dysfunction note that, in the hospital setting, other comorbidities such as volume status, medications, and end organ failure may limit or change how tests may be interpreted.[5,17]

## CLASSIFICATION OF CAN

Based on diagnostic testing, CAN can be classified into three categories: (1) "early involvement" with one abnormal HR test or two borderline results; (2) "definite involvement" with two or more abnormal results; and (3) "severe involvement" when orthostatic hypotension is present.[5,6,18] CAN is also divided into two stages: subclinical and clinical. The classification of subclinical CAN is based on changes in HR variability, baroreflex sensitivity, and cardiac imaging showing increased torsion of the left ventricle without any significant changes on standard CARTs discussed above.[4,19] The clinical stage is diagnosed when sympathetic activity is predominant and symptoms such as decreased exercise tolerance and resting state tachycardia are evident. As clinical CAN progresses, orthostatic hypotension becomes apparent.[5,18,20] The standard CARTs may be used to obtain an autonomic neuropathy score to assess the severity of CAN and monitor its progression.[1,5,19]

## CLINICAL MANIFESTATIONS

Clinical manifestations of CAN depend on the progression of the disease. Reduced HR variability is the earliest manifestation in subclinical CAN. In clinical CAN, resting tachycardia and reduced exercise tolerance may be seen in the early stages as sympathetic tone increases.[1,5,9] In early clinical CAN, an HR of 90 to 130 bpm may be noted.[1,3] An HR that does not change with sleep, stress, or exercise and exhibits a poor response to adenosine suggests complete sympathetic loss seen in severe CAN and is associated with a higher risk of mortality.[1,5,6]

Impaired cardiac output, BP, and HR lead to exercise intolerance; therefore, cardiac stress testing is recommended before starting an exercise program.[1,9] Orthostatic hypotension and sympathetic denervation of the heart are manifestations of severe CAN.[3,5] Orthostatic hypotension is estimated to be present in 6% to 32% of patients with DM. Along with objective criteria such as a fall in BP ≥ 20 mm Hg, other symptoms such as dizziness, syncope, changes in vision, frequent falls, and nocturnal hypertension due to a paradoxical increase in sympathetic tone may also be seen in CAN.[1,5,9]

## COMPLICATIONS

Based on a meta-analysis of 15 studies, the relative mortality risk in diabetics with CAN is 3.65. In addition, the EURODIAB study of T1DM suggests that CAN is a strong predictor of mortality even compared to other common risk factors.[1,9,21,22] Specific symptoms associated with severe CAN, such as orthostatic hypotension, suggest a poor prognosis and higher risk of mortality in diabetic patients with CAN.[5,23] Multiple studies have also identified an association between CAN and silent myocardial ischemia (MI). This is important because patients with DM may not report classic ischemic chest pain but may instead present with dyspnea, nausea, fatigue, cough, or other nonspecific symptoms that may be missed as symptoms of MI. A reduction in left ventricular systolic and especially diastolic function in CAN may further contribute to diabetic cardiomyopathy.[1,5,21,24]

Although CAN predisposes diabetic patients to life-threatening arrhythmias and sudden death, it is still not known whether it is an independent predictor of mortality.[1,21,25,26] Diabetes is associated with almost a threefold higher risk of peri- and intraoperative cardiovascular complications, and diabetes-related CAN confers an added risk of hemodynamic compromise and cardiac arrest, especially with the use of anesthesia.[1,2,6] Some studies suggest an association between ischemic stroke and abnormalities in HR variability or with a diagnosis of CAN in general.[5,9,27] Most studies also report that CAN may be an independent predictor of progressive nephropathy associated with DM.[1,4]

## PREVENTION AND TREATMENT

In general, there are two therapeutic approaches targeting CAN: one aimed at preventing the development or progression of CAN and one targeting symptomatic control of CAN in DM.[25] In the DCCT/EDIC study, intensive glycemic control in T1DM reduced the incidence of CAN by more than 50% initially, and although CAN prevalence increased, the benefit was maintained 13 to 14 years out.[1,5,8,9,28] It is less extensively proven that tighter glucose control may be able to reduce the progression of CAN

in T2DM; however, weight loss and exercise are known to have a favorable effect.[4-6,29,30] Vitamin E and C peptide have been evaluated in smaller studies and have demonstrated some benefit in slowing the progression of CAN.[5,6,30] In addition, selective beta blockers may be used effectively in patients with resting tachycardia.[2,6,28]

Orthostatic hypotension associated with severe CAN is treated symptomatically.[5,6,23,31] Nonpharmacological treatments include physical maneuvers such as squatting, slow changes in posture, or lifestyle changes such as avoiding heavy carbohydrate-rich meals or increasing fluid intake.[5,31] Pharmacological interventions may be necessary if the former fail. Midodrine, an alpha-1 adrenergic agonist, is the only drug approved by the U.S. Food and Drug administration for symptomatic hypotension.[1,18] The main adverse effects are paresthesia, supine hypertension, bradycardia, urinary retention, and piloerection. Fludrocortisone is a mineralocorticoid that retains sodium and water, enhances plasma volume, and increases the adrenergic sensitivity of blood vasculature.[1,5,9] The adverse effects of this drug include supine hypertension, hypokalemia, heart failure, and fluid retention.[1,5,9] Erythropoietin, desmopressin, somatostatin analogs, and nonselective beta blockers are other drugs that may be used for symptomatic hypotension.[5,18] Therapies to reverse CAN are limited; however, early detection and lifestyle modification are important in limiting the deleterious effects from severe DM-associated CAN.[32]

## CONCLUSION

Diabetes-related CAN causes significant morbidity and mortality and is common in both type 1 and type 2 DM. The pathophysiological mechanisms leading to CAN are multifactorial and need further study. CAN in DM can be subclinical or present with a wide range of symptoms, ranging from resting tachycardia to orthostatic hypotension. Although CAN in DM is difficult to diagnose in the hospital setting, multiple tests of autonomic function are available in the outpatient setting for screening and definitive diagnosis. CAN in DM can lead to significant morbidity and carries an increased risk of silent ischemia and perioperative mortality. Current treatment of CAN is mainly limited to glycemic control to slow progression and symptomatic treatment of orthostatic hypotension.

*Conflict of Interest Disclosure:*
The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

*Keywords:*
cardiac autonomic neuropathy, diabetes, resting tachycardia, orthostatic hypotension, heart rate variability, cardiac autonomic reflex tests, CARTs, hyperglycemia, parasympathetic, cardiovagal, sympathetic, Valsalva, silent ischemia, DCCT study, EDIC study, perioperative mortality, exercise intolerance, EURODIAB study, glycosylation, reactive oxygen species, microvascular complications, diabetic neuropathy, Toronto Consensus Panel

### KEY POINTS

- Cardiac autonomic neuropathy (CAN) is a known complication in diabetes mellitus (DM) that remains underdiagnosed despite the high risk of morbidity and mortality associated with this disease.
- CAN is a progressive disease that may initially remain subclinical, affecting only cardiovagal function, but can progress to more severe manifestations that affect sympathetic function.
- Diagnostic testing is done through cardiac autonomic reflex tests (CARTs), which are based on heart rate, blood pressure, and sudomotor responses.
- Treatments strategies for CAN in DM are limited to preventing progression of disease and symptomatic control.

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