

Cardiac autonomic neuropathy in patients with diabetes mellitus: current perspectives

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Abstract: Cardiac autonomic neuropathy (CAN) is a common and often-underdiagnosed complication of diabetes mellitus (DM). CAN is associated with increased mortality, cardiovascular disease, chronic kidney disease, and morbidity in patients with DM, but despite these significant consequences CAN often remains undiagnosed for a prolonged period. This is commonly due to the disease being asymptomatic until the later stages, as well as a lack of easily available screening strategies. In this article, we review the latest developments in the epidemiology, pathogenesis, diagnosis, consequences, and treatments of CAN in patients with DM.

Keywords: cardiovascular, autonomic, neuropathy, orthostatic hypotension, postural hypotension, hyperglycemia, heart-rate variability, sympathetic, parasympathetic, deep breathing, Valsalva ratio, 30:15 ratio, Ewing tests, Ewing criteria

Introduction

Diabetes mellitus (DM) is a global health epidemic thought to be affecting 415 million people worldwide, with a further 318 million suffering with glucose intolerance and an increased risk of developing the disease.¹ Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in patients with DM, but diabetes-related microvascular complications also have a significant impact on morbidity and mortality.²⁻⁴

Cardiac autonomic neuropathy (CAN) is a common underdiagnosed complication of DM.^{5,6} The impact of CAN on patients with DM can be devastating, with CAN shown to be associated with increased mortality, CVD, chronic kidney disease (CKD), and morbidity of DM.⁶⁻⁸ The aim of this manuscript is to review the latest developments related to the epidemiology, pathogenesis, diagnosis, consequences, and treatment of CAN in patients with DM.

Search strategies

A review of literature was conducted using PubMed, Google Scholar, and Medline. Several terms were used in combination, including “cardiac”, “autonomic”, “neuropathy”, “dysfunction”, “cardiomyopathy”, “diabetes”, “treatment”, “diagnosis”, “definition”, “pathophysiology”, and “pathology”. These results were limited to studies published in the English language between 2012 and 2017, but references from within those texts were also used. In addition, we also consulted our previous review of this topic that was published in 2014.⁹

CAN epidemiology

Several studies examined the prevalence of CAN in patients with type 1 DM (T1DM) and type 2 DM (T2DM) (Table 1). These studies showed a large variation in CAN prevalence:

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17%–66% in patients with T1DM and 31%–73% in patients with T2DM. This is thought to be due to discrepancies and variation in the criteria used to diagnose CAN, study populations, and variation in CAN risk factors, as shown in Table 1.⁹

CAN risk factors

CAN has several risk factors that are common to other diabetes-related vascular complications, such as glycemic control, diabetes duration, and CVD risk factors, among others.

Duration of diabetes

Diabetes duration is a major risk factor for the development of CAN in patients with T1DM and T2DM.^{6,14–16} The incidence of CAN has been reported to be 6% and 2% annually in patients with T1DM and T2DM, respectively.⁹ The prevalence of CAN increased from 9% at the close of the DCCT study to 31% 1 year later.²⁴ Similarly, the prevalence of CAN increased from 19.8% in patients with prediabetes to 32.2% in patients newly diagnosed with T2DM,²⁵ with higher prevalence reported in patients with T2DM and longer diabetes duration.^{14,26,27} The prevalence of CAN is often reported to be higher in T2DM compared to T1DM, despite the longer diabetes duration in patients with T1DM; this is likely a reflection of patients with T2DM often being older and more likely to have more CVD risk factors for CAN than patients with T1DM.

Glycemic control

Hyperglycemia plays an important role in the pathogenesis of diabetes-related microvascular complications,²⁸ and hence it is not surprising that hyperglycemia has an unfavorable impact on the development and progression of CAN. DCCT showed a 50% decrease in CAN incidence over a 6.5-year follow-up in its intensive-therapy cohort.¹⁵ The benefits of intensive glycemic control during DCCT persisted for at least 14 years after the end of the study, despite glycated hemoglobin (HbA_{1c}) differences between the intensive- and conventional-therapy arms disappearing after the end of randomization.²⁹ Furthermore, participants in the DCCT intensive-therapy group who were free from CAN at the end of the study had a 31% reduction in risk of incident CAN when compared to those in the control arm (OR 0.69; 95% CI 0.51–0.93).¹⁵ However, those individuals diagnosed with CAN at the end of DCCT showed a higher risk of suffering CVD events in follow-up, which was not independent of previous glycemic exposure or the effect of metabolic memory.²⁴

Cardiovascular risk factors

CVD risk factors, including obesity, smoking, hypertension, and hyperlipidemia, have all been associated with

CAN development.^{14,30,31} In the EURODIAB prospective complications study, risk factors related to CAN development were investigated over a 7.3-year follow-up in patients with T1DM. The study showed that systolic blood pressure (SBP; OR 1.1/10 mmHg, 95% CI 1–1.3), HbA_{1c} (OR 1.2 per percentage point, 95% CI 1.1–1.4), and age (OR 1.3 per decade, 95% CI 1.1–1.7) were associated with a higher risk of developing CAN.³¹ A cross-sectional study of 2,230 participants with T2DM also showed that CAN patients had a higher prevalence of hypertension vs patients without CAN (57% vs 49%, $P<0.001$).³²

One study suggested that central obesity was associated with CAN, alongside age, postprandial glycemia, and diastolic blood pressure (DBP).²⁵ Another study of 245 T1DM and 151 T2DM patients showed that CAN was independently associated with obesity ($P=0.034$) and that specifically in T2DM there was higher prevalence of CAN in obese patients ($P=0.033$).³³ It may thus be suggested that weight loss might have a favorable impact on CAN.³⁴

Microvascular complications

Microvascular complications share common mechanisms, and several studies have shown that microvascular complications predict CAN development. For example, the EURODIAB study showed that the presence of retinopathy and albuminuria was associated with CAN.¹³ A large cohort study of 1,021 T2DM patients with CAN demonstrated that over a 7.5-year follow-up diabetic retinopathy (OR 1.513, 95% CI 1.028–2.226; $P=0.036$) and higher levels of microalbuminuria (OR 1.515, 95% CI 1.031–2.228; $P=0.035$) predicted CAN progression.³⁵ Similar results were found in a more recent study.³⁶

Sex

The impact of sex on CAN epidemiology is controversial. The ACCORD trial, which included >8,000 patients with T2DM, showed higher CAN prevalence in women compared to men across all definitions of CAN used within the study.³⁷ A more recent study, though not statistically significant, also showed women had higher prevalence of CAN than men (65.2% vs 34.8%, $P=0.059$).³⁸ However, other studies have shown no difference in CAN prevalence between men and women.^{13,32,39}

Ethnicity

The impact of ethnicity on CAN prevalence has also been widely discussed in the literature, being cited as a possible risk factor for CAN, as lower rates of peripheral neuropathy (PN) were detected in South Asians when compared to white

Table 1 Summary of studies on prevalence of cardiac autonomic neuropathy

Study	Diagnostic test	Criteria	Cutoffs	Prevalence (%)	Patients, n	DM type	Population	Ethnicity	Notes
O'Brien et al ¹⁰	1. HRV response to rest 2. E:I ratio 3. Valsalva maneuver 4. 30:15 ratio 5. CV of HRV	Two or more abnormal tests	HR responses below percentile 2.5 (abnormal)	17	506	T1DM	Mean age 45 years Diabetes duration 15 years	NA	
Navarro et al ¹¹	1. E:I ratio 2. Valsalva ratio	Two abnormal tests	1. HRV ≥ 15 bpm 2. ≥ 1.43	65.9	545	T1DM	Mean age 33.4 years Diabetes duration 19.4 years	NA	
Chen et al ¹²	1. E:I ratio 2. HRV during six consecutive breaths 3. 30:15 ratio 4. Valsalva maneuver 5. Postural drop	Scoring 3 or more	1. HRV < 8 bpm (1) 2. HRV < 7 bpm (2) 3. HRV < 17 bpm (1) 4. HRV < 13 bpm (1) 5. SBP fall > 25 mmHg or DBP fall > 10 mmHg	60.6	612	T2DM	Mean age 63.1 years Diabetes duration 10.4 years	Data collected from a Taiwanese hospital	Numbers in parentheses represent score given to each CART
Kempler et al ¹³	1. 30:15 ratio 2. SBP postural drop	One abnormal test	1. < 1.04 2. Drop > 20 mmHg	36	3,010	T1DM	Mean age 32.7 years Diabetes duration 14.7 years	Data collected in European countries	
Low et al ¹⁴	1. Sudomotor axon-reflex test 2. HRV during Valsalva maneuver 3. SBP postural drop and 30:15 4. E:I ratio	CASS ≥ 1 in two domains or ≥ 2 in one domain (sudomotor, cardiovascular, adrenergic)	CASS is 10-point score divided into adrenergic (0–4), sudomotor (0–3), and cardiovascular (0–3). No specific cutoffs were quoted in the paper	54 (T1DM) 73 (T2DM)	68 (T1DM) 134 (T2DM)	T1DM T2DM	Mean HbA _{1c} 6.7% Mean age 59 years HbA _{1c} 7.4% (T1DM) and 7.2% (T2DM)	T1DM – 100% white T2DM – 98% white	Recruited from Rochester Diabetic Neuropathy Study; CASS corrected for confounding effects of age and sex
Pop-Busui et al ¹⁵	1. E:I ratio 2. Valsalva maneuver 3. DBP postural drop	Abnormal HRV combined with abnormal Valsalva ratio or DBP drop	1. HRV < 15 bpm 2. ≤ 1.5 3. Drop > 10 mmHg	29 (intensive-Tx group) 35 (conventional-Tx group)	620 (intensive-Tx group) 591 (conventional-Tx group)	T1DM	Mean age 47 years Diabetes duration 26 years HbA _{1c} 7.9% (intensive), 7.8% (conventional)	NA	Primary and secondary care

(Continued)

Table 1 (Continued)

Study	Diagnostic test	Criteria	Cutoffs	Prevalence (%)	Patients, n	DM type	Population	Ethnicity	Notes
Eze et al ¹⁷	1. Resting HR 2. Valsalva ratio 3. HRV to deep breathing 4. 30:15 ratio 5. Postural drop	Score ≥ 3 out of 5 Borderline = 0.5 Abnormal = 1	1. ≥ 100 bpm (abnormal) 2. ≤ 1.1 (abnormal), 1.11–1.2 (borderline) 3. ≤ 10 bpm (abnormal), 11–14 bpm (borderline) 4. ≤ 1 (abnormal), 1.01–1.03 (borderline) 5. SBP ≥ 20 mmHg (abnormal), DBP ≥ 10 mmHg (abnormal)	44.3	70	T2DM	Mean age 55.76 years Diabetes duration 7.67 years Male 38.6%	Nigerian	Secondary care
Tahrani et al ¹⁸	1. E:I ratio 2. Valsalva ratio 3. 30:15 ratio 4. Postural drop	Two or more abnormal tests	Abnormal values not given, except postural drop of SBP >20 mmHg or DBP >10 mmHg	42.2	204	T2DM	Mean age 59.5 years Diabetes duration 15 years Male 60.5% HbA _{1c} 8.2%	White European – 43.6% South Asian – 56.4%	Secondary care
Lerner et al ¹⁹	1. Valsalva maneuver 2. SBP postural drop 3. 30:15 ratio 4. E:I ratio	Two or more abnormal tests	1. <1.2 2. 10–29 mmHg (borderline), >30 mmHg (abnormal) 3. <1.03 4. HRV <10 bpm	37	384	T2DM	Mean age 57.6 years	Peru	Primary and secondary care
Mendivil et al ²⁰	1. E:I ratio 2. Valsalva maneuver 3. 30:15 ratio	One or more abnormal or borderline tests	1. HRV ≤ 10 (abnormal), 11–14 (borderline) 2. ≤ 1.1 (abnormal), 1.11–1.2 (borderline) 3. ≤ 1 (abnormal), 1.01–1.03 (borderline)	68	154	T2DM	Mean age 61.4 years Diabetes duration 12.2 years HbA _{1c} 7.7%	Latin American	Secondary care
Razanskaite-Virbickiene et al ²¹	1. E:I ratio 2. 30:15 ratio 3. SBP postural drop 4. DBP change to isometric exercise	Two or more abnormal tests	1. ≤ 1.1 2. ≤ 1.1 3. Drop ≤ 20 mmHg 4. Drop ≤ 10 mmHg	32.2	208	T1DM	Mean age 20 years Diabetes duration 15.1 years HbA _{1c} 9.46%	Data collected from a Lithuanian–Swiss project	

(Continued)

Table 1 (Continued)

Study	Diagnostic test	Criteria	Cutoffs	Prevalence (%)	Patients, n	DM type	Population	Ethnicity	Notes
Menon et al ²²	1. E:1 ratio 2. 30:15 ratio 3. SBP postural drop 4. DBP change to isometric exercise	One abnormal test = possible CAN Two abnormal tests = definite CAN	1. 20–24 years, 1.17; 25–29, 1.15; 30–34, 1.13; 35–39, 1.12; 40–44, 1.1; 45–49, 1.08; 50–54, 1.07; 55–59, 1.06; 60–64, 1.04; 65–69, 1.03; 70–75, 1.02 2. <1.03 3. Drop >30 mmHg 4. Difference between highest and resting DBP of ≤15 mmHg	31 (possible) 66.2 (definite)	74	T2DM	Mean age 61.1 years Diabetes duration 10.2 years HbA _{1c} 8.9%	NA	Secondary care
Tahrani et al ²³	1. E:1 ratio 2. Valsalva ratio 3. 30:15 ratio 4. SBP and DBP postural drop	Two or more abnormal tests	Abnormal values not given, except postural drop of SBP >20 mmHg or DBP >10 mmHg	40.9 in both South Asians and Caucasians	126 (South Asian) 140 (Caucasian)	T2DM	Mean age 59.5 years (South Asians), 59.2 years (Caucasians) Diabetes duration 11 years (South Asian), 10.5 years (Caucasians) HbA _{1c} 8%	White Caucasian – 52.6% South Asian – 47.4%	Secondary care

Abbreviations: HRV, heart-rate variability; DM, diabetes mellitus; E:1, expiration:inspiration; CASS, composite autonomic severity score; CV, coefficient of variation; T1DM, type 1 DM; T2DM, type 2 DM; CAN, cardiac autonomic neuropathy; Tx, treatment; SBP, systolic blood pressure; DBP, diastolic blood pressure; NA, not applicable; HbA_{1c}, glycated hemoglobin.

Europeans with DM.⁴⁰ This was further supported in a recent study that showed white Caucasians were twice as likely to have diabetic PN (DPN) as South Asians, although this did become nonsignificant when adiposity and height were adjusted for.²³ However, unlike PN, CAN prevalence has not been shown to be different between ethnicities, despite these ethnic differences in PN prevalence.²³ This suggests that despite similarities in the pathogenesis of PN and autonomic neuropathy (AN) in patients with DM, there remain specific mechanisms that might affect one and not the other that need to be further explored.

Pathogenesis of CAN

CAN pathogenesis is complex, multifactorial, and still under much debate. Many of the proposed mechanisms are centered on models of neuronal injury based on somatic neuropathy, rather than AN. There are similarities between somatic neuropathy and AN, but there are also differences, as was shown by the STENO-2 trial,⁴¹ in which the most recent follow-up showed that multifactorial intervention (including intensive therapy or CVD risk factors) can prevent the progression of AN, while the effects on somatic neuropathy were limited.⁴¹

Hyperglycemia

Hyperglycemia can activate multiple pathways involved in the pathogenesis of CAN. Of these pathways, the majority are related to the metabolic and/or oxidative state of neuronal cells. Although these alone can cause excessive damage, when combined they result in mitochondrial dysfunction and formation of reactive oxygen species (ROS).⁴² Oxidative stress can induce DNA damage, leading to activation of PARP and inhibition of GAPDH.⁴³ This in turn can activate multiple pathways, including the polyol pathway, the hexosamine pathway, as well as activation of PKC and increased production of advanced glycation end products, which in turn correlate with the severity of autonomic nerve abnormalities in patients with DM.^{42,44–47}

Recent studies have supported the theory that hyperglycemia also impairs neuronal regeneration, and suggested that an increase in plasma superoxide generation may be able to predict decline in cardiac nerve function, and in particular may be the main determinant in early cardiac autonomic dysfunction.^{48–50} In relation to CAN, increased ROS is thought to depress autonomic ganglion synaptic transmission, contributing to increased risk of fatal cardiac arrhythmias, as well as to sudden death after myocardial infarction due to posttranslational protein modifications.⁵¹

Autoimmunity

CAN might occur as a result of autoimmune autonomic ganglionopathy. This is where autonomic failure occurs in the presence of antibodies to the nicotinic acetylcholine receptor of autonomic ganglia, leading to severe autonomic manifestations, eg, orthostatic intolerance, syncope, constipation, gastroparesis, urinary retention, dry mouth, dry eyes, anhidrosis, and cognitive impairment.^{52,53} However, the role of autoimmunity in patients with diabetes and CAN remains controversial.^{54–57} A recent small cross-sectional study did show that the presence of IgG antibodies was associated with AN (OR 9, 95% CI 1.3–61.03).⁵⁸ However, there remains no clear consensus on the role of autoimmunity in CAN progression, and most studies showing a positive association have been in patients with T1DM. Therefore, whether autoimmunity contributes to CAN in patients with T2DM is still not clear.^{57,59}

Genetics

Several genes have been linked to the development and progression of diabetic polyneuropathy and CAN, among which are *TCF7L2*, *APOE*, and *ACE*.⁶⁰ Ciccacci et al showed an association between miR1146a and miR27a single-nucleotide polymorphisms and CAN susceptibility.⁶¹ However, a twin study by Osztoivits et al found that genetic factors did not have a substantial influence on CV autonomic function, and the authors went on to say that environmental factors played a bigger role.⁶²

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is known to be common in patients with DM and believed to be associated with DPN in patients with T2DM.^{63,64} While obesity is a major risk factor for OSA, Janovsky et al showed that OSA was common in lean patients with T1DM and that OSA can be associated with CAN.⁶⁵ Unpublished data from our group showed that OSA was associated with weaker sympathetic and parasympathetic tone in patients with T2DM and that patients who were compliant with OSA treatment (continuous positive airway pressure) had improvements in several autonomic parameters over the follow-up period.^{66,67}

The pathophysiology and relationship between OSA and CAN might differ between patients with T1DM and T2DM. The intermittent hypoxia that occurs with OSA could result in increased ROS and impaired microvascular function, leading to CAN.⁶⁴ On the other hand, the relationship may be bidirectional, with CAN causing changes in respiratory drive and upper-airway tone, increasing the risk of OSA.

Inflammation

Inflammation plays an important role in the pathogenesis of diabetes and its related micro- and macrovascular complications. CAN has been associated with increased inflammatory markers such as CRP, IL6, and TNF α , and adipose-tissue inflammation.⁴⁷ However, the direction of the relationship between inflammation and CAN is not clear and could be bidirectional.^{47,68} Vinik et al suggested that the inflammatory response is controlled by a neural circuit in which the afferent arc consists of nerves that sense injury and transmits the information via the vagus nerve to the brain stem, which in turn activates the cholinergic anti-inflammatory pathways modulating the response.⁴⁷ Increased activity in the vagus nerve to the spleen reduces the innate immune system's response to damage-associated molecular patterns and suppresses inflammation.⁴⁷ Therefore, changes in vagal activity due to AN might have an impact on inflammatory responses.

Clinical manifestations and consequences of CAN

CAN only becomes symptomatic in the later stages of the disease as it advances (Figure 1).^{6,47} The denervation of both the autonomic and peripheral nervous systems occurs in an ascending length-dependent manner.^{9,69,70} Therefore, the vagus nerve is usually the first nerve to be affected in CAN, resulting in patients presenting with symptoms of sympathetic predominance. However, this is initially limited to baroreceptor abnormalities and changes in heart-rate variability (HRV), but as the disease progresses cardiac involvement becomes more evident and symptomatic.

Resting tachycardia

One of the earliest signs of CAN is asymptomatic abnormalities in heart rate (HR), which later progresses to resting

tachycardia (90–130 bpm).^{47,71} A fixed and unresponsive HR to breathing is associated with complete cardiac denervation and severe CAN.^{47,72} Therefore, resting HR can be used as a diagnostic and prognostic tool in patients with DM after excluding other causes of tachycardia.⁹ Furthermore, a study of 11,400 T2DM patients concluded that resting tachycardia is associated with an increased risk of death and CV complications (HR 1.15/10, 95% CI 1.08–1.21; $P < 0.001$). However, it was unclear whether this increased risk was a direct result of a higher resting HR or just a marker of other factors that may determine a poor outcome.⁷³

Reduced exercise tolerance

Parasympathetic denervation and sympathetic predominance are known to impair exercise tolerance by reducing HR and blood pressure (BP) response to activity, as well as blunting the appropriate increases in cardiac output.^{47,71} Patients with CAN who are undertaking an exercise program should be warned that HR cannot be used as an indicator of exercise intensity.^{47,74}

Orthostatic hypotension

Orthostatic hypotension is defined as a reduction in SBP > 20 mmHg or DBP > 10 mmHg following a postural change from supine to standing, and is deemed to be a late sign in CAN.^{71,74} In diabetes, it is thought to be the result of efferent sympathetic vasomotor denervation leading to a defective reflex arc, culminating in an inadequate HR response and peripheral vasodilation when a person stands.^{14,75} Symptoms can include faintness, dizziness, and light-headedness, and in severe cases a syncopal episode.⁷² Several medications given to patients with diabetes can aggravate these symptoms, including diuretics, vasodilators, tricyclic antidepressants, and insulin.^{74,76}

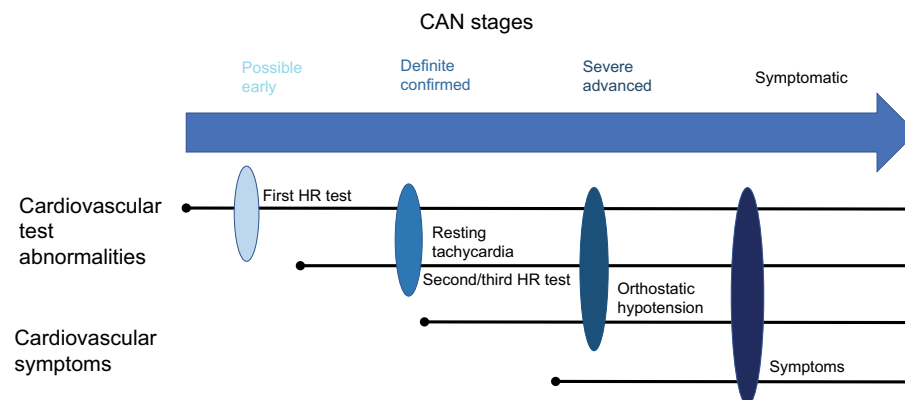


Figure 1 Stages of CAN.

Notes: CAN symptoms can include reduced exercise tolerance, silent ischemia, interoperative complications, and lower-limb complications. Adapted from Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. *J Diabetes Invest.* 2013;4(1):4–18. © 2013 Asian Association for the Study of Diabetes and Wiley Publishing Asia Pty Ltd.⁴⁷

Abbreviations: CAN, cardiovascular autonomic neuropathy; HR, heart rate.

QT prolongation

QT prolongation is associated with cardiac arrhythmias and sudden death.⁷⁷ Its pathogenesis is multifactorial, but includes an imbalance in cardiac sympathetic innervation and left-ventricular hypertrophy, as is often seen in CAN.⁷⁸

Silent ischemia and CVD

Silent coronary artery disease has been reported with varied prevalence (12%–34%) in patients with DM, and is dependent on age, diabetes duration, and the presence of other risk factors.^{79–82} In the DIAD study, CAN (based on Valsalva ratio) was strongly associated with silent myocardial ischemia independently of traditional CVD risk factors.^{47,81} CAN was also associated with a prolonged subjective angina threshold, meaning that electrocardiography changes occur prior to the onset of angina pectoris, and thus CAN patients may be more susceptible to silent myocardial ischemia and/or infarction.⁸³

A study by Valensi et al showed that CAN was a better predictor of a major cardiac event than silent ischemia ($P=0.04$ vs $P<0.05$), but that patients with CAN and associated silent ischemia had the highest risk.⁸⁴ A meta-analysis of 12 cross-sectional studies showed that CAN was associated with silent ischemia in patients with DM; the Mantel–Haenszel test estimated the prevalence risk ratio was 1.96 (95% CI 1.53–2.51, $P<0.001$) for patients with CAN vs no CAN when CAN was defined using two or more measures.⁷⁴ The pathophysiology linking these two conditions is still unclear, with several proposed mechanisms, including reduced pain threshold, changes to the myocardial autonomic pathways or ischemic processes, and a causative relationship with both conditions being the product of coronary artery disease present in diabetes.⁹

In the EURODIAB study, CAN was independently associated with CVD in patients with T1DM.³¹ Similarly, the DCCT and EDIC studies showed that CAN predicted long-term CVD events during follow-up.²⁴ CAN was also found to be a predictor of cerebrovascular disease over 5–10 years of follow-up in patients with T2DM.^{85–87}

Cardiomyopathy

Diabetic cardiomyopathy results in systolic and diastolic dysfunction in the absence of structural and valvular cardiac disease, hypertension, or coronary vessel disease.⁸⁸ The perceived mechanisms include left-ventricular hypertrophy, increased oxidative stress, altered substrate utilization, and mitochondrial dysfunction.⁸⁹ The combination of sympathetic predominance and autonomic myocardial denervation leads

to reduced coronary blood flow and thus diastolic and eventually systolic dysfunction.^{5,90}

Peri- and intraoperative complications

Patients with CAN have a greater risk of anesthetic-related complications. Sufferers of CAN may have varied hemodynamic response to induction and tracheal intubation, leading to intraoperative hypotension, which is thought to be due to an inability to vasoconstrict correctly after the use of vasodilatory agents, such as anesthesia.^{91,92} Furthermore, patients with CAN have been shown to have a two- to three-fold increase in perioperative morbidity and mortality as a result of severe intraoperative hypothermia.^{91–93} It is thus vital that all patients with a diabetes diagnosis are subject to a thorough preoperative assessment to minimize any of these complications perioperatively.⁹¹

Lower-limb complications

Sudomotor dysfunction, which can lead to foot ulceration, is due to both PN and AN.⁹ A study over 5 years of 595 patients with T2DM showed that the development of foot ulcers was independently associated with CAN after adjustment for possible confounding factors (normal vs definite CAN, HR 4.45, 95% CI 1.29–15.33).⁹⁴ In addition, a study by Chahal et al suggested that there may be an association between sudomotor dysfunction and peripheral artery disease, which can contribute to foot ulceration and lower-limb amputations.⁹⁵ Autonomic dysfunction has been suggested to play an important role in the pathogenesis of Charcot neuroarthropathy in addition to periphery sensory and motor neuropathy.⁹

Chronic kidney disease

A recent study of 755 patients showed that CAN was an independent predictor for developing CKD in patients with T2DM after a 9.6-year follow-up (HR 2.62, 95% CI 1.87–3.67; $P<0.001$).⁹⁶ CAN was also an independent predictor of estimated glomerular filtration-rate decline in patients with T2DM in another study.¹⁸ Similarly, in patients with T1DM, CAN predicted the development of albuminuria and estimated glomerular filtration-rate decline over a 14-year period.⁹⁷

Anemia

Anemia is positively associated with CAN in patients with T2DM, despite adjustment for sex, age, smoking habits, body-mass index, ALT, hyperlipidemia, hypertension, DM duration, HbA_{1c}, retinopathy, and nephropathy.³²

Mortality

Longitudinal studies have shown a 5-year mortality rate of 16%–50% in both T1DM and T2DM once CAN had been diagnosed, with most of these attributed to sudden cardiac death.^{9,72} This large range was due to differences in study population and methodologies used to diagnose CAN. These include changes in the perception of myocardial ischemia, altered hemodynamic response to stress on the CV system (eg, surgery, infection, or anesthesia), QT-interval dispersion leading to cardiac arrhythmias, variations in autonomic cardiac innervation balance and focal regions of sympathetic denervation, and reinnervation of the myocardium.⁸

A meta-analysis of 15 studies including studies with a baseline assessment of HRV using one or more tests and follow-up mortality data showed that the pooled estimated relative mortality risk was 3.45 (95% CI 2.66–4.47, $P < 0.001$) when CAN was defined as the presence of two or more abnor-

malities in cardiac autonomic function.^{9,98} The ACCORD trial also showed CAN to be an independent predictor of all-cause mortality (HR 2.14, 95% CI 1.37–3.37) and CVD mortality (HR 2.62, 95% CI 1.4–4.91) after a mean follow-up of 3.5 years,³⁷ while the EURODIAB IDDM complication study demonstrated that CAN had the strongest association with mortality when compared to other risk factors.⁹⁹

Diagnosis and screening of CAN

Cardiac autonomic reflex tests

Cardiac autonomic reflex tests (CARTs) were first described by Ewing et al in 1980 (Table 2).^{71,100} The CAN Subcommittee of the Toronto Consensus Panel defined CAN as the presence of at least two abnormal CARTs, presence of one abnormal CART as possible CAN, and presence of orthostatic hypotension with two or more abnormal CARTs as indicative of advanced CAN.⁶ CARTs are the gold standard in clinical

Table 2 Summary of Ewing tests

CART	What does it assess?	Which branch of the autonomic nervous system does it measure?	Interpretation and definition	Cutoffs (age-dependent) ¹⁰²	Diagnostic performance ¹⁰¹
HR response to deep breathing (E:I ratio) ^{103,111}	Assesses beat-to-beat variation (R-R variation) during paced deep breathing	Tests for defects in parasympathetic activity by assessing ability of vagal nerve to slow HR	Gives an E:I ratio: longest R-R during expiration divided by shortest R-R during inspiration	1.22–1.1 (15–65 years)	$S_1 = 19\%$ $S_2 = 98\%$ $P = 0.115$ OR (95% CI) = 2.34 (1.19–4.77)
HR response to standing (30:15 ratio) ^{103,111}	Assesses beat-to-beat variation (R-R variation) following standing	Tests for defects in parasympathetic activity by assessing ability of vagal nerve to slow HR	Gives the 30:15 ratio: R-R interval around 30th heartbeat divided by R-R interval around the 15th heartbeat	1.17–1.06 (15–65 years)	$S_1 = 96\%$ $S_2 = 65\%$ $P < 0.001$ OR (95% CI) = 44.07 (12.68–153.25)
Valsalva maneuver (Valsalva ratio) ¹⁰⁴	Evaluates HR response during and after provoked increase in intrathoracic/abdominal pressure	Assesses both parasympathetic and sympathetic activity, but mainly parasympathetic	Gives Valsalva ratio: longest R-R interval in Phase IV divided by shortest R-R interval in Phase II and at very beginning of Phase III	1.23–1.16 (15–65 years)	$S_1 = 62\%$ $S_2 = 92\%$ $P = 0.001$ OR (95% CI) = 18.56 (5.55–62.1)
BP response to standing (reduction in SBP) ^{103,106,110}	Assesses the baroreceptor reflex	Tests for defects in sympathetic activity by assessing ability to provide suitable HR and BP response to activity	Test result presented as difference in both SBP and DBP between sitting and standing	20 drop in SBP or 10 drop in DBP	$S_1 = 51\%$ $S_2 = 71\%$ $P = 0.061$ OR (95% CI) = 2.5 (1.28–4.88)
BP response to sustained muscle contraction (rise in DBP) ^{103,105}	DBP increases caused by sustained muscle contraction with the use of a handgrip dynamometer	Tests for defects in sympathetic activity by assessing ability to provide suitable HR and BP response to activity	Test result presented as difference between highest DBP during examination and average DBP at rest	Should normally be >15 mmHg	$S_1 = 64\%$ $S_2 = 75\%$ $P = 0.002$ OR (95% CI) = 5.22 (2.6–10.55)

Notes: Phase I is a transient increase in BP and resulting bradycardia due to a mechanical rise in transthoracic pressure. Phase II is concomitant compensatory tachycardia due to reduced venous return and stroke volume leading to a decrease in BP. Phase III is a further transient reduction in BP and resulting tachycardia at the end of expiration due to pulmonary vasculature expansion. Phase IV is an abrupt rise in BP above baseline values with resulting bradycardia, thought to be the result of baroreceptor activation. Based on changes to hemodynamic parameters, various indices can be calculated, including the Valsalva ratio, which is derived from the longest R-R interval in Phase IV divided by the shortest R-R interval at the end of Phase II/beginning of Phase III.¹⁰⁷ Normal values for cutoffs are age-dependent; some software manufacturers (such as Ansar) also provide their own normative values. S_1 is sensitivity and S_2 is specificity.

Abbreviations: HR, heart rate; CART, cardiac autonomic reflex test; E:I, expiration:inspiration; SBP, systolic blood pressure; DBP, diastolic blood pressure.

autonomic testing, as they are all noninvasive, safe, and well standardized.^{21,100} While CARTs are measures of CAN, they are also measures of cardiac function, which can be affected in patients with CAN.

Pafili et al compared the results from each individual CART and their combination against Ewing's battery of tests. The study included 152 patients with a median diabetes duration of 12 years and mean age of 64.51±7.85 years. It was concluded that the 30:15 ratio demonstrated the best diagnostic indicator for CAN, with 96% sensitivity, 65% specificity, 94% negative predictive value, and OR of 21.14. It also suggested that if a 30:15 ratio indicated CAN, diagnostic accuracy could be increased if combined with the Valsalva ratio, a rise in DBP, and/or E:I ratio.¹⁰¹

In a study in a rural area of south India, 126 patients with T2DM were compared with 152 age- and sex-matched healthy controls. CAN prevalence was 53.2% in patients with T2DM, and HRV to deep breathing and DBP response to isometric exercise were the most sensitive tests for detecting parasympathetic and sympathetic AN when compared to all other Ewing CARTs.¹⁰⁸ Abnormal values in Valsalva ratio, HRV to deep breathing, and immediate HR response to standing were used to diagnose parasympathetic dysfunction, and abnormal values in BP response to standing and BP response to isometric exercise were used to diagnose sympathetic dysfunction.¹⁰⁸ Another study that evaluated patients with T1DM vs age- and sex-matched healthy controls demonstrated that HRV parameters and HR recovery were significantly reduced in T1DM patients when compared to their healthy counterparts and that HRV parameters also correlated with HR recovery.¹⁰⁹

Spectral analysis of heart-rate variability

As previously discussed, CAN often remains subclinical before clinical manifestations are present. Subclinical CAN can be detected through a reduction in HRV.²¹ In healthy individuals, there is normal beat-to-beat variation during inspiration and expiration, which is driven by sympathetic and parasympathetic activity.^{9,110} Therefore, abnormal beat-to-beat variations may be indicative of early changes to myocardial autonomic innervation. HRV may be assessed by time-domain analysis or frequency-domain analysis, with the former looking at statistical analysis of R-R intervals (SD of all normal R-R intervals and root-mean square of the difference of successive R-R intervals) and the latter at spectral analysis.²¹ Studies have shown that HRV abnormalities can be present at the time of diagnosis and that time- and frequency-domain analysis may permit more accurate evalu-

ation of CV parasympathetic and sympathetic activity.^{21,76} Power spectral analysis of HRV can be carried out under resting conditions with demonstration of low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.4 Hz) components. The LF component of the power spectrum of HRV primarily reflects sympathetic activity, whereas the HF component (also termed the respiratory frequency [RF]) primarily reflects parasympathetic activity. LF:RF ratios are calculated, and provide a measure of sympathetic/parasympathetic activity (Figure 2).³

Scintigraphy

Scintigraphy allows the quantitative evaluation of sympathetic cardiac innervation through the use of single-photon-emission computed tomography ± positron-emission tomography and sympathetic neurotransmitter analogues, such as ¹²³I-metaiodobenzylguanide and ¹¹C-metahydroxyephedrine, respectively.^{9,76} However, these tests are specialized and expensive, and hence most of their use is limited to research studies, rather than routine clinical care.

Baroreflex sensitivity

An increase in BP is normally detected by baroreceptors, inducing a reflective increase in vagal activity and reduction in sympathetic activity.⁹ This results in a reduction in cardiac output, as well as peripheral vasodilation to control the increase in BP.⁹ The opposite occurs when there is a reduction in BP, and thus baroreflex sensitivity (BRS) can assess both sympathetic and parasympathetic activities.⁹

BRS can be examined using pharmacological methods (such as intravenous bolus injection of epinephrine) or non-pharmacological techniques (physical maneuvers, such as postural change).⁹ The former is considered the gold standard to date for evaluating BRS. Both techniques require a continuous measure of BP and a continuous and synchronized measure of HR (R-R interval).⁹ Furthermore, BRS can be estimated spontaneously through the observation of fluctuations of BP and R-R intervals.¹¹¹

The use of BRS as a method of CAN diagnosis has also been looked at in comparison to healthy controls. Kamińska et al found that BRS was significantly lower in T1DM patients with CAN than those without CAN and that BRS did not differ significantly between those without CAN and the sex- and age-matched control group.¹¹² This was further supported by a study showing that T1DM patients had decreased mean BRS in both ms/mmHg and mHz/mmHg when compared to age-matched controls ($P=0.05$ and $P=0.17$, respectively).¹¹³

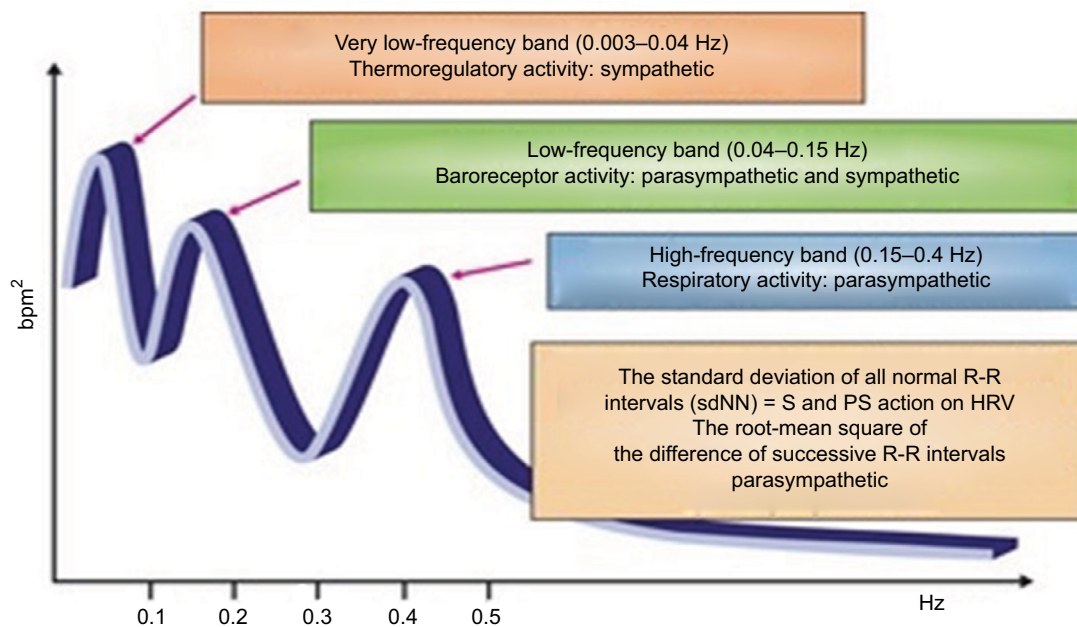


Figure 2 Spectral analysis of HRV.

Note: Reproduced from Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. *J Diabetes Invest*. 2013;4(1):4–18. © 2013 Asian Association for the Study of Diabetes and Wiley Publishing Asia Pty Ltd.⁴⁷

Abbreviations: HRV, heart-rate variability; PS, parasympathetic; S, sympathetic; sdNN, standard deviations of all normal beat-to-beat intervals.

Corneal confocal microscopy

Corneal confocal microscopy (CCM) is an ophthalmic imaging technique that can accurately determine damage to corneal nerve fibers in patients with diabetes. These fibers have been shown to have a similar structure to type A δ and small autonomic C fibers, and thus CCM may be able to detect CAN.¹¹⁴ Tavakoli et al found that CCM may be used to diagnose subclinical and overt diabetic AN (DAN; based on the composite autonomic scoring scale).¹¹⁵ There were progressive and significant reductions in nerve-fiber density, nerve-branch density, and nerve-fiber length in patients with DAN vs healthy control and patients without DAN. Another study showed that CCM could represent a new and noninvasive tool in the diagnosis of CAN in T1DM, as corneal nerve-fiber density was lower in patients with CAN vs without CAN (based on HRV and postural hypotension).¹¹⁶ This is still an evolving area of research, but could present a new noninvasive method for CAN screening and diagnosis in the future.

Screening

The Toronto Consensus Panel recommended screening for CAN, as it can be used as a risk-stratification tool for diabetes-related complications and CV mortality and morbidity.⁶ The American Diabetes Association also recommended screening for CAN at the time of diagnosis for T2DM and

within 5 years of diagnosis for T1DM, particularly if other complications are present.¹¹⁷ CAN screening should also be considered in patients with DM who are undergoing elective surgery, as well as those patients who have suffered from cardiac events, including following myocardial infarction, as CAN predicted adverse outcomes.^{3,29}

Treatment of CAN

Early determination of CAN is vital to the success of therapeutic input, as it has been suggested that CV denervation may be reversible if diagnosed soon after onset.¹¹⁸ The aim of CAN treatment is symptom control or slowing progression. Current methods use a combination of nonpharmacological and pharmacological approaches, including lifestyle modification, intensive glycemic control, and treating underlying risk factors, such as hyperlipidemia and hypertension.

Despite similarities in the pathogenesis of CAN and DPN, they are not the same disease. The STENO-2 trial showed improvements in CAN, but not DPN.⁴¹ In addition, CAN and DPN do not always coexist, despite similar pathogenesis, suggesting that these two conditions are not the same. It has also been shown that the ethnic differences seen in DPN prevalence between South Asians and white Caucasians are not seen in CAN. This could contribute to the differences observed between CAN and DPN responses to treatment. However, when considering treatment, it is important to consider the

treatment modality and how responses were measured. For example, an improvement in the gold standard for DPN – nerve-conduction studies – does not necessarily correlate with an improvement in CAN and vice versa, whereas if CCM, discussed earlier, were used as a measure of DPN, it may lead to a different result. Indeed, following islet-cell transplant, CCM shows improvements in corneal nerves.^{115,116}

Lifestyle modifications

Increased physical activity has been demonstrated to improve HRV and lower resting HR.¹¹⁹ Even simple activity, such as dog walking, could improve parasympathetic activity.¹²⁰ The Diabetes Prevention Program demonstrated that lifestyle modifications were superior to metformin or placebo in regard to improvement in autonomic dysfunction (assessed with HRV and QT indices).¹²¹ A review by Voulgari et al concluded that moderate endurance and aerobic exercise improved HRV and parasympathetic dominance in patients with T1DM or T2DM.¹²² Esposito et al suggested that improvement in autonomic function following physical activity may be related to improvements in tissue hypoxia.¹²³

Intensive glycemic control

The DCCT trial showed that intensive glycemic control reduced CAN incidence by 50% in T1DM over a 6.5-year follow-up when compared to conventional therapy (7% vs 14%, $P < 0.004$).^{15,29,124} These beneficial effects of intensive glycemic control in DCCT persisted during long-term follow-up in the EDIC study,¹⁵ and thus early intervention with intensive therapy in patients with T1DM may help reduce the progression and development of CAN. Additionally, the SEARCH CVD study looked at subclinical autonomic dysfunction in 354 young T1DM patients. Dysfunction was assessed with HRV testing and the presence of parasympathetic loss with sympathetic override, and $HbA_{1c} > 7.5\%$ was independently associated with the presence of subclinical CAN when compared to a control group without DM.¹²⁵

The effects of intensive glycemic control on CAN in patients with T2DM is still unclear.⁵ The Veterans Affairs Cooperative Study suggested no impact of intensive glycemic control on CAN.¹²⁶ In another randomized controlled trial (RCT), intensive glycemic control in newly diagnosed T2DM in primary care did not have an impact on CAN prevalence at 6-year follow-up.³⁹ Conversely, the STENO-2 trial demonstrated that intensive multifactorial treatment (including behavior modification and intensive therapy targeting hyperglycemia and CVD risk factors) lowered progression to AN (based on HRV during paced breathing and orthostatic

hypotension) in T2DM (OR 0.32, 95% CI 0.12–0.78);¹²⁷ these benefits were sustained at the 2-year follow-up.⁴¹

Pathogenesis-based pharmacotherapy

As discussed in the pathogenesis of CAN, hyperglycemia results in the production of excessive ROS, resulting in endothelial dysfunction and neuronal disease.³⁴ Therefore, several antioxidants have been suggested as treatment for CAN. Small studies using α -lipoic acid and vitamin E suggested that these agents might have a favorable impact on CAN.^{6,34,128,129} However, a more recent RCT that used a triple-antioxidant regime (allopurinol, α -lipoic acid, and nicotinamide) over the course of 2 years failed to prevent progression of CAN and had no effect on myocardial perfusion, as demonstrated with scintigraphic imaging modalities.¹³⁰ The effects of α -lipoic acid in the DEKAN RCT were only modest and only seen at 4 months.¹²⁸ A small RCT in patients with T1DM also showed that C-peptide treatment might improve CAN over a 6-month period.¹³¹

Aldose reductase inhibitors, which block the polyol pathway, have been shown to improve autonomic function in three or more of the standardized CARTs, but were ineffective in advanced CAN.¹³² Another study found that aldose reductase inhibitors stabilized or partially reversed left-ventricular abnormalities in patients with CAN.¹³³ ACE inhibitors, particularly quinapril, have also been shown to improve parasympathetic/sympathetic imbalance.^{30,133,134} ACE inhibitors may also be combined with α -lipoic acid to increase HRV, as demonstrated by Ziegler et al.¹³⁵ Cardioselective β -blockers can have a positive effect on autonomic dysfunction.¹³⁶ Ebbehøj et al found that metoprolol improved autonomic function in patients with T1DM when used in combination with an ACE inhibitor.¹³⁷ In the Beta-Blocker Heart Attack trial, propranolol was given to patients with DM following myocardial infarction, and was shown to improve parasympathetic tone and decrease morning sympathetic predominance.¹³⁸

Treatment of orthostatic hypotension

Management of orthostatic hypotension in CAN is complex, and the condition is difficult to treat.⁵ Nonpharmacological interventions include increasing water consumption, avoiding sudden changes in body posture, reducing physical maneuvers that increase intra-abdominal and intrathoracic pressure, use of stockings of the lower extremities, and eating smaller and more frequent meals.^{5,80} Additionally, certain medications have been associated with orthostatic hypotension and should thus be stopped in patients who are symptomatic, including tricyclic antidepressants, diuret-

ics, and α -adrenoreceptor antagonists.^{5,9} If these methods are unsuccessful, then pharmacological methods should be considered on a risk–benefit basis: weighing up an increase in standing BP against prevention of supine hypotension.^{9,80}

Midodrine is a peripheral selective α_1 -adrenergic agonist that causes peripheral vasoconstriction of arterioles and veins and is the only Food and Drug Administration-approved drug, hence its common use.⁹ Other pharmacological agents used in the treatment of orthostatic hypotension include fludrocortisone, which is a synthetic mineralocorticoid, octreotide, which inhibits the release of vasoactive peptides in the gastrointestinal tract, leading to an increase in splanchnic vasoconstriction and a rise in mean arterial BP, erythropoietin, which increases intravascular volume and blood viscosity, and pyridostigmine, which is a cholinesterase inhibitor.¹³⁹

Conclusion

CAN is very common and often undiagnosed in patients with DM. Intensive multifactorial intervention targeting lifestyle, glycemic control, and CVD risk factors prevents the development and slows the progression of CAN. Identifying patients with CAN is important, as CAN is associated with increased mortality, CVD, CKD, perioperative morbidity, and lower-limb complications. As such, these patients should receive appropriate follow up and preventive treatments to prevent or slow the progression of these complications. CAN should be diagnosed as per the Toronto Consensus Panel statement using standardized CARTs. Further research into the pathogenesis of CAN is important, in order to identify novel treatment targets and develop new therapies.

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Disclosure

The authors report no conflicts of interest in this work.

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