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## Cardiovascular autonomic neuropathy in diabetes: Pathophysiology, clinical assessment and implications

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### Abstract

Cardiovascular autonomic neuropathy (CAN) is a debilitating condition that mainly occurs in long-standing type 2 diabetes patients but can manifest earlier, even before diabetes is diagnosed. CAN is a microvascular complication that results from lesions of the sympathetic and parasympathetic nerve fibers, which innervate the heart and blood vessels and promote alterations in cardiovascular autonomic control. The entire mechanism is still not elucidated, but several aspects of the pathophysiology of CAN have already been described, such as the production of advanced glycation end products, reactive oxygen species, nuclear factor kappa B, and pro-inflammatory cytokines. This microvascular complication is an important risk factor for silent myocardial ischemia, chronic kidney disease, myocardial dysfunction, major cardiovascular events, cardiac arrhythmias, and sudden death. It has also been suggested that, compared to other traditional cardiovascular risk factors, CAN progression may have a greater impact on cardiovascular disease development. However, CAN might be subclinical for several years, and a late diagnosis increases the mortality risk. The duration of the transition period from the subclinical to clinical stage remains unknown, but the progression of CAN is associated with a poor prognosis. Several tests can be used for CAN diagnosis, such as heart rate variability (HRV), cardiovascular autonomic reflex tests, and myocardial scintigraphy. Currently, it has already been described that CAN could be detected even during the subclinical stage through a reduction in HRV, which is a non-invasive test with a lower operating cost. Therefore, considering that diabetes mellitus is a global epidemic and that

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diabetic neuropathy is the most common chronic complication of diabetes, the early identification and treatment of CAN could be a key point to mitigate the morbidity and mortality associated with this long-lasting condition.

**Key Words:** Cardiovascular autonomic neuropathy; Cardiac autonomic neuropathy; Diabetes mellitus; Heart rate variability; Sympathetic autonomic nervous system; Parasympathetic autonomic nervous system

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**Core Tip:** Cardiovascular autonomic neuropathy (CAN) is an important risk factor for cardiovascular events. However, CAN may be subclinical for several years, worsening its potential contribution to increased mortality due to late diagnosis. Even during the subclinical stage, CAN could be detected through reduction in heart rate variability, a non-invasive test. Therefore, considering that diabetes mellitus is a global epidemic and that diabetic neuropathy is the most common chronic complication of diabetes, the early identification and treatment of CAN could be a key point to mitigate the morbidity and mortality impact from this long-lasting condition.

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## INTRODUCTION

Cardiovascular autonomic neuropathy (CAN) is a microvascular complication defined as the impairment of cardiovascular autonomic control in persons with diabetes, with no other causes[1]. The prevalence of CAN varies from nearly 2% in patients with newly diagnosed or well-controlled diabetes, up to 60% of patients with long-standing type 2 diabetes mellitus and 90% of pancreas transplantation candidates with type 1 diabetes[2,3]. The heterogeneity of evaluation methods used to classify CAN is a possible cause of this wide variation in prevalence, making it difficult to compare epidemiological data across different studies. CAN prevalence also increases with age, duration of diabetes, and poor glycemic control[4].

Despite CAN manifesting as a subclinical condition for several years until the development of symptoms, it is a risk factor for silent myocardial ischemia, chronic kidney disease, myocardial dysfunction, major cardiovascular events, cardiac arrhythmias, and sudden death. Moreover, it is associated with increased morbidity and mortality risk and poor long-term diabetes prognosis[5-8]. The etiology of CAN is multifactorial, and several conditions are associated with CAN, such as hyperglycemia, insulin resistance, prediabetes, obesity, hypertension, dyslipidemia, metabolic syndrome, and obstructive sleep apnea (OSA). However, it is mainly recognized as a major complication of type 1 and type 2 diabetes mellitus[8], since diabetic neuropathies are the most prevalent chronic microvascular complications of diabetes. Of these, autonomic neuropathies (mainly CAN) and distal symmetric polyneuropathy are the most studied to date[3,9].

An increase in the incidence of CAN is expected to occur due to the progression of diabetes as a global epidemic[10,11]. In 2019, diabetes mellitus affected 463 million people worldwide. This scenario is predicted to grow to over 592 million by 2035; based on the International Diabetes Federation, this number will rise to 700 million (10.9% prevalence) by 2045[12,13]. These projections are worrying considering that, in 2016, diabetes was directly responsible for 1.6 million deaths, representing the seventh leading cause of death worldwide[14]. In addition, diabetes commonly coexists with obesity, and nearly 85% of people with diabetes are type 2 diabetics; of those, 90% are obese or overweight[15]. The burden of these chronic diseases leads to a cardiometabolic epidemic, with a staggering increase in the global prevalence of diabetes mellitus, obesity, and metabolic syndrome[16-18]. Therefore, early identification and

treatment of CAN could be a key point to minimize the morbidity and mortality associated with this long-lasting pandemic. The aim of this study was to review the latest content on the epidemiology, pathophysiology, and clinical assessment of CAN and to encourage healthcare workers to be aware of this clinical entity, considering that CAN is still an under-recognized condition[19].

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## CAN IN DIABETES

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### **Definition**

CAN is a debilitating condition that occurs mainly among diabetic patients, especially those with a long duration of diabetes[19], but can manifest earlier, even before the diagnosis of diabetes[20]. Among its clinical manifestations, resting tachycardia, orthostatic hypotension, light-headedness, visual impairment, syncope, and exercise intolerance are the most common[21,22]. In 1892, Eichhorst suggested that persistent tachycardia in diabetic individuals may be due to damage to the vagus nerve[23]. Bradbury and Eggleston[24] first described the clinical syndrome of orthostatic hypotension and orthostatic tachycardia in 1925, and in 1945, Rundles described these physiological abnormalities as manifestations of diabetic neuropathy[25,26]. Since 1980, several studies have evaluated cardiac autonomic denervation as a possible late-stage complication of CAN and demonstrated that it is associated with increased mortality[23,26-28].

Total cardiac denervation – the loss of sympathetic and parasympathetic innervation – is not frequent, but can occur as a result of diabetic neuropathy and, in turn, results in a blunted heart rate response. Vagal denervation is usually more common and occurs at an earlier stage before sympathetic denervation. Thus, it reverberates in abnormalities of normal heart rate variation and vascular dynamics, which are regulated by the sympathetic autonomic nervous system (SANS) and parasympathetic autonomic nervous system (PANS)[2,20,23]. The interaction and the equilibrium between SANS and PANS result in sympathovagal balance, which is responsible for modulating the sinus node; promoting adjustments of heart rate; controlling chronotropism, dromotropism, bathmotropism, and inotropism; altering the systolic and diastolic volumes; and promoting the control of vascular smooth muscle cells, contributing to peripheral vascular resistance[29-31].

Chronic modifications in the existing equilibrium between the SANS and PANS therefore cause autonomic dysfunction. The mechanisms of autonomic dysfunction are complex and multifactorial, involving degenerative, inflammatory, ischemic, and metabolic abnormalities, which compromise the intrinsic cardiac innervation as well as other structures of the autonomic nervous system[4,32,33]. As cardiovascular autonomic dysfunction is potentially arrhythmogenic, it may predispose to atrial and ventricular arrhythmias and sudden cardiac death[8,34,35]. Although CAN progression is currently considered an independent prognostic factor for cardio-vascular disease[36], it is frequently considered a subclinical condition, which may aggravate its potential contribution to the increased probability of mortality due to late diagnosis. Therefore, it is important to understand the pathophysiological mechanisms that trigger CAN, as well as which clinical assessments are currently available and recommended, in order to contribute to morbidity and mortality reduction associated to CAN[37].

### **Pathophysiology**

CAN results from lesions of the autonomic nerve fibers that innervate the heart and blood vessels, promoting abnormalities in cardiovascular autonomic control[4]. The pathophysiological mechanism responsible for this lesion is multifactorial. Although the mechanisms associated with CAN development remain uncertain in their entirety, the main mechanism is hyperglycemia. Hyperglycemia directly favors an increase in the production of reactive oxygen species (ROS) and advanced glycation end products (AGEs), which are a heterogeneous group of compounds[7,32].

The formation of AGEs occurs mainly due to the Maillard reaction, which is a non-enzymatic reaction between the carbonyl groups of reducing sugars and free amino groups of proteins, and depends directly on the concentration of glucose[38]. This process, which takes weeks to months, is reversible in the early phases, but becomes irreversible in its final stage. After its formation, AGEs accumulate inside and outside the cells. AGEs have been described as being able to bind to receptors for AGEs (RAGE), stimulating phosphatidylinositol-3 kinase (PI3-K) and mitogen-activated protein kinases (MAPK), and, consequently, activating nuclear factor kappa B (NF-κB)

[39].

NF- $\kappa$ B enhances the stimulation of RAGE expression in the cell membrane of cardiomyocytes, neurons, adipocytes, vascular cells, immune cells, glomerular epithelial cells, and lung epithelial cells, promoting a positive feedback response. Moreover, this transcription factor amplifies the production of tumor necrosis factor  $\alpha$  and interleukin 6, which are pro-inflammatory cytokines, and vascular cell adhesion molecule 1, which promotes transendothelial migration of leukocytes [39-41]. In addition to hyperglycemia caused by type 1 and type 2 diabetes, other factors can also increase the production of NF- $\kappa$ B and pro-inflammatory cytokines, such as fatty acid accumulation, obesity, and atherosclerosis [40,42]. NF- $\kappa$ B also plays a crucial role in obesity-induced inflammation and insulin resistance [42].

AGE/RAGE signaling promotes nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation, expanding the production of ROS and oxidative stress [39]. Oxidative stress is defined as an imbalance between ROS production and antioxidant defense systems (superoxide dismutase, catalase, and glutathione peroxidase). Thus, the complex of NADPH oxidase produces superoxide, which, together with hydroxyl radicals, singlet oxygen, and hydrogen peroxide, represent ROS. They have the ability to act as highly reactive free radicals, promote protein, lipid, and nucleic acid oxidation, and induce cellular damage. Moreover, the increase in oxidative stress activates NF- $\kappa$ B and, consequently, increases the expression of RAGEs in the cell membrane, emphasizing AGE/RAGE signaling and promoting positive feedback [39,43].

In particular, it has been demonstrated that plasma superoxide anion is a primary biomarker of oxidative stress, and its increased production works as a predictor of cardiac autonomic dysfunction progression and even all-cause mortality [44]. Thus, chronic increased oxidative stress has a dangerous impact on the autonomic fibers and  $\beta$ -pancreatic cells, triggering the insulin resistance process and the development of type 2 diabetes mellitus. In addition, the increase in oxidative stress is associated not only with the progression of diabetes, but also with dyslipidemia, atherosclerosis, cancer, and cardiovascular diseases [43-45].

Another component that may be associated with the pathogenesis of CAN is OSA [46]. OSA can be defined as a syndrome marked by frequent pauses in breathing during sleep that is usually accompanied by loud snoring, which occurs due to upper airway collapse [47,48]. Although the exact mechanism remains obscure, this disorder can lead to intermittent hypoxia that increases oxidative stress, contributing to CAN development [46]. Moreover, OSA is associated with increased cardiovascular morbidity and is commonly present in diabetic patients [46,48].

### **CAN, diabetes, and mortality**

Several studies have demonstrated the relationship between CAN and increased morbidity and mortality in patients with diabetes [49-51]. In 1991, Ewing *et al* [50] investigated the association between QT interval and corrected QT interval (QTc) length and sudden death in patients with diabetes. They showed that among 71 diabetic subjects, 13 died unexpectedly within three years of follow-up, and the QT and QTc intervals were significantly increased in these 13 participants. Thus, QT and QTc interval prolongation were associated with an increased risk of unexpected death in diabetic individuals with CAN [50].

Thereafter, in 2005, the Rochester diabetic neuropathy study (RDNS) evaluated CAN and the risk factors for sudden cardiac death. Suarez *et al* [52] demonstrated an association between an increase in the QTc interval and sudden cardiac death *via* univariate analysis, but this significance was not observed in the multivariate analysis. Thus, they suggested that other conditions could have influenced this worse prognosis, such as nephropathy. This microvascular complication could be a marker of generalized vascular dysfunction and was marked as an independent risk factor for sudden death in the RDNS study.

Despite the RDSN findings, the Diabetes Heart Study demonstrated that QTc interval predicted all-cause and cardiovascular disease mortality in participants with type 2 diabetes mellitus [53], confirming the results previously obtained by Ewing *et al* [50]. In addition, in 2010, Pop-Busui *et al* [54] evaluated the mortality risk in participants with CAN and reported that CAN participants had a twofold all-cause mortality risk compared to individuals without CAN.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial demonstrated that participants with CAN had similar mortality rates when following both standard and intensive treatments for glycemic control, suggesting that severe glycemic control could promote hypoglycemia and increase the probability of mortality in diabetic patients [54]. Another study developed by Tang *et al* [51] based on

the ACCORD trial evaluated the effects of intensive treatment of hyperglycemia, hypertension, and dyslipidemia as a prevention strategy to reduce cardiovascular events. Considering that these three conditions are important cardiovascular risk factors that must be controlled, the study showed that intensive control of blood pressure and glycemia promotes protective effects on CAN[51]. These findings reinforce that poor glycemic control, the duration of diabetes, and lifestyle factors play a crucial role in CAN development[19]. A brief description of relevant studies on CAN and diabetes is provided in Table 1.

### **Clinical assessment**

Currently, it is estimated that about 50% of people with diabetes mellitus remain undiagnosed[46] and, among those diagnosed, the diagnosis usually happens very late, approximately 20 years after the onset of the disease[55]. Thus, considering that CAN may present even before the onset of diabetes, it is a markedly underdiagnosed and underestimated microvascular complication[20,56]. The natural progression of CAN comprises an asymptomatic, subclinical, and reversible phase, which represents the initial stage. Subsequently, CAN progresses to more advanced stages, with symptoms and a greater impairment of cardiac autonomic fibers[20,33,46].

Autonomic neuropathy battery tests, known as cardiovascular autonomic reflex tests (CARTs), are used to assess stages of and monitor the progression of CAN. They are composed of tests that evaluate autonomic responses through changes in heart rate, blood pressure, and sudomotor responses after several maneuvers[22]. Some of the available tests were described by Ewing *et al*[57-60] in the 1970s and the 1980s and are known as Ewing's Battery composed of five tests as follows: Valsalva maneuver, heart rate response to standing (30:15 ratio), heart rate response to deep breathing (maximum-minimum heart rate), blood pressure response to standing up (orthostatic hypotension test), and blood pressure response to sustained handgrip (isometric handgrip test)[60].

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## **EWING'S BATTERY**

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### ***Heart rate response to deep breathing***

The deep breathing test is associated with respiratory arrhythmia and evaluates PANS function. Patients are asked to breathe at a rate of six times per minute, with approximately 5 s of inhalation and 5 s of exhalation per breath. The examiner must calculate the difference between the average of the largest accelerations (inspiration time) and the average of the largest decelerations (expiration time), and the expected result is at least 10 breaths/min to 15 breaths/min, which can decrease with aging. Moreover, it allows the calculation of the expiratory-inspiratory ratio (E:I ratio), which represents the ratio of the longest RR interval during expiration divided by the shortest RR interval during inspiration from five cycles. The result should be at least 1.2 in young individuals[4,61,62].

### ***Heart rate response to standing***

The heart rate response to standing is referred to as the 30:15 ratio, another test designed to assess PANS function. The protocol consists of asking the patient to rest in the supine position for a specified amount of time, then to change this posture to an erect position. It is calculated based on the ratio between the longest RR interval (between the 20<sup>th</sup> and 40<sup>th</sup> beat, around the 30<sup>th</sup> heartbeat) and the shortest RR interval (between the 5<sup>th</sup> and 25<sup>th</sup> beat, around the 15<sup>th</sup> heartbeat) after standing up. The RR intervals are measured using an electrocardiogram record, and the result should be at least 1.04. In addition, sinus tachycardia, neurocardiogenic syncope, and abnormalities in baroreceptor function could also be detected with this test[4,61,62].

### ***Valsalva maneuver***

The Valsalva maneuver represents voluntary forced expiration against resistance. The test is performed with an electrocardiogram record and evaluates the PANS function with high sensitivity. During expiration, the patient should maintain a mercury column at 40 mmHg for 15 s. Subsequently, physiological tachycardia commonly occurs. The electrocardiogram remains recording for 30 s to 45 s, when physiological bradycardia commonly occurs. The ratio of the shortest RR intervals (maximum heart rate) divided by the longest RR intervals (slowest heart rate) represents the Valsalva ratio, and values below 1.21 are considered abnormal results[4,62].

**Table 1 Characteristics of different studies evaluating cardiovascular autonomic neuropathy and diabetes**

Study	Ref.	Sample size and type of study	CAN assessment	Main findings
Pittsburgh Epidemiology of Diabetes Complications Study III	Maser <i>et al</i> [49], 1990	168 participants with type 1 diabetes; Cross-sectional study	Heart rate response to deep breathing, 30:15 ratio and Valsalva maneuver	The association of CAN with increased cardiovascular risk factors may explain the high mortality of CAN patients
EURODIAB IDDM Complications Study	Kempler <i>et al</i> [85], 2002	3,007 participants with type 1 diabetes; Cross-sectional study	Orthostatic hypotension test and 30:15 ratio	CAN is associated to cardiovascular disease and vascular factors may have an important role in the pathogenesis of CAN
EURODIAB Prospective Complications Study	Witte <i>et al</i> [86], 2005	956 participants with type 1 diabetes; Prospective cohort study (mean follow-up of 7 yr)	Orthostatic hypotension test and 30:15 ratio	Glycated hemoglobin level, hypertension, distal symmetrical polyneuropathy and retinopathy, predict the risk of CAN development
MONICA/KORA Augsburg Cohort Study	Ziegler <i>et al</i> [87], 2008	1720 participants (1560 non-diabetic and 160 diabetic subjects); Prospective cohort study (mean follow-up of 9 yr)	HRV, corrected QT interval and QT dispersion (difference between the longest and shortest QT intervals in 12-lead electrocardiogram)	Prolonged corrected QT interval is an independent predictor of mortality in the non-diabetic and diabetic population, while reduced HRV appears to be a prognostic index only in the presence of diabetes
ACCORD Trial	Pop-Busui <i>et al</i> [54], 2010	10251 participants with type 2 diabetes; Clinical Trial	HRV, resting heart rate and QT index (observed/predicted QT duration)	CAN patients had a 1.55-2.14 increased relative risk of all-cause mortality compared to those without CAN
First Joslin Kidney Study	Orlov <i>et al</i> [88], 2015	370 participants with type 1 diabetes; Prospective cohort study (mean follow-up of 14 yr)	Heart rate response to deep breathing	CAN is a strong independent predictor of the long-term risk of early decline of renal function
ACCORD Trial	Tang <i>et al</i> [51], 2021	7725 participants with type 2 diabetes; Clinical Trial	HRV and QT index	The intensive blood pressure and glycemic control demonstrated favorable impact in patients with CAN

CAN: Cardiovascular autonomic neuropathy; HRV: Heart rate variability.

**Blood pressure response to standing up**

The blood pressure response to standing up is the so-called orthostatic hypotension test or postural hypotension test. This test evaluates variations in blood pressure between the rest period and after standing for three min, corresponding to the evaluation of the SANS function. A decrease in systolic blood pressure  $\geq 20$  mmHg and/or diastolic blood pressure  $\geq 10$  mmHg upon standing should be considered as an abnormal result. Moreover, several other symptoms or conditions can be identified with this test, such as weakness, faintness, dizziness, and visual impairment[4,62,63].

**Blood pressure response to sustained handgrip**

The isometric handgrip test consists of pressing the handgrip with nearly 30% of the maximum contraction strength for 3-5 min. This maneuver could be performed with the dominant arm and/or the non-dominant arm and is supposed to promote an increase in diastolic blood pressure. Blood pressure is measured in the contralateral arm, and an increase of at least 15 mmHg between the rest and peak effort values is expected. This test mainly evaluates the SANS response due to isometric exercise[4,62].

The Ewing’s Battery tests represent a framework of CAN and its severity assessment in a simple, fast, and non-invasive manner[60]. Based on the diagnostic tests and clinical stages, CAN could be classified as follows: subclinical stage, possible or early CAN [decreased heart rate variability (HRV) or one abnormal cardiovascular test from CARTs], definite or confirmed CAN (presence of two or more abnormal CARTs results and often accompanied by resting tachycardia), and severe or advanced CAN (presence of definite or confirmed CAN and orthostatic hypotension, often accompanied by evidence of cardiomyopathy with left ventricular dysfunction on echocardiography and silent myocardial ischemia)[8,10]. Symptomatic CAN may be considered as severe or advanced CAN with exercise intolerance, postural dizziness, palpitations, or presyncope[8].

According to these stages, Ewing *et al*[60] suggested that early involvement, definite involvement, and severe involvement should be interpreted as early parasympathetic, definite parasympathetic, and parasympathetic with additional sympathetic compromise, respectively. In addition, each Ewing’s test can be scored as 0 for a

normal result, 0.5 for a borderline result, and 1 for an abnormal result. Therefore, a total score of 0-5 can be attributed to the standard battery performance, as previously described[60,64]. The progression of CAN stages is associated with a worse prognosis, emphasizing the need for tests for early diagnosis[8].

However, there are some criticisms about the feasibility of Ewing's tests, such as the difficulty in performing some tests in patients with osteoarthroarticular conditions or other mobility difficulties. Moreover, the results of the orthostatic hypotension test could not be reliable in patients with fluid retention, and the Valsalva maneuver directly depends on the patient's comprehension[65]. On the other hand, a potentially useful framework that overcomes these limitations is nuclear imaging, despite the high cost being a major limitation. It is a functional assessment tool used to evaluate presynaptic sympathetic nervous system function using myocardial scintigraphy[63].

### **Myocardial scintigraphy**

Myocardial scintigraphy with  $^{123}\text{I}$ -metaiodobenzylguanidine ( $^{123}\text{I}$ -MIBG) allows for the evaluation of sympathetic presynaptic integrity[63]. After being injected,  $^{123}\text{I}$ -MIBG diffuses into synaptic spaces and is absorbed into pre-synaptic terminals just like norepinephrine. Thus, considering that  $^{123}\text{I}$ -MIBG is a false neurotransmitter, it is not catabolized and allows the visualization and quantification of norepinephrine transporter-1 function and, consequently, cardiac sympathetic innervation[66]. Several studies demonstrated abnormalities in sympathetic innervation in diabetic patients through myocardial scintigraphy with  $^{123}\text{I}$ -MIBG[67-70]. In addition to CAN evaluation in diabetic patients, cardiac sympathetic imaging has other potential clinical applications, such as heart failure, transplantation, ischemic heart disease, and chemotherapy-induced cardiotoxicity[66].

The clinical use of  $^{123}\text{I}$ -MIBG for cardiac and non-cardiac imaging has already been approved in some countries. However, this technique has an elevated cost and its clinical use is still limited[71]; therefore, CARTs continue to be the most commonly used methods for CAN diagnosis[36], providing a quick and non-invasive assessment of cardiac autonomic function at a lower operating cost[72], despite the increased sensitivity of  $^{123}\text{I}$ -MIBG scintigraphy[69].

### **HRV**

The HRV test is a cost-effective measurement based on the RR interval oscillation analysis of consecutive heartbeats. The duration of the RR intervals is not fixed, and reflects the combined performance of the SANS and PANS[73]. Thus, HRV is a marker of cardiac autonomic function, which is suitable for cardiovascular risk stratification. Its reduction is associated with increased cardiovascular risk[63,73]. In addition, HRV is recognized as a predictive factor of silent myocardial infarction and postmyocardial infarction mortality[36].

HRV can be evaluated using linear or nonlinear methods. The nonlinear methods comprise the detrended fluctuation analysis, Hurst exponent, fractal dimension, and Lyapunov exponent. Although these indices are good morbidity and mortality markers, they require long periods of analysis. On the other hand, linear methods can be evaluated in a short period and are divided into two groups: those analyzed in the time domain and those analyzed in the frequency domain[74]. The parameters of these domains are listed in [Table 2](#).

Despite the fact that HRV indices and their respective interpretations are well-established in the literature, there is still no standardization of their reference values. In 1996, the European Society of Cardiology and the North American Society of Pacing and Electrophysiology published guidelines with standardized values of HRV measurements and their clinical associations. However, some of the ranges came from studies with small sample sizes, and the values were not adjusted for potential confounders, such as sex, age, or environmental factors. Thus, they should be considered as estimate values that requires more robust physiological and clinical validation[75].

Another criticism of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology guidelines is the statement that HRV is a simple tool. Although the technique has spread mainly due to devices that provide an automated measurement of HRV, the guidelines generate complex parameters and should be interpreted with caution in order to avoid incorrect data conclusions and extrapolations[33]. Nevertheless, despite criticism and the absence of standardized reference values, HRV remains a method widely associated with the body's self-regulatory capacity and the early identification of autonomic alterations and increased cardiovascular risk[76-78]. Moreover, HRV has been reported as a tool to identify cardiovascular risk, even in individuals without previous cardiovascular diseases[77,

**Table 2 Heart rate variability time and frequency domain measures[89,90]**

Linear indices - time domain		
Parameters	Abbreviation meaning	Interpretation
MNN (ms)	Mean of NN intervals	Long RR intervals are related to a lower heart rate, while short RR intervals denote a high heart rate. It reflects SANS and PANS modulations
SDNN (ms)	Standard deviation of all NN intervals	Reflects the activity of both SANS and PANS
rMSSD (ms)	The square root of the mean squared differences of successive NN intervals	Reflects the PANS activity
NN50 (count)	Number of interval differences of successive NN intervals greater than 50 ms	Reflects the PANS activity
pNN50 (%)	Percentage of successive RR intervals that differ by more than 50 ms	The proportion of NN50 divided by total number of NN, which also represents the PANS activity
Linear indices - frequency domain		
ULF (ms <sup>2</sup> , Hz, %)	Ultra low frequency	Frequency range: 0-0.003 Hz. Commonly, it is not present in HRV results
VLF (ms <sup>2</sup> , Hz, %)	Very low frequency	Frequency range: 0.003-0.04 Hz. It is related to renin-angiotensin-aldosterone system, thermoregulation, peripheral vasomotor tonus and PANS activity
LF (ms <sup>2</sup> , Hz, nu, %)	Low frequency	Frequency range: 0.04-0.15 Hz. It represents the SANS and PANS activity, with a predominance of SANS influence
HF (ms <sup>2</sup> , Hz, nu, %)	High frequency	Frequency range: 0.15-0.4 Hz. It represents the PANS activity
LF/HF	Ratio of LF-to-HF power	So-called sympathovagal index. It represents the sympathovagal balance, the autonomic state resulting from the SANS and PANS influences
Total power (ms <sup>2</sup> )	Total power	It reflects both SANS and PANS influences, representing the components with frequency range ≤ 0.4 Hz

SANS: Sympathetic autonomic nervous system; PANS: Parasympathetic autonomic nervous system; LF: Low frequency; HF: High frequency; ULF: Ultra low frequency; VLF: Very low frequency; MNN: Mean of NN; SDNN: Standard deviation of all NN.

79].

## CRITICAL REFLECTION

Diabetes mellitus is a global epidemic[46], and diabetic neuropathy is the most common chronic complication[63]. Among the types of diabetic neuropathy, CAN is one of the most studied and disabling conditions[19]. Considering that CAN is a major marker for silent myocardial ischemia, myocardial dysfunction, cardiac arrhythmias, and sudden death[5-8], it is surprising that CAN is still an under-investigated condition in patients with diabetes[1].

CAN may present in a subclinical form for many years while the parasympathetic denervation process already occurs in diabetic patients[80]. Moreover, CAN is associated with increased morbidity and mortality risks[4]. However, there is no universal standard method for detecting CAN, and it is suggested that more than one test should be conducted to enhance the sensitivity and reliability of CAN diagnosis [19]. In this setting, several tests with different degrees of accuracy, such as CARTs, HRV, and nuclear imaging, are available[61,69,81,82].

According to the position statement of the American Association of Clinical Endocrinologists (AAACE) and American College of Endocrinology (ACE), CAN screening should be performed at the time of diagnosis in patients with type 2 diabetes mellitus and five years after diagnosis in patients with type 1 diabetes mellitus. Nevertheless, there are still some controversies regarding the guidelines for CAN screening. For instance, the position statement of the American Diabetes Association (ADA) considers a patient eligible for CAN assessment only if they have microvascular complications and/or hypoglycemia unawareness. On the other hand, the Italian Society of Diabetology (SID) and the Italian Association of Clinical Diabetologists (AMD) reported that patients should be evaluated if they have high cardiovascular risk and complications, while the Toronto Consensus emphasizes that screening for symptoms and signs of CAN should be universal[10].

There is also disagreement about the use of HRV tests for the diagnosis of CAN. According to the ADA, SID, and AMD statements, this technique is mainly used for research purposes. In contrast, the AACE, ACE, and Toronto Consensus recognize the clinical and prognostic value of the HRV test[10]. Despite the importance of early detection, there is no harmonized definition of CAN, and CAN is frequently diagnosed late[83].

Therefore, early recognition of CAN is essential to minimize the risk of morbidity and mortality in patients with diabetes. CARTs, HRV, and the <sup>123</sup>I-mIBG myocardial scintigraphy should be used in combination for the CAN diagnosis in diabetic patients [63,84]. A harmonized definition among scientific societies is urgently needed to recommend standardized methods for CAN screening in patients with low, medium, and high cardiovascular risk. In view of the autonomic alterations associated with hyperglycemia, the early identification of sympathovagal imbalance in CAN may change treatment strategies for diabetic patients. Moreover, HRV analysis may be used as a potential tool to identify the first signs of CAN, even in asymptomatic individuals [84].

## CONCLUSION

Although CAN is considered a condition associated with increased risks of morbidity and mortality, there are still many disagreements regarding the recommendations in the CAN guidelines. The existence of complex mechanisms, the wide variety of tools for assessing CAN, and the lack of a harmonized definition among the scientific societies contribute to the reduced clinical investigation of this complication, which can increase the risk of silent myocardial ischemia, myocardial dysfunction, cardiac arrhythmias, and sudden death.

CAN assessment methodologies (HRV, CARTs, and <sup>123</sup>I-mIBG myocardial scintigraphy) need to become more available, widely accessible, and easy to interpret. Considering that CAN is an under-recognized condition, it is also necessary to stimulate the discussion about this microvascular complication in college or university programs in the healthcare field. Investing in education and stimulating the assessment of this complication can be a promising key point for early identification and reducing morbimortality of CAN, mainly in the current scenario of diabetes and cardiometabolic epidemics.

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