Diabetic Cardiovascular Autonomic Nerve Dysfunction

a report by

Aaron I Vinik, MD, PhD, FCP, FACP,[1] **Raelene E Maser**, PhD, MT(ASCP)[2] *and* **Abhijeet A Nakave**, MBBS[3]

1. Director, Strelitz Diabetes Research Center; 2. Associate Professor, Department of Medical Technology, University of Delaware;
3. Research Associate, Strelitz Diabetes Research Center

Introduction to Cardiovascular Autonomic Nerve Dysfunction

Cardiovascular autonomic neuropathy (CAN), a serious complication of diabetes,[1–3] is often overlooked. CAN encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, which may result in abnormalities in heart-rate control and vascular dynamics.[4] There is now an appreciation that, prior to the advent of structural changes in the autonomic nervous system (ANS), there may be dysfunction (CAND), which can produce quite debilitating symptoms. If recognized for what it is, dysfunction of the ANS can be treated by therapeutic manipulations of the ANS using agents that restore balance to the sympathetic and parasympathetic nervous system. If left unbridled, persistent overactivity of the ANS will result in irreparable damage, culminating in hypertension, cardiac muscle dysfunction, and even ultimate failure.

This review discusses the clinical manifestations (e.g. resting tachycardia, orthostasis, orthostatic tachycardia and bradycardia syndromes, hyperhidrosis, sleep apnea, exercise intolerance, intra-operative cardiovascular liability, silent myocardial infarction, and increased risk of mortality) of CAN and CAND. Clinical manifestations of CAN and CAND may affect daily activities and promote life-threatening outcomes. With advances in technology for measuring the ANS, however, early stages of autonomic dysfunction can be identified with the use of independent, simultaneous measurements of sympathetic and parasympathetic function. This review, therefore, also addresses potential therapeutic choices that are available for the correction of functional defects of the ANS.

Epidemiology of Cardiovascular Autonomic Nerve Dysfunction

Determination of the prevalence of any form of neuropathy including CAND is difficult due to methodology differences that occur across studies. Factors that account for the variability of prevalence rates include but are not limited to:

- differences with regard to the criteria used to define CAND;
- various assessment modalities (type and number of tests performed) used to determine its presence; and
- different patient cohorts studied (e.g. clinic versus tertiary referral centers), some of which have known biases.

A review of the literature[1,5] confirms the effect of these factors, as prevalence rates ranging from approximately 1% for people with type 1 diabetes with short duration of diabetes[6] to 90% for individuals undergoing a pancreatic transplant have been reported.[7] Adding to the disparity in reported prevalence rates is the potential for the presence of confounding variables that are risk factors (e.g. age, gender, duration of diabetes, glycemic control, type of diabetes, obesity, hypertension, and history of smoking) and a variety of physiological and pathophysiological factors modulating heart rate variability (HRV) or the development of CAND and the presence of other diabetic complications (e.g. distal symmetric polyneuropathy, retinopathy).[8–10] While the variation of prevalence rates across studies illustrates the difficulty of determining the true prevalence of CAND, it has been shown that:

- autonomic dysfunction can occur early after diagnosis or even before diagnosis of diabetes;[11]
- the prevalence of CAND increases with age, duration of diabetes, and poor glycemic control; and
- other comorbid conditions influence prevalence.

Risk Factors for Altered Heart Rate Variability

Table 1 illustrates some of the risk factors for altered HRV. There is now further evidence that genetic factors may influence the balance between the two major subdivisions of the ANS. Acetylcholine is produced by the enzyme choline acetyltransferase, which uses coenzyme A (AcCoA) and choline as substrates for the formation of Ach. Upon release, Ach is

Aaron I Vinik, MD, PhD, FCP, FACP, is Director of the Diabetes Research Institute at the Strelitz Diabetes Center, Scientific Director of the Department of Medicine, and Professor of Medicine at Eastern Virginia Medical School. He is one of the leading diabetes researchers in the world and his focus of attention is the prevention and reversal of diabetic neuropathy and the development of islet cell regeneration research as a cure for diabetes. He spearheaded the discovery of ilotropin, a chemical substance that can reawaken a cell's potential to produce insulin, and the gene INGAP, the protein responsible for this reawakening. Dr Vinik has received research funding for his studies from the National Institutes of Health (NIH), the National Cancer Institute, the Kroc Foundation, the American Diabetes Association (ADA), and pharmaceutical industries.

E: vinikai@evms.edu

Raelene E Maser, PhD, MT(ASCP), is an Associate Professor of Medical Technology at the University of Delaware, Newark, where she teaches hematology and hemostasis. She is also an endocrinology research consultant for the Diabetes and Metabolic Research Center at Christiana Care Health Services, Newark. Her main research interests include complications of diabetes mellitus, with a particular focus on diabetic neuropathy. Specifically, Dr Maser has performed clinical trials in the areas of cardiovascular autonomic neuropathy and distal symmetric polyneuropathy. She also has an interest in the role of coagulation and fibrinolysis as it relates to the development and/or progression of diabetic complications. Dr Maser has published over 40 papers on the complications of diabetes.

Figure 1: Autonomic Neuropathy—Disease Initiation/Progression
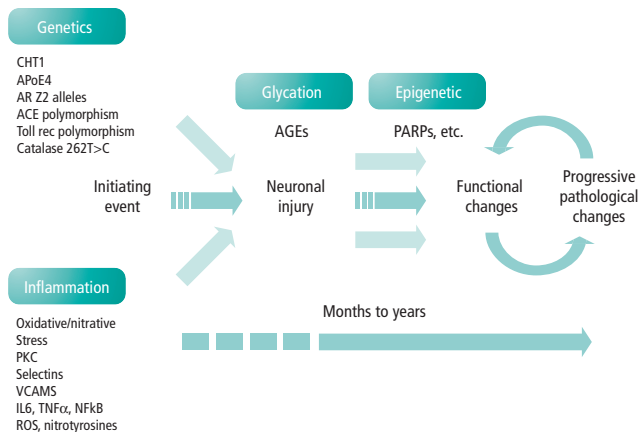
Modified from Vinik and Mehrabyan, *Med Clinics North America, 2004.*

Table 1: Risk Factors for Altered Heart Rate Variability

Physiological Factors	Pathophysiological Factors
Age	Hyperglycemia
Heart rate	Diabetes duration
Blood pressure	Coronary heart disease and heart failure
Sitting	Smoking
Standing	Drugs
Pregnancy	Hyperinsulinemia and insulin resistance
Physical activity	Obesity
Genetic	Genetic

Table 2: Cardiovascular Effects of Autonomic Nerve Dysfunction

Central	
	Tachycardia/bradycardia
	Systolic and diastolic dysfunction
	Decreased exercise tolerance
	Orthostasis, orthostatic tachycardia, and orthostatic bradycardia
	Sleep apnea
	Anxiety/depression
	Cardiac denervation syndrome
Peripheral	
	Decreased thermoregulation
	Decreased sweating
	Altered blood flow
	Impaired vasomotion
	Edema

metabolized into choline and acetate by acetylcholine esterase and other non-specific esterases. Choline is then transported back into the neuron, creating a reservoir for further synthesis of Ach. A G/T translocation of the genotype for the choline transporter ~CHT1) has now been shown to be associated with a marked reduction in the low/high-frequency measures of HRV, which indicates disturbed sympathetic/parasympathetic balance.[12] It has also become apparent that there is a long prodromal phase prior to the advent of structural damage to the ANS in which there is evidence of an inflammatory state preceding the advent of hyperglycemia. Furthermore, it is evident that a variety of polymorphisms

are conducive to increasing or decreasing susceptibility to ANS dysfunction, culminating in CAN, as illustrated in *Figure 1*.

Table 2 summaries the cardiovascular effects of ANS dysfunction. These conditions may manifest as functional syndromes initially, but evolve into structural changes within the ANS.

Resting Tachycardia

Vagal impairment results in resting tachycardia and a fixed heart rate.[13] Resting heart rates of 90–100 beats/min and occasional heart rate increments up to 130 beats/min occur. In those with evidence for combined vagal and sympathetic involvement, heart rate returns toward normal, but remains elevated. A fixed heart rate unresponsive to moderate exercise, stress, or sleep indicates almost complete cardiac denervation.[14] Thus, heart rate may not provide a reliable diagnostic criterion of CAN unless it is increased (i.e. >100 beats/min in the absence of other causes).

Exercise Intolerance

An impaired ANS affects an individual's ability to tolerate exercise.[15] Specifically, heart rate and blood pressure responses are reduced,[16] along with a blunted increase in cardiac output.[17] For diabetic people likely to have CAN, it has been recommended that cardiac stress testing be performed before beginning an exercise program.[18] Furthermore, when healthcare providers discuss an exercise program with patients who have autonomic dysfunction, it should be emphasized that the use of heart rate as a gauge of exercise intensity is not appropriate. For these patients the intensity of physical activity can be monitored by using the Rating of Perceived Exertion scale.[19,20] This scale utilizes an individual's subjective feeling of intensity. Alternately, the percent heart rate reserve, an accurate predictor of percent VO_2 reserve, can be used to prescribe and monitor exercise intensity.[19] Although currently there are insufficient data to recommend routine screening using an exercise electrocardiogram (ECG) test for asymptomatic patients, there are some data to support the use of stress imaging to identify diabetic individuals with pre-clinical coronary artery disease, particularly those with other comorbid conditions.[21]

Primary Hyperhidrosis

Activity of the sympathetic nervous system is essential in maintaining cardiovascular homeostasis.[22] An imbalance in ANS activity can, however, result in a number of disturbing clinical manifestations. For example, hyperhidrosis and postural tachycardia syndrome (POTS) may result from overactivity of the sympathetic nervous system.[22,23] Primary hyperhidrosis is characterized by profuse sweating and can affect the axillae, face, palmar surface of the hands, soles of the feet, and other areas of the body. It is a problem of sympathetic dysregulation of unknown cause characterized by excessive discharge of sympathetic cholinergic sudomotor nerves.[24] The prevalence of hyperhidrosis in a survey sample of 150,000 households, with a response rate of 64%, was 2.9%.[23] The prevalence of hyperhidrosis in the US was therefore projected to be ~2.8%.[23]

Orthostatic Tachycardia Syndromes

POTS is a mild form of autonomic dysfunction characterized by fatigue, exercise intolerance, light-headedness, and near syncope.[25] A hallmark of POTS is that, during syncope, an individual's blood pressure is maintained, while heart rate increases dramatically. During tilt table testing, individuals

with POTS had an increase of heart rate of ≥30 beats/min or a maximum heart rate of 120 beats/min within the first 10 minutes of being upright that was unassociated with profound hypotension.[25] Although the pathogenesis of POTS is complex and heterogenous, POTS appears to be a manifestation of increased cardiac sympathetic nerve traffic and has been hypothesized to reflect compensatory sympathetic activation in response to decreased venous return to the heart.[26] Suggested causes for reduced venous return include volume depletion, venous pooling, extravasation, or local sympathetic denervation.[27] Although the prevalence of POTS is not clear, studies of POTS patients have reported an increased prevalence in females. For example, in a retrospective study of patients who presented to the Mayo Clinic with POTS during an 11-year period, 132 of the 152 patients (86.8%) were female.[28] Bonyhay and Freeman have reported recently that there are physiological differences between males and females in muscle sympathetic nerve discharge characteristics.[22] These differences may be responsible for the greater vulnerability of females to the effects of sympathetic fiber loss, contribute to the pathophysiology of POTS, and help to explain the greater prevalence of POTS in female individuals.

Sleep Apnea

Prevalence surveys in the general population estimate that 2% of middle-aged females and 4% of middle-aged males have obstructive sleep apnea (OSA),[29] while in another study of males with type 2 diabetes a prevalence rate of 17% for OSA was reported.[30] Furthermore, one in four diabetic patients with CAN have been shown to have OSA.[31]

Individuals with OSA have altered cardiovascular variability,[32] with increased levels of sympathetic nerve traffic.[33] Specific abnormalities of HRV evaluated via power spectral analysis for individuals with moderate to severe OSA compared with controls have been shown to include:

- a decrease in the high-frequency component (measure of efferent vagal activity);
- an increase in low-frequency normalized units (considered a marker of sympathetic modulation); and
- an increase in the ratio of low to high frequency (an indirect index of sympathovagal balance).[32]

> Surgically induced weight loss has also been recently shown to improve measures of parasympathetic nervous system function six months and one year post-surgery.

Autonomic nervous system imbalance can predispose individuals with OSA to the development of cardiac arrhythmias.[34]

During sleep, increased sympathetic drive is a result of repetitive episodes of hypoxia, hypercapnia, and obstructive apnea acting through chemoreceptor reflexes.[33] Increased sympathetic drive has been implicated in increased blood pressure variability with repetitive sympathetic activation and blood pressure surges impairing baroreflex and cardiovascular reflex functions.[32]

Figure 2: Role of Overactivation of the Autonomic Nervous System

Sympathetic dysfunction, POTS, hyperhidrosis hypertension and LV dysfunction in diabetes
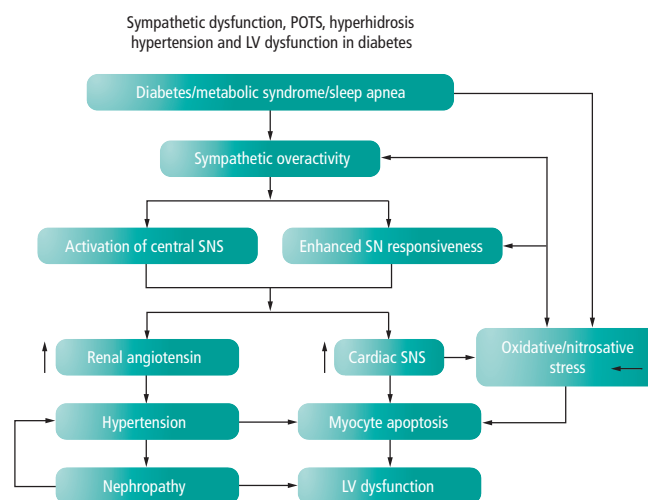
Several cross-sectional studies have shown a strong association between OSA and hypertension,[35–38] with indications that OSA contributes to the genesis of hypertension,[39,40] perhaps through an increase in sympathetic tone in the peripheral vasculature caused by chronically occurring repetitive hypoxia and arousal, initiating a rise in blood pressure.[41] The etiological link between OSA and the development of hypertension has not, however, gone without debate. The debate has focused mainly around the association between OSA and obesity.[42] It may be that the association between OSA and blood pressure involves both an obesity–hypertension link (sympathetic activation induced by obesity exerts tonic vasoconstriction that contributes to the increased blood pressure)[43] and an independent role of OSA in the chronic rise in blood pressure.[42] A direct relationship between the severity of OSA and the increase in blood pressure has been noted. Furthermore, the use of continuous positive airway pressure (CPAP) for the treatment of OSA has been shown to lower blood pressure[44,45] and improve cardiovascular autonomic nerve fiber function for individuals with OSA.[46,47] Withdrawal of CPAP for even a short period (i.e. one week) has been shown to result in a marked increase in sympathetic activity.[48]

A recent systematic review and meta-analysis of studies following effective weight loss in morbidly obese patients after undergoing bariatric surgery has shown that surgical treatment of obesity has striking effects on OSA (i.e. 85.7% of patients experienced resolution of OSA) and hypertension (i.e. 78.5% of patients experienced resolution or improvement of hypertension).[49] Surgically induced weight loss has also been recently shown to improve measures of parasympathetic nervous system function six months and one year post-surgery.[50] With weight loss, patients with OSA experience increased oxygen saturation and arterial oxygen content while decreasing arterial carbon dioxide levels. These physiological changes affect the neurological pathways (improving autonomic balance) and cerebral centers responsible for respiration. Appropriate therapeutic strategies for the treatment of OSA are patient-dependent. However, measuring HRV during sleep has the potential to determine a patient's sympathovagal balance, identify at-risk patients, and assess the effect of various intervention strategies.[51]
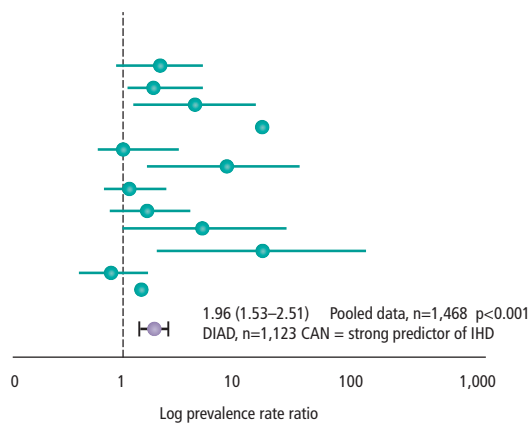
Table 3: Diagnostic Assessment of Cardiovascular Autonomic Function

Parasympathetic	Sympathetic
Resting heart rate	Resting heart rate
Beat-to-beat variation with deep breathing (E:I ratio)	Spectral analysis of heart-rate variation, very low-frequency power (VLFP 0.003–0.04)
30:15 heart rate ratio with standing	Orthostasis BP
Valsalva ratio	Hand grip BP
Spectral analysis of heart rate variation, high-frequency power (HFP 0.15–0.40Hz)	Cold pressor response
	Sympathetic skin galvanic response (cholinergic)
Spectral analysis of HRV respiratory frequency	Sudorimetry (cholinergic)
	Cutaneous blood flow (peptidergic)

VLFP/HFP = sympathetic/parasympathetic balance.

Figure 3: Association between Cardiovascular Autonomic Neuropathy and Silent Myocardial Infarction

1.96 (1.53–2.51)   Pooled data, n=1,468 p<0.001
DIAD, n=1,123 CAN = strong predictor of IHD

Log prevalence rate ratio

Source: Vinik et al., Diabetes Care, 2003; Wackers et al., Diabetes Care, 2003.

The role of overactivation of the autonomic nervous system is illustrated in *Figure 2*.

Intra-operative and Peri-operative Cardiovascular Liability

Individuals with diabetes have a two- to three-fold increase in peri-operative cardiovascular morbidity and mortality. In diabetic patients undergoing general anesthesia, heart rate and blood pressure may decline to a greater degree during induction of anesthesia and increase to a lesser degree following tracheal intubation and extubation compared with non-diabetic subjects. It was recently reported, from a study of 50 diabetic patients who underwent an ophthalmosurgical procedure, that the incidence of hypotension during anaesthetic induction for patients with autonomic dysfunction (i.e. an abnormal expiration/inspiration (E/I) ratio) was 51.9% compared with 8.7% for those with normal E/I ratio (p=0.0019).[52] Vasopressor support is needed more often in diabetic individuals with CAN than in those without.[53] Normally, the autonomic response of vasoconstriction and tachycardia will compensate for the vasodilating effects of anesthesia. This response is, however, reduced in those with CAN. Reduced hypoxic-induced ventilatory drive[54] and severe intra-operative hypothermia, causing reduced metabolism of medications and slow wound healing,[55] have also been shown to be associated with CAN. Pre-operative

screening for reduced HRV will alert the anesthesiologist and surgeon to patients who are at risk for potential intraoperative complications.

Orthostatic Hypotension

Orthostatic hypotension is defined as a fall in blood pressure (i.e. >30mmHg systolic or >10mmHg diastolic blood pressure) in response to postural change (i.e. from supine to standing).[56] In some patients the fall in blood pressure may be asymptomatic, while in others it is disabling.[57] Normally, a postural change results in activation of a baroreceptor-initiated centrally mediated sympathetic reflex resulting in an increase in peripheral vascular resistance and cardiac acceleration. Damage to the efferent sympathetic vasomotor fibers, particularly those in splanchnic vasculature,[58] may result in orthostatic hypotension. In a recent study of 45 males with type 2 diabetes, the presence of sympathetic dysfunction and higher supine blood pressure was shown to be independently associated with the fall in systolic blood pressure during the transition from supine to standing.[59]

> Silent ischemia in diabetic individuals may result either from cardiovascular autonomic neuropathy or from autonomic dysfunction due to coronary artery disease itself, or both.

A decrease in total vascular resistance, reduced norepinephrine response relative to the fall in blood pressure, decreased cardiac acceleration and cardiac output, low blood volume, or reduced red cell mass may all contribute to the pathogenesis of orthostatic hypotension. In addition, other factors such as post-prandial blood pooling, the hypotensive role of insulin, and treatment of kidney or heart failure with diuretics leading to volume depletion may aggravate orthostatic symptoms.[60] Symptoms of orthostatic hypotension may include weakness, faintness, dizziness, visual impairment, and even syncope following the change from lying to standing. Orthostatic symptoms can be misjudged as hypoglycemia and be aggravated by a number of medications (e.g. vasodilators, diuretics, phenothiazines, tricyclic antidepressants, insulin).

Silent Myocardial Ischemia/Cardiac Denervation Syndrome

Recognition of myocardial ischemia or infarction can be impaired as a result of reduced appreciation for ischemic pain. *Figure 3* shows the results of 12 cross-sectional studies in which the frequency of silent myocardial ischemia was compared for those with and without autonomic dysfunction.[1] An increased frequency of silent myocardial ischemia was shown in five of the studies. The point estimates for the prevalence rate ratios in the 12 studies ranged from 0.85 to 15.53. In a meta analysis, the Mantel-Haenszel estimates for the pooled prevalence rate risk for silent myocardial ischemia was 1.96, with 95% confidence interval of 1.53–2.51 (p<0.001; n=1,468 total subjects). Thus, a consistent association between CAN and the presence of silent myocardial ischemia was shown.

Silent ischemia in diabetic individuals may result either from CAN or from autonomic dysfunction due to coronary artery disease itself, or both. Thirty-nine percent of diabetic patients and 22% of non-diabetic individuals in the Framingham Study had unrecognized myocardial

infarctions. The difference was not, however, statistically significant.[61] Results from the National Registry of Myocardial Infarction 2 did, however, show a difference. In this study, there were a total of 434,877 patients with a confirmed myocardial infarction. The results indicated that 33% did not have chest pain on presentation to the hospital. Of those presenting without chest pain, 32.6% had diabetes versus 25.4% (p<0.001) in the group with chest pain.[62]

In diabetic patients with exertional chest pain, a prolonged anginal perceptual threshold (i.e. the time from onset of 0.1mV ST depression to the onset of angina pectoris during exercise), was associated with autonomic dysfunction.[63] The prolonged perception of anginal pain permits patients with CAN and coronary artery disease to continue exercising despite increasing ischemia.
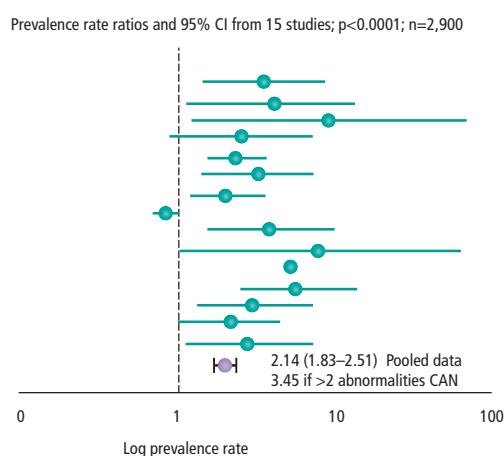
Mechanisms that cause silent myocardial ischemia are complex and not completely understood. Possible mechanisms that have been suggested include: altered pain thresholds, subthreshold ischemia insufficient to induce pain, and dysfunction of the afferent cardiac autonomic nerve fibers.[64] Results from the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, an investigation that included 1,123 patients with type 2 diabetes, showed that cardiac autonomic dysfunction was a strong predictor of ischemia.[65] Thus, cardiovascular autonomic function testing may be an important component in the coronary artery disease risk assessment of patients with diabetes.

Increased Risk of Mortality

Figure 4 summarizes the results from 15 studies that evaluated the association between CAN and mortality. The follow-up intervals in these studies ranged from one to 16 years. In all 15 studies, the baseline assessment for cardiovascular autonomic function was made on the basis of one or more of the tests described by Ewing.[66] Total mortality rates were higher in subjects with CAN at baseline than in those whose baseline assessment was normal, with statistically significant differences in 11 of the studies. The pooled estimate of the relative risk, based on 2,900 total subjects, was 2.14, with 95% confidence intervals 1.83–2.51 (p<0.0001).[1] However, if CAN was defined by the presence of >2 abnormal cardiovascular autonomic function tests, the risk increased to 3.45 (confidence interval 2.66–4.47).[2]
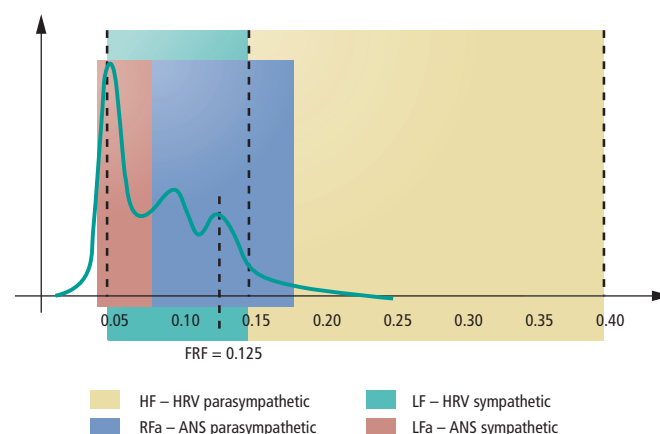
The mechanisms by which CAN leads to increased mortality remain obscure. Three large longitudinal cohort studies addressed the risk of mortality as a result of autonomic dysfunction. The Hoorn Study (a population-based study with 159 persons with type 2 diabetes) demonstrated that impaired autonomic function was associated with an approximately doubled risk of mortality.[67] The Pittsburgh Epidemiology of Diabetes Complications Study, a large population-based cohort of 487 type 1 diabetic subjects followed for two years, revealed a relative risk for mortality of 4.03 for subjects with CAN compared with those without CAN.[68] Adjustments in differences for markers of renal function, coronary heart disease, and hypertension determined at baseline reduced the relative risk of mortality to 1.37 for this cohort. In another investigation, a study cohort of 197 type 1 diabetic individuals with diabetic nephropathy were matched with 191 type 1 diabetic individuals with normoalbuminuria.[69] During the 10 years of follow-up, 35 and 14% of the patients with and without nephropathy and abnormal HRV, respectively, died. In patients with nephropathy and reduced HRV, the investigators showed an adjusted hazard ratio of 6.4 (95%

Figure 4: Relative Risk of Mortality from Cardiovascular Autonomic Neuropathy

Prevalence rate ratios and 95% CI from 15 studies; p<0.0001; n=2,900

2.14 (1.83–2.51) Pooled data
3.45 if >2 abnormalities CAN

Log prevalence rate

Source: Vinik et al., Diabetes Care, *2003; Maser et al.,* Diabetes Care, *2003.*

Figure 5: Sample Power Spectrum of the Heart Rate Variability Signal from a Subject Breathing at an Average Rate of 7.5 Breaths per Minute (fundamental respiratory frequency, FRF = 0.125 Hz)

FRF = 0.125

HF – HRV parasympathetic
RFa – ANS parasympathetic
LF – HRV sympathetic
LFa – ANS sympathetic

The method using HRV alone defines two fixed spectral regions for the low-frequency (LF) and high-frequency (HF) measure (green and yellow, respectively). It is clear that the high-frequency (yellow) region includes very little area under the HRV spectral curve, suggesting very little parasympathetic activity. The great majority of the HRV spectral activity is under the low-frequency (green) region, suggesting primarily sympathetic activity. These representations are incorrect because the slow-breathing subject should have a large parasympathetic component reflective of the vagal activity. This parasympathetic component is represented correctly by the method using both HRV and respiratory activity, which defines the red and blue regions of the spectrum in the graph. The blue region defined by the fundamental respiratory frequency (FRF; 0.125Hz) represents purely parasympathetic activity, whereas the remainder of the lower frequency regions (red region) represent purely sympathetic activity.

confidence interval 1.5–26.3; p=0.010) for a composite end-point of cardiovascular morbidity and mortality.

CAN has also been shown to be a significant predictor of death after Cox regression adjustment for perfusion defects.[70] Finally, ^{123}I-metaiodobenzyl-guanidine myocardial scintigraphy and CAN were independent predictors of a cardiac event. These data suggest that alteration of sympathetic innervation may be a contributing factor to mortality.[71] Collectively, the results of these studies provide evidence that CAN increases the risk of mortality for people with diabetes.

Table 4: Diagnosis and Management of Autonomic Nerve Dysfunction

Symptoms	Assessment Modalities	Management
Resting tachycardia, exercise intolerance, early fatigue and weakness with exercise	HRV, respiratory HRV, MUGA thallium scan, ^{123}I MIBG scan	Graded supervised exercise, beta-blockers, ACE-inhibitors
Postural hypotension, dizziness, light-headedness weakness, fatigue, syncope, tachycardia/bradycardia	HRV, blood pressure measurement lying and standing	Mechanical measures, clonidine, midodrine, octreotide, erythropoietin, pyridostigmine
Hyperhidrosis	Sympathetic/parasympathetic balance	Clonidine, amitryptylline, trihexyphenidyl, propantheline or scopolamine, botox, glycopyrrolate

Figure 6: Effects of Dog Walking on Vagal Activity (High-frequency Power) in Senior Citizens
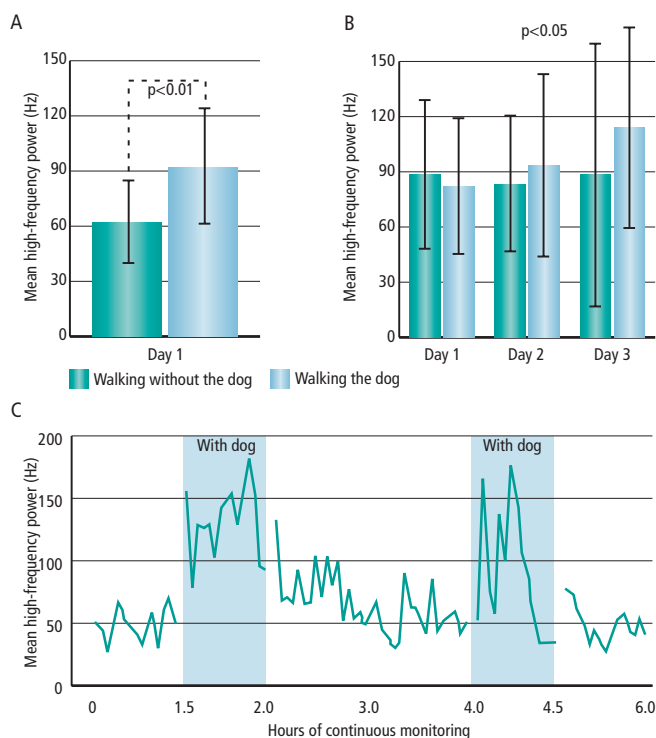
A: 80-minute walking program including two 30-minute walks without and with the dog (n=13). B: 80-minute walking program over three consecutive days (n=3). C: Interaction with the dog at home during six hours of continuous monitoring (n=4).
Source: Motooka et al., MJA, 2006, with permission.

Diagnostic Assessment of Autonomic Function

The assessment of ANS should be based on the results of a battery of autonomic tests rather than on one single test. Both branches of the ANS can be evaluated, as shown in *Table 3*. HRV can be assessed either by calculation of indices based on statistical analysis of RR intervals (time domain analysis) or by spectral analysis (frequency domain analysis) of an array of RR intervals (see *Figure 5*). However, HRV alone is only one measure of a system (the ANS) with two independent components (sympathetic and parasympathetic). A second measure is required to fully characterize the two ANS branches, independently and simultaneously. Spectral analysis of both HRV and respiratory activity provides quantitative, independent, simultaneous, non-invasive measures of both autonomic branches (see *Figure 5*).

Spectral analysis involves decomposing the series of sequential RR intervals into its various frequency components. Traditionally, the sum of sinusoidal functions of different amplitudes and frequencies by several possible mathematical approaches such as the fast Fourier transformation (FFT) has been employed. However, the FFT requires assumptions and approximations to be made about the HRV and respiratory activity signals that are clinically limiting and affect the fidelity of the results. These assumptions and approximations include the need for a compromise between time and frequency fidelity and for the signal to be 'stationary' over the analysis interval. Continuous wavelet transforms (CWT) remove these assumptions and approximations and fundamentally enhance the fidelity of the results. The results (power spectrum) can be displayed with the magnitude of variability as a function of frequency. In other words, the power spectrum reflects the amplitude of the heart rate fluctuations present at different oscillation frequencies.[72]

The HRV spectrum without respiratory frequency analysis mixes sympathetic and parasympathetic components.[73,74] Clinically, this is represented in the cardiogram as a mix of the sympathetically mediated mean heart rate changes coupled with the parasympathetically mediated respiratory sinus arrhythmia (RSA) changes. By adding spectral analysis of respiratory activity, the frequency of RSA is identified, eliminating the mixed measures.[72–74] This second independent measure identifies the frequency range of parasympathetic influence on HRV. This frequency range is called the respiratory frequency range. The area under the HRV spectral curve over the respiratory frequency range is a measure of parasympathetic activity. The respiratory frequency range often overlaps the low-frequency range *(see Figure 5)*. The area under the HRV spectral curve over the remaining low frequency range is the sympathetic activity.[72]

The combination of spectral analysis of HRV with spectral analysis of respiratory activity enables realtime, quantitative, non-invasive, independent, simultaneous measures of parasympathetic and sympathetic activity, both at rest and in response to various challenges. This technique enables early detection and quantification of CAND and CAN in terms that are clinically trendable and reflective of disease progression, therapeutic intervention, and outcomes.[75]

Commercially available computer programs (e.g. NeuroDiag II, ANSAR) are usually employed to assess autonomic nerve function. Conventional ECG equipment has also be used to compute:

1) coefficient of variation (CV) of RR intervals or spectral power in the high-frequency band at rest;
2) spectral power in the very low-frequency band;
3) spectral power in the low-frequency band;
4) HRV during deep breathing, including mean circular resultant of vector analysis or expiration/inspiration (E/I) ratio;
5) maximum–minimum 30:15 ratio;
6) Valsalva ratio; and
7) postural change in systolic blood pressure.

However, metrics (1) to (3) are measures that mix sympathetic and parasympathetic activity. Metrics (4) to (6) are approximations of changes

in parasympathetic activity. The age-related normal ranges of the seven indices included in this battery have been determined. CAN has been defined as the presence of ≥3 abnormalities among these seven parameters (specificity: 100%). Borderline or incipient CAN is assumed when ≥2 abnormal findings are present (specificity: 98%).[72,73] However, the progression or severity of CAN cannot be quantified using these measures. If a computer system is not available, the last four parameters should be determined. In this case definite CAN is diagnosed in the presence of ≥2 abnormal findings.

Potential Therapeutic Modalities for Cardiovascular Autonomic Neuropathy (CAN) and CAN Dysfunction

Table 4 summarizes the approach to diagnosis and symptomatic management of autonomic nerve dysfunction.[1,74] Several studies have reported that it is possible to improve HRV. Results of the Diabetes Control and Complications Trial showed that improvement in glycemic control reduced the incidence of CAN and slowed the deterioration of autonomic dysfunction over time.[6] A reduction of HbA_{1c} from 9.5±0.4% to 8.4±0.5% has also been shown to improve HRV for individuals with early CAN, but autonomic function continued to deteriorate in patients with advanced CAN.[75] In the Diabetes Prevention Program, lifestyle intervention (e.g. increased physical activity) improved autonomic function compared with the metformin or placebo arms of the study.[76] Support for the notion that lifestyle intervention (e.g. diet, stress management, physical activity) has salutary effects on autonomic function was shown in patients with established coronary artery disease where baroreflex sensitivity increased by 2ms/mmHg.[77] Although not all studies have found improved autonomic function as a result of exercise, several studies have shown beneficial effects. For example, *Figure 6* demonstrates that walking a dog can shift an individual's ANS activity in favor of parasympathetic activity.[78] Improvement in vagal activity with endurance training has also been shown in insulin-requiring diabetic individuals with early CAN.[79] Perhaps a potential mechanism for improved nerve function is associated with enhanced cutaneous blood flow, as was found for type 2 diabetic individuals who were chronic exercisers.[80]

The development of CAN and CAND is a multifactorial process. Thus, it is likely that combination therapies directed at the various components of the pathogenic pathway will be needed to reduce the development of autonomic nerve fiber dysfunction. The Steno-2 study clearly showed that targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria reduced the development of CAN.[81]

Angiotensin-converting enzyme (ACE) inhibition with quinapril for 12 months improved the parasympathetic/sympathetic balance in patients with CAN.[82] Angiotensin receptor blockage (ARB) with 100mg/day of losartan for one year has also been shown to improve autonomic dysfunction.[83] Furthermore, the investigators in this study showed that the combination of an ACE inhibitor and ARB may be slightly better than monotherapies. Although not studied yet, it would be interesting to examine the effect of even greater blockade of the renin–angiotensin–aldosterone system via the use of the new renin inhibitor. A more comprehensive review of other agents including aldosterone, calcium-channel, and beta blockers and their effect on HRV can be found elsewhere.[84] Given that there are therapies that can reorient the functional abnormalities of the ANS toward improved function, the importance of determining the presence of CAN and CAND early cannot be overemphasized.

> Given that there are therapies that can reorient the functional abnormalities of the autonomic nervous system toward improved function, the importance of determining the presence of cardiovascular autonomic neuropathy (CAN) and CAN dysfunction early cannot be overemphasized.

Summary

Autonomic dysfunction can now be divided into a prodromal functional phase manifesting as an imbalance in the autonomic nervous division of the sympathetic and parasympathetic nervous systems. Clinical presentations include hyperhidrosis, orthostatic tachycardia and bradycardia, sleep apnea, and anxiety/depression/panic disorders that, left untreated, culminate in structural changes in a variety of organ systems. Structural damage to the ANS, found in approximately one-quarter of type 1 and one-third of type 2 diabetic patients, is associated with a number of serious complications, including an increased risk of mortality. Various assessment modalities are available to determine the presence of CAND and CAN. Once determination of the presence of autonomic dysfunction has occurred, a number of therapeutic agents are available for the correction of functional defects in the ANS. ■

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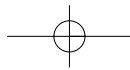
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