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Diabetic Cardiovascular Autonomic Neuropathy

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One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN),[1–3] which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics.[4]

The present report discusses the clinical manifestations (eg, resting tachycardia, orthostasis, exercise intolerance, intraoperative cardiovascular liability, silent myocardial infarction [MI], and increased risk of mortality) in the presence of CAN. It also demonstrates that autonomic dysfunction can affect daily activities of individuals with diabetes and may invoke potentially life-threatening outcomes. Advances in technology, built on decades of research and clinical testing, now make it possible to objectively identify early stages of CAN with the use of careful measurement of autonomic function and to provide therapeutic choices that are based on symptom control and that might abrogate the underlying disorder.

Epidemiology of CAN

Little information exists as to frequency of CAN in representative diabetic populations. This is further complicated by the differences in the methodology used and the lack of standardization. Fifteen studies using different end points report prevalence rates of 1% to 90%.[1] The heterogenous methodology makes it difficult to compare epidemiology across different studies. CAN may be present at diagnosis, and prevalence increases with age, duration of diabetes, and poor glycemic control. CAN also cosegregates with distal symmetric polyneuropathy, microangiopathy, and macroangiopathy. Age, diabetes, obesity, and smoking are risk factors for reduced heart rate variability (HRV)[5] in type 2 diabetes. Thus, there may be selectivity and sex-related differences among the various cardiovascular risk factors as to their influence on autonomic dysfunction.[6] HbA1c, hypertension, distal symmetrical polyneuropathy, retinopathy, and exposure to hyperglycemia were shown to be risk factors for developing CAN in type 1 diabetes.[7]

Clinical Manifestations of CAN

Resting Tachycardia

Whereas abnormalities in HRV are early findings of CAN, resting tachycardia and a fixed heart rate are characteristic late findings in diabetic patients with vagal impairment.[8] Resting heart rates of 90 to 100 bpm and occasional heart rate increments up to 130 bpm occur. The highest resting heart rates have been found in patients with parasympathetic damage, occurring earlier in the course of CAN than sympathetic nerve function; in those with evidence for combined vagal and sympathetic involvement, the rate returns toward normal but remains elevated. A fixed heart rate that is unresponsive to moderate exercise, stress, or sleep indicates almost complete cardiac denervation.[8] Thus, heart rate may not provide a reliable diagnostic criterion of CAN in the absence of other causes unless it is increased by more than 100 bpm.

Exercise Intolerance

Autonomic dysfunction impairs exercise tolerance,[9] reduces response in heart rate and blood pressure (BP),[10] and blunts increases in cardiac output in response to exercise.[11,12] Diabetic patients who are likely to have CAN should be tested for cardiac stress before undertaking an exercise program.[9] Patients with CAN need to rely on their perceived exertion, not heart rate, to avoid hazardous levels of intensity of exercise.[13] Presently, there is inadequate evidence to recommend routine screening of asymptomatic diabetic patients with an exercise ECG test. Emerging data support the utility of stress imaging testing in identifying diabetic patients with preclinical coronary artery disease, particularly patients with high-risk features, and comorbidities such as long-standing disease, CAN, multiple chronic renal failures, resting ECG abnormalities, and peripheral artery disease.[14]

Intraoperative and Perioperative Cardiovascular Instability

Perioperative cardiovascular morbidity and mortality are increased 2- to 3-fold in patients with diabetes. Compared with nondiabetic subjects, diabetic patients undergoing general anesthesia may experience a greater degree of decline in heart rate and BP during induction of anesthesia and less of an increase after tracheal intubation and extubation.

Vasopressor support is needed more often in diabetic individuals with CAN than in those without CAN.[15] The normal autonomic response of vasoconstriction and tachycardia does not completely compensate for the vasodilating effects of anesthesia. There is an association between

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CAN and more severe intraoperative hypothermia[16] that results in decreased drug metabolism and impaired wound healing. Reduced hypoxic-induced ventilatory drive[17] requires preoperative CAN screening for loss of HRV. The anesthesiologist and surgeon should be alerted to this risk.

Orthostatic Hypotension

Orthostatic hypotension is defined as a fall in BP (ie, >30 mm Hg systolic or >10 mm Hg diastolic BP) in response to a postural change from supine to standing.[18] Symptoms include weakness, faintness, dizziness, visual impairment, and even syncope after a change from a lying to a standing posture. Orthostatic hypotension may become disabling, but the BP fall may also be asymptomatic.[19] Orthostatic symptoms can be misjudged as hypoglycemia and can be aggravated by a number of drugs, including vasodilators, diuretics, phenothiazines, and particularly tricyclic antidepressants and insulin. A change from lying to standing normally results in activation of a baroreceptor-initiated, centrally mediated sympathetic reflex, resulting in an increase in peripheral vascular resistance and cardiac acceleration. In patients with diabetes, orthostatic hypotension is usually attributable to damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature.[20] In addition, a decrease in total vascular resistance contributes to pathogenesis of this disorder.

In individuals with orthostatic hypotension, there may be a reduced norepinephrine response relative to the fall in BP. Reduced cardiac acceleration and cardiac output may also be important, as well as low blood volume or reduced red cell mass. Other factors such as postprandial blood pooling, the hypotensive role of insulin, and treatment of kidney or heart failure with diuretics, leading to volume depletion, could aggravate orthostatic symptoms.[21]

Orthostatic Tachycardia and Bradycardia Syndromes

Symptoms compatible with orthostasis, such as feeling faint or dizzy, circumoral paresthesia, and headache, may occur on changes from a supine to an erect position and may be caused by postural tachycardia syndrome (POTS), inappropriate sinus tachycardia, neurocardiogenic syncope, or abnormalities in baroreceptor function. The hallmark of these abnormalities is the absence of a fall in BP with standing, but a tachycardia or bradycardia with the change in posture. The pathogenesis of POTS is obscure. Some patients have defective peripheral vasoconstriction and an increase in calf blood flow, whereas others have increased peripheral arterial resistance and decreased blood flow.[22,23] POTS is associated with a selective defect in intraepidermal nerve fiber in the skin. Norepinephrine concentrations have been significantly related to the estimate of the severity of autonomic neuropathy,[24] and loss of peripheral sympathetic C fiber tone seems to translate to inadequate cardiac venous return with thoracic hypovolemia.[25] POTS patients have paradoxically unchanged plasma renin activity and low aldosterone, given their marked reduction in plasma volume. These patients also have a significant reduction in plasma erythropoietin, suggesting that the kidney may play a role in the pathogenesis of this condition.[26] POTS patients have exaggerated muscle sympathetic nerve activity with baroreceptor-reflex challenges.[27] A cadre of POTS patients have shown normal peripheral resistance and blood volume in the supine position but thoracic hypovolemia and splanchnic pooling in the upright position. Selective and maintained orthostatic pooling in the splanchnic bed occurs in low-flow POTS despite marked peripheral vasoconstriction in these patients. Local splanchnic vasoregulatory factors may counteract the vasoconstriction in these patients.[28] In addition to these syndromes, there are selected patients with orthostatic symptoms who have a paradoxical bradycardia on standing; the symptoms closely mimic those of hypotension. It is important to recognize these differences because each is amenable to simple intervention.

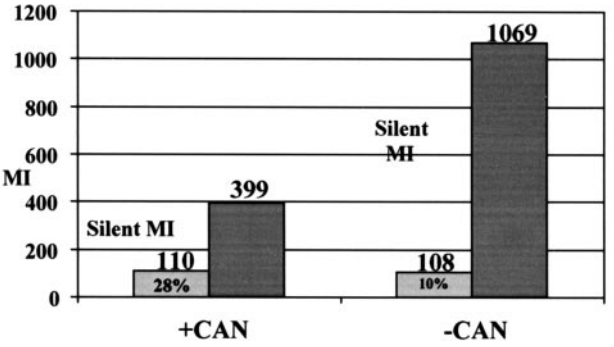

Figure 1. Prevalence rate ratios and 95% confidence intervals for association between CAN and silent myocardial ischemia in 12 studies. Adapted from Vinik et al,[1] with permission from the American Diabetes Association. Copyright © 2003.

Silent Myocardial Ischemia/Cardiac Denervation Syndrome

Reduced appreciation for ischemic pain can impair timely recognition of myocardial ischemia or infarction, thereby delaying appropriate therapy. Figure 1 summarizes the results of 12 cross-sectional studies comparing the presence of silent myocardial ischemia, generally measured by exercise stress tests, between diabetic individuals with and without CAN. Five of the 12 studies showed a statistically significant increased frequency of silent myocardial ischemia in those with CAN compared with those without CAN. The point estimates for the prevalence rate ratios in these 12 studies ranged from 0.85 to 15.53. Mantel-Haenszel estimates for the pooled prevalence rate risk for silent myocardial ischemia in meta-analysis was 1.96, with a 95% confidence interval of 1.53 to 2.51 ($P<0.001$; n=1468 total subjects), demonstrating a consistent association between CAN and the presence of silent myocardial ischemia.

In the ECGs of diabetic patients with exertional chest pain, a prolonged anginal perceptual threshold (ie, the time from onset of 0.1 mV ST depression to the onset of angina pectoris during exercise) was associated with the presence of CAN.[29] Hence, patients with CAN and coronary artery disease are jeopardized because the longer threshold permits them to continue exercising despite increasing ischemia.

Silent ischemia in diabetic patients may either result from CAN, from autonomic dysfunction attributable to coronary artery disease itself, or from both. In the Framingham Study,

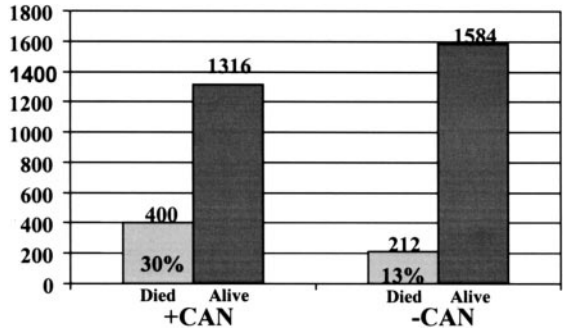

Figure 2. Relative risks and 95% confidence intervals for association between cardiovascular autonomic neuropathy and mortality in 15 studies.

the rates of unrecognized MIs were 39% in diabetic patients and 22% in nondiabetic subjects, but the difference was not significant.[30] In a survey from the National Registry of Myocardial Infarction 2 (NRMI-2), of 434 877 patients presenting with MI, 33% did not have chest pain. Among those presenting without chest pain, 32% had diabetes versus 25.4% in the group with chest pain.[31]

The mechanisms of painless myocardial ischemia are, however, complex and not fully understood. Altered pain thresholds, subthreshold ischemia not sufficient to induce pain, and dysfunction of the afferent cardiac autonomic nerve fibers have all been suggested as possible mechanisms.[32] Positron emission tomography to measure regional cerebral blood flow as an index of regional neuronal activation has shown that impaired afferent signaling resulting from autonomic dysfunction is associated with failed signal transmission from the thalamus to the frontal cortex.[33] In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study of 1123 patients with type 2 diabetes, cardiac autonomic dysfunction was a strong predictor of ischemia.[34] Thus, patients with CAN warrant more careful attention, and cardiovascular autonomic function testing may be an important component in the risk assessment of diabetic patients with coronary artery disease.[21] Given the complex and controversial mechanisms of silent myocardial ischemia, even in the absence of diabetes, further studies are needed to clarify the exact role of CAN in this context.

Features of an MI in patients with CAN are:

- silence,
- cough,
- nausea and vomiting,
- dyspnea,
- tiredness, and
- ECG changes.

Increased Risk of Mortality

Figure 2 summarizes the results from 15 different studies that have included a follow-up of mortality. The follow-up intervals in these studies ranged from 1year to 16 years. In all 15 studies, the baseline assessment for cardiovascular autonomic function was made on the basis of 1 or more of the tests described by Ewing et al.[35] 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 2900 total subjects, was 2.14, with a 95% confidence interval of 1.83 to 2.51 ($P<0.0001$). If CAN is defined by the presence of >2 abnormal quantitative autonomic function tests, however, the risk increases to 3.65 (95% confidence interval, 2.66 to 4.47)

The mechanisms by which CAN leads to increased mortality remain obscure. A number of studies have shown a 2.3-fold increased risk of CAN in diabetic patients showing a prolonged QT interval, leading to speculation that CAN might also predispose to malignant ventricular arrhythmias and to sudden death from cardiac arrest caused by torsades de pointes, as in long QT syndrome. It is difficult to determine the independent effects of CAN on mortality because of the coexistence of cardiovascular disease (CVD). Symptomatic patients with CAN have increased mortality from renal failure and a variety of other causes. However, several studies showing increased mortality from CAN have excluded CHD. If duration, renal disease, hypertension, and CVD were controlled for, the relative risk would decrease from 4.03 to 1.39, but it would remain significant.[36] Furthermore, symptomatic CAN at 5 years of diabetes predicted mortality at 10 years, even after adjusting for conventional CVD risk factors. CAN remained a significant predictor of death after Cox regression adjustment for perfusion defects.[37] Stepwise Cox regression with backward selection for smoking, sex, age, CVD, cholesterol, triglyceride, albumin excretion rate, systolic blood pressure, glycemic control, and HRV still gave a hazard ratio of 6.4 for CAN.[38] Finally, meta-iodobenzylguanidine (MIBG) scan and CAN were independent predictors according to multivariate analysis for a cardiac event, suggesting that maldistribution of sympathetic innervention may contribute.[39]

HRV was found to be an independent predictor of all-cause mortality during a period of 9 years, in a population-based study using Cox proportional hazard models including dyslipidemia, diabetes, age, physical activity, alcohol intake, smoking, and CVD as independent variables.[40] Moreover, the Hoorn study by Gerritsen et al[41] demonstrated that impaired autonomic function is associated with increased all-cause and cardiovascular mortality and that CAN in patients already at risk (diabetes, hypertension, or history of CVD) may be especially hazardous.

Association of CAN With Major Cardiovascular Events

The relationship between CAN and major cardiovascular events has been assessed in 2 prospective studies. Specifically, the relationship between baseline CAN and the subsequent incidence of a fatal or nonfatal cardiovascular event, defined as an MI, heart failure, resuscitation from ventricular tachycardia or fibrillation, angina, or need for coronary revascularization, was examined.[42] The relative risks associated with CAN in these studies were 2.2 and 3.4, respectively, with the latter result just achieving statistical significance ($P<0.05$). There seems to be an association between CAN and major cardiovascular events, but given the small number

of events that occurred in each of these studies, more follow-up studies are required.

CAN and Sudden Death

Sudden, unexpected deaths occur among subjects with CAN. One potential cause may be severe but asymptomatic ischemia, which can induce lethal arrhythmias. QT prolongation may also predispose individuals to life-threatening cardiac arrhythmias and sudden death. Results from the European Diabetes Insulin-Dependent Diabetes Mellitus (IDDM) Complications Study showed that male patients with impaired HRV had a higher corrected QT prolongation than males without this complication.[43] Imaging of myocardial sympathetic innervation with various radiotracers (eg, MIBG) has shown that predisposition to arrhythmias and an association with mortality may also be related to intracardiac sympathetic imbalance.[44,45]

The significance of CAN as an independent cause of sudden death has, however, been questioned recently. In the Rochester Diabetic Neuropathy Study,[45a] the investigators found that all cases of sudden death in individuals with and without diabetes had severe coronary artery disease or left ventricular (LV) dysfunction. They suggested that although CAN could be a contributing factor, it was not a significant independent cause of sudden death. Heart failure is, however, common in individuals with diabetes; it is identified in these patients by the presence of neuropathy, even in those without evidence of coronary artery disease or LV dysfunction. The association of CAN in the absence of coronary disease and cardiomyopathy requires further study.

Increased Mortality After MI

Mortality rates after an MI are higher for diabetic compared with nondiabetic patients.[46] A simple bedside test that measured 1-minute HRV during deep breathing was a good predictor of all-cause mortality for 185 patients (17.8% with diabetes) after a first MI.[47] Autonomic function testing is a valuable tool in identifying a subgroup of post-MI patients who are at high risk for death.

Association of Cerebrovascular Disease and CAN

Abnormalities of parasympathetic and sympathetic autonomic function were found to be independent predictors of stroke in a group of 133 type 2 diabetic patients for 10 years.[48] Clearly, other studies examining all the multivariate factors contributing to stroke are needed to confirm or refute this report.

Progression of CAN

Although much remains to be learned about the natural history of CAN, previous reports can be coalesced into a few observations that provide some insights with regard to progression of autonomic dysfunction.

- It can be detected at the time of diagnosis.[49]
- Neither age nor type of diabetes are limiting factors in its emergence; it has been found both in young people with newly diagnosed type 1 diabetes and in older people newly diagnosed with type 2 diabetes.[49–53]
- Poor glycemic control plays a central role in development and progression.[49,54]
- Intensive therapy can slow the progression and delay the appearance of abnormal autonomic function tests.[55]
- Subclinical autonomic neuropathy can be detected early using autonomic function tests.[49]
- Autonomic features that are associated with sympathetic nervous system dysfunction (eg, orthostatic hypotension) are relatively late complications of diabetes.
- There is an association between CAN and diabetic nephropathy that contributes to high mortality rates.[49]

Even with consensus regarding these general observations, much remains unclear.

- Some individuals with symptoms associated with autonomic neuropathy die suddenly and unexpectedly.[49]
- Clinical signs and symptoms of autonomic dysfunction do not always progress. This underscores the need for performance of quantitative autonomic function tests to identify individuals at risk for premature death.[56]
- Type 1 and type 2 diabetes may have different progression paths.
- The relationship between autonomic damage and the duration of diabetes is not clear, although numerous studies (eg, Vinik et al[21]) support an association.
- Prevalence and mortality rates may be higher among individuals with type 2 diabetes, possibly because of the longer duration of glycemic abnormalities before diagnosis.[9]

Autonomic Cardiopathy

CAN may be associated with abnormalities in LV systolic and particularly diastolic function in the absence of cardiac disease in diabetic patients. A review of diabetic cardiopathy other than that ascribed to CAN has recently been published[57] and is beyond the scope of this review. Echocardiographic studies have shown a significant correlation of the severity of CAN with reduced peak diastolic filling rate and with an augmented atrial contribution to diastolic filling as assessed by Doppler echocardiography. It is difficult to judge, however, whether CAN is an independent contributor to these abnormalities, because other factors such as interstitial myocardial fibrosis and microangiopathic or metabolic changes (discussed in the pathogenesis of diabetic heart muscle disease) may also be responsible for LV dysfunction. CAN is associated with LV diastolic dysfunction (LVDD) at rest, both in patients with long-term type 2[58] or type 1 diabetes.[10,59] LVDD may progress to heart failure, mainly with preserved LV systolic function (diastolic heart failure), which is also related to high morbidity and mortality rates.[60,61]

The pathophysiology of LVDD includes delayed relaxation, impaired LV filling, and/or increased stiffness.[62] Diabetes mellitus can produce functional, biochemical, and morphological myocardial abnormalities independent of coronary atherosclerosis and hypertension,[63] contributing to heart failure with normal LV systolic function.[63] There may be no evidence of ischemic, hypertensive, or valvular heart disease, yet patients may develop cardiac dysfunction and,

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 Hz)
30:15 Heart rate ratio with standing	Orthostasis blood pressure
Valsalva ratio	Hand grip blood pressure
Spectral analysis of heart rate variation, high-frequency power (HFP; 0.15–0.40 Hz)	Cold pressor response
	Sympathetic skin galvanic response (cholinergic)
	Sudorometry (cholinergic)
	Cutaneous blood flow (peptidergic)

Sympathetic/parasympathetic balance=VLFP/HFP.

finally, congestive heart failure, suggesting the presence of diabetic cardiomyopathy.[64] In patients with CAN, vagal impairment can lead to a relative predominance of sympathetic activity in the sympathovagal balance. Sympathetic overactivity stimulates the renin–angiotensin–aldosterone system and increases heart rate, stroke volume, and peripheral vascular resistance, thus contributing to LV dysfunction.[65] The latter is promoted by the deleterious effects of the renin–angiotensin–aldosterone and adrenergic systems on systemic and coronary hemodynamics, myocyte hypertrophy and fibroblast growth, and myocyte necrosis and apoptosis.[66] Such a sympathetic hyperactivity, in combination with regional myocardial sympathetic denervation, has been shown recently to lead to diminished coronary blood flow reserve and diastolic dysfunction in diabetic patients with early microangiopathy.[67] Analogous to the situation with neurohormones, the overexpression of cytokines is sufficient to contribute to LV dysfunction and, eventually, to heart failure.[68]

Diagnostic Assessment

Cardiovascular autonomic reflex tests

The diagnosis of CAN should be based on the results of a battery of autonomic tests rather than one single test, and the function of both branches of the autonomic nervous system can be evaluated as indicated in the Table.

HRV can be assessed either by calculation of indices based on statistical analysis of R-R intervals (time-domain analysis) or by spectral analysis (frequency-domain analysis) of an array.

Spectral analysis involves decomposing the series of sequential R-R intervals into a sum of sinusoidal functions of different amplitudes and frequencies by several possible mathematical approaches, such as fast Fourier transformation or autoregressive models. The result (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. The power spectrum of HRV has been shown to consist of 3 major peaks: (1) very-low-frequency component (below 0.04 Hz), which is related to fluctuations in vasomotor tone associated with thermoregulation; (2) low-frequency (LF) component (around 0.1 Hz), which represents the so-called 10-s rhythm (Mayer waves) associated with the baroreceptor reflex; and (3) high-frequency (HF) component (around 0.25 Hz), which is related to respiratory activity (Figure 3). The very-low-frequency heart rate fluctuations are thought to be mediated primarily by the sympathetic system, and the LF fluctuations are predominantly under sympathetic control with vagal modulation, whereas the HF fluctuations are under parasympathetic control. Because spectral analysis is carried out under resting conditions, it has the advantage that active cooperation of the patient is not required. Numerous factors may influence the test results: age, heart rate, respiratory rate, BP, eating, drinking coffee, smoking, body position, volume status, mental stress, drugs, exercise, and time of day.

Commercially available computer programs (eg, Neuro-Diag II, Ansar) are usually employed to assess autonomic nerve function, but conventional ECG equipment can also be used: (1) coefficient of variation of R-R intervals or spectral power in the HF band at rest; (2) spectral power in the very-low-frequency band; (3) spectral power in the LF band; (4) HRV during deep breathing, including mean circular resultant of vector analysis or expiration/inspiration ratio; 5) maximum/minimum 30:15 ratio; 6) Valsalva ratio; and 7) postural change in systolic BP. The age-related normal ranges of the 7 indices included in this battery have been determined. CAN is defined as the presence of ≥3 abnormalities among

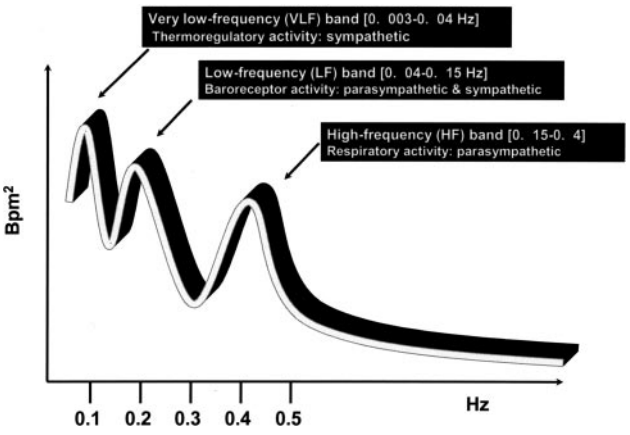

Figure 3. R-R intervals.

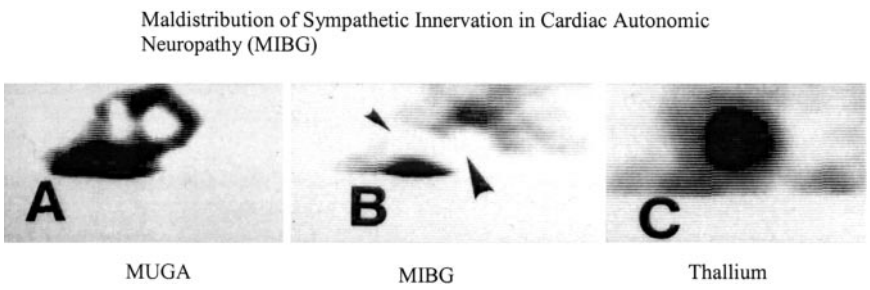

Figure 4. Maldistribution of sympathetic innervation in cardiac autonomic neuropathy (MIBG). MUGA indicates multiple gated acquisition scan.

these 7 parameters (specificity: 100%). Borderline or incipient CAN is assumed when ≥2 abnormal findings are present (specificity: 98%).[69,70] If a computer system is not available, the last 4 parameters should be determined. In this case, definite CAN is diagnosed in the presence of ≥2 abnormal findings. Among the series of HRV indices, the most sensitive in detecting abnormality in diabetic patients under resting conditions were the coefficient of variation and spectral power in the LF band. Among the reflex tests, the mean circular resultant or expiration/inspiration ratio during deep breathing, maximum/minimum 30:15 ratio to standing up, and Valsalva ratio showed the highest sensitivity.

Twenty-Four Hour HRV

Using power spectral analysis of heart rate applied to 24-hour ECG recordings, a circadian rhythm of sympathovagal balance has been observed in the general population. Whereas the LF power spectrum component is predominant at daytime, a prominent increase of the HF component occurs during the night, resulting in a marked decrease in the LF/HF ratio from day to night. This can be explained by the dominance of sympathetic activity influencing the LF component during the day, which decreases during the night in coincidence with vagal arousal. Diabetic patients with autonomic neuropathy display an impairment in absolute values of both HF and LF oscillations. Blunting of nocturnal increases in the HF component, however, which expresses vagal modulation of the heart, seems to be the earliest and most prominent event. This leads to a relative predominance of sympathetic activity during the night. The abnormal circadian pattern of sympathovagal balance has been shown to be related to a similar abnormality in the BP pattern. These 2 abnormalities could be relevant to the excess cardiovascular mortality rates described in the diabetic population and in patients with CAN.[71]

During the last decade, 24-hour HRV using multichannel ECG recorders has been increasingly used for risk stratification after acute MI and congestive heart failure. In 1996, the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology published standards for the measurement and clinical use of HRV.[72] Several studies in diabetic patients suggest that assessment of 24-hour HRV may be more sensitive in detecting CAN than standard autonomic reflex tests.[73]

Spontaneous Baroreflex Sensitivity

The development of a technique based on servoplethysmomanometry that measures BP in the finger on a beat-to-beat basis has expanded the diagnostic spectrum in diabetic patients with CAN. This method (Finapress) is becoming an integral constituent in the assessment of autonomic nervous system function, allowing the assessment of neural modulation of the sinus node by arterial baroreceptors. Previously, the baroreceptor–cardiac reflex sensitivity was quantified by measuring R-R interval changes produced in response to short-term, pharmacologically induced changes in BP. More recently, it has been shown that the analysis of spontaneous baroreflex sequences gives results equivalent to the pharmacological methods.[74] Two analyses for spontaneous baroreceptor–cardiac reflex sensitivity have been proposed. The first consists of analyzing recordings of simultaneous BP and R-R intervals for sequences in which BP or R-R are either rising (+BP/+R-R) or falling (−BP/−R-R) in parallel for at least 3 beats. The second method involves spectral analysis enabling the linkage or cross-spectrum between the BP and R-R interval signals to be quantified in terms of amplitude or gain, phase (the time shifts between 2 signals), and coherence. It has been suggested that coherence is acceptable in 2 frequency bands (LF, 0.05 to 0.15; and HF, 0.20 to 0.35).[74] Studies in diabetic patients with or without CAN indicate that both time- and frequency-domain measures of spontaneous baroreceptor–cardiac reflex sensitivity could allow earlier detection of CAN than autonomic function tests,[75–77] but further studies providing information on normal ranges, reproducibility, and sensitivity are required.

Cardiac Radionuclide Imaging

Radionuclide techniques for cardiac mapping have recently been used to directly quantify cardiac sympathetic innervation in various diseases, including CAN (Figure 4).

The nonmetabolized norepinephrine analogue MIBG participates in norepinephrine uptake in postganglionic sympathetic neurons. Several studies have demonstrated decreased myocardial MIBG uptake in patients with CAN as assessed by autonomic reflex tests.[10] There is evidence to suggest that scintigraphic assessment using MIBG and single–photon emission computed tomography is more sensitive in detecting CAN than indirect autonomic reflex testing, because MIBG uptake is reduced in patients with normal autonomic tests.[78–81] The MIBG uptake defects are localized predominantly in the LV posterior and inferior segments. In advanced CAN, completely absent MIBG uptake may be observed.

The norepinephrine analogue [^{11}C] hydroxyephedrine (HED) has also been employed to examine cardiac innervation defects. In diabetic patients, attenuated HED retention is related to the severity of CAN and is most pronounced in the inferior, apical, and lateral segments.[81] In severe CAN, the

myocardial retention of HED was remarkably heterogenous, and as the extent of distal deficits increased, HED retention became paradoxically increased in the proximal myocardial segments, which showed the highest deficits in coronary blood flow reserve.[82] Such a proximal hyperinnervation relative to the distal denervation could result in potentially life-threatening myocardial electrical instability. Because the myocardial dysinnervation correlated with impairments in myocardial blood flow regulation such as reduced blood flow reserve, it has been suggested that augmented cardiac sympathetic tone and impaired myocardial perfusion may contribute to myocardial injury in diabetes.[67]

Long-term poor glycemic control constitutes an essential determinant in the progression of LV adrenergic innervation defects that may be prevented by near normoglycemia in type 1 diabetic patients. Global and regional MIBG defect scores in the inferior, posterior, and apical walls were increased in poorly controlled patients. Well-controlled patients showed enhanced global MIBG uptake compared with the poorly controlled group after 4 years. In contrast, no such differences were noted for autonomic function testing, suggesting that direct assessment of myocardial innervation defects by MIBG scintigraphy may be more appropriate than indirect autonomic function testing for evaluating the effect of metabolic intervention in CAN. Similar results have been reported in a 3-year study using HED.[83]

Thus, cardiac radionuclide imaging provides a unique, sensitive tool for direct assessment of the pathophysiology and progression of early sympathetic innervation defects not accessible by indirect autonomic function testing. This asymmetry of innervation is thought to be responsible for the predisposition to arrhythmias, and it provides a tool for the determination of the success of intervention on reinnervation of the myocardium. Additional studies using tracers of parasympathetic cardiac neurons will allow a more complete, direct quantitative characterization of CAN in the near future.

Diagnostic Testing for Orthostatic Symptoms

A standard test for establishing the cause of postural symptoms is the head-up tilt-table study.[84] Although this is technician- and physician intensive, it often resolves the cause of the symptoms.

Typically, autonomic labs will combine tilt-table and other studies with HRV measures obtained during deep breathing and Valsalva.[85] Other functional syndromes may also be revealed, such as the vasoconstrictor syndrome (paradoxic orthostatic hypertensive syndrome, also known as orthostatic hypertension) and paradoxic orthostatic bradycardia syndrome.

Treatment Interventions for Orthostatic Hypotension

Treatment of orthostatic hypotension comprises nonpharmacological and pharmacological measures. Nonpharmacological measures such as increasing consumption of water[86,87] and the use of lower-extremity stockings to reduce symptoms (eg, dizziness, dyspnea)[87] should be encouraged when treating orthostatic hypotension attributable to autonomic dysfunction. Pharmacological therapies must balance an increase in standing BP against prevention of supine hypotension.

Orthostatic hypotension can be aggravated by different forms of therapy (eg, tricyclic antidepressant [amitriptyline]) used for the treatment of other complications (eg, painful sensory neuropathy). Therefore, careful attention to other medications that may aggravate orthostatic hypotension in these patients is mandatory.[88]

Recently, some novel approaches using other pharmacological agents have been investigated in nondiabetic individuals with orthostatic symptoms. Enhancement of ganglionic transmission via the use of pyridostigmine (inhibitor of acetylcholinesterase) improved symptoms and orthostatic BP with only modest effects in supine BP for 15 patients with POTS.[89] Similarly, the use of β-adrenergic blockers may benefit the tachycardia and anticholinergics, the orthostatic bradycardia.

Pyridostigmine has also been shown to improve HRV in healthy young adults.[89] Fluoxetine, a selective serotonin reuptake inhibitor, improved hemodynamic parameters and symptoms of orthostatic hypotension in patients with Parkinson disease.[90] In patients with pooling of blood in the splanchnic bed, somatostatin may be of value, and in patients with contracted plasma volume, treatment with erythropoietin is recommended.[11,12]

Management of Exercise Intolerance

In diabetic individuals with CAN, exercise tolerance is limited as a result of impaired parasympathetic/sympathetic responses that would normally enhance cardiac output and direct peripheral blood flow to skeletal muscles.[9] Reduced ejection fraction, systolic dysfunction, and a decrease in the rate of diastolic filling also limit exercise tolerance.[9] In diabetic patients without evidence of heart disease but with asymptomatic vagal CAN, exercise capacity (greatest tolerable workload and maximal oxygen uptake), heart rate, BP, cardiac stroke volume, and hepatosplanchnic vascular resistance are diminished. A further decrease in exercise capacity and BP is seen in patients with both vagal CAN and orthostatic hypotension. The severity of CAN correlates inversely with the increase in heart rate at any time during exercise and with the maximal increase in heart rate. Thus, CAN contributes to diminished exercise tolerance. Therefore, autonomic testing offers a useful tool to identify patients with potentially poor exercise performance and may help prevent hazards when patients are introduced to exercise training programs.

For diabetic persons likely to have CAN, it has been suggested that cardiac stress testing should be performed before beginning an exercise program.[11] When discussing exercise instructions and goals with patients with CAN, health care providers need to emphasize that the use of heart rate is an inappropriate gauge of exercise intensity, because maximal heart rate is lower in persons with CAN. Recently, it has been shown that percent heart rate reserve, an accurate predictor of percent $\dot{V}O_2$ reserve, can be used to prescribe and monitor exercise intensity in diabetic individuals with CAN.[13] An alternate method for monitoring intensity of physical activity is the rated perceived exertion scale.[13,91] The

rated perceived exertion scale, which uses the individual's subjective feelings of intensity, can be used in settings where maximal heart rate is not easily measured.

Perioperative Management

There is a 2- to 3-fold increase in cardiovascular morbidity and mortality intraoperatively for patients with diabetes. Patients with severe autonomic dysfunction have a high risk of BP instability,[92,93] and intraoperative BP support is needed more often in those with greater impairment.[15] Intraoperative hypothermia[16] (which may decrease drug metabolism and affect wound healing) and impaired hypoxic induced ventilatory drive[17] have also been shown to be associated with the presence of CAN. Noninvasive diagnostic methods assessing autonomic function allow identification of at-risk patients preoperatively and may better prepare the anesthesiologist for potential hemodynamic changes.

Potential for Reversal of CAN

Several studies have reported that it is possible to improve HRV. In patients with minimal abnormalities, endurance training under strict supervision and lifestyle intervention associated with weight loss improve HRV.[94]

Johnson et al[95] have reported improved LV function in patients with diabetic autonomic neuropathy (DAN) by using an aldose reductase inhibitor, but this still needs to be shown on a larger scale. Surprisingly, LV ejection fractions improved without a change in quantitative autonomic function test scores.

β-Blockers such as bisoprol improved HRV in heart failure.[96] The addition of spironolactone to enalapril, furosemide, and digoxin in patients with heart failure improved sympathovagal balance.[97]

Angiotensin-converting enzyme (ACE) inhibition with quinapril increases total HRV and improves the parasympathetic/sympathetic balance in patients with mild but not advanced autonomic neuropathy.[98]

ACE inhibition improves the prognosis of chronic heart failure,[99] but plasma concentrations of angiotensin 11 remain elevated,[100] which may be related to non-ACE pathways that convert angiotensin 1 to angiotensin 11.[101,102] Hence, addition of an angiotensin receptor blockade may overcome this problem,[103] ostensibly effecting greater blockade of the renin–angiotensin–aldosterone system.[101] Indeed, there are now several reports of beneficial effects on hemodynamic and neurohumoral effects of adding losartan,[104] valsartan,[105] or candesartan[106] to an ACE inhibitor.

To investigate the effect of ACE inhibition or angiotensin receptor blockade and their combination on both DAN and LVDD in asymptomatic patients with diabetes, Didangelos et al[106a] examined 62 patients (34 women) with long-term diabetes mellitus (24 with type 1 diabetes mellitus and DAN). The patients, who were aged 51.7±13.9 years and were free of coronary artery disease and arterial hypertension at baseline, were studied for a 12-month period. Early ACE inhibition or angiotensin receptor blockade improved both DAN and LVDD after 1 year of treatment in asymptomatic patients with type 1 or 2 diabetes mellitus. The combination may be slightly better than monotherapies on DAN and LVDD, auguring well for the patient with established CAN. The clinical importance of these effects should be validated by larger studies, however.

Improvement in glycemic control reduces the incidence of CAN and slows the progression thereof.[107] Glycemic control with a reduction of HbA1c from 9.5 to 8.4 has also been shown to improve HRV with mild autonomic abnormalities; this was not so in cases of advanced autonomic abnormalities.[108]

The use of aldose reductase inhibitors such as sorbinil improved resting and maximum cardiac output, and epalrestat improved MIBG uptake and HRV in patients with mild abnormalities but not in those with advanced CAN.[109]

The most salutary lesson, however, derives from the Steno memorial study by Gaede et al,[110] in which intensive multifactorial management aimed at control of BP, lipids, HBA1c, use of aspirin, vitamins E and C, and ACE inhibitors reduced CAN by 68%. Thus, it is important to diagnose CAN because the outlook is not as dismal as was once perceived; there are now symptomatic therapies that can reorient the functional abnormalities toward improved function, as well as therapies that provide prospects for reversal.

Conclusions

Diabetic CAN, a serious complication found in one fourth of type 1 and one third of type 2 diabetic patients, is associated with increased mortality and silent myocardial ischemia and may even predict the development of stroke. CAN is associated with a poor prognosis and may result in severe orthostasis, postural hypotension, exercise intolerance, enhanced intraoperative instability, and an increased incidence of silent MI and ischemia. It may be attributable to a functional abnormality or to organic structural damage to the different components of the autonomic nervous system. There are simple bedside tests to diagnose CAN using HRV, responses to breathing, the Valsalva maneuver, and standing. Functional abnormalities and imbalance between the sympathetic and parasympathetic nervous system are discerned with respiratory modulation of different-frequency oscillations in HRV. Measurement of 24-hour HRV may be more sensitive and reliable in detecting CAN than single tests. Additionally, 24-hour recording of HRV may provide insights into abnormal patterns of circadian rhythms modulated by sympathovagal activity. Simultaneous beat-to-beat measurement of R-R intervals and BP is useful to detect spontaneous baroreceptor–cardiac reflex sensitivity and to evaluate the relationship between spontaneous changes in BP and R-R interval in the time domain (sequence method) and in the frequency domain (cross-spectral method). These estimates can be obtained under conditions suitable for routine outpatient evaluation. Radionuclide techniques for cardiac mapping directly quantify myocardial sympathetic innervation. The nonmetabolized guanethidine derivative MIBG, the diolabeled analogue of norepinephrine, and the norepinephrine analogue HED have been employed to examine cardiac innervation defects. These techniques are research tools that are not available for clinical routine use, however.

Several agents have become available for the correction of functional defects in the autonomic nervous system. Studies

have shown improvement of HRV with graded exercise, using a variety of cardioactive drugs as well as intensification of treatment for the multiple risk factors for autonomic neuropathy that are shared with those for macrovascular disease. Most important, knowing the HRV number may help emphasize the need for intensive control of cardiovascular risk factors, thereby reducing the risk of premature mortality.

Disclosures

Dr Vinik serves on the advisory panels or gives lectures on behalf of Sanofi Aventis, Takeda Corporation, Lilly, Pfizer, and Merck. Dr Ziegler reports no conflicts.

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