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What Do We Know and We Do Not Know About Cardiovascular Autonomic Neuropathy in Diabetes

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Abstract

Cardiovascular autonomic neuropathy (CAN) in diabetes is generally overlooked in practice, although awareness of its serious consequences is emerging. Challenges in understanding the complex, dynamic changes in the modulation of the sympathetic/parasympathetic systems' tone and their interactions with physiologic mechanisms regulating the control of heart rate, blood pressure, and other cardiovascular functions in the presence of acute hyper-or-hypoglycemic stress, other stressors or medication, and challenges with sensitive evaluations have contributed to lower CAN visibility compared with other diabetes complications. Yet, CAN is a significant cause of morbidity and mortality, due to a high-risk of cardiac arrhythmias, silent myocardial ischemia and sudden death. While striving for aggressive risk factor control in diabetes practice seemed intuitive, recent reports of major clinical trials undermine established thinking concerning glycemic control and cardiovascular risk. This review covers current understanding and gaps in that understanding of the clinical implications of CAN and prevention and treatment of CAN.

Keywords

Cardiovascular autonomic dysfunction; Diabetes mellitus; Neuropathy

Definition and Epidemiology

The autonomic nervous system plays a major role in the regulation of cardiovascular function (Fig. 1). Cardiovascular autonomic neuropathy (CAN) is defined as the impairment of the autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes. Diabetes mellitus affects more than 26 million people in the USA (www.diabetes.org) and an estimated 366 million worldwide (www.who.int/diabetes). Diabetic neuropathies are the most common chronic complication of type 1 (T1DM) and type 2 diabetes (T2DM). Although the prevalence of CAN is as low as 2.5% in patients with newly diagnosed T1DM, as observed in the primary prevention cohort in the Diabetes Control and Complications Trial (DCCT) [1], it does increase substantially with diabetes duration regardless of diabetes type [2–4]. The follow-up of the DCCT participants enrolled in the observational Epidemiology of Diabetes Interventions and Complications (EDIC), demonstrated CAN prevalence rates as high as 35 % in the former conventional-treated DCCT cohort [3]. The EURODIAB IDDM Complications Study, a cross-sectional clinic-based study involving 3,250 randomly selected patients with T1DM from 16 European countries, autonomic dysfunction was present in one third of T1DM subjects at follow-up

[5]. Prevalence rates of 60 % and higher were reported in cohorts of patients with long-standing T2DM [4, 6] and in patients with long-standing T1DM who were potential candidates for a pancreas transplantation [7]. Evidence of changes in measures of CAN and possible shift in the sympathetic/parasympathetic balance favoring the sympathetic tone were also described even in subjects with pre-diabetes range hyperglycemia in the Framingham Heart Study [8] and confirmed more recently in a large cohort of subjects with impaired glucose tolerance [9]. However, prevalence data are highly dependent on the diagnostic criteria, type of tests and normative data sets used, age, and gender [4].

Clinical Implications

Mortality Risk

One of the most serious consequences of CAN is its relationship with mortality risk. Earlier longitudinal studies of subjects with CAN have shown 5-year mortality rates as high as 16–50 % in T1DM and T2DM, with a high proportion attributed to sudden cardiac death [10–12]. A more recently published meta-analysis of 15 studies that included 2,900 subjects with diabetes reported a pooled relative risk of mortality of 3.45 (95 % CI, 2.66–4.47) in patients with CAN [13]. In the EURODIAB IDDM Complications Study, CAN was the strongest predictor for mortality during a 7-year follow-up, exceeding the effect of traditional cardiovascular risk factors [14]. The Hoorn study reported that presence of diabetic CAN doubled 9-year mortality risk in an elderly cohort [15]. Maser et al. found a progressive increase in the mortality risk with the increase in the number of abnormal CAN function tests [13]. The higher predictive value of increased number of CAN abnormalities was confirmed in two other cohorts of T1DM and T2DM reporting that a combined abnormality in heart rate variability (HRV) and QT index was a strong predictor of mortality [16, 17].

Because CAN is associated with multiple factors including duration of diabetes, severity of hyperglycemia, as well as the presence of coronary artery disease, the exact contribution of CAN to the increased mortality risk has been however difficult to quantify in prior studies, given their relatively small sample size that prevented adjustments for multiple covariates. However, we confirmed in a large and carefully characterized cohort of more than 8,000 participants with T2DM enrolled in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, that the presence of CAN strongly predicts all-cause (hazard ratio=2.14; 95 % CI, 1.37–3.37) and CVD mortality (hazard ratio=2.62; 95 % CI, 1.4–4.91) independently of baseline CVD, diabetes duration, multiple traditional CVD risk factors and medication (Table 1) [18]. A possible explanation for the effects of CAN on mortality risk is by promoting life threatening arrhythmias and sudden death in response to a variety of insults including drug side-effects, hypoglycemia, hypokalemia, hypotension, or ischemia [18–21]. A most feared consequence of rigorous glycemic control is an increased incidence of hypoglycemia [22, 23]. Hypoglycemia impairs hormonal and autonomic responses to subsequent hypoglycemia [24] and hypoglycemia unawareness may promote a reduced threshold for malignant arrhythmias and subsequent sudden cardiac death. Evidence that exposure to hypoglycemia leads to impaired CAN function was recently described in healthy volunteers [25]. Although no association between antecedent hypoglycemia and CAN-increased mortality was shown in the ACCORD trial [18], striving to achieve lower glycemic, blood pressure and other CVD risk factor targets, may induce significant additional challenges in the presence of CAN.

CAN and Silent Myocardial Ischemia

In a meta-analysis of 12 published studies, Vinik et al. reported a consistent association between CAN and the presence of silent myocardial ischemia, measured by exercise stress testing, with point estimates for the prevalence rate ratios from 0.85 to 15.53 [26]. In the

Detection of Ischemia in Asymptomatic Diabetics (DIAD) study of 1123 patients with T2DM, CAN was a strong predictor of silent ischemia and subsequent cardiovascular events [27]. A slow heart rate (HR) recovery after exercise, which is proposed to indirectly reflect CAN, was also shown to be associated with silent myocardial ischemia [28]. The association between CAN and silent ischemia has important implications, as reduced appreciation for ischemic pain impairs timely recognition of myocardial ischemia or infarction, thereby delaying appropriate therapy. In patients with diabetes, presence of symptoms such as acute onset dyspnea with/without coughing, severe fatigue, and/or acute onset of nausea and vomiting should raise a high index of suspicion for an ischemic event and prompt the appropriate measures [29].

CAN and Myocardial Dysfunction

The presence of CAN was also linked to development of diabetic cardiomyopathy. The autonomic innervation is the primary extrinsic control mechanism regulating HR and cardiac performance. The vagus nerve (parasympathetic), the longest autonomic nerve, mediates approximately 75 % of all parasympathetic activity. Because neuropathy is seen first in the longest fibers (as also discussed below), the earliest manifestations of autonomic neuropathy in diabetes tend to be associated with various degrees of parasympathetic denervation. As such, the initial development of CAN in diabetes is characterized by early augmentation of sympathetic tone [30]. A prevalent cardiac sympathetic activity with subsequent abnormal norepinephrine signaling and metabolism, increased mitochondrial oxidative stress [31], and calcium-dependent apoptosis [32] may contribute to myocardial injury [31, 33] and explain the high cardiovascular risk in these patients. The sympathetic imbalance associated with CAN may also critically influence myocardial substrate utilization [34] and contribute to mitochondrial uncoupling [35], regional ventricular motion abnormalities, functional deficits, and cardiomyopathy [36]. Sympathetic toxicity induces insulin resistance and may compromise regional glucose utilization [37]. This, together with the increased FFA supply due to catecholamine-induced fatty acid extraction and oxidation [38, 39], switches cardiac energy generation to the utilization of FFA. Therefore, FFA metabolism, an inefficient energy source [40], may contribute to more than 90 % of the myocardial oxygen (O_2) consumption in the diabetic heart [41, 42], which may induce mitochondrial uncoupling [35, 43], increased O_2 demand [35, 43] and generation of reactive oxygen species (Fig. 1). Mitochondrial uncoupling, when associated with deficits in glucose metabolism, may also predispose to programmed cell death and fibrosis [44–46]. All these changes in metabolic substrate usage in the presence of sympathetic activation may reduce cardiac efficiency- the ratio of cardiac work to myocardial O_2 consumption [47–51], with energy deficits, and subsequent left ventricle hypertrophy and remodeling (Fig. 2).

Evidence from patients with T1DM showed that left ventricle dysfunction often precedes or occurs in the absence of significant coronary artery disease or hypertension. Alterations of diastolic [36, 52] and systolic [53] function are reported in otherwise healthy diabetic subjects, and often predate the development of macrovascular complications. Our group has identified that diastolic dysfunction occurring early in the course of T1DM was correlated with abnormal cardiac sympathetic function as assessed by cardiac sympathetic imaging [36]. In a separate study, Sacre et al. reported that in patients with T2DM, measures of both systolic and diastolic function were associated with measures of CAN [54]. Diastolic dysfunction, characterized by impairment in LV relaxation and passive filling, was also shown by others to be the earliest manifestation of diabetic cardiomyopathy [55, 56]. This is possibly due to possibly due to increased LV wall thickness and LV hypertrophy. CAN may promote LV hypertrophy through several mechanisms including its impact on sympathovagal balance and baroreflexes. The vagal component of the baroreflex is a major protective mechanism that adjusts HR, stroke volume and blood pressure (BP) to minimize

myocardial stress. A depressed baroreflex is associated with an unopposed sympathetic tone, increased systolic BP [57], LV wall stress, and subsequent LV hypertrophy and increased risk of heart failure and CVD [58–60]. Attenuation (non-dipping) or complete loss of the nocturnal fall in BP (reverse dipping) in diabetes was also associated with left ventricle hypertrophy in cross-sectional studies, and with increased risk of cardiovascular and renal events in some longitudinal studies [4]. In a subgroup analysis of ~300 patients with T2DM enrolled in the prospective AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF), the presence of CAN at baseline, defined as a heart-to-mediastinum ratio <1.6 as assessed by I-123 metaiodobenzylguanidine imaging, was associated with a significantly greater 2-year rate of heart failure progression, compared with non-diabetic patients enrolled in the same trial [61]. We have recently reported in a large cohort of patients with T1DM participants in the DCCT/EDIC, that the presence of CAN was associated with increased LV mass and with concentric remodeling as assessed by cardiac MRI independent of age, sex, and other factors [62].

Ongoing studies may help to clarify the complex interactions between CAN and development of cardiomyopathy in diabetes.

Other Cardiovascular Risk Implications

Intraoperative and Perioperative Cardiovascular Instability—Observations in diabetic patients undergoing general anesthesia reported that individuals with CAN required vasopressor support more often than those without CAN [29]. Individuals with CAN may experience a greater decline in HR and BP during induction of anesthesia and more severe intraoperative hypothermia resulting in decreased drug metabolism and impaired wound healing [29].

Stroke—A recent study in 1,458 patients with T2DM reported that presence of CAN, assessed by standard HRV testing was one of the strongest predictor of ischemic stroke. Four longitudinal studies documented that CARTs abnormalities or QT_i prolongation imposes a twofold risk of stroke [4, 29].

CAN and Metabolic Syndrome—Several cross-sectional studies in adults without diabetes provide evidence that markers of autonomic function are inversely associated with obesity, insulin resistance, and fasting glucose [8, 63–65], all components of the metabolic syndrome. Other prospective studies have shown that autonomic dysfunction correlates with poor cardiorespiratory fitness and is associated with the development of diabetes [66]. In a recent study evaluating more than 1200 subjects, Chang et al. reported that altered cardiac autonomic function was found even in subjects with one or two metabolic abnormalities, suggesting that CAN may precede insulin resistance in the metabolic syndrome [67]. In the Finnish Diabetes Prevention Study, measures of CAN were associated with higher triglycerides and higher waist circumference, both features of metabolic syndrome [68]. Ongoing studies will provide further insight on the association between CAN and metabolic syndrome.

CAN and Chronic Kidney Disease

The sympathetic activation associated with CAN may also play a central role in the pathogenesis of chronic kidney disease (CKD), due to changes in glomerular haemodynamics and in the circadian rhythms of BP and albuminuria [30, 69, 70]. A higher resting HR was reported to be associated with overt nephropathy development in type 1 diabetic patients. In the Atherosclerosis Risk in Communities (ARIC) Study, that included more than 1,500 adults with diabetes followed for 16 years, higher resting HR and lower HRV indices were associated with the highest risk of developing end-stage renal disease

[71]. Moreover, erythropoietin-deficiency anemia and early dysregulation of erythropoietin production have been described in patients with CAN [72]. Anaemia is a predictor of nephropathy and CKD progression and erythropoietin exerts direct renoprotective effects. Thus, both anaemia and erythropoietin deficit may contribute to kidney damage in diabetes.

In patients with diabetes and CKD or ESRD on dialysis, cardiovascular events represent the leading cause of mortality [73–75] with a high incidence of sudden cardiac death. An association between compromised autonomic function and sudden cardiac death in patients awaiting kidney transplantation has been reported [76, 77]. It is proposed that an imbalance between sympathetic and parasympathetic activities in diabetic dialysis patients is further augmented by the effects and consequences of uremia [78]. If impairment of cardiovascular autonomic function is combined with left ventricular hypertrophy, an independent risk factor for shortened survival in CKD patients as well as for cardiovascular disease [79, 80], the mortality of CKD patients increased further [81].

Pathogenesis

Hyperglycemia plays a key role in the activation of various biochemical pathways related to the metabolic and/or redox state of the cell, which, in concert with impaired nerve perfusion, contribute to the development and progression of diabetic neuropathies. Strong experimental data implicate a number of pathogenic pathways that may impact autonomic neuronal function in diabetes including: formation of advanced glycation end products (AGE), increased oxidative/nitrosative stress with increased free radical production, activation of the polyol and protein kinase C pathways, activation of polyADP ribosylation, activation of genes involved in neuronal damage [26, 82, 83]. In addition, significantly lower levels of the soluble receptor for AGE (sRAGE) were reported in patients with advanced CAN [84]. Recent evidence also suggests that low-grade inflammation plays an important role in the pathogenesis of diabetic neuropathies some mediated by NF- κ B activation and downstream effects [85, 86] with deficits in peripheral and autonomic nerve fibers [86, 87]. A role of inflammatory cytokines and adipocytokines on the autonomic imbalance present in diabetes and even in prediabetes was also more recently described and is amply covered in [65]. Emerging data in human studies reported that changes in both sympathetic and parasympathetic system function may occur prior to the development of diabetic range hyperglycemia in individuals with features of the metabolic syndrome, changes that correlated with an increase in adipose-tissue derived inflammatory markers [67, 88]. The involvement of autoimmune responses in the pathogenesis of CAN was also postulated. For instance, lymphocytic and macrophages infiltration within sympathetic ganglia and other autonomic nerve structures was described in diabetic patients with severe symptomatic autonomic neuropathy [89, 90], and the presence of autoantibodies to autonomic nerve structures has been reported independently from several different laboratories [91–94]. A detailed review of these mechanisms and their complex interactions is however beyond the scope of this manuscript. In spite of the large body of experimental evidence supporting a role for each of these described mechanisms, interventions targeting these various pathways in humans have failed to provide an effective pathogenetic treatment for CAN. This raises the question whether unknown processes exist which have yet to be elucidated, presenting therefore an intriguing opportunity for new research.

It is in general accepted that in human diabetes, the development of CAN is a function of complex interactions among degree of glycemic control, disease duration, age-related neuronal attrition, and systolic and diastolic BP [2, 95, 96]. These promote progressive autonomic neural dysfunction in a fashion which parallels the development of peripheral neuropathy, e.g., beginning distally, and progressing proximally. Our data [36] and others [97] confirmed that, early in the progression of CAN complicating T1DM, there is a

compensatory increase in the cardiac sympathetic tone in response to subclinical peripheral denervation. Later, sympathetic denervation follows beginning at the apex of the ventricles and progressing towards the base (Figs. 1 and 3).

Clinical Signs

The clinical symptoms of CAN are usually manifest with advanced disease and longer diabetes duration as exercise intolerance, resting tachycardia and orthostatic hypotension. Subclinical CAN is heralded by changes in HRV and abnormal cardiovascular reflex testing and may be detected within a year of diagnosis in T2DM and 2 years of diagnosis in T1DM [98].

Exercise Intolerance

Patients with CAN may present with an initial asymptomatic reduced HR, BP, and cardiac output in response to exercise, as a consequence of diabetes-induced vagal denervation even in the absence of other signs of cardiovascular disease [29]. In later stages the combined parasympathetic-sympathetic deficits lead to more severe declines, severely blunted maximal HR response and symptoms of orthostatic hypotension [4]. It is recommended that diabetic patients who are likely to have CAN be tested with cardiac stress test before undertaking an exercise program and be advised to rely on their perceived exertion, not HR, to avoid hazardous levels of intensity of exercise [29].

Resting Tachycardia

Resting HR of 100–130 bpm are a manifestation of later stages of the disease and reflect the relative increase in the sympathetic tone associated with vagal impairment. However, resting tachycardia is a nonspecific sign for CAN, as may be present in several other conditions such as anemia, thyroid dysfunction, underlying cardiovascular disease including heart failure, obesity and poor fitness. A fixed HR that is unresponsive to moderate exercise, stress, or sleep indicates almost complete cardiac denervation [29] and is indicative of severe CAN. However, a blunted HR response to adenosine receptor agonists was described in both patients with diabetes and patients with metabolic syndrome and attributed to earlier stages of CAN [28]. Higher resting HR was shown to be an independent risk predictor for all-cause and CVD mortality in several prospective cohorts [99]. Emerging evidence has demonstrated the prognostic value of resting HR as a useful tool for cardiovascular risk stratification and as therapeutic target in high-risk patients [4].

Abnormal Blood Pressure Regulation

Nondiabetic subjects present with predominance of vagal tone and decreased sympathetic tone at night associated with reduction in nocturnal BP [100]. In diabetic CAN, this pattern is altered resulting in nocturnal sympathetic predominance during sleep and subsequent nocturnal hypertension, also known as non-dipping and reverse dipping [101]. These are associated with a higher frequency of LV hypertrophy and fatal and severe nonfatal cardiovascular events in diabetic CAN subjects [102, 103].

Orthostatic Hypotension

Symptoms associated with orthostatic hypotension include: lightheadness, weakness, faintness, dizziness, visual impairment, and in most severe cases, syncope on standing. These symptoms can be aggravated by a number of drugs that may be commonly prescribed in diabetes such as: vasodilators, diuretics, insulin (through endothelium-dependent vasodilatation), and tricyclic antidepressants, a class of drugs commonly used for symptomatic relief of pain associated with painful diabetic neuropathy [29]. Orthostatic hypotension is defined as a reduction of systolic BP of at least 20 mmHg or diastolic BP of

at least 10 mmHg within 3 min of standing or a systolic fall in BP of 30 mmHg beds [4, 104]. In diabetes, orthostatic hypotension occurs largely as a consequence of efferent sympathetic vasomotor denervation, causing reduced vasoconstriction of the splanchnic and other peripheral vascular beds [104].

Clinical Evaluation and Diagnosis Criteria

Several diagnostic approaches with a varying degree of complexity are available and have been used to diagnose CAN in practice or research including assessment of cardiovascular reflex testing, HRV, 24-h BP profiles, orthostatic hypotension, baroreflex sensitivity, cardiac sympathetic imaging, microneurography or occlusion plethysmography (Table 2).

However, based on strongest lines of evidence available to date, the recent Toronto Consensus Panel on Diabetic Neuropathy concluded that the cardiovascular autonomic reflex testing (discussed below) are sensitive, specific, reproducible, safe and standardized [26, 105–107], and recommended their use as the gold standard for clinical autonomic testing [4].

Cardiovascular Autonomic Reflex Tests

The cardiovascular autonomic reflex tests first described in the 1970s [12] assess the cardiovascular autonomic function using provocative physiological maneuvers and measuring the HR and BP changes. These tests are non-invasive, safe, and comprise several simple bedside assessments that include: changes in R–R with deep breathing, a measure of sinus arrhythmia during quiet respiration reflecting primarily parasympathetic function [106]; R–R response to standing inducing reflex tachycardia followed by bradycardia which is jointly vagal and baroreflex-mediated; Valsalva ratio which evaluates cardiovascular function in response to a standardized increase in intrathoracic pressure (Valsalva Maneuver); orthostatic hypotension; and the BP response to a Valsalva manoeuvre and sustained isometric muscular strain providing indices of sympathetic function, although the BP response to sustained isometric muscular strain is now used in clinical research only [4].

Although a clear evidence of a striking superiority in diagnostic characteristics of a cardiovascular reflex test over the others is missing, [4], the deep breathing test is the most widely used test due to its high reproducibility, ~80 % specificity [108] and easy to use [4, 106, 108]. The deep breathing test may be expressed as HR range, heart period range, E/I ratio (shortest R–R during inspiration/longest R–R during expiration), or mean circular resultant computed by vector analysis. The later appears to be most sensitive analysis because eliminates the effects of trends in HR over time, attenuating the effect of basal HR and ectopic beats [106]. The Valsalva and postural tests are analyzed as the quotient of the largest and shortest R–R intervals recorded during each respective maneuver.

The Valsalva maneuver needs greater patients' cooperation and due to the associated increase in intrathoracic, intraocular and intracranial pressures may theoretically be associated with a small risk of intraocular haemorrhage or lens dislocation and cannot be universally performed [4].

A variety of factors including caffeine and tobacco products, food, or prescription and over-the-counter medicines may alter cardiovascular autonomic responses, therefore these tests should be performed under strict standardized conditions.

As far as staging CAN, one single abnormal test may indicate early CAN, but the presence of abnormalities in more than one test, preferably three tests, is recommended for a definite

diagnosis [4]. Test abnormalities should be defined strictly using age-based and technique-specific normative data [4].

Assessment of Heart Rate Variability

A decrease in HRV is earliest clinical indicator of CAN, although it is in general asymptomatic. In normal individuals the high degree of beat-to-beat variability with respiration, increasing with inspiration and decreasing with expiration, are due to direct influence by sympathetic and parasympathetic stimuli. Besides the sympathetic and parasympathetic efferences to the sinus node, other continuous tonic, phasic and transient external and internal stimuli may affect HR including neurohumoral influences (e.g., catecholamines and thyroid hormones), stretch of the sinus node, changes in local temperature, or ionic changes in the sinus node [109]. However, under resting conditions, the sympathetic and parasympathetic efferences to the sinus node play a critical role in short-term HRV [109]. Initial clinical relevance of HRV emerged due to observations that fetal distress is preceded by alterations in beat-to-beat intervals before any appreciable change occurred in HR itself. Later, it was confirmed that HRV was a strong, independent predictor of mortality after acute myocardial infarction [110].

The HRV can be evaluated in the time and frequency domain, derived from ECG recordings, ideally under paced breathing. Incorporating respiratory signal analysis enables one to independently measure both sympathetic and parasympathetic branches of the autonomic nervous system. Longer ECG recordings (e.g., 24 h) were used exclusively initially, but shorter recordings were also shown to provide reliable information on the cardiovascular autonomic function [2, 105, 109].

Time domain measures of the normal R–R intervals, basically reflecting parasympathetic activity, include: the difference between the longest and shortest R–R interval, standard deviation of 5-min average of normal R–R intervals (SDANN), root-mean square of the difference of successive R–R intervals (rMSSD). With 24-h recordings, the number of instances per hour in which two consecutive R–R intervals differ by more than 50 ms over 24 h (pNN50), standard deviation of all normal R–R intervals (SDNN) and the variation during the difference between night and day HR [110] may also be obtained. The accuracy of these measures is affected by various arrhythmias, and the analysis requires normal sinus rhythm and atrioventricular-nodal function.

The frequency domain measures are obtained by spectral analysis of R–R interval and other respiratory and cardiovascular signals [29, 109]. It is traditionally accepted that the parasympathetic system affects the overall variability (e.g., variance and total power), the high-frequency components (0.15–0.4 Hz). The sympathetic activity essentially influences a rather narrow band around 0.1 Hz (LF), equivalent to a fluctuation of approximately six cycles/min [109]. The very-low-frequency components (<0.04 Hz) are essentially related to fluctuations in vasomotor tone associated with thermoregulation or activity [109]. Different mathematical methods have been used to analyze HRV including Fourier transform, the most commonly chosen due to algorithm simplicity and high processing speed [110], or more complex equations that perform a time-frequency decomposition of the signal yielding a time-dependent version of the low-and high-frequency peaks, equations suggested to be superior in the analysis of nonstationary conditions [111, 112]. A detailed analysis of the various methods of HRV testing and interpretation is beyond the scope of this review and it was broadly covered recently by Bernardi et al. [109].

However, it is generally accepted that the critical factor to avoid important bias in the interpretation of HRV, is the control for respiration [109]. Without respiration control, spectral analysis cannot provide additional information as compared to the simpler indices

of global variability. Several commercially available software programs are available for assessment of HRV (Hokanson Inc. WA, ANSAR Inc. PA), but for the moment given that application of the technique is critically depending upon understanding of the underlying physiology, the mathematical analyses used, and the many confounders and possible technical artifacts, the use of HRV testing is recommended for research and in conjunction with the cardiovascular autonomic reflex testing [109].

Imaging Techniques for CAN

Quantitative scintigraphic assessment of sympathetic innervation of the human heart is possible with positron emission tomography (PET) and either [^{123}I]*meta*-iodobenzylguanidine (MIBG) [^{11}C]-*meta*-hydroxy-ephedrine [^{11}C]HED, 6- ^{18}F -dopamine, and [^{11}C]-epinephrine. [29, 113].

Deficits of LV [^{123}I]MIBG and [^{11}C]HED retention have been identified in T1DM and T2DM subjects [114–116] with [114–116] and without [36] abnormal cardiovascular reflex testing.

Regional myocardial [^{123}I]-MIBG “uptake” is semi-quantitative and not a clean index of neuronal uptake, which occurs extremely rapidly. The interpretation of early myocardial [^{123}I]-MIBG retention is further complicated by increased body mass index (BMI) and diastolic BP which have been reported to reduce myocardial MIBG uptake [109]. The delivery of tracers is critically influenced by myocardial perfusion, so myocardial retention of tracers should be performed with a quantitative analysis of myocardial blood flow [109].

Metabolically stable [^{11}C]HED undergoes highly specific uptake into sympathetic nerve varicosities via norepinephrine transporters and quantitative [^{11}C]HED retention may be assessed in 480 independent LV regions [113]. The striking consistency of the evolution of the pattern of denervation in T1DM supports the reliability of [^{11}C]HED to monitor changes in cardiac sympathetic nerve populations and evaluate early anatomical regional deficits of sympathetic denervation [36, 113, 114]. As an example, Fig. 1 shows the polar map analysis of LV [^{11}C]HED retention in subjects with T1DM expressed as *Z*-score analysis vs. controls [36]. The washout rates from the myocardium of [^{11}C]-epinephrine or 6- ^{18}F -dopamine can give information on vesicular integrity. In subjects with type 1 diabetes and CAN, the washout rates of [^{11}C]-epinephrine parallels those of [^{11}C]-HED, suggesting regional differences in vesicular uptake or retention [109]. The interpretation of findings using sympathetic neurotransmitter analogues is complicated by the fact that alterations in sympathetic nervous system tone may also affect the retention of these tracers, and this fact is often not considered as an explanation for the clinical findings. In the isolated rat heart model, elevated norepinephrine concentrations in the perfusion increased neuronal HED clearance rates consistent with the concept that neuronal “recycling” of HED can be disrupted by increased synaptic norepinephrine levels [113]. Alternatively at high norepinephrine concentrations non-neuronal uptake of HED into myocardial cells and impaired retention may be a factor. Quantitative regional measurements of myocardial beta-adrenoreceptor density can be assessed using PET and the high affinity beta-adrenoreceptor radioligand [^{11}C] CGP-12177 [117] but was never assessed in human diabetes.

Although a very valuable research tool, considering that scintigraphic studies are very costly, requires highly specialized infrastructure and personnel, the methodology is not standardized and robust data sets of normative values are not yet available, the use of these techniques is not yet recommended for standard clinical care.

Baroreflex Sensitivity

The baroreflex sensitivity (BRS) technique evaluates the capability to reflexively increase vagal activity and decrease sympathetic activity in response to a sudden increase in BP and is used in research protocols to assess cardiac vagal and sympathetic baroreflex function. An increase in BP reduces the firing of sympathetic vascular and cardiac efferents and increases the firing of vagal cardiac efferents, resulting in a rapid reduction in HR and in BP. The reduction in BP is due to both a reduction in cardiac output caused by bradycardia and to a slower direct vasodilation secondary to sympathetic withdrawal. A reduction in BP induces opposite responses [109]. Thus, to correctly define the baroreflex function, one has to consider both the vagal efferent activity (evidenced by changes in HR in response to changes in BP), and the sympathetic efferent activity (mainly directed to the arterial vessels) [109]. The measurement of the cardiac-vagal arm BRS can be done with several drugs or physical maneuvers can be applied to modify BP; alternatively, the spontaneous BP variations can be used. In all cases the response in HR to the changes in BP is quantified. None of these methods, that have been described in detail in [109], have shown so far a definite advantage over the others, or a clinically relevant difference [109].

The BRS was a significant independent risk predictor of cardiac mortality in several large cohorts of patients with heart failure or patients with a recent myocardial infarction [58, 59]. Other longitudinal studies confirmed its independent prognostic value in patients with diabetes [15].

Muscle Sympathetic Nerve Activity

This technique is based on recording electrical activity emitted by skeletal muscle (peroneal, tibial, and radial) at rest or in response to various physiological perturbations, via microelectrodes inserted into a fascicle of a distal sympathetic nerve to the skin or muscle (microneurography), and identification of sympathetic bursts. Bursts have a characteristic shape consisting of a gradual rise and fall that is usually constrained by the cardiac cycle and at least twice the amplitude of random fluctuations [118]. Recently available fully automated sympathetic neurogram techniques provide a rapid and objective method that is minimally affected by signal quality and preserves beat-by-beat sympathetic neurograms [118].

Due to its invasiveness and the time-consuming nature of the procedure, muscle sympathetic nerve activity is not indicated for routine autonomic assessment. However, by being the most direct measure of sympathetic activity it is an important research tool [109].

Head-Up-Tilt-Table Testing

Head-up-tilt-table testing with/without pharmacological provocation is another tool for the investigation of CAN or of predisposition to neurally mediated (vasovagal) syncope due to the wide range of changes in the autonomic input to the heart and in the R-R intervals induced by the rapid postural changes during this test. This test requires specialized personnel and is not readily available in general practice.

Assessment of Symptoms

Symptoms associated with CAN include exercise intolerance, orthostatic intolerance and syncope [6]. The correlation between symptom scores and deficits is generally weak in mild CAN as these symptoms usually occur late in the disease process. Low et al., using a validated self-report measure of autonomic symptoms in a population-based study, found that autonomic symptoms were present more commonly in T1DM than in T2DM [6].

Treatment Considerations

CAN and Risk Factor Control

Glycemic Control—The DCCT demonstrated that intensive insulin therapy for T1DM reduced the incidence of CAN by 53 % compared with conventional therapy [1]. The EDIC, the prospective observational study of the DCCT cohort, has shown persistent beneficial effects of past glucose control on microvascular complications despite the loss of glycemic separation [119]. CAN was re-evaluated recently in more than 1,200 well-characterized EDIC participants during the 13th–14th year of EDIC follow-up. Although during EDIC, CAN progressed substantially in both former treatment groups, but the prevalence and incidence of CAN in EDIC remained significantly lower in the former intensive group than in the former conventional group, despite similar levels of glycemic control [3]. Treatment group differences in the mean HbA1c level during DCCT and EDIC explained virtually all of the beneficial effects of intensive versus conventional therapy on risk of incident CAN supporting that intensive treatment of T1DM should be initiated as early as is safely possible [3].

In T2DM, the effects of glycemic control are less conclusive. The VA Cooperative Study demonstrated no difference in the prevalence of autonomic neuropathy in T2DM patients after 2 years of tight glycemic control compared to those without tight control [120]; similar results were reported by the Veterans Affairs Diabetes Trial (VADT) [121], although some could argue that the CAN outcome measures used may not have been the most sensitive.

Multiple Risk Factor Intervention—In the STENO 2 study, an intensive multifactorial cardiovascular risk intervention targeting glucose, blood pressure, lipids, smoking and other lifestyle factors, reduced the progression or the development of CAN among type 2 diabetic patients with microalbuminuria [122]. However, a beneficial effect of the intensive glycaemic intervention alone on CAN, in this cohort of patients with type 2 diabetes has not been specifically proven.

Data regarding the impact of lifestyle interventions in preventing progression of CAN are emerging [123, 124]. Strictly supervised endurance training combined with dietary changes was associated with weight loss and improved HRV in patients with minimal abnormalities [29]. In the Diabetes Prevention Program, indices of CAN improved most in the lifestyle modification arm compared with the metformin or placebo arm [123]. Weight loss in obese patients is accompanied by improvement in cardiovascular autonomic function [125]. A few small—mostly open—interventional studies in diabetes showed a beneficial effect of aerobic training on cardiovascular autonomic indices, with some indication that mild physical exercise may be effective only in patients with less severe CAN [4].

Therapies Targeting Pathogenetic Pathways and Autonomic Tone Modulation

—Evidence on the effects of agents targeting pathogenetic pathways shown to contribute to CAN development is limited. Phase II randomized controlled trials have shown favorable effects on HRV indices using the antioxidant α -lipoic acid, vitamin E, and C-peptide [4]. Further studies are needed to confirm these findings as well as to unveil effective potential pathogenetic treatments.

A number of drugs may adversely affect the autonomic tone by reducing HRV with consequent potential proarrhythmic effect [4]. On the other hand, an increase in HRV has been described—with some controversy—in diabetic patients with ACE inhibitors, angiotensin II type 1 receptor blockers, cardioselective β blockers without intrinsic sympathomimetic activity (e.g., metoprolol, nebivolol, and bisoprolol), digoxin, and verapamil [2, 4, 29]. Some have proposed the use of cardioselective β blockers to treat

resting tachycardia associated with CAN, but to date there is no clear evidence on their efficacy in diabetic CAN.

Symptomatic Treatment of Orthostatic Hypotension—Treatment of orthostatic hypotension is required in general only when patients are symptomatic. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Although quite challenging in severe cases, the rate of success is dependent on the use of both non pharmacological and pharmacological measures described in brief in Table 3.

Conclusions

CAN is a serious chronic complication of diabetes and is an independent predictor of cardiovascular disease mortality. CAN is also associated with high morbidity and poorer quality of life. Conclusive clinical evidence from randomized prospective trials supports a central role for hyperglycemia in the pathogenesis of CAN, although other cardiovascular risk factors contribute to the disease state. The clinical presentation of CAN comprises a broad constellation of symptoms and deficits. Assessment of CAN includes a broad battery of diagnostic methods and varies between research and clinical practice, however it is generally accepted that the cardiovascular autonomic reflex tests are the gold standard. Strong clinical evidence continues to prove the benefits of glycemic control in preventing CAN in patients with T1DM. Intensive multifactorial cardiovascular risk intervention retards the development and progression of CAN in type 2 diabetes, while the benefits of lifestyle interventions are emerging.

Additional studies are needed to clarify the natural history of CAN in diabetes and pre-diabetes, to fully understand its clinical implications, and to develop CAN targeted pharmacological and lifestyle interventions.

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Fig. 1. The anatomy of the autonomic nervous system. *Ach* acetylcholine, *NE* norepinephrine, α α -adrenoceptor, β β -adrenoceptor, *M* muscarinic receptor

Fig. 2.
Proposed model linking CAN and myocardial dysfunction

Fig. 3. Polar maps of $[^{11}\text{C}]$ HED retention in normal control (*left*) and a T1DM patients with CAN (*right*). The color table is set to a maximum $[^{11}\text{C}]$ HED RI value of $0.09 \text{ mL blood min}^{-1} \text{ mL}^{-1} \text{ tissue}$. To quantify the ‘extent’ of cardiac sympathetic denervation, patients’ RI data are statistically compared with our normal population database using *Z*-score analysis

Table 1

Hazard ratios and 95 % confidence interval for all-cause and CVD mortality in participants with CAN vs. participants without CAN [18]

Measure	All-cause mortality ^a			CVD mortality ^a		
	Hazard ratio CAN+/CAN-	95 % CI	P value	Hazard ratio CAN+/CAN-	95 % CI	P value
CAN1	1.55	1.09, 2.21	0.016	1.94	1.20, 3.12	0.007
CAN2	2.14	1.37, 3.37	0.0009	2.62	1.40, 4.91	0.003
CAN3	2.07	1.14, 3.76	0.02	2.95	1.33, 6.53	0.008

CAN1: the lowest quartile of standard deviation of normally conducted R-R intervals (SDNN); **CAN2:** CAN1 + highest quartile of heart rate; **CAN3:** CAN2 + DPN

^a Adjusted for treatment allocation, CVD history, baseline age, gender, ethnicity, diabetes duration, HbA1c, BMI, systolic and diastolic blood pressure, LDLc, triglycerides, microalbumin/creatinine ratio, and use of TZD, insulin, beta-blockers, ACE inhibitors/angiotensin-receptor blockers, statins, alcohol, and cigarettes

Table 2**Evaluation of CAN****Cardiovascular autonomic reflex tests**

Changes in R–R interval with deep breathing

Valsalva maneuver

R–R response to standing (lying-to-standing test)

Blood pressure response to standing

Blood pressure response to sustained handgrip (reserved for research)

Heart rate variability**Time domain measures**

Standard deviation of all normal R–R intervals (SDNN)

Root-mean square of the difference of successive R–R intervals (rMSSD)

Difference between the longest and shortest R–R interval

Standard deviation of 5-min average of normal R–R intervals (SDANN)

Frequency domain measures

High-frequency components (0.15–0.4 Hz)

Low-frequency components (0.1 Hz)

Very low-frequency components (<0.04 Hz)

Resting heart rate

Used in research and may be used in practice for cardiovascular risk stratification

24-h blood pressure profiles**Baroreflex sensitivity**

Use is reserved for research to assess cardiac vagal and sympathetic baroreflex function

Scintigraphic imaging techniquesPositron emission tomography with [¹²³I]meta-iodobenzylguanidinePositron emission tomography with [¹¹C]-meta-hydroxyephedrine [¹¹C]HED**Muscle sympathetic nerve activity**

Use is reserved for research

Head-up-tilt-table testing**Assessment of symptoms**

Autonomic symptom profile

Table 3**Treatment of orthostatic hypotension****Lifestyle and supportive measures**

- Avoiding sudden changes in body posture to the head-up position
- Avoiding medications that aggravate hypotension (i.e., tricyclic antidepressants, phenothiazines, and diuretics)
- Eating small, frequent meals
- Avoiding activities that involve straining
- Elevating the head of the bed 18 in. at night
- Using a compressive garment over the legs and abdomen
- Using an inflatable abdominal band
- Using a low portable chair, as needed for symptoms
- Physical countermeasures, such as leg crossing, squatting, and muscle pumping
- Increase fluid and salt intake if not contraindicated

Pharmacologic therapy**Midodrine**

- A peripheral-selective direct alpha-1-adrenoreceptor agonist
- Activates alpha-1 receptors on arterioles and veins, thereby increasing total peripheral resistance. Several double-blind, placebo-controlled studies have documented its efficacy in the treatment of orthostatic hypotension [104–106]
- The only FDA approved agent approved for the treatment of orthostatic hypotension
- Doses of 2.5–10 mg 34 times/day are usually recommended
- First dose to be taken before arising
- Avoid to take several hours before planned recumbent position
- Does not cross the blood–brain barrier
- Main adverse effects include: piloerection, pruritus, paresthesias, supine hypertension, and urinary retention

Fludrocortisone

- A synthetic mineralocorticoid, with a long duration of action, which induces plasma expansion
- It may also enhance the sensitivity of blood vessels to circulating catecholamines
- The effects are not immediate, occur over a 1-to 2-week period
- Treatment usually begins with 0.05 mg at bedtime, and may be titrated gradually to a maximum of 0.2 mg/day. Higher doses are associated with higher risk for side effects
- Main adverse effects include supine hypertension, hypokalemia, hypomagnesemia, congestive heart failure, peripheral edema
- Caution must be used in patients with congestive heart failure, to avoid fluid overload

Erythropoietin

- May improve standing blood pressure in patients with orthostatic hypotension
- Possible mechanisms of action include increase in red cell mass and central blood volume; correction of the normochromic normocytic anemia that frequently accompanies diabetic autonomic neuropathy; alterations in blood viscosity; and a direct or indirect neurohumoral effect on the vascular wall and vascular tone regulation, which are mediated by the interaction between hemoglobin and the vasodilator nitric oxide
- It can be administered in diabetic patients with orthostatic hypotension and hemoglobin levels under 11 g/dl subcutaneously or intravenously at doses between 25 and 75 U/kg 3 times/week until the hemoglobin reaches target of 12 g/dl followed by lower maintenance doses
- Risk of serious cardiovascular events should be considered

Somatostatin analogues

- May attenuate the postprandial BP fall and reduce orthostatic hypotension in patients with autonomic failure
- Mechanisms of action include a local effect on splanchnic vasculature, by inhibiting the release of vasoactive GI peptides; enhanced cardiac output; and an increase in forearm and splanchnic vascular resistance
- Usually 25–200 µg/day octreotide are given subcutaneously in divided doses every 8 h

Long-acting depot preparation may be used, 20–30 mg intramuscularly once monthly

Adverse events include severe hypertension

Caffeine citrate

A methylxanthine with well-established pressor effect, primarily due to blockade of vasodilating adenosine receptors

May improve orthostatic hypotension and attenuate postprandial hypotension

Recommended dose 100–250 mg orally 3 times daily. *Dose expressed as anhydrous caffeine*

May be taken as tablets or caffeinated beverage

Tachyphylaxis occurs with continuing use of caffeine