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REVIEW ARTICLE

Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management

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Summary

The Cardiovascular Autonomic Neuropathy (CAN) Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy worked to update CAN guidelines, with regard to epidemiology, clinical impact, diagnosis, usefulness of CAN testing, and management. CAN is the impairment of cardiovascular autonomic control in the setting of diabetes after exclusion of other causes. The prevalence of confirmed CAN is around 20%, and increases up to 65% with age and diabetes duration. Established risk factors for CAN are glycaemic control in type 1 and a combination of hypertension, dyslipidaemia, obesity, and glycaemic control in type 2 diabetes. CAN is a risk marker of mortality and cardiovascular morbidity, and possibly a progression promoter of diabetic nephropathy. Criteria for CAN diagnosis and staging are: (1) one abnormal cardiovagal test result identifies possible or early CAN; (2) at least two abnormal cardiovagal test results are required for definite or confirmed CAN; and (3) the presence of orthostatic hypotension in addition to abnormal heart rate test results identifies severe or advanced CAN. Progressive stages of CAN are associated with increasingly worse prognosis. CAN assessment is relevant in clinical practice for (1) diagnosis of CAN clinical forms, (2) detection and tailored treatment of CAN clinical correlates (e.g. tachycardia, orthostatic hypotension, non-dipping, QT interval prolongation), (3) risk stratification for diabetic complications and cardiovascular morbidity and mortality, and (4) modulation of targets of diabetes therapy. Evidence on the cost-effectiveness of CAN testing is lacking. Apart from the preventive role of intensive glycaemic control in type 1 diabetes, recommendations cannot be made for most therapeutic approaches to CAN.

Keywords diabetic autonomic neuropathy; cardiovascular; epidemiology; diagnosis; prognosis; treatment

Abbreviations: ABPM, ambulatory blood pressure monitoring; CAD, coronary artery disease; CART, cardiovascular autonomic reflex test; CAN, cardiovascular autonomic neuropathy; HRV, heart rate variability; SCD, sudden cardiac death; SMI, silent myocardial ischaemia

Introduction

This consensus document on diabetic cardiovascular autonomic neuropathy (CAN) is the work product of the CAN Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy. The aims were to (1) update the current guidelines on the assessment and management of CAN [1]; (2) revise the data on epidemiology and clinical impact of CAN [2,3]; (3) propose uniform and standardized diagnostic modalities for CAN; (4) evaluate the clinical usefulness of autonomic testing in diabetes in terms of its cost-effectiveness and potential impact on outcomes; (5) propose sensitive and reproducible measures of CAN to be used as end-points in prospective observational and

clinical trials; and (6) review the available therapeutic approaches to CAN.

Methodology

The CAN Subcommittee addressed these issues using the following methods: (1) extensive literature search (Appendix S1); (2) applying a defined system for rating the levels of evidence and strengths of recommendations; (3) preparation of a shared preliminary evidence-based referenced report to be discussed during a 2-day Consensus Meeting (held in Toronto); and (4) development of this final document.

The methodology adopted for rating the quality of evidence and strength of recommendations was that suggested by the American Academy of Neurology [4] for diagnostic studies and by the American College of Cardiology and the American Heart Association Task Force on Practice Guidelines [5] for therapeutic studies (Appendix S1).

Definition of CAN

CAN is defined as the impairment of autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes [6]. CAN is usually documented using several cardiovascular autonomic reflex tests (CARTs) [7].

Epidemiology of CAN

Prevalence

The reported prevalence of CAN varied greatly depending on the tests, the diagnostic criteria used, the use of age-related normative values, and the population studied. In clinic-based studies in unselected populations, including both type 1 and type 2 diabetic patients, the prevalence of confirmed CAN (based on at least two abnormal cardiovascular heart rate test results) varied from 16.6 to 20% [8,9].

Prevalence rates, however, increased both with age (up to 38% in type 1 and 44% in type 2 patients aged 40–70 years) and diabetes duration (up to 35% in type 1 and 65% in type 2 patients with long-standing diabetes) [10,11]. Abnormal CART results were present at the time of diagnosis in about 7% of both type 1 and type 2 patients [2]. The available longitudinal studies indicated an annual increase in prevalence of CAN of about 6% in type 2 diabetes and of about 2% in type 1 diabetes [2,11,12].

Predictors and clinical correlates

In addition to age and diabetes duration, other diabetes-related clinical correlates or predictors of CAN (as documented in cross-sectional or longitudinal studies) were glycaemic control, the presence of diabetic polyneuropathy, diabetic retinopathy, microalbuminuria or diabetic nephropathy, and renal failure [2,3,9,10,13].

The role of several cardiovascular risk factors has also been increasingly reported: blood pressure or hypertension, smoking (only in cross-sectional studies), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, body weight or obesity in type 2 diabetes (with some controversy), waist circumference, insulin levels in type 2 diabetes, cardiovascular disease, and use of anti-hypertensive drugs [2,3,10,13]. Data on the relationship between gender and CAN was controversial (see also Appendix S2).

Conclusions

Establishing the prevalence of CAN is hampered by heterogeneous and inadequate diagnostic criteria and population selection. The prevalence of confirmed CAN in unselected people with type 1 and type 2 diabetes is around 20%, but figures as high as 65% are reported with increasing age and diabetes duration. Because many studies were hospital based, referral bias cannot be excluded (classes II and III).

Clinical correlates or risk markers for CAN are age, diabetes duration, glycaemic control, microvascular complications (peripheral polyneuropathy, retinopathy, and nephropathy), hypertension, and dyslipidaemia (classes I and II).

Established risk factors for CAN are glycaemic control in type 1 diabetes (class I), and a combination of hypertension, dyslipidaemia, obesity, and glycaemic control in type 2 diabetes (class II).

Recommendation

Suitable candidates for CAN screening are asymptomatic type 2 diabetic patients at diagnosis and type 1 diabetic patients after 5 years of disease, in particular those at greater risk for CAN due to a history of poor glycaemic control (haemoglobin $A_{1c} > 7\%$), or the presence of one major cardiovascular risk factor (among hypertension, dyslipidaemia, and smoking), or the presence of macro- or microangiopathic complications (level B).

CAN screening may be also required in asymptomatic patients for pre-operative risk assessment before major surgical procedures (level C).

Clinical impact of CAN

Clinical manifestations of CAN

Symptomatic manifestations of CAN include sinus tachycardia, exercise intolerance, and orthostatic hypotension. Orthostatic hypotension was present in 6–32% of diabetic patients depending on diagnostic cut-offs for fall in systolic

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Table 1. Abnormalities associated with cardiovascular autonomic neuropathy at the level of cardiovascular system and peripheral vascular function

Cardiovascular system
Perioperative unstability
Resting tachycardia
Loss of reflex heart rate variations
Hypertension
Exercise intolerance
Orthostatic hypotension
Postprandial hypotension
Silent myocardial ischaemia
Left ventricular dysfunction and hypertrophy
QT interval prolongation
Impaired baroreflex sensitivity
Non-dipping, reverse dipping
Sympathovagal imbalance
Dysregulation of cerebral circulation
⇓ Sympathetically mediated vasodilation of coronary vessels
↑ Arterial stiffness
Peripheral vascular function
↑ Peripheral blood flow and warm skin
↑ Arteriovenous shunting and swollen veins
↑ Venous pressure
Leg and foot oedema
Loss of protective cutaneous vasomotor reflexes
Loss of venoarteriolar reflex with microvascular damage
↑ Transcapillary leakage of macromolecules
Medial arterial calcification

blood pressure (20 or 30 mmHg) and the diabetic populations studied [2,9,10,14–16]. Symptoms of orthostatic intolerance were present in 4–18% of diabetic patients [9,15]. Orthostatic symptoms, such as light-headedness, dizziness, blurred vision, fainting, or pain in the neck or shoulder when standing, may be worse in the early morning, after meals, during a rise in core temperature, during prolonged standing, or with activity [16]. Symptoms may be disabling, are often a barrier to an effective anti-hypertensive treatment, and may lead to falls in the elderly.

A number of other cardiovascular abnormalities were found in association with CAN [17,18]. These may play a role in excess mortality and morbidity and contribute to the burden associated with CAN (Table 1).

CAN and mortality

A meta-analysis of 15 longitudinal studies, which included a total of 2900 patients followed up for 1–16 years, showed that the diagnosis of CAN based on at least two abnormal CART results determined a relative risk of mortality of 3.65 (95% confidence interval 2.66–4.47) [17]. Subsequent studies confirmed the predictive value of CAN on mortality [19–24] (Table 2). These studies provided even stronger support that CAN is an independent predictor of mortality corrected for multiple confounding factors (including cardiovascular risk factors). Moreover, the pooled relative risk of mortality in clinic-based studies that used more than one index was considerably higher than in studies that used only one [17,22].

In diabetic patients the presence of orthostatic hypotension impaired the prognosis and increased the mortality rate over that associated with vagal cardiac test abnormalities [17]. Tachycardia was associated with total and/or cardiovascular mortality in the diabetic population as well as in the general, cardiac or hypertensive population [25].

There is also strong evidence, based on 12 out of 13 studies in 1319 patients with type 1 diabetes and 3396 patients with type 2 diabetes with a mean follow-up of 9.2 years, that QT interval (QTi) prolongation is an independent predictor of mortality for all-cause and cardiovascular deaths [17,18,21,26] (see also Appendices S4 and S5).

CAN as a predictor of cardiovascular morbidity

An association between CAN and silent myocardial ischaemia (SMI) is well documented [2,27]. In a meta-analysis of 12 studies including 1468 diabetic patients, SMI was present in 20% of those with CAN compared with 10% of those without CAN with a prevalence rate ratio of 1.96 (95% confidence interval 1.53–2.51) [2]. At baseline, the Detection of Ischaemia in Asymptomatic Diabetics (DIAD) study showed that in 1123 type 2 diabetic patients the lowest quartile of the Valsalva ratio was the strongest determinant of SMI, which was defined as abnormal stress adenosine Tc-99m sestamibi Single Photon Emission Computed Tomography myocardial perfusion imaging [28]. Over a mean follow-up of 4.8 years, the lowest quartile of lying-to-standing test was associated with an adjusted hazard ratio of 4.33 (95% confidence interval 2.14–8.75) for cardiac death or non-fatal myocardial infarction [27].

CAN was reported to be a predictor of cardiovascular morbidity and mortality in type 1 diabetes [20] and to provide prognostic information for death and/or cardiac events incremental to that offered by perfusion defects or by the presence of SMI [29].

Moreover, CAN was associated with left ventricular systolic and particularly diastolic dysfunction in the absence of cardiac disease [18,30]. However, it is difficult to evaluate the independent role of CAN in these disorders and in chronic heart failure, as other factors such as interstitial myocardial fibrosis, microangiopathic or metabolic changes may also be responsible for diabetic heart muscle disease and left ventricular dysfunction.

Four longitudinal studies documented that CART abnormalities or QTi prolongation [18] imposes a twofold risk of stroke. In the Pittsburgh Epidemiology of Diabetes Complications study, CAN was associated with increased arterial stiffness in type 1 diabetic patients 18 years later [31].

Increased risk for perioperative morbidity and mortality is well described in diabetes, and in seven out of eight studies CAN was associated with haemodynamic instability during general anaesthesia, cardiorespiratory arrests, and abnormal cardiovascular reactions even

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Table 2. Cardiovascular autonomic neuropathy as a risk marker for mortality in recent studies

Author (year)	Country or study	Type	Number	Follow-up (years)	Cardiovascular autonomic neuropathy test	Mortality	Relative risk
Wheeler [19]	USA	Type 1–2	532 males	3.5	Deep breathing test	All-cause	1.49
Astrup [20]	Denmark	Type 1	388 (197 macro-, 191 normo-albuminuric)	10	Deep breathing test	Cardiovascular disease mortality and morbidity	4.9[a]
Soedamah- Muthu [23]	EURODIAB Prospective Complications Study	Type 1	2787	7	Lying to standing test +/− orthostatic hypotension	All-cause	2.4
Lykke [22]	Denmark	Type 1	391 (199 macro-, 192 normo-albuminuric)	10	Deep breathing test QTc Deep Breathing test + QTc	All-cause	2.5 (not significant) 2.3 (not significant) 7.9
Ziegler [21]	MONICA/KORA Ausburg Cohort study	Type 1–2	160	9	Max-min heart rate QTc	All-cause	1.74 ($p = 0.075$[b]) 3.0
Pop-Busui [24]	Action to Control Cardiovascular Risk in Diabetes study	Type 2	8135	3.5	Heart rate + standard deviation of R-R interval + QTc	All-cause Cardiovascular disease	1.55–2.14 1.92–2.95

QTc, QT interval corrected for rate; MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease; KORA, Cooperative Health Research in the Region of Augsburg.
[a]Not significant in normoalbuminuric group.
[b]After multiple adjustment.

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during minor surgery [18,32] (see Appendix S5 for references).

Attenuation (non-dipping) or complete loss of the nocturnal fall in blood pressure (reverse dipping) in diabetes was associated with left ventricle hypertrophy in cross-sectional studies or two- to eight-fold increase in risk of cardiovascular or renal events in some longitudinal studies [2,18].

CAN as a promoter of nephropathy progression

Several studies (with one exception) showed that CAN and autonomic pupillary abnormalities independently predicted the progression of diabetic nephropathy [20]. It was suggested that this could be mediated by CAN-induced changes in glomerular haemodynamics and in the circadian rhythms of blood pressure and albuminuria. Moreover, erythropoietin-deficiency anaemia and early dysregulation of erythropoietin production have been described in patients with CAN [33] as in different dysautonomic conditions. Anaemia is a predictor of nephropathy progression and erythropoietin exerts direct renoprotective effects. Thus, both anaemia and erythropoietin deficit may contribute to kidney damage in diabetes. Resting heart rate was reported to be associated with overt nephropathy development in type 1 diabetic patients. In the Atherosclerosis Risk in Communities (ARIC) study in 13 241 adults (1523 with diabetes) followed up for 16 years, higher resting heart rate and lower heart rate variability (HRV) indices were associated with the highest risk of developing end-stage renal disease [34].

Moreover, non-dipping and reverse dipping were found to predict, independent of 24-h blood pressure level, the progression from overt nephropathy to renal failure or dialysis in type 2 patients and – with some controversy – the development of microalbuminuria in type 1 patients (see Appendix S5 for references).

Conclusions

There is definitive evidence for a predictive value of CAN on overall mortality (class I).

There is some evidence for a predictive value of CAN on morbidity (class II).

Orthostatic hypotension, when due to advanced CAN, is associated with an additional increase in mortality risk over that driven by HRV abnormalities (class III).

Some cardiovascular abnormalities, closely linked to CAN, are associated with increased mortality: tachycardia (class II), QTi prolongation (class II), and non-dipping status (class III).

Recommendations

CAN is a risk marker of mortality (level A) as well as a risk marker and likely a risk factor for cardiovascular morbidity (level B), and possibly a progression promoter of diabetic nephropathy (level C).

Orthostatic hypotension is associated with a worse prognosis than cardiovagal neuropathy (level C).

QTi prolongation has prognostic value in diabetes (level B). Non-dipping status is associated with an adverse cardiovascular prognosis in diabetes (level C).

Non-dipping status predicts the progression from micro- and macroalbuminuria to renal failure in type 2 diabetes (level C).

CAN assessment

Methods of CAN assessment in clinical practice include assessment of symptoms and signs, CARTs based on heart rate and blood pressure, and ambulatory blood pressure monitoring (ABPM).

Assessment of symptoms

Questionnaires have been developed to investigate orthostatic symptoms and their severity in dysautonomic conditions, although they have not been specifically validated for CAN and validated translations in different languages are lacking. In the Rochester Diabetic Neuropathy Study the correlation between the autonomic symptoms and the autonomic deficits was weak in type 1 and absent in type 2 diabetic patients [10]. Orthostatic symptoms were poorly related to fall in systolic blood pressure on standing [35]. For their clinical impact, orthostatic symptoms should be looked for regularly together with other dysautonomic symptoms in diabetic patients.

Assessment of signs

Some clinical findings observed during routine clinical evaluation or obtained as incidental data in clinical tests as electrocardiography or ABPM can alert the physician on the presence of CAN.

Tachycardia. Resting heart rate is a straightforward and readily available clinical measurement. Tachycardia may reflect diabetic autonomic dysfunction [18]. It can also reflect vagal impairment and/or sympathetic overactivity present in cardiac diseases, poor fitness, obesity, or anaemia.

Emerging evidence on the prognostic value of heart rate have led to the advice in the current hypertension guidelines to measure heart rate in clinical practice [36] and to use it for cardiovascular risk stratification and as therapeutic target in high-risk patients [25,36].

Exercise intolerance. In diabetic patients without evidence of heart disease, but with asymptomatic cardiac vagal neuropathy, exercise capacity and heart rate, blood pressure, and cardiac stroke volume responses to exercise were diminished. A further decrease in exercise capacity and blood pressure response was seen in patients

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with both vagal neuropathy and orthostatic hypotension. The severity of CAN correlated inversely with maximal heart rate increase during exercise [37], suggesting CAN contribution to diminished exercise tolerance.

Orthostatic hypotension may result from various pathophysiological conditions and is affected by drugs, hypovolaemia, and deconditioning. Orthostatic hypotension is defined as a reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 min of standing [38,39] and a fall in systolic blood pressure of 30 mmHg [35,40].

The presence of orthostatic hypotension after exclusion of other causes suggests advanced CAN that should be confirmed by CARTs. For its ease and prognostic value, orthostatic hypotension should be assessed routinely in diabetic patients even without symptoms, in particular after the age of 50 [36].

QTi prolongation. QTi prolongation has been defined as a QTc (corrected QT for heart rate) $\geq$460 ms in women and $\geq$450 ms in men, although in most studies less strict criteria were used. The pathogenesis of QTi prolongation is multifactorial and includes imbalance in cardiac sympathetic innervation, intrinsic metabolic and electrolytic myocardial changes, left ventricular hypertrophy, coronary artery disease (CAD), and genetic factors [26].

The day–night modulation of the QT/relative risk relation – on 24-h electrocardiogram recordings – was altered in CAN patients free of coronary artery disease, left ventricular dysfunction, or hypertrophy, with a reversed day–night pattern and an increased nocturnal QT rate dependence [41].

Reversible QTi prolongation may be induced by hyperinsulinaemia in healthy subjects, by hyperglycaemia [42] and by acute hypoglycaemia in both healthy and diabetic subjects [26]. In type 1 diabetic patients, prolonged QTc was shown to occur frequently during overnight hypoglycaemia and to be associated with cardiac rate/rhythm disturbances. These findings support an arrhythmic basis for the 'dead in bed' syndrome and possibly a provocative role in cardiovascular events of hypoglycaemia-induced sympathetic activation [43].

In a meta-analysis of 17 studies including 4584 diabetic patients, QTc prolongation (>441 ms) was a specific (86%) albeit insensitive (28%) index of CAN [44].

Non-dipping and reverse dipping. ABPM is a standard tool in hypertension research and management with regard to diagnostic, prognostic, and therapeutic issues [36]. It allows the assessment of the diurnal blood pressure pattern, which is mainly regulated by sleep–awake changes in the autonomic cardiovascular function. ABPM may be used for research purposes to (1) evaluate the circadian blood pressure pattern and its abnormalities (e.g. non-dipping, nocturnal hypertension, extreme dipping, morning surge); (2) study its relationship with autonomic dysfunction, sleep disturbances, and kidney function; (3) assess the 24-h blood pressure response to treatment; and (4) evaluate the longer term prognostic implications of circadian blood pressure abnormalities. Non-dipping and reverse dipping patterns were associated with CAN, which was the major determinant of the circadian variation in blood pressure. Several observations in both diabetic and non-diabetic patients linked non-dipping to a disruption of the circadian variation in sympathovagal activity, i.e. a diminished increase in vagal activity and a sympathetic predominance during the night [45]. The day–night difference in systolic blood pressure was a moderately accurate diagnostic tool for CAN, and reverse dipping as a specific (95%) – albeit insensitive (25%) – marker of CAN [46]. In clinical practice, ABPM in the general population is useful for diagnostic purposes and provides unique and additional information for risk stratification with regard to hypertension-related organ damage and cardiovascular events, and for the extent of blood pressure response to treatment [36]. The European Society of Hypertension acknowledges that ABPM may improve predictions of cardiovascular risk in hypertensive patients and recommends that 24-h ABPM should be considered in the presence of either noticeable variability of office blood pressure values or a marked discrepancy between office and home blood pressure values, and in case there is resistance to drug treatment or hypotensive episodes are suspected [36]. Thus, in patients with CAN, ABPM may be particularly useful in detecting non-dipping or reverse dipping conditions, daytime postural blood pressure changes, and postprandial hypotension, and in achieving blood pressure control for the whole 24-h period. Conversely, in clinical practice, the presence of reverse dipping in ABPM may suggest the presence of CAN and thus requires CAN testing (see Appendix S5 for references).

Conclusions

Resting heart rate is not a specific sign of CAN (class IV).

After exclusion of other causes orthostatic hypotension suggests an advanced CAN that should be confirmed by CARTs (class I).

Orthostatic hypotension (class III), QTi prolongation (class II), and reverse dipping on ABPM are specific but insensitive indices of CAN (class III).

Recommendations

The presence of symptoms and/or signs is not a sufficient criterion for CAN diagnosis but should provide the motivation to perform CAN testing to get a definite diagnosis (level B).

Screening of orthostatic symptoms is advisable in any diabetic patient (level B).

Regardless of the presence of orthostatic symptoms, the orthostatic hypotension test is recommended yearly, in particular in patients over the age of 50 and in hypertensive diabetic patients (level B).

CAN testing offers a useful tool to identify patients with potentially poor exercise performance and to prevent

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adverse outcomes when patients are introduced to exercise training programs (level C).

Diabetic patients with unexplained tachycardia should undergo CAN testing (level C).

Resting heart rate may be used in clinical practice for cardiovascular risk stratification (level C).

QTi prolongation alone is an insufficient measure of CAN but should prompt further testing (level B).

QTc may be used for cardiovascular risk stratification (level B).

ABPM should not be routinely employed for the diagnosis of CAN (level C). However, it is a reliable research tool to explore 24-h blood pressure patterns in different conditions (level B).

In the presence of reverse dipping, referral for CAN testing is advisable (level C).

ABPM may be useful in patients with CAN to detect non-dipping, to determine risk stratification for cardiovascular mortality and nephropathy progression, and to adjust anti-hypertensive treatment (level C).

Cardiovascular autonomic reflex tests

CARTs assess cardiovascular autonomic function through provocative physiological manoeuvres and by measuring the end-organ response, i.e. heart rate and blood pressure changes. Although indirect autonomic measures, they are considered the gold standard in autonomic testing. Heart rate variations during deep breathing, Valsalva manoeuvre, and lying-to-standing (heart rate tests) are indices mainly of parasympathetic function, whereas the orthostatic hypotension, the blood pressure response to a Valsalva manoeuvre and sustained isometric muscular strain provide indices of sympathetic function [1,7,14]. These tests are non-invasive, safe, clinically relevant (they correlate with tests of peripheral nervous system function), easy to perform, sensitive, specific, reproducible, and standardized, and therefore they are considered consolidated, gold-standard measures of autonomic function [7]. Blood pressure response to sustained handgrip is no longer regarded as an established clinical test but as an investigational test [7], whereas the orthostatic hypotension test still represents an essential part of the standard assessment of CAN, despite its low sensitivity [35].

Valsalva manoeuvre increases intrathoracic, intraocular, and intracranial pressure and may theoretically be associated with a small risk of intraocular haemorrhage or lens dislocation [7]. In the absence of data on the occurrence of retinal complications induced by CARTs, avoiding the Valsalva manoeuvre in patients with proliferative retinopathy may be appropriate [35].

There is no statistical evidence of a striking superiority in diagnostic characteristics of a cardiovascular heart rate test over the others [18]. It is also worthy of consideration that (1) the deep breathing test is certainly the most widely used test; (2) the Valsalva manoeuvre needs greater cooperation from patients and cannot be universally performed, and heart rate response depends on the blood pressure response to the manoeuvre; and (3) the orthostatic hypotension test is affected by a number of confounding factors [35].

CARTs have a number of confounding factors [35]. Table 3 contains a list of these confounders with corresponding recommendations (see also Appendix S3).

Diagnosis and staging of CAN

How many and which tests to use for diagnosis?

There is no evidence that one individual heart rate test may substitute for the other two, or have such a clear diagnostic superiority as to be used on its own [4]. Moreover, the diagnostic definition of CAN based on several tests reduces the probability of false positives. The need to use several tests of both vagal and sympathetic functions is reaffirmed in the available guidelines [1,3].

The prognostic value of CAN for mortality and cardiovascular events differs according to the number of tests used for its diagnosis [17,18,47]. The number of abnormal results most likely represents an indication of severity or progression of the disease and affords a more robust definition of CAN.

Test abnormalities should be defined using age-based and technique-specific normative data (see Table 3 and Appendix S3) [35].

Diagnostic criteria for CAN

No unanimous criteria for diagnosis of CAN have been adopted to date. A single abnormal result among the two or three heart rate tests actually performed was considered a sufficient criterion for early CAN diagnosis [1–3]. However, the presence of abnormalities in more than one test on several occasions was indicated as preferable for diagnosis [1]. In addition, the presence of two or three abnormal results (two for borderline, three for definite) among the seven autonomic cardiovascular indices (including the five standard CARTs and other time and frequency domain indices of HRV) was recommended as a criterion for CAN diagnosis [8].

Staging of CAN

Ewing *et al*. originally proposed a classification based on 'early involvement' (one abnormal result on heart rate test or two borderline results), 'definite involvement' (two or more abnormal results on heart rate tests), and 'severe involvement' (presence of orthostatic hypotension) [14]. An 'autonomic neuropathy score' – obtained by scoring the results of CARTs – has been used with the dual advantage of quantifying the progression of CAN and providing an overall quantitative result [35].

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Table 3. Confounding factors on cardiovascular autonomic testing

Physiological confounders	Advice	Recommendation
Standardization	Follow the standard procedures in performing tests and control or minimize the influence of confounding factors	Standardization of testing procedure and control of confounding factors are essential to the reliability of cardiovascular tests
Patients' compliance	Provide detailed information to the subject	Instructions to patients and their familiarization with the tests allow a better standardization of stimuli
Age	Use normal age-related values	Age-related normal reference values are strictly required to correctly interpret the results of all the heart rate-based cardiovascular tests (level B)
Respiratory pattern	Control for respiratory pattern	Accurate instruction on timed deep breathing and on avoidance of deep or irregular breaths after the Valsalva manoeuvre and after standing is advisable (level C)
Body position	Allow a sufficient supine rest before orthostatic test	Adequate supine rest before standing is necessary to increase reproducibility and test reliability
Basal heart rate and blood pressure	Caution in interpreting the results of heart rate tests with a resting heart rate $>$100 bpm and of orthostatic hypotension test with supine systolic blood pressure $>$160 mmHg or $<$120 mmHg	No correction is needed for the resting heart rate (level C), the possible confounding effect of supine systolic blood pressure should be taken into account when evaluating orthostatic hypotension test (level B)
Physical exercise	Avoid strenuous exercise 24 h before testing.	Patients should be requested to avoid strenuous physical exercise in the 24 h preceding the tests
Coffee, alcohol, smoking	Avoid consumption of coffee and alcohol, and smoking before testing	Patients should be requested to avoid caffeine beverages, smoking, and alcohol at least 2 h prior to the tests
Meals	Avoid testing just after main meals	It is advisable to perform the tests at least 2 h after a light meal
Pathophysiological confounders		
Intercurrent diseases	Avoid testing in the presence of intercurrent diseases associated with fever, infection, or dehydration	It is advisable to avoid testing during acute disease, stressful condition, fever, infection, dehydration
Hypoglycaemia, hyperglycaemia	Avoid testing during hypoglycaemia or marked hyperglycaemia	Tests should not be performed during hypoglycaemia or marked hyperglycaemia (level C)
Insulin	Avoid testing just after short-acting insulin administration	Tests should be performed at least 2 h after short-acting insulin administration (level C)
Respiratory and cardiovascular disease	Control for associated diseases	Test results should be interpreted with caution in presence of respiratory or cardiovascular diseases, in particular heart failure (level C)
Drugs	Control for medications	An appropriate wash-out of interfering drugs, particularly diuretics, sympatholytic agents and psychoactive drugs should be pursued, if not feasible, results should be interpreted with caution

While an abnormal orthostatic hypotension test result generally occurs late in diabetes and subsequent to abnormalities in the heart rate tests, no chronological order or a markedly different prevalence of abnormalities among the heart rate tests has been found [8,35]. Considering progression from an early to an advanced involvement, instead of from parasympathetic to sympathetic neuropathy, would appear to be the most appropriate approach to CAN staging (Figure 1), although orthostatic hypotension may on rare occasions precede abnormalities in heart rate tests [2,14,35]. The available information regarding the duration required to progress from an earlier to a later

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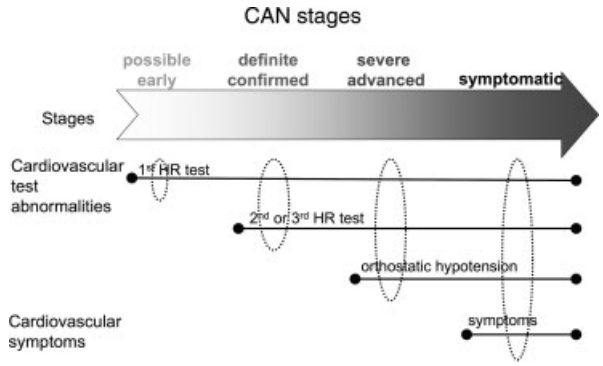

Figure 1. Stages of cardiovascular autonomic neuropathy

stage of CART impairment is scant and it is not documented that a progression to orthostatic hypotension and symptomatic forms invariably occurs in all patients.

The combination of CARTs with tests for sudomotor function may provide a more accurate diagnosis of diabetic autonomic neuropathy [4].

Conclusions

The following CARTs are the gold standard for clinical autonomic testing: heart rate response to deep breathing, standing, and Valsalva manoeuvre, and blood pressure response to standing (class II) (Table 4).

These CARTs are sensitive, specific, reproducible, easy to perform, safe, and standardized (classes II and III).

The Valsalva manoeuvre is not advisable in the presence of proliferative retinopathy and when there is an increased risk of retinal haemorrhage (class IV).

CARTs are subject to a number of confounding or interfering factors (class III). Age is the most relevant factor affecting heart rate tests (class I).

A definite diagnosis of CAN and CAN staging requires more than one heart rate test and the orthostatic hypotension test (class III).

Recommendations

Diagnosis of CAN is based on the use of CARTs for heart rate response to deep breathing, standing, Valsalva manoeuvre, and for blood pressure response to standing (level A).

For the diagnosis and monitoring of CAN, more than one heart rate test and the orthostatic hypotension test are required (level B).

Performance of CARTs should be standardized and the influence of confounding variables minimized (level A).

Age-related normal ranges of heart rate tests are strictly required (level A).

CAN diagnosis and staging: (1) the presence of one abnormal cardiovagal test result identifies the condition of possible or early CAN, to be confirmed over time; (2) at least two abnormal cardiovagal results are required for a definite or confirmed diagnosis of CAN; and (3) the presence of orthostatic hypotension in addition to heart rate test abnormalities identifies severe or advanced CAN (level B).

CARTs allow CAN staging from early to advanced involvement (level C).

Progressive stages of CAN are associated with increasingly worse prognosis (level B).

Usefulness of CAN diagnosis in clinical practice

The detection of CAN may help tailor therapeutic strategies for patients with diabetes

For instance it may help in the individualized treatment of orthostatic hypotension, tachycardia, non-dipping and nocturnal hypertension [25]. In the presence of CAN, blood pressure should not be measured only in the seated position when adjusting anti-hypertensive treatment (particularly in patients with orthostatic hypotension); and drugs with adverse autonomic consequences should be avoided. Drugs with the potential to prolong QTi should be avoided where possible in patients with CAN.

CAN testing and exercise program

Given the association between CAN and symptoms of exercise intolerance, decreased cardiac responsiveness to exercise and exercise-induced orthostatic hypotension, the estimate of exercise intensity should be based on ratings of perceived exertion scale rather than heart rate increase in CAN patients [18]. Therefore, CAN testing should be considered before a stress exercise test.

Testing should also be considered before beginning a program of more vigorous physical activity than brisk walking. The presence of severe CAN may contraindicate certain types of exercise or predispose patients to injury [48].

CAN testing for the evaluation of perioperative anaesthetic risk

CAN may be considered as a risk marker for anaesthetic haemodynamic instability thus highlighting the need for a careful haemodynamic monitoring during the operative and perioperative periods [32] (see Appendix S5 for references).

CAN testing for risk stratification for morbidity and mortality

CAN is a risk marker for all-cause and cardiac mortality, for stroke, coronary events, SMI, heart failure, arrhythmia, sudden death, and nephropathy progression [2,17,18,27–30,33,34].

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Table 4. Cardiovascular autonomic tests and suggested indications for their use

	Clinical diagnosis	Research	End-point in clinical trials
Heart rate cardiovascular tests	Yes	Yes	Yes
Orthostatic hypotension test	Yes	Yes	No (low sensitivity)
QT interval	Yes (additional information and risk stratification)	Yes	No (low sensitivity)
Ambulatory blood pressure monitoring for dipping status	Yes (risk stratification)	Yes	No (low sensitivity)
Heart rate variability time and frequency domain indices	Yes (early additional information and risk stratification)	Yes	Yes
Baroreflex sensitivity measures	No (early additional information and risk stratification but low availability)	Yes	Yes
Scintigraphic studies	No (low availability, limited standardization)	Yes	Yes
Muscle sympathetic nerve activity	No (low availability, limited data in cardiovascular autonomic neuropathy)	Yes	Possible (used in lifestyle intervention trials in obesity)
Catecholamine assessment	No (low availability)	Yes	Possible (used in lifestyle intervention trials in obesity)

CAN testing for risk stratification before screening for CAD

In light of recent data [27], generalized and routine screening for CAD in asymptomatic type 2 patients no longer appears to be justified, whereas testing for SMI and silent coronary stenoses should be performed exclusively for individuals at very high risk [49].

CAN may play a pivotal role in the identification of these high-risk diabetic patients for its association with a twofold risk for SMI [2] and its predictive value on cardiac events [27–29]. Thus, CAN testing may be considered a main component of a diabetes-specific risk pattern to identify high-risk subjects in whom CAD screening is more effective [49]. CAN testing may also improve patient adherence to risk-reducing therapies [49].

CAN testing for risk stratification for sudden death following myocardial infarction

Type 2 diabetes is associated with a twofold to fourfold increase in the risk of sudden cardiac death (SCD) in particular after a myocardial infarction. CAD is the most common pathologic substrate for SCD in adults. Ventricular fibrillation is the most common electrophysiological mechanism, with impaired cardiac autonomic modulation considered as a key factor in the development of a cardiac arrest [50]. Some autonomic indices, i.e. HRV, baroreflex sensitivity, heart rate turbulence, deceleration capacity, heart rate recovery after exercise, were independent predictors of cardiac death after myocardial infarction, with better predictive value when used in combination [50]. However, it has not been proved that any of them can effectively identify patients likely to benefit from prophylactic therapy with implantable cardioverter defibrillator [50].

Robust and conclusive data assessing the predictive value of HRV for SCD after myocardial infarction in diabetic patients is still lacking [51]. A risk stratification scheme for the prevention of SCD in diabetic patients has not yet been identified [51], and the role of CAN testing in SCD risk stratification needs to be clarified.

CAN testing to define the target of glycaemic control

Hypoglycaemia has a proarrhythmogenic effect through QTi prolongation, attenuation of cardiovagal baroreflex function [52], and Ca^{2+} overload consequent to sympathetic activation. Diabetes and cardiovascular disease contribute to both changes [53]. Although definitive evidence that hypoglycaemia can be regarded as a proarrhythmogenic event leading to malignant ventricular tachyarrhythmias and SCD does not exist, there are indications of an association between hypoglycaemia and SCD, in particular in patients with cardiac disease [54,55]. The role of CAN in this setting is still undefined. Severe CAN may attenuate the sympathetic response to hypoglycaemia and is also associated with QTi prolongation and baroreflex impairment which may predispose to cardiac death. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, although self-reported history of neuropathy was associated with an increased mortality risk in the group on intensive diabetes therapy, the presence of abnormal autonomic indices derived from a resting electrocardiogram (CARTs were not formally performed) did not account for the difference in mortality

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rate between intensive and standard glycaemia treatment groups [24].

The presence of CAN may identify diabetic patients more prone to the dangerous effects of hypoglycaemia, in particular among the group with cardiac disease. Thus, CAN testing may serve to define the target of glycaemic control according to the patient's risk profile and also to weigh up the advantage of aggressive diabetes treatment against the risk. However, it is still unproven that the presence of CAN should be a contraindication for intensive glycaemic control.

CAN testing to overcome clinical inertia and patient non-adherence

The presence of CAN may promote a proactive behaviour in health providers and patients, although this is unproven.

Likewise, there is a lack of prospective studies that assess the cost-effectiveness of CAN testing in the asymptomatic stages of CAN, the impact of therapeutic changes on ultimate or surrogate endpoints as a consequence of CAN diagnosis, and which patients could benefit most from CAN testing.

Conclusions

CAN assessment is relevant in clinical practice for

- Diagnosis of symptomatic and clinical forms of CAN and explaining symptoms suggestive of diabetic dysautonomia (classes II and III);
- detection and tailored treatment in the presence of CAN clinical correlates: tachycardia, orthostatic hypotension, non-dipping, QTi prolongation (classes III and IV);
- risk stratification for diabetes-related complications (class III);
- risk stratification for cardiovascular morbidity and mortality (classes II and III); and
- tailoring of targets of diabetes therapy (class IV).

There is a lack of prospective studies assessing the cost-effectiveness of CAN testing.

Recommendations

In symptomatic and clinical forms of CAN, diagnosis may allow a directed treatment of the clinical consequences of CAN and may provide insight into the general therapeutic strategy in diabetic patients (level B).

In asymptomatic patients, CAN assessment may be required for the evaluation of perioperative risk (level C).

In asymptomatic patients, CAN assessment may be used for cardiovascular risk stratification (level C).

CAN may be assumed to be a component of a diabetes-specific risk pattern to identify high-risk diabetic subjects in whom screening for CAD is cost effective (level U).

CAN diagnosis may serve to modulate targets of therapeutic intervention and to address clinical inertia and foster patient adherence (level U).

CAN diagnosis may be useful if followed by a modification of disease management and/or therapeutic strategies.

Management of CAN

Glycaemic control and multifactorial risk intervention

In the Diabetes Control and Complications Trial (DCCT) study intensive insulin treatment in type 1 diabetic patients reduced the incidence of CAN by 53% compared to conventional therapy [12]. In the Epidemiology of Diabetes Interventions and Complications (EDIC) study, at the 13th–14th year after DCCT closeout, although CAN progressed substantially in both treatment groups, its prevalence and incidence remained significantly lower in the former intensive than in the former conventional group [11], supporting that intensive treatment of type 1 diabetes should be initiated as early as is safely possible.

In the Steno 2 study, an intensive multifactorial cardiovascular risk intervention reduced the progression or the development of CAN among type 2 diabetic patients with microalbuminuria [56]. However, the beneficial effect of intensive glycaemic control on CAN in type 2 diabetes has not been specifically proven [57].

Lifestyle modification

In the Diabetes Prevention Program, autonomic function indices improved in subjects with pre-diabetes randomized to the lifestyle modification arm aimed at weight reduction and at engaging physical activity [58]. Weight loss in obese patients is accompanied by improvement in cardiovascular autonomic function [59]. A few small – mostly open – interventional studies in diabetes showed a beneficial effect for aerobic training on cardiovascular autonomic indices, with some indication that mild physical exercise may be effective only in patients with less severe CAN.

Treatment based on pathogenetic concepts

Only limited data on a pathogenetically oriented pharmacotherapy are available in CAN patients [18]. Phase II randomized controlled trials have shown favourable effects on HRV indices using the anti-oxidant α-lipoic acid [60], vitamin E, and C-peptide. Further studies are needed to confirm these findings as well as to evaluate other potential pathogenetic treatments.

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Pharmacological modulation of autonomic tone

A number of drugs may adversely affect the autonomic tone by reducing HRV with consequent potential pro-arrhythmic effect [61]. On the other hand, an increase in HRV has been described – with some controversy – in diabetic patients with angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, cardioselective β blockers without intrinsic sympathomimetic activity (e.g. metoprolol, nebivolol, bisoprolol), digoxin, and verapamil [18,35,60]. Cardioselective β blockers can be used to treat resting tachycardia associated with CAN.

Symptomatic treatment of orthostatic hypotension

Treatment of orthostatic hypotension is required only when symptomatic with the therapeutic goal to minimize postural symptoms rather than to restore normotension. The first step encompasses non-pharmacological measures with the attempt to (1) identify other causes of orthostatic hypotension, e.g. volume depletion, and avoid, when possible, drugs exacerbating postural symptoms, such as psychotropic drugs, diuretics, and α-adrenoreceptor antagonists; (2) educate patients regarding behavioural strategies such as gradual staged movements with postural change, mild isotonic exercise, head-up bed position during sleep, physical counter-manoeuvres (e.g. leg-crossing, stooping, squatting, and tensing muscles), use of portable folding chairs, increased fluid and salt intake if not contraindicated, drinking water rapidly, and avoidance of large meals rich in carbohydrates; (3) use of elastic garment over the legs and abdomen. If symptoms persist despite these measures, a pharmacological treatment should be considered. Several drugs have efficacy in the treatment of neurogenic orthostatic hypotension [39,61]. The potential risks of a drug should be weighed against its possible benefit, including the balance between the goal of increasing standing blood pressure and the avoidance of a marked supine hypertension.

The peripheral selective α_1-adrenergic agonist midodrine is a first-line drug that exerts a pressor effect through both arteriolar constriction and venoconstriction of the capacitance vessels. The dosing should be individually tailored (up to two to four times 10 mg/day, with the first dose taken before arising and use avoided several hours before planned recumbency particularly in patients with documented supine hypertension). Adverse events are pilomotor reactions, pruritus, supine hypertension, bradycardia, gastrointestinal symptoms, and urinary retention. Midodrine is the only medication approved by the Food and Drug Administration for the treatment of symptomatic orthostatic hypotension and is now under reconsideration.

The 9-α-fluorohydrocortisone is another first-choice drug that acts through sodium retention, a direct constricting effect on partially denervated vessels, and an increase in the water content of the vessel wall leading to a reduced distensibility. Possible adverse effects include supine hypertension, hypokalaemia, congestive heart failure, and peripheral oedema. The initial dose should be 0.05–0.1 mg daily with individual titration to 0.1–0.3 mg daily [62].

Erythropoietin was proposed to increase standing blood pressure via several mechanisms: (1) increasing red cell mass and central blood volume, (2) correcting the anaemia frequently associated with severe CAN, and (3) neurohumoral effects on the vascular wall and vascular tone regulation. It can be administered in diabetic patients with haemoglobin levels under 11 g/dL subcutaneously or intravenously at doses between 25–75 U/kg three times/week with an haemoglobin target of 12 g/dL followed by lower maintenance doses [62].

Other possible treatments include (1) desmopressin acetate, a vasopressin analogue useful to correct nocturnal polyuria and morning orthostatic hypotension; (2) somatostatin analogues aimed at inhibiting the release of vasoactive gastrointestinal peptides, enhancing cardiac output, and increasing forearm and splanchnic vascular resistance, with severe cases of hypertension as possible adverse events in diabetic patients; (3) caffeine and (4) acarbose, both useful in attenuating postprandial hypotension in autonomic failure [39,62].

Conclusions

Intensive diabetes therapy retards the development of CAN in type 1 diabetes (level A).

Intensive multifactorial cardiovascular risk intervention retards the development and progression of CAN in type 2 diabetes (level B).

Lifestyle intervention may improve HRV in pre-diabetes (level B) and diabetes (level B).

Symptomatic orthostatic hypotension may be improved by non-pharmacological measures (level B) and by midodrine (level A) and/or fludrocortisone (level B).

Drug treatment of symptomatic orthostatic hypotension in diabetic patients with CAN may be challenging and should be thoroughly balanced between the goal of increasing standing blood pressure and the avoidance of a marked increase in supine blood pressure (level C).

Recommendations

Diabetes therapy in patients with type 1 and type 2 diabetes should consider the individual risk profile and comorbidities (class I).

Lifestyle intervention should be offered as a basic preventive measure (class I).

Given the limited evidence from very few large-scale randomized clinical trials, recommendations cannot be given for pharmacological and non-pharmacological treatments of CAN.

Drugs that may reduce HRV should be avoided in patients with CAN (class III).

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Resting tachycardia associated with CAN can be treated with cardioselective β blockers (class I).

The first therapeutic approach in symptomatic orthostatic hypotension should consider the exclusion of drugs exacerbating orthostatic hypotension, correction of volume depletion (class I), and other non-pharmacological measures (class IIa).

Pharmacotherapy of symptomatic orthostatic hypotension should include midodrine (class I) or fludrocortisone or a combination of both in non-responders to monotherapy (class IIa).

Because of the limited evidence, the potential risk of any pharmacological treatment should be thoroughly weighed against its possible benefit (class I).

CARTs should be used as end-points in prospective observational and clinical trials.

Issues for future research

Longitudinal studies are needed (1) to clarify the natural history of CAN, in particular in type 2 diabetes and prediabetes; (2) to evaluate the impact of pharmacological and lifestyle interventions targeting CAN; and (3) to determine the effect of CAN on clinical outcomes and its long-term prognostic relevance.

Supporting information

Supporting information may be found in the online version of this article.

Conflict of interest

Nothing to declare.

Appendix

The Toronto Consensus Panel on Diabetic Neuropathy

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