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MEETING CONTRIBUTION

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Clinical consequences of cardiovascular autonomic neuropathy in diabetic patients

Abstract A wide range of clinical consequences of cardiovascular autonomic neuropathy (CAN) can be observed in diabetic patients and contributes to the clinical picture of the diabetic heart. Resting heart rate and cardiovascular reflexes as well as circadian heart rate variability may be altered by CAN in diabetes. Moreover, blood pressure is also influenced by sympathovagal imbalance. Postural hypotension is a clinical characteristic in diabetic subjects with CAN. Painless myocardial infarction, ischaemia and left ventricular dysfunction are also observed in some cases. Impairment of cardiac parasympathetic and sympathetic innervation as well as QT-interval prolongation may play a partial role in the pathogenic mechanism of sudden unexpected death in diabetic patients. The risk of surgical intervention and that of anaesthesia are increased due to abnormal cardiovascular reactions. Clinical symptoms and signs of CAN should be assessed as severe diabetic complication and the therapy is difficult in some cases. Taken together, symptoms and signs of CAN carry a poor prognosis in diabetic patients.

Key words Diabetes mellitus • Autonomic neuropathy • Cardiovascular reflex tests • Postural hypotension • Sudden cardiac death

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Introduction

Different physiological functions are affected by autonomic neuropathy in diabetes. Nevertheless, the cardiovascular, especially the cardiac complications of autonomic neuropathy in diabetic patients can be considered important in terms of clinical and prognostic consequences. The clinical importance of cardiovascular autonomic neuropathy (CAN) can also be justified by its high prevalence rate. The prognosis of CAN is serious and the therapy can often be difficult.

Prevalence of cardiovascular autonomic neuropathy

It is obvious that the prevalence of CAN is dependent upon the screening method as well as on the population investigated. The prevalence of autonomic neuropathy in the EURODIAB IDDM Complications Study of 3007 patients was 36% [1]. Significant correlation was observed between the presence of CAN with age, duration of diabetes, HbA_{1C}, presence of retinopathy and microalbuminuria, severe hypoglycaemia and ketoacidosis, cigarette smoking, low serum HDL cholesterol, total cholesterol/HDL cholesterol ratio, diastolic blood pressure and fasting serum triglycerides. It is noteworthy, however, that the number of tests for identifying CAN was limited in this study [1].

A higher prevalence of CAN was documented in hospital-based studies. Most likely this observation is due to two main reasons: on the one hand, the glycaemic control of these patients was poor and, on the other hand, autonomic function in these studies was assessed by the full battery of cardiovascular reflex tests. Alterations of cardiorespiratory reflexes indicating parasympathetic impairment of cardiac innervation can often be found in diabetic patients without clinical signs of autonomic neuropathy. These alterations are

frequently observed in diabetic patients with distal symmetrical neuropathy or in patients with one or more clinical signs of late specific complications [2]. Recently, CAN has also been documented in newly diagnosed diabetic patients [3]. In these cases, the long-lasting unrecognised or untreated metabolic disturbances are the most probable causes of CAN. When two or more pathological abnormalities are documented (i.e. alcoholism, thiamine deficiency, diabetes), the prevalence of CAN is extremely high. In a recent study, the frequency of CAN reached 85.7% in alcoholic diabetic patients [4]. CAN is also documented in patients with gestational diabetes, and data in the paediatric literature indicate that CAN is observed in adolescent diabetic patients [5]. In general, parasympathetic (vagal) impairment precedes sympathetic dysfunction during the natural course of CAN in diabetic patients.

Clinical consequences of CAN in diabetes

Changes in heart rate and blood pressure

Resting tachycardia due to parasympathetic damage may represent one of the earliest signs of CAN. In addition to the stable "fixed" tachycardia, no increase of heart rate occurs in the standing posture or during exercise. Therefore, cardiac output is only increased by increasing stroke volume in these cases. Fortunately, total cardiac denervation occurs rarely.

Abnormal circadian rhythm is characteristic of diabetic patients with CAN. A reduction in circadian heart rate variability was documented in diabetic patients with signs of CAN [4]. This phenomenon has primarily been a consequence of more frequent nocturnal heart rate due to dominant impairment in cardiac parasympathetic innervation. Apart from reduced nocturnal fall of heart rate, higher mean hourly rate and lower heart rate variability were documented in studies with Holter monitoring. The physiological circadian pattern of blood pressure may also be altered in diabetic subjects with CAN. A decrease in the circadian rhythm of blood pressure in association with nocturnal sympathetic predominance may be observed in diabetic patients with CAN. Normally, a decrease from day to night of >10% of daytime blood pressure identifies subjects with physiological blood pressure patterns (dippers), whereas a fall <10% identifies subjects with abnormal circadian patterns (non-dippers). The "non-dipper" phenomenon is registered not only in normotensive but also in hypertensive diabetic patients with asymptomatic autonomic neuropathy [6]. Clinical investigations with diabetic patients documented that non-dippers carry poorer prognosis than dippers in terms of target organ damage. The diminished circadian heart rate variability as well as the blunted or absent day-night blood pressure variation is considered a potential explanation for mechanism leading to acute cardiovascular diseases with specific diurnal pattern in patients with CAN [7].

Postural hypotension is a characteristic, albeit not frequent, clinical feature of CAN in diabetes and generally occurs rather late in the natural course. Dizziness, fainting, blackouts or visual impairment on standing are clinical presentations of postural hypotension. In most serious cases, postural hypotension results in disability. As for the pathogenic mechanism, the impairment of peripheral and, less importantly, splanchnic vasoconstrictor mechanism caused by sympathetic autonomic neuropathy should be considered. Many hormonal (e.g. renin, vasopressin) abnormalities have also been reported but their importance in the pathogenesis remains uncertain. Clinical symptoms may occur when systolic blood pressure falls below 70 mmHg or the fall is >50 mmHg in the upright position. The severity of postural hypotension is characterised by substantial intra-individual variability and symptoms often occur intermittently. The cause of this fluctuation is unknown, nevertheless it is documented that fluid retention from deteriorating renal function may mitigate, while insulin administration due to decrease of systematic blood pressure may aggravate the symptoms of postural hypotension. In addition, postural hypotension can be exacerbated by many drugs, such as antihypertensives, diuretics and different psychotherapeutic agents.

It should be noted that the prevalence of postural hypotension is largely dependent on the diagnostic criteria used. Classically, a 30-mmHg drop in systolic blood pressure after standing was considered diagnostic while other data suggested that the use of 20 mmHg as diagnostic criterion could be more appropriate.

Hypertension (permanent blood pressure elevation) is also associated with CAN, however it is uncertain whether this relationship is causative. Undoubtedly, it is plausible that a relative sympathetic overdrive due to predominant parasympathetic neuropathy may partly be responsible for hypertension in diabetic subjects with CAN. It is noteworthy, however, that alterations in heart rate variability are also documented in essential hypertension.

Silent myocardial infarction and ischaemia

Myocardial infarction (MI) is one of the leading causes of death in diabetic patients, especially those with type 2 diabetes. Nevertheless, MI may be painless or may occur with atypical pain in some cases. Although silent MI or ischaemia is a well-defined clinical condition, the exact pathogenic mechanism for the absence of symptoms is far from clear [8]. Impairment of myocardial parasympathetic and sympathetic fibres was demonstrated more than two decades ago in a post-mortem histological study of diabetic subjects with

painless MI. On the other hand, painless ischaemia in non-diabetic subjects and in diabetic subjects without CAN may also be observed, indicating a possible role of factors other than autonomic neuropathy in the pathogenic mechanism of painless MI/ischaemia. A change in central pain perception may be supposed in such cases.

Asymptomatic ischaemia can be registered on exercise electrocardiography (ECG), 24-h ECG recording or dynamic thallium scintigraphy. Recently, isotope studies (meta-iodo-benzyl-guanidine [MIBG] scintigraphy) suggested that the lack of ischaemic pain can be attributed to the impairment of sympathetic cardiac innervation in diabetic patients [9].

Left ventricular dysfunction

Cardiac dysfunction at rest or during exercise may be associated with CAN even in the absence of ischaemic heart disease. In a cross-sectional study, a correlation between the degree of left ventricular dysfunction and the severity of CAN was demonstrated. In general, impaired diastolic relaxation precedes the development of systolic dysfunction in diabetic patients. All these alterations are easily visualised with echocardiography. Diastolic abnormalities can be assessed by E/A ratio while systolic dysfunction results in a decrease of ejection fraction. An association between sympathetic neuropathy and ventricular dysfunction was also suggested by a MIBG scintigraphy study.

QT-interval lengthening, prolonged ventricular late potentials, cardiac arrhythmia, sudden cardiac death

QT-interval prolongation predisposes subjects to cardiac arrhythmia and even to sudden death. It is important in this context that QT-interval prolongation was found in type 1 and type 2 diabetic patients with CAN. While early cross-sectional studies only suggested that the prolongation of the electrical systole might be a cause of cardiac arrhythmia and death [10], the higher mortality rate of diabetic subjects with both CAN and QT-interval prolongation was documented by subsequent prospective clinical studies. Because the QT-interval is rate-dependent, the data should be corrected for actual heart rate. This correction is usually performed by using Bazett's formula. Generally, QT_c values >440 ms are considered to be prolonged. Nowadays, measurement of QT-dispersion (the difference between the longest and the shortest QT-intervals on the 12-lead electrocardiogram) increasingly replaces determination of the QT-interval. Similarly to QT-interval prolongation, the increased value of QT-dispersion reflects electric instability of the left ventricle [11]. The prolongation of QT-interval (or the increase of QT-dispersion) is characteristic of the presence of CAN. In a recent meta-analysis, the prolongation of QT-interval was considered as a specific but not sufficiently sensitive marker of CAN in diabetes [12]. It should be kept in mind, therefore, that QT-interval can be affected by other factors (such as serum electrolytes and other heart diseases). It is obvious, on the other hand, that CAN should be taken into consideration when the aetiology of a QT-interval prolongation is not clear.

In addition to prolongation of the QT-interval, prolonged ventricular late potentials have also been implicated in the aetiology of cardiac arrhythmia and sudden death in diabetic patients with CAN. Unfortunately, data are insufficient for drawing a final conclusion in this regard.

Although cardiac arrhythmia due to electrical instability of the left ventricle in diabetic subjects with CAN represents an attractive pathogenic mechanism, sudden death of diabetic patients may also be caused by unrecognised hypoglycaemia. The exact cause of "dead in bed syndrome" may remain unexplored due to typically uncharacteristic autopsy findings in some cases [13]. It is noteworthy, however, that hypoglycaemia is occasionally accompanied by an increased QT-dispersion. The possible factors associated with high mortality and sudden death due to CAN in diabetic patients are summarised in Table 1 [4].

Table 1 Factors associated with high mortality and sudden death due to CAN in diabetic patients (From [4], with permission)

Silent myocardial infarction and ischaemia
Cardiorespiratory arrest
Increased perioperative and peri-intubation risk
Obstructive sleep apnea syndrome
Ventricular arrhythmia – prolonged QT-interval
Abnormal diastolic or systolic left ventricular function
Resting tachycardia
Decreased heart rate variability
Reduced baroreflex sensitivity
Alteration of the circadian rhythm of heart rate and blood pressure (non-dipper phenomenon)
Hypertension
Exaggerated blood pressure responses to supine position and exercise
Postural hypotension
Poor exercise tolerance
Reduced heat tolerance
Increased risk of severe hypoglycaemia
Susceptibility to foot ulceration and amputations due to arteriovenous shunting and sudomotor dysfunction

Increased risk of anaesthesia and surgical intervention

Cardiorespiratory arrest during anesthesia and surgical intervention has been described in diabetic subjects with CAN. Therefore, any diabetic patient with CAN is at an increased risk during anaesthesia. The potential pathogenic mechanism includes the increased susceptibility to fatal ventricular arrhythmia and the increased risk for other cardiovascular events.

Diagnosis

Early detection of CAN is of great importance in prevention of the more advanced symptomatic stages. Undoubtedly, simple, noninvasive and reproducible tests can only be considered for testing alterations of cardiovascular innervation. In the past, a number of bedside cardiovascular tests were widely used. The so-called Ewing battery tests (Table 2) were popular due to their simplicity and reliability [14]. There is no doubt that the diagnosis of CAN should be based on the results of a battery of tests rather than on a single test. Yet, rational diagnostic models were developed later in order to reduce the number of tests applied. Despite some criticisms, the Ewing battery tests are still in clinical use.

Recently, measuring heart rate variability became a popular method in characterising autonomic dysfunction. The time domain analysis is based on calculation of different indices of R-R intervals while frequency domain analysis is provided by power spectral analysis [15, 16]. Measuring baroreflex sensitivity is another way to detect autonomic dysregulation. Interestingly, the Ewing battery tests have been used mainly in diabetology while, on the contrary, measuring heart rate variability and assessing baroreflex sensitivity became popular predominantly in cardiology. Age-specific reference values should be applied in both diabetology and cardiology [17].

Isotope mapping (MIBG scintigraphy) of heart muscle innervation has recently been used to characterise cardiac sympathetic innervation in diabetic subjects with CAN. Although the method is attractive, it is used for research purposes only [9].

Therapy

Long-term poor glycaemic control plays a pivotal role in the pathogenic mechanism of diabetic microvascular complications including CAN. Therefore, achieving and maintaining near-normoglycaemia is essential. Interestingly, early intervention studies with intensive conservative insulin treatment, continuous subcutaneous insulin infusion (CSII) or pancreatic transplantation resulted in inconsistent conclusions for clinical improvement of CAN. On the other hand, DCCT and some other smaller prospective studies indicated that long-term near-normoglycaemia may delay or prevent the onset of abnormalities of CAN [18]. It can be assumed, therefore, that the advanced stages of CAN are more resistant to antihyperglycaemic treatment than are the early stages.

A wide range of drugs has been tested but only a few have been extensively investigated in clinical trials for treating CAN in diabetic subjects. Previous clinical studies with aldose reductase inhibitors were negative or controversial. Recently, the use of α-lipoic acid proved to be promising for treating diabetic subjects with CAN [19].

In particular, postural hypotension often needs symptomatic treatment. In clinical practice fludrocortisone proved to be most effective. The utility of other drugs (e.g. pindolol, midodrine, diltiazem, octreoide, indomethacin, erythropoietin) remains questionable. In some cases, non-pharmacological therapy (e.g. elevation of headrest of the bed, use of elastic stockings) and avoiding hypotensive drugs (diuretics, vasodilators, etc.) are useful.

Prognosis

Cardiovascular autonomic integrity is important to control heart rate, blood pressure and myocardial contractility and, consequently, plays a pivotal role in the regulation of the cardiovascular system. It is not surprising that CAN represents a serious complication in diabetes and may carry a poor prognosis. This was first documented by a follow-up

Table 2 The battery of cardiovascular reflex tests. (Adapted from [14])

Method	Parameter	Normal value	Borderline value	Abnormal value
Tests to investigate parasympathetic function				
Deep inspiration and expiration	Beat-to-beat variation	≥15 beats/min	11–14 beats/min	≤10 beats/min
Valsalva manoeuvre	Valsalva ratio	≥1.21	1.11–1.20	≤1.10
Lying-to-standing	30:15 ratio	≥1.04	1.01–1.03	≤1.00
Tests to investigate sympathetic function				
Lying-to-standing	Decrease in systolic pressure	≤10 mmHg	11–29 mmHg	≥30 mmHg
Handgrip test	Increase of diastolic pressure	≥16 mmHg	11–15 mmHg	≤10 mmHg

study in 1980. Although the numerical results of this pioneer work were challenged later, a recent meta-analysis showed that mortality after 5.8 years in diabetic patients with CAN was as high as 29% while it was only 6% in those without CAN [20].

Conclusions

Cardiac innervation is affected by autonomic neuropathy, and a wide range of clinical consequences of CAN are observed in diabetic patients. The symptoms and signs of CAN should be assessed as severe diabetic complication and they carry a poor prognosis. The therapy of diabetic subjects with symptoms of CAN is difficult in some cases. To achieve and maintain long-term near-normoglycaemia is the most effective strategy for preventing CAN in diabetes.

References

1. Kempler P, Tesfaye S, Chaturvedi N, Stevens LK, Webb DJ, Eaton S, Kerenyi Z, Tamas G, Ward JD, Fuller JH, EURODIAB IDDM Complications Study Group (2002) Autonomic neuropathy is associated with increased cardiovascular risk factors: the EURODIAB IDDM Complication Study. Diabet Med 19:900–909
2. Jermendy G, Tóth L, Vörös P, Király M, Perényi J, Kammerer L, Pogátsa G (1990) Impairment of cardiorespiratory reflexes and its association with distal somatic neuropathy in diabetic patients free from clinical symptoms of autonomic neuropathy. Exp Clinic Endocrinol 96:199–206
3. Kempler P, Váradi A, Tamás GY (1993) Autonomic neuropathy in newly diagnosed diabetes mellitus. Diabetes Care 16:848–849
4. Kempler P, Jermendy G (2002) Cardiovascular autonomic neuropathy in diabetes: clinical experiences in Hungary. Diabetol Hung 10:37–43
5. Barkai L, Madácsy L (1995) Cardiovascular autonomic dysfunction in diabetes mellitus. Arch Dis Child 73:515–518
6. Jermendy G, Ferenczi J, Hernandez E, Farkas K, Nádas J (1996) Day-night blood pressure variation in normotensive and hypertensive NIDDM patients with asymptomatic autonomic neuropathy. Diabetes Res Clin Pract 34:107–114
7. Jermendy G (1995) Sympathovagal balance and cardiovascular diseases in diabetic patients with autonomic neuropathy. Diab Nutr Metab 8:123–124
8. Airaksinen KEJ (2001) Silent coronary artery disease in diabetes – a feature of autonomic neuropathy or accelerated atherosclerosis? Diabetologia 44:259–266
9. Muhr-Becker DD, Weiss M, Tatsch K, Wolfram G, Standl E, Schnell O (1999) Scintigraphically assessed cardiac sympathetic dysinnervation in poorly controlled type 1 diabetes mellitus: one-year follow-up with improved metabolic control. Exp Clin Endocrinol Diabetes 107:306–312
10. Jermendy G, Tóth L, Vörös P, Koltai MZ, Pogátsa G (1991) Cardiac autonomic neuropathy and QT interval length - a follow-up study in diabetic patients. Acta Cardiol (Bruxelles) 46:189–200
11. Sawicki PT, Kiwitt S, Bender R, Berger M (1998) The value of QT interval dispersion for identification of total mortality risk in non-insulin-dependent diabetes mellitus. J Intern Med 243:49–56
12. Whitsel EA, Boyko EJ, Siscovick DS (2000) Reassessing the role of QTc in the diagnosis of autonomic failure among patients with diabetes: a meta-analysis. Diabetes Care 23:241–247
13. Weston PJ, Gill GV (1999) Is undetected autonomic dysfunction responsible for sudden death in type 1 diabetes mellitus? The "dead in bed" syndrome revisited. Diabet Med 16:626–631
14. Ewing DJ, Marty CN, Young RJ, Clarke BF (1985) The value of cardiovascular autonomic function tests: 10 years experiences in diabetes. Diabetes Care 8:491–498
15. Bellavere F, Balzani I, De Masi G, Carraro M, Carenza P, Cobelli C, Thomaseth K (1992) Power spectral analysis of heart-rate variations improves assessment of diabetic cardiac autonomic neuropathy. Diabetes 41:633–640
16. Ziegler D, Laux G, Dannehl K, Spüler M, Mühlen H, Mayer P, Gries FA (1992) Assessment of cardiovascular autonomic function: age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses. Diabet Med 9:166–175
17. Gerritsen J, Ten Voorde BJ, Dekker JM, Kingma R, Kostense PJ, Bouter LM, Heethaar RM (2003) Measures of cardiovascular autonomic nervous function: agreement, reproducibility, and reference values in middle age and elderly subjects. Diabetologia 46:330–338
18. The Diabetes Control and Complications Trial Research Group (1998) The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). Diabetologia 41:416–423
19. Ziegler D, Schatz H, Conrad F, Ulrich H, Reichel G, Gries FA (1997) The DEKAN Study Group. Effects of treatment with the antioxidant alpha-lipoic acid on cardiac autonomic neuropathy in NIDDM patients. Diabetes Care 20:369–373
20. Ziegler D (1994) Diabetic cardiovascular autonomic neuropathy: Prognosis, diagnosis and treatment. Diabetes Metab Rev 10:339–383