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Cardiovascular autonomic neuropathy associated with carotid atherosclerosis in Type 2 diabetic patients

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Abstract

Aims To clarify if cardiovascular autonomic neuropathy is associated with carotid artery atherosclerotic plaques in Type 2 diabetic patients.

Methods Cardiovascular autonomic nerve function was related to carotid artery ultrasound in 61 Type 2 diabetic patients 5–6 years after diagnosis of diabetes.

Results Cardiovascular autonomic neuropathy [abnormal age corrected expiration/inspiration (E/I) ratio or acceleration index (AI)] was found in 13/61 (21%) patients. Patients with cardiovascular autonomic neuropathy showed increased degree of stenosis in the common carotid artery (24.6 ± 13.2% vs. 14.7 ± 9.2%; $P = 0.014$) and a tendency towards a higher plaque score (4.0 ± 1.7 vs. 3.2 ± 1.6; $P = 0.064$). Controlled for age, AI correlated inversely with degree of stenosis ($r = -0.39$; $P = 0.005$), plaque score ($r = -0.39$; $P = 0.005$), and mean ($r = -0.33$; $P = 0.018$) and maximum ($r = -0.39$; $P = 0.004$) intima-media thickness in the common carotid artery. In contrast, E/I ratio correlated only slightly with mean intima-media thickness in the common carotid artery ($r = -0.28$; $P = 0.049$).

Conclusions Cardiovascular autonomic neuropathy was associated with carotid atherosclerosis in Type 2 diabetic patients. Abnormal E/I ratios reflect efferent structural damage to parasympathetic nerves whereas abnormal AI reflects afferent autonomic dysfunction possibly due to impaired baroreceptor sensitivity secondary to carotid atherosclerosis.

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Keywords Type 2 diabetes mellitus, carotid atherosclerosis, autonomic neuropathy

Abbreviations AI, acceleration index; E/I ratio, expiration/inspiration ratio; SD, standard deviation

Introduction

Autonomic neuropathy is a serious complication of diabetes [1], implicated in sudden death [2], nephropathy [3–5] and proliferative retinopathy [6,7]. Moreover, cardiac complications such as silent myocardial infarction [8], reduced pain threshold for myocardial ischaemia [9], cardiac hypertrophy [10], impaired cardiac function during exercise [11], and disturbed coronary blood flow [12] have also been associated. We have shown connections between cardiovascular autonomic neuropathy and hyperinsulinaemia [13] and increased plasminogen activator inhibitor 1 activity [14], indicating a link between cardiovascular autonomic neuropathy and the metabolic syndrome. Others [15,16] have recently confirmed these assumptions. Hence, there is evidence that cardiovascular autonomic neuropathy may damage the vasculature in diabetic patients [17].

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Recently, Töyry *et al.* reported an association between stroke and cardiovascular autonomic neuropathy in Type 2 diabetic patients [18]. We therefore evaluated whether carotid artery atherosclerosis was associated with cardiovascular autonomic neuropathy as evaluated by the heart rate reactions to deep breathing [19] and tilting [20], amongst Type 2 diabetic patients in whom we previously found associations between parasympathetic neuropathy and the metabolic syndrome [14]. The aims of this study were to clarify the relationship between atherosclerotic plaques in the carotid artery and cardiovascular autonomic neuropathy.

Patients and methods

Patients

From a population-based study of the diabetes incidence in Malmö between 1990 and 1992 [21], all Type 2 diabetic patients below 60 years of age at diagnosis ($n = 91$) were invited to an assessment of cardiac autonomic nerve function and biochemical risk profile 5 years after diagnosis, and 76 accepted [14]. One year later, 61/76 (80%) patients underwent carotid ultrasound examination for quantification of atherosclerosis. Their age then ranged from 40 to 64 years, median 54. In this report, data from all 61 patients that underwent carotid ultrasound examination are reported.

Informed consent was obtained from all subjects. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the University of Lund.

Methods

Body mass index was measured as weight (kg)/height (m^2). Blood pressure was defined in the supine position with a sphygmomanometer in the right upper arm after 10 min rest.

Autonomic nerve function tests, deep breathing test (R–R interval variation)

Six maximal expirations and inspirations were performed during 1 min in the supine position during the recording of a continuous ECG, and the R–R intervals were recorded. The expiration/inspiration (E/I) ratio, a test of parasympathetic vagal nerve function, was calculated as the mean of the longest R–R interval during expiration (E) divided by the mean of the shortest R–R interval during inspiration (I) [19].

The immediate heart rate reaction to tilt

After 10 min of supine rest, the subject was rapidly tilted (< 2 s) to the upright position (head up 90°) and remained there for 8 min. The initial heart rate reaction to tilt, an immediate acceleration followed by a transient deceleration, was evaluated by continuous ECG recording and determination of the acceleration and brake indices [20]. In the formulae below A indicates mean R–R interval before tilt, B indicates the shortest R–R interval during the immediate acceleration, and C indicates the longest R–R interval during the deceleration. The acceleration index (AI) is $(A - B)/A \times 100$ and the brake index (BI) is $(C - B)/A \times 100$. Although the immediate postural acceleration (AI) in heart rate reflects withdrawal of parasympathetic nerve activity and the later transient deceleration reinstitution of parasympathetic nerve activity, the indices also evaluate sympathetic and not only parasympathetic nerve function [22,23]. The difference between tests (repeatability) of AI is 24% and of BI 29%.

Definitions of abnormalities

The E/I ratio, AI, and BI, were expressed in age corrected values [i.e. z-scores in standard deviations (SD)] [24]. Values < –1.64 SD (95% confidence interval, one-sided test) below the age-related reference values were considered abnormal.

Ultrasound investigation

Ultrasound investigation of the right carotid artery was performed using Acuson 128/XP10 (Acuson, Mountain View, CA, USA) equipped with a linear array 7-MHz transducer with subjects supine and the head turned 45° to the left. The right carotid artery was scanned for the presence of plaques, defined as focal thickenings of the arterial wall. The extent of atherosclerosis was determined on-line according to a semi-quantitative scale as a plaque score ranging from '0' (representing a vessel without plaques or wall thickenings, the latter defined as intima media thickness (≥ 1.25 mm) to '5' (representing a vessel containing two or more plaques ≥ 10 mm^2 or one circumferential plaque or a plaque causing ≥ 50% stenosis). The degree of stenosis was decided based on blood flow velocity at the location of maximum lumen diameter reduction. When no increase in flow velocity (change in Doppler shift) could be detected, the degree of stenosis was subjectively decided from eye-balling the plaque on-line and determining to what extent the plaque protruded into the lumen (maximum 30%, otherwise an increase in flow velocity should be possible to detect). From R-trigging in an ECG-tracing, end-diastolic images were recorded for off-line analysis of intima-media thickness and lumen diameter in the common carotid artery, and intima-media thickness in the bulb of the carotid bifurcation in a computer-assisted analysing system with the identity of the subject coded.

This method has been described previously [25,26]. It has been proven valid in measurements of atherosclerosis [27,28] and the reproducibility is acceptable [29].

Statistical analysis

Differences between groups were evaluated with the Mann–Whitney U-test. Differences in frequency were evaluated with the χ^2 test. Partial correlations were evaluated, controlled for age. Tests were two-tailed and P-values < 0.05 were considered significant. Results are presented as mean ± SD. SPSS, version 10.0 software (Chicago, IL, USA) was used for the statistical calculations.

Results

Patient characteristics are shown in Table 1. Cardiovascular autonomic neuropathy (an abnormal age corrected E/I ratio

Table 1 Patient characteristics 5 years after diagnosis of diabetes and results of carotid ultrasound investigation 1 year later in 61 Type 2 diabetic patients

	Cardiovascular autonomic neuropathy		
	With $n = 13$	Without $n = 48$	P-value
Age (years)	53 ± 6	53 ± 7	0.685
Females [n (%)]	3 (23)	18 (37)	0.320
Body mass index (kg/m^2)	31.9 ± 6.7	28.6 ± 4.8	0.159
Systolic blood pressure (mmHg)	145 ± 16	144 ± 18	0.853
Diastolic blood pressure (mmHg)	89 ± 8	89 ± 10	0.930
Common carotid artery			
Plaque score	4.0 ± 1.7	3.2 ± 1.6	0.064
Degree of stenosis (%)	24.6 ± 13.2	14.7 ± 9.2	**0.014**
Mean intima-media thickness (mm)	0.994 ± 0.288	0.866 ± 0.146	0.267
Maximum intima-media thickness (mm)	1.291 ± 0.382	1.081 ± 0.250	0.120
Mean lumen diameter (mm)	7.200 ± 1.175	6.589 ± 0.980	0.074

Mean standard deviation if not stated otherwise. Significant difference shown in bold.

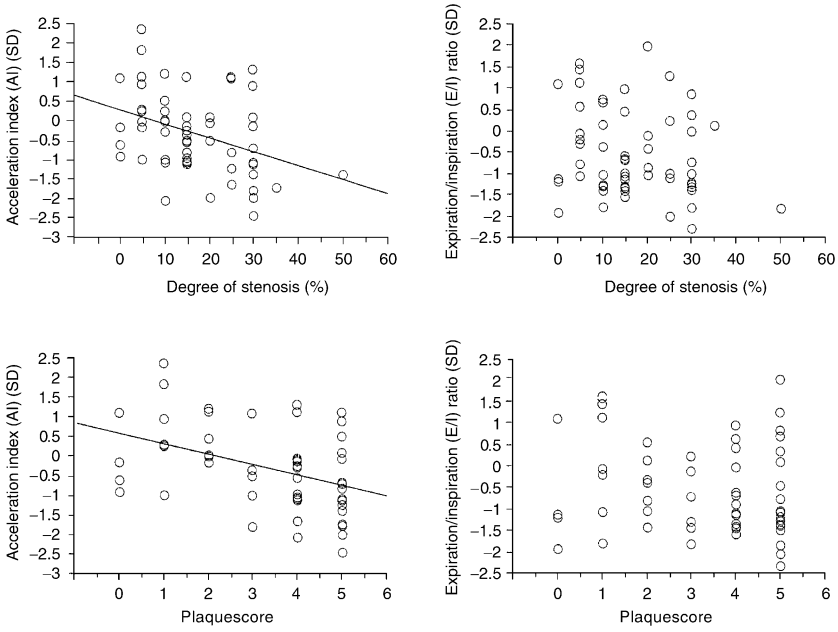

Figure 1 Degree of common carotid artery stenosis and plaque score vs. autonomic nervous function; acceleration index (AI), $[A - B]/A \times 100$, where A indicates mean R–R interval before tilt, B indicates the shortest R–R interval during immediate acceleration [20]) and expiration/inspiration (E/I) ratio [mean of the longest R–R interval during expiration (E) divided by the mean of the shortest R–R interval during inspiration (I)] in 61 Type 2 diabetic patients 5–6 years after diagnosis. AI correlated significantly with the degree of stenosis and plaque score ($r = -0.39$; $P = 0.005$ for both), whereas there were no such correlations for the E/I ratio ($r = -0.20$; $P = 0.14$ and $r = -0.11$; $P = 0.44$, respectively).

or AI) was found in 13/61 (21%). There were no age or sex differences between patients with and without cardiovascular autonomic neuropathy (Table 1). Patients with cardiovascular autonomic neuropathy showed significantly increased degree of stenosis at plaque sites in the common carotid artery (24.6 ± 13.2% vs. 14.7 ± 9.2%; $P = 0.014$, Table 1) and a non-significant tendency towards a higher plaque score (4.0 ± 1.7 vs. 3.2 ± 1.6; $P = 0.064$, Table 1). In age-controlled partial correlation, AI correlated inversely with degree of stenosis ($r = -0.39$; $P = 0.005$), plaque score ($r = -0.39$; $P = 0.005$), and mean ($r = -0.33$; $P = 0.018$) and maximum ($r = -0.39$; $P = 0.004$) intima-media thickness in the common carotid artery. In contrast, E/I ratio correlated only and slightly with mean intima-media thickness in the common carotid artery ($r = -0.28$; $P = 0.049$, Table 2 and Fig. 1).

Table 2 Age-controlled partial correlations between expiration/inspiration (E/I) ratio and acceleration index (AI) 5 years after diagnosis of diabetes vs. carotid ultrasound investigation 1 year later in 61 Type 2 diabetic patients

	E/I ratio	AI
Common carotid artery		
Plaque score	−0.11; 0.44	**−0.39; 0.005**
Degree of stenosis	−0.20; 0.14	**−0.39; 0.005**
Mean intima-media thickness	**−0.28; 0.049**	**−0.33; 0.018**
Maximum intima media thickness	−0.13; 0.35	**−0.39; 0.004**
Lumen diameter	−0.02; 0.87	−0.26; 0.07

R; P-values. Significant correlations shown in bold.

Discussion

We have previously shown in this group of patients with Type 2 diabetes [14] and another [13] that Type 2 diabetic patients with cardiovascular autonomic neuropathy, as defined by an abnormal E/I ratio (i.e. an established sign of parasympathetic neuropathy [22]) display signs of the metabolic syndrome. This suggested that cardiovascular autonomic neuropathy by mechanisms related to the metabolic syndrome may affect the vasculature in Type 2 diabetic patients, and is supported by the current study. Type 2 diabetic patients with cardiovascular autonomic neuropathy had increased degree of stenosis and plaque score in the common carotid artery compared with those without. Most interestingly AI, and not the E/I ratio, was associated with these changes as well as with carotid intima-media thickness. The weak negative relationship between AI and the lumen diameter of the common carotid artery ($r = -0.26$; $P = 0.07$) might seem puzzling at first glance. However, artery diameters increase in the presence of both atherosclerotic risk factors and atherosclerosis [30], presumably as a compensatory regulatory mechanism to preserve luminal area [30,31]. Consequently, our study shows that cardiovascular autonomic neuropathy is associated with atherosclerotic plaques in the carotid artery. However, we cannot draw any conclusions about causality from cross-sectional results in a limited cohort, especially as the time delay of 1 year between the autonomic function tests and the ultrasound examinations in the study might have affected our results.

Carotid artery atherosclerosis and increased intima-media thickness often occur together with atherosclerosis in coronary [32] and peripheral [33,34] arteries, and increased carotid intima-media thickness predicts myocardial infarction and stroke [35]. The present study of relationships between cardiovascular autonomic neuropathy and carotid intima-media thickness was performed 5–6 years after the clinical diagnosis of diabetes, a disease in which macrovascular complications are known to develop steadily over time [36]. Follow-up of this cohort will reveal whether carotid artery plaques associated with cardiovascular autonomic neuropathy and the metabolic syndrome [13–16] indicate increased risk of atherosclerotic events with increasing diabetes duration [18].

The correlation between carotid plaque variables and autonomic dysfunction was mainly confined to AI and not to the E/I ratio. AI reflects a fast inhibition of parasympathetic nerve tone when a subject is tilted [20], whereas a disturbed heart rate reaction during deep breathing, as expressed by an abnormal E/I ratio, is believed to reflect efferent parasympathetic nerve damage [37]. These assumptions are supported by the current study. The association between low AI and carotid plaques is a strong argument that afferent nerve activity secondary to postural changes in baroreceptor activity is the mechanism behind the immediate acceleration after tilt. Our study further supports the idea that the E/I ratio reflects efferent and most likely structural degeneration of the vagal nerve [38]. Previously we suggested that AI also might reflect sympathetic nerve activity [23]. Withdrawal of parasympathetic nerve activity in combination with increased sympathetic nerve activity is probably involved in the postural heart rate reaction. We speculate that parasympathetic neuropathy as manifested by an abnormal E/I ratio through factors related to the metabolic syndrome induces an early atherosclerosis in the carotid artery and, by impairing baroreceptor function, leads to an afferent autonomic dysfunction as demonstrated by a low AI.

In conclusion, cardiovascular autonomic neuropathy in Type 2 diabetic patients was associated with atherosclerosis and narrowing of the carotid artery. This association could be due to factors related to the metabolic syndrome present, a feature of autonomic neuropathy in Type 2 diabetic patients.

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