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Decreased heart rate variability in patients with type 1 diabetes mellitus is related to arterial wall stiffness

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Objective. Low heart rate variability (HRV) is, in several patient groups, related to poor prognosis. The underlying mechanisms are still unclear. The aim was to study if there is a relationship between HRV, which is a measure of baroreceptor function, and atherosclerosis.

Design. The relationship between heart rate variability and carotid arterial wall stiffness was studied in subjects with type 1 diabetes mellitus in which autonomic dysfunction and early atherosclerosis are common. HRV was assessed from power spectral analysis of 24-h Holter recordings and arterial wall stiffness was assessed from an ultrasound study of the right common carotid artery.

Setting. A university hospital.

Subjects. Fifty-nine patients (41 ± 8 years) from the Stockholm Diabetes Intervention Study (SDIS) were investigated. These patients were randomized to intensified conventional treatment or standard treatment approximately 12 years before this study.

Results. Patients with stiffer arteries had lower HRV in all spectral bands ($r = -0.32$ to -0.40, $P = 0.06$–0.001). This relation remained on correcting for age. All spectral parameters of HRV correlated with the mean HbA1c from 10 years of study ($r = -0.37$ to -0.40, $P = 0.004$–0.001).

Conclusions. In patients with type 1 diabetes mellitus, heart rate variability and arterial wall stiffness are related to each other. The results suggests that the autonomic nervous system could be a link between diabetes and vascular disease.

Keywords: arterial baroreceptors, arterial wall stiffness, atherosclerosis, heart rate variability, insulin-dependent diabetes mellitus.

Introduction

In several patient groups, such as post-infarction patients [1,2], other patients with ischaemic heart disease and patients with diabetes mellitus [3], low heart rate variability (HRV) is related to increased mortality. The prognostic value of HRV in post-infarction patients is independent of other measures such as low ejection fraction or frequent ventricular dysrhythmias [1,4]. With autonomic dysfunction follows a poor prognosis both in patients with ischaemic heart disease and in patients with type 1 diabetes mellitus. The relation between low HRV and increased mortality is not clear but there is evidence that reduced parasympathetic activity or attenuated parasympathetic reflexes contribute to electrical instability which could predispose for ventricular dysrhythmias with possible sudden cardiac death [5].

The major cause of death in patients with type 1 diabetes mellitus is coronary heart disease [6], and diabetic patients with autonomic neuropathy have a poorer prognosis than diabetic patients without signs of neuropathy [3].

If there is a causal relationship between HRV and atherosclerosis it has not been studied. In two recent articles it was suggested that power spectral analysis of HRV is a sensitive indicator of baroreflex control, particularly of vagal control [7,8]. If so, a stiff arterial wall could affect baroreceptor function, and consequently HRV. This could be a link between

atherosclerosis and decrease of HRV.

This study investigates the relation between HRV and arterial wall stiffness. We studied subjects with type 1 diabetes mellitus in which autonomic dysfunction and early atherosclerosis are common. Patients from the Stockholm Diabetes Intervention Study (SDIS) [9] were investigated. These patients were randomized to intensified conventional treatment or standard treatment approximately 12 years before this study.

Subjects and methods

Subjects

Fifty-nine patients (41 ± 8 years) from the SDIS had both carotid artery stiffness measures and Holter recordings. Microvascular complications have been described [9,10]. Serious retinopathy was defined as retinopathy requiring photocoagulation, nephropathy was defined as an albumin excretion rate of at least 200 $\mu g\ min^{-1}$. Peripheral neuropathy ($n = 10$) was defined as clinical symptoms from the legs combined with at least one nerve (tibial, peroneal or sural) in the dominant leg with a reduced nerve conduction velocity ($< 41\ m\ s^{-1}$) [9]. All patients with hypertension (blood pressure $> 140/90$) received antihypertensive treatment, primarily with an ACE inhibitor, a loop diuretic and/or a calcium-blocking agent. Fifteen patients used ACE inhibitors.

The experimental protocol was approved by the institutional ethics committee and the patients gave their informed consent before they participated.

Protocol

Arterial wall stiffness was assessed by ultrasound investigation of the patients' right common carotid artery (CCA) and heart rate variability by analysis of 24-h Holter registration. Patients had no change in their normal meal or insulin intake but were asked not to drink coffee or tea for at least 2 h before the ultrasound study.

Heart rate variability

Long-term ECG recording was made using a cassette-based two-channel ECG recorder (Reynolds Sherpa, Reynolds Medical, Hertford, England). Electrode positions similar to V_1 and V_5 were used. All subjects were monitored for 24 h. The ECG signal was digitized and stored using a commercially available PC-based system (Aspect Holter System, Daltek, Borlänge, Sweden). An automatic analysis of dysrhythmias was first made and the QRS complexes classified. The consecutive *R–R* intervals expressed in centiseconds and their corresponding classification code were exported to an ASCII text file.

Five-minute periods of data were analysed with a custom-made software. The time series of *R–R* intervals were resampled at a sampling frequency of two samples per second. Gaps in the time series due to non-normal *R–R* intervals (QRS-labelled by the Aspect System classification as noise or ectopic beats) were filled with values calculated by linear interpolation between the adjacent normal *R–R* intervals. The computer program also automatically checked for misclassified dropped beats deviating more than three standard deviations from the mean normal *R–R* interval of each epoch. Epochs with more than 4% non-normal *R–R* intervals were excluded from further analysis. An autoregressive method was used for analysing the frequency domain of the time series of *R–R* intervals. The power spectrum of the frequency domain was divided into four different frequency bands according to Bigger *et al.* [11]: total power (TP), 0.0033–0.40 Hz (ms^2); very low frequency power (VLF), 0.0033–0.04 Hz (ms^2); low-frequency power (LF), 0.04–0.15 Hz (ms^2); high-frequency power (HF), 0.15–0.40 Hz (ms^2). The different spectral parameters of HRV were analysed for the whole 24-h period.

Day-to-day variablity expressed as the coefficient of variation (CV) for total power was 9–12%, the other HRV variables had similar CV.

Arterial wall stiffness

Ultrasound scans were made using a duplex scanner (Acuson 128XP) with a 7.0 MHz ART linear array transducer in a quiet semi-darkened room with the subject supine after at least 10 min rest.

The subject's head was tilted in order to get the CCA just proximal to the bulb placed horizontally across the screen. The CCA 5–15 mm proximal to the bulb was used for stiffness calculations. The M-mode cursor was placed perpendicularly to the vessel walls guided by B-mode. The intima-media lines of the near and far walls were identified. Vessel diameters were calculated from the leading edge of the echogenic near wall intima-media echo to the leading edge of the far wall during three consecutive

heartbeats [12]. Brachial blood pressure was measured sphygmanometrically immediately before and after the M-mode scan and the mean of the measurements was used. The brachial blood presssure was estimated for the common carotid artery pressure. D is the vessel diameter (maximum and minimum) and ln ($P_{systolic}/P_{diastolic}$) is the natural logarithm for the systole/diastole pressure ratio. Wall stiffness was calculated according to Kawasaki *et al.* [13]:

$$\text{Stiffness} = \ln(P_{systolic}/P_{diastolic})/[(D_{systolic} - D_{diastolic})/D_{diastolic}]$$

The CV for intra- and inter-operator variability of arterial wall stiffness was around 7% [14].

Statistics

Non-normal distributed values (HRV measures) were logarithmically transformed before analysis. Univariate and multiple linear regression analyses were used. Values are means + SD.

Results

Heart rate variability

All patients but one had adequate Holter recordings. Mean heart rate was 81 ± 10 beats min^{-1} over 24 h. TP was 1366 ± 1224 ms^2, VLF was 558 ± 441 ms^2, LF was 498 ± 481 ms^2 and HF was 248 ± 324 ms^2. The ratio between LF and HF was 2.87 ± 1.16. TP, VLF, LF and HF are means from 5-min segments over the entire 24-h ECG recording.

The mean HbA1c from 10 years of study (mean of 29 values during 10 years) correlated with all spectral parameters of HRV ($r = -0.37$ to -0.43, $P = 0.001$–0.004).

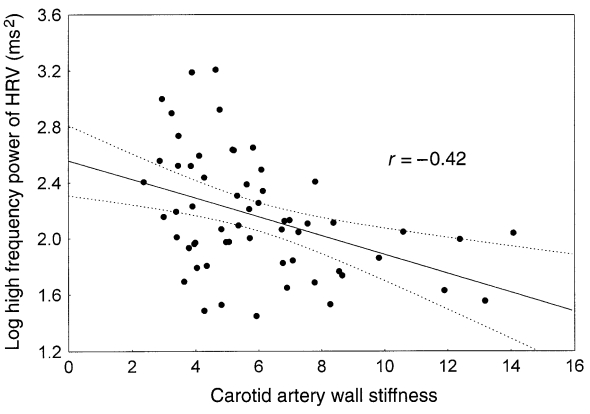

Fig. 1 The correlation between high-frequency power (HF) of heart rate variability (HRV) and arterial wall stiffness index (dimensionless) in 59 patients with type 1 diabetes mellitus.

Arterial wall stiffness

Sixty patients were investigated; one study was excluded due to technical problems. The stiffness index (dimensionless) was 5.8 ± 2.6 (range 2.4–14.1). There was a correlation between arterial wall stiffnes and neuropathy ($r = 0.32$, $P = 0.014$) but not with retinopathy ($P = 0.24$) or albuminuria ($P = 0.95$). Arterial wall stiffness correlated with the mean HbA1c from 10 years of study ($r = 0.34$, $P = 0.009$). These results have been published before [15].

Correlations between heart rate variability and arterial wall stiffness

All spectral parameters of heart rate variability correlated with arterial wall stiffness ($r = -0.37$ to -0.40, $P = 0.004$–0.001). The highest *r*-value was for the correlation to HF (Fig. 1). When the 10 patients with peripheral neuropathy were excluded from the calculations, the relation was unchanged. In a multiple regression analysis with HF power against stiffness and age, stiffness was the only factor with an independent contribution to the prediction of HF power ($P = 0.044$). When TP, VLF and LF were entered in the equation instead of HF, the correlations were similar ($P = 0.022$, 0.027 and 0.023, respectively).

Discussion

The present study shows that heart rate variability and arterial wall stiffness are related to each other. The relationship can be a parallel phenomenon of two variables both related to metabolic control, but heart rate variability and arterial wall stiffness might also have a causal relationship.

The physiological background to the variability in *R–R* interval length is incompletely known. By using power spectral analysis of HRV, the amount of variability in different frequency bands can be assessed. The spectral power obtained at the frequency of the respiration (HF), the sinus dysrhythmia, is thought to be vagally mediated [16–18], whereas the oscillations with around 10 s periodicity (LF) have been associated with baroreflex control of sympathetic activity [17,20]. The ratio of these has been thought

to reflect the balance between sympathetic and vagal tone. However, parasympathetic activity might also influence LF [20] and Kleiger *et al.* [21] showed that in young subjects LF is predominantly affected by parasympathetic tone.

In two recent articles it was discussed whether the low-frequency peak of HRV was generated by the baroreflexes, but with a time delay due to the slower response of the sympathetic nervous system [7,8]. It was suggested that HRV is not a central phenomenon but rather an indicator of baroreflex control, particularly of vagal control. In support of this view Piepoli *et al.* [22] recently reported that respiratory sinus dysrhythmia could be mimicked by stimulation of the baroreceptors at breathing frequency, suggesting an important role of the baroreflexes in generating the sinus dysrhythmia.

If HRV is largely a measure of baroreceptor function then a stiff arterial wall could lead to an attenuated baroreceptor function and thus a decreased HRV. In the present study we found that carotid arterial wall stiffness was correlated to all spectral indices of HRV, both those that are thought to reflect vagal function and those that are thought to reflect sympathetic function. Patients with stiffer arteries had lower HRV.

Arterial wall stiffness increases [13] and heart rate variability declines with age [23], but the relation remained after correcting for age. It is therefore possible that the carotid artery stiffness could be a factor affecting the baroreceptor function. Other factors such as hypertension could have an effect on both heart rate variability and arterial wall stiffness, but it is not possible to tell what would be the cause and the effect in that case. This study shows an association between arterial wall stiffness and HRV where further studies are warranted to prove any causal relationship.

If decreased HRV reflects an attenuated baroreceptor function partly due to stiff arteries, the association between low HRV and increased mortality found in studies of post-infarction patients [1,2] could be due to the fact that the patients with low HRV had a more advanced atherosclerotic disease. HRV could thus partly be a measure of the degree of atherosclerosis *per se*. This hypothesis is supported by the findings of Hayano *et al.* [24] who found that low HRV is associated with the extent or severity of coronary atherosclerosis in patients with coronary heart disease. La Rovere *et al.* [25] found a similar relation between severity of coronary atherosclerosis and decreased baroreceptor function, which is in line with our findings.

Another possibility is that carotid artery stiffness could be closely related to the function of the autonomic nervous system. The autonomic nervous system plays a major role in regulating blood flow and pressure, and consequently a malfunction of this system causes disturbances in regulation of blood flow. As flow, blood pressure and resistance are interrelated, the disturbed arterial blood pressure regulation might cause stretch of the arterial wall, which could, as suggested by Thubrickar *et al.* [26], be a primary factor for the development of atherosclerosis.

In the present study, HRV was related to long-term blood glucose control. The patients with better blood glucose control had better HRV. We have previously shown that good long-term blood glucose control retards development of atherosclerosis [15], indicating a common denominator. Heart rate variability can be influenced by therapies such as beta-blocking agents or physiological variables such as physical training. Whether arterial wall stiffness and heart rate variability could both be altered with some kind of intervention needs further study.

In conclusion we find a correlation between HRV and arterial wall stiffness in patients with type 1 diabetes mellitus, which might be due to a causal relationship in which low HRV could be a sign of a more advanced atherosclerotic disease or due to dysfunction of the autonomic nervous system, which in turn could affect arterial wall stiffness. The function of the autonomic nervous system could be an important link between diabetes and vascular disease.

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