The effects of diabetes, hypertension and their coexistence on cardiovascular autonomic function

Is there a need for the measurement of blood pressure changes in response to sustained handgrip in the assessment of autonomic neuropathy?

PhD Thesis

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1. INTRODUCTION

1.1. Clinical and prognostic significance of cardiovascular autonomic neuropathy

Diabetic neuropathy is of special importance among the microvascular complications of diabetes mellitus: it occurs in about half of our diabetic patients with time and it is the only microvascular complication that may be present at the time or even before diabetes is diagnosed. Damage of autonomic nerve fibres encompassing our whole organism may lead to variable clinical symptoms.

Given its prevalence, diagnostic and prognostic relevance, cardiovascular autonomic neuropathy (CAN) can be considered the leading complication of diabetes mellitus. Cardiovascular autonomic neuropathy belongs to the progressive forms of neuropathy and carries a multiple increase in mortality among diabetic patients. Several factors could contribute to its poor prognosis. Parasympathetic impairment leads to elevated heart rate that is one of the most important risk factors of developing atrial fibrillation and ventricular arrhythmias. Moreover, elevated heart rate was found to be associated with more rapid progression of coronary sclerosis and higher incidence of acute coronary syndrome. Orthostatic hypotension attributed to the sympathetic denervation of peripheral vessels was proven to be the predictor of stroke, myocardial infarction and all-cause mortality in prospective studies.

Silent myocardial ischaemia and infarction play an immense role in the higher mortality of patients with cardiovascular autonomic neuropathy. The repeating episodes of symptomless ischaemia result in myocardial fibrosis presenting clinically as left ventricular dysfunction and malignant ventricular tachyarrhythmia. It has been previously proposed that parallel increase in sympathetic activity and diminishment of parasympathetic tone could be the key alteration preceding the occurrence of non-sustained ventricular tachycardia and sudden cardiac death. Imbalance in the autonomic innervation of the heart causes substantial inhomogenity in depolarization and repolarization. QT-prolongation is considered the cause of ventricular arrhythmias during hypoglycaemic events and enhanced QT-dispersion was found to be independent predictor of sudden cardiac death.

Intra-and perioperative cardiac and respiratory arrest is more common in patients with cardiovascular autonomic neuropathy. In addition, impaired awareness of hypoglycaemia and diminished counterregulatory response to hypoglycaemia also show some associations with the presence of cardiovascular autonomic dysfunction.

1.2. The relationship between autonomic neuropathy and hypertension

Research of the past decades revealed novel findings related to the associations between diabetes, hypertension and cardiovascular autonomic neuropathy. Still, specific nature of the association remained unclear. On the one hand, a body of evidence shows that parasympathetic autonomic neuropathy and relative sympathetic overactivity might play an important role in the development of hypertension, especially, in its early phase. The absence of physiological decrease in heart rate and blood pressure during night-time are attributable to the lack of increased vagal activity and sympathetic shift of the autonomic balance at night as well. The ARIC (Atherosclerosis Risk in Communities) study found decreased heart rate variability (HRV) a reliable predictor of future hypertension. On the other hand, hypertension and higher systolic blood pressure values were proven risk factors of diabetic neuropathy in the EURODIAB IDDM Prospective Study. The increased vascular resistance associated with essential hypertension has been hypothesized the reason why baroreceptor afferentation is decreased in hypertension leading to increased sympathetic activity. In this case, autonomic neuropathy is rather consequence than cause of essential hypertension.

There are many theories on the causal relationship between diabetes, hypertension and autonomic neuropathy. Some authors propose hyperglycaemia or hyperinsulinaemia as the primary alterations; other concepts assume a pre-existent parasympathetic autonomic impairment leading to relative sympathetic overactivity, enhanced anabolism and finally to insulin resistance and hypertension. Causal role of autonomic damage in the development of these disorders has been confirmed by epidemiologic studies.

There is certain controversy in literature data regarding effects of coexistent diabetes and hypertension on cardiovascular autonomic function as well. Légrády et al found cardiovascular autonomic impairment of similar severity in hypertensive patients with and without diabetes. However, in the ARIC Study, reduced heart rate variability was independently associated with diabetes and hypertension with their effects being additive.

1.3. Diagnostic facilities of cardiovascular autonomic neuropathy

Although there are several diagnostic methods for the evaluation of cardiac autonomic function, traditional cardiovascular reflex tests and analysis of heart rate variability are the most widely used in clinical practice.

The cardiovascular reflex tests (CARTs) standardized by Ewing are safe, non-invasive, clinically relevant, reproducible and easy-to-perform procedure. Hence, they are considered gold standard measures of CAN. The San Antonio Consensus conference (1988) advocated that a battery of quantitative tests including both parasympathetic and sympathetic function tests should be performed and more than one of these tests should be abnormal to verify the diagnosis of CAN. The need to use more tests has been confirmed in recent guidelines. However, only four of the five tests are currently suggested being performed - measuring diastolic blood pressure response to sustained handgrip is no longer recommended as an established clinical test in recent guidelines.

According to the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN), the handgrip test has limited sensitivity and specificity in diagnosing CAN. Furthermore, confounding variables influencing the result of handgrip test are not well known and evidence is lacking to judge its clinical usefulness. The confounding factors and associations of sustained handgrip test with the other CARTs have not been studied previously.

Measurement of heart rate variability is a novel, non-invasive and sensitive approach currently available to evaluate CAN in clinical research. Heart rate variability has a strong negative predictive value for cardiovascular morbidity and mortality. Reduced HRV is an early sign of cardiovascular autonomic neuropathy and is considered the appropriate method for the assessment of sympathetic and parasympathetic activity separately.

Reduced heart rate variability was proven to be a predictor of future hypertension as well. The parasympathetic autonomic impairment leads to elevated heart rate before hypertension occurs; diminished heart rate variability has been demonstrated in normotensive patients genetically predisposed to hypertension supporting the role of autonomic impairment in the pathogenesis of hypertension.

2. OBJECTIVES

Based on literature data summarized in the introduction, I have been working to elucidate the answers for the following questions:

1. What kind of effects do diabetes, hypertension and their coexistence exert on measures of heart rate variability and results of the cardiovascular reflex tests?

2. Which of these two conditions, hypertension or diabetes, could play the decisive role in the diminishment of cardiovascular autonomic function?

3. What is the diagnostic performance of measuring diastolic blood pressure response to sustained handgrip exercise (sustained handgrip test)? Is there any relationship between results of the sustained handgrip test and the results of the other cardiovascular reflex tests?

4. What are the confounding factors that may influence handgrip test results in diabetic patients?

5. What kind of association does exist between results of the handgrip test and the presence of hypertension? Is this association independent of antihypertensive medication?

6. Are office systolic blood pressure values of importance when performing handgrip test? Is there any correlation between initial diastolic blood pressure values and diastolic blood pressure increase in response to sustained handgrip? Could adjustment for these initial blood pressure values improve the associations between handgrip test and the other cardiovascular test measures?

3. PATIENTS AND METHODS

3.1. Patient population

The studies were accomplished in patients attending the 1st Department of Medicine, Semmelweis University. In case of diabetic patients, inclusion criteria were the presence of type 1 or type 2 diabetes according to the WHO (1999) criteria. Patients hospitalized for acute intercurrent diseases or for acute metabolic derangements such as diabetic ketoacidosis or hyperglycaemic hyperosmolar state were excluded from our study. Further exclusion criteria included other diseases or conditions that may affect autonomic or sensory function, such as thyroid and liver diseases, chronic kidney failure, autoimmune or haematological disorders, Parkinson’s disease, etc. Subjects with a history of arrhythmia, bundle branch block, heart failure, valvular disease, acute coronary syndrome, ischaemic heart disease or pulmonary disorders (COPD) were also excluded.

Eligible patients were requested to avoid strenuous physical exercise, caffeine beverages, smoking and alcohol in the 12h preceding cardiovascular autonomic testing. The examinations took place in the morning hours; diabetic patients were examined at least one hour after insulin administration and breakfast.

3.1.1. Evaluation of cardiovascular autonomic function in diabetic patients with hypertension and without hypertension and in non-diabetic hypertensive subjects

We have recruited 102 Type 2 diabetic patients, 74 non-diabetic patients with essential hypertension (mean age: 53±12,3 years; median duration of hypertension: 5 years (interquartile range:8)) and 25 healthy control subjects (mean age: 52,2±9,1 years) into the study. Type 2 diabetic patients were divided into two subgroups based on the presence or absence of hypertension. Hypertension was defined as use of antihypertensive medication or blood pressure over 135/85mmHg during ambulatory blood pressure monitoring. Sixty-two patients had coexisting hypertension (mean age: 55,2±6,6 years; median diabetes duration: 3 years (interquartile range:9,6); median duration of hypertension: 7 years (interquartile range: 6)), the remaining 40 patients were assigned to the normotensive diabetic (mean age: 52,8±8,1 years; median diabetes duration: 3 years (interquartile range: 6)) group.

Patients with essential hypertension had normal fasting (≤6mmol/l) and two-hour (<7,8mmol/l) glucose levels on oral glucose tolerance test according to WHO criteria. Patients taking antihypertensive drugs that may influence heart rate variability, such as beta blockers or non-dihydropyridine type calcium channel blockers were excluded from the study. Patients with newly diagnosed hypertension were not receiving any medication at the examination. Diabetic patient groups did not differ regarding HbA1c (8,27±2,3 versus 8,46±2,4,%), and diabetes duration, hypertensive groups regarding duration of hypertension. The four groups were age-matched and they did not differ in respect of total cholesterol. However, they differed in respect of BMI and smoking. Hence, these two parameters were included as covariates in the analyses.

Patients were asked to omit all medications – except for insulin injection- that may influence autonomic function in the 48 hours preceding Cardiotens examination and cardiovascular autonomic neuropathy assessment.

3.1.2. The handgrip test in the assessment of cardiovascular autonomic function

Our study involved 353 patients with diabetes (age: 60,2±7,4 years; female: 57,2%; BMI: 29,3±2,1 kg/m2; diabetes duration: 15,6±9,9 years; HbA1c: 8,2±1,9%; with type 1 diabetes: 18,1%). 225 (63,7%) diabetic patients had coexisting hypertension. Among patients with hypertension, 30 patients had type 1 and 195 patients had type 2 diabetes. Diabetic patients taking antihypertensive medication were defined as hypertensive.

Patients taking antihypertensive agents that might influence the results of the CARTs based on heart rate changes were asked to omit interfering medication, particularly beta-receptor blockers and non-dyhidropyridine-type calcium channel blockers in the 24h interval before CARTs were performed.

Diabetic patients with poor physical status making them unable to perform sustained isometric muscular strain and patients with proliferative retinopathy being at risk of intraocular haemorrhage during Valsalva and handgrip manoeuvre were not included, either.

3.2. Methods

Data on age, glycaemic control (HbA1c), diabetes duration, antidiabetic and antihypertensive medication and insulin treatment were obtained. Weight and height of eligible subjects were measured and body mass index (BMI) calculated (expressed in kg/m2). Measurements of office blood pressure and blood pressure values during the manoeuvres were accomplished by OMRON M2 automatic upper hand-cuff sphygmomanometer. Office blood pressure values were obtained after a minimal period of five minutes of resting state.

3.2.1. Cardiovascular autonomic function assessment

3.2.1.1. Cardiovascular autonomic reflex tests

Traditional cardiovascular autonomic reflex tests are the gold standard in the assessment of cardiovascular autonomic function. CARTs are safe, non-invasive, clinically relevant, reproducible and easy-to-perform. CARTs based on heart rate changes – the deep-breathing test, 30/15 ratio and Valsalva ratio- mainly reflect parasympathetic function while those based on BP response to manoeuvres (orthostatic hypotension test and handgrip test) explore sympathetic function. Confirmed diagnosis of CAN was defined as the presence of ⩾2 abnormal test results as recommended by recent guidelines

To evaluate severity of cardiovascular autonomic dysfunction, an overall autonomic neuropathy score (CAN score) was obtained by scoring the results of the reflex tests: 0, 1 and 2 for normal, borderline and abnormal test result, according to age-related reference values for heart rate based tests. Similarly, a parasympathetic impairment score was derived from the results of the parasympathetic function tests based on heart rate changes.

Cardiovascular autonomic function tests were analysed by the 5 CARTs using Cardiosys 12.1 diagnostic station and Cardiosys-A01 software (MDE Heidelberg GMBH, Heidelberg, Germany).

3.2.1.2. Heart rate variability (HRV) analysis

The 24-hour heart rate variability of diabetic patients with and without hypertension, non-diabetic patients with hypertension and healthy control subjects was assessed by using Meditech Cardiotens 1.34 device and Medibase software.

Heart rate variability of the studied groups was evaluated by frequency domain parameters of HRV and the HRV triangular index (time domain measure of HRV). The frequency domain parameters of HRV are calculated from spectral analysis of NN intervals using fast Fourier transformation. Among spectral parameters, total power (TP:0.01-1.0 Hz) characterize the overall heart rate variability, the low frequency component characterizes the slow-, while the high frequency component characterizes the quick changes of HRV (respiratory component). Fluctuations in the high frequency component (HF: 0.15-0.40Hz) are synchronic to respiration and are attributable to changes in parasympathetic activity. Low-frequency component (LF: 0.04-0.15 Hz) is a result of both sympathetic and parasympathetic tone. Sympathetic function can only be evaluated by the relative proportion of the LF and HF components (that is: LF divided by the sum of LF and HF). HRV triangular index being the most sensitive among time domain parameters derives from the geometric processing of NN intervals and is attributable to total variability.

3.2.2. Sensory function assessment

Sensory nerve function was assessed by measuring current perception thresholds (CPT) on the median and peroneal nerves using the Neurometer device (Neurotron Inc., Baltimore, USA). CPTs measured at high frequency stimulation (200 Hz, 250 Hz) reflect the function of large and small myelinated nerve fibres while CPTs at lower frequency (5 Hz) describe function of small unmyelinated fibres.

Sensory loss was defined as the presence of abnormal CPT values (hypaesthesia or hyperaesthesia) on at least one sensory nerve fibre type of any extremity. The extent of sensory impairment was weighed by calculating sensory scores (one point for abnormal CPT per sensory nerve type, scores ranging from 0 to 12 points).

3.2.3. Statistical analysis

Kolmogorov-Smirnov's test for normality was performed on all variables to guide subsequent analysis. Normally distributed data are expressed as mean±SD while non-normally distributed variables are described as median/geometric mean and interquartile range where appropriate. Categorical variables are reported as n (%). For comparison of categorical variables between two different groups, 2x2 contingency tables and $\chi 2$ test or Fisher's exact test were used. For the between-group comparison of continuous variables, Mann-Whitney U-test or paired t-test for continuous variables were performed as required.

Comparison of spectral parameters of heart rate variability among the four patients groups of diabetic patients with and without hypertension, non-diabetic patients with hypertension and healthy controls was carried out with ANOVA on ranks. As the four groups differed in respect of BMI and smoking, these parameters were included as covariates in the analyses.

Association between the results of the handgrip test and clinical parameters were analysed using Spearman's rank correlation (rho). Kendall monotony coefficient gamma (γ) was used to evaluate the association between abnormality of the handgrip test and abnormality of the other tests.

In order to adjust for the confounding effect of antihypertensive medication on the association between handgrip test results and hypertension, additional multiple logistic regression analysis was performed. Variables associated ($p<0.1$) with abnormal handgrip test result were included in the analysis.

As baseline diastolic blood pressure values showed a significant inverse association with blood pressure response during handgrip test, multiple linear regression was performed with the diastolic blood pressure response to sustained handgrip as depending variable and baseline diastolic blood pressure values and results of each cardiovascular reflex test as predictors.

All analyses were performed using STATISTICA 12.5 software. Statistical significance was defined at a level of $p<0.05$.

4. RESULTS

4.1. Assessment of cardiovascular autonomic function among diabetic patients with and without hypertension and in non-diabetic hypertensive patients

4.1.1. Heart rate variability impairment in diabetic patients with and without hypertension and non-diabetic hypertensive patients

According to the two-way ANOVA on ranks with covariates, diabetes proved to have a significant negative effect on heart rate variability, including HRVti ($p<0,001$), LF ($p<0,0001$), HF ($p<0,001$) and TP ($p<0,0001$), while hypertension was associated only with the low frequency component ($p<0,05$). These results were independent of age, BMI, smoking and serum total cholesterol. LF/HF ratio was influenced neither by diabetes nor by hypertension. The interaction between diabetes and hypertension has not proven to be significant in any of the evaluated HRV parameters, that is, the negative effects of hypertension and diabetes on HRV are additive.

To enhance sensitivity, analyses were performed even on original data (not on ranks), and led to similar results with an additional significant association between hypertension and the total power ($p<0,05$). The normalized unit of LF (LF/LF+HF) was not influenced by either diabetes or hypertension. The lowest values of HRV reflecting the most severely impaired cardiovascular autonomic function were measured in patients with both diabetes and hypertension.

4.1.2. Cardiovascular reflex tests in in diabetic patients with and without hypertension and in non-diabetic hypertensive patients

Among the five standard cardiovascular reflex tests, only the most sensitive test, the deep breathing test was influenced negatively by hypertension ($p<0,05$) and diabetes ($p<0,001$), with their effects being additive (interaction of diabetes and hypertension was not significant: $p=0,357$).

Although there was a trend toward lowest values of Valsalva ratio and 30/15 ratio in the group of diabetic patients with hypertension, the between-group difference was statistically not significant.

4.2. The handgrip test in the assessment of cardiovascular autonomic neuropathy

4.2.1. The diagnostic performance of handgrip test and its associations with the other reflex tests

Diagnosis of CAN was present in 36.8% of the patients. Abnormal results of the deep-breathing test, the Valsalva ratio, 30/15 ratio, handgrip and orthostatic hypotension test were proven in 59.5, 19.5, 4.5, 22 and 32.3%, respectively. Given the small number of patients with abnormal 30/15 ratio, 30/15 ratio was not included in the further statistical analysis.

Compared with the definition of CAN based on the presence of at least 2 abnormal reflex tests, sensitivity of the handgrip test for detecting CAN was 24.6% and specificity was 79.4% ($p = 0.384$), respectively.

Abnormal results of the handgrip test did not show any association with abnormality of the deep-breathing test ($\gamma = 0.004$, $p = 0.563$), Valsalva ratio ($\gamma = -0.058$, $p = 0.436$), 30/15 ratio ($\gamma = 0.282$, $p = 0.357$) and the parasympathetic impairment score ($\gamma = 0.059$, $p = 0.465$), respectively. An association between results (scores) of the handgrip and the OHT failed to be proven ($\gamma = -0.026$, $p = 0.833$).

4.2.2. Influencing factors of handgrip test results

4.2.2.1. Association between handgrip test results and demographic and clinical parameters of the study population

In order to identify factors influencing handgrip test results, patients with and without handgrip test abnormality were compared in terms of demographic and clinical characteristics. Patients with abnormal handgrip test result had significantly higher mean office systolic BP (140 vs 130 mmHg, $p = 0.007$) and higher mean baseline diastolic BP (83 vs 76 mmHg, $p = 0.0004$) than those with normal handgrip test result. In contrast, diagnosis of hypertension was more frequent in patients without handgrip test abnormality [186 (67.7%) vs 39 (50%), $p = 0.0076$]. These associations hint to the fact that higher blood pressure values were not necessarily measured in patients with hypertension which allowed the assessment of the impact of hypertension as comorbidity itself and the effect of casual blood pressure values on handgrip test results separately.

Handgrip test results did not show any association with BMI, glycaemic control, diabetes duration, presence and the extent of sensory loss, insulin treatment and the presence of neuropathic pain. However, use of diuretics and alpha-receptor antagonists was significantly more frequent among patients with normal handgrip test results.

4.2.2.2. Independent association between handgrip test results and the presence of hypertension

Sustained handgrip exercise was rarely accompanied by reduced diastolic blood pressure increase in diabetic patients with hypertension indicating an inverse association between abnormal handgrip test result and the presence of hypertension. As use of some antihypertensive agents showed a significant (diuretics, alpha-receptor antagonists) or nearly significant (ACEis/ARBs) association with handgrip test result, a multivariate analysis was to perform.

In multiple logistic regression analysis, handgrip test abnormality was inversely related to the presence of hypertension (OR: 0.42, 95% CI: 0.23 - 0.78, $p = 0.006$), with these relationships being independent of antihypertensive medication.

4.2.2.3. Impact of office blood pressure and initial blood pressure values on the scale of diastolic blood pressure increase in response to sustained handgrip exercise

Diastolic BP changes during handgrip test correlated negatively to baseline diastolic BP values (rho = - 0.286, $p < 0.01$), while office systolic BP had no effect (rho = - 0.0169, NS) on the scale of BP increase during handgrip test.

Remarkably, adjustment for baseline diastolic blood pressure resulted in no improvement of the statistical association between handgrip test and the other cardiovascular reflex tests.

5. Conclusions

1. Both diabetes and hypertension has a significant negative effect on cardiovascular autonomic function. Among these two factors, the presence of diabetes might play the decisive role.

2. Diabetes and hypertension have additive effects on the deterioration of cardiovascular autonomic function. Most severe impairment of heart rate variability is to be expected in patients with diabetes and hypertension. Hence, early assessment of cardiovascular autonomic function is suggested in diabetic patients with hypertension.

3. The measurement of diastolic blood pressure changes in response to sustained handgrip exercise (handgrip test) has low sensitivity in the detection of cardiovascular autonomic neuropathy and shows no association with the other cardiovascular autonomic reflex tests established for assessing cardiovascular autonomic neuropathy in patients with diabetes.

4. Handgrip test abnormality is inversely related to the presence of hypertension. This inverse relationship is independent of antihypertensive medication.

5. Diastolic blood pressure changes during handgrip test show a significantly negative correlation with baseline diastolic blood pressure values. However, the adjustment for baseline diastolic blood pressure does not improve the association between handgrip and the other reflex tests.

6. According to our data, the presence of the comorbidity hypertension appears to be the major determinant of handgrip test results in diabetic patients. The handgrip test should no longer be suggested for the assessment of the cardiovascular autonomic function in diabetes.

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7. Publications

7.1. Publications directly related to the dissertation

1. Istenes I‡, **Körei AE‡**, Putz Zs, Németh N, Martos T, Keresztes K, Kempler MS, Vági O E, Vargha P, Kempler P. Heart rate variability is severely impaired among type 2 diabetic patients with hypertension Diabetes Metabolism Research and Reviews 2004; 30:(4):305-312.

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7.2. Publications indirectly related to the dissertation

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