Relationship between hypertension, autonomic neuropathy and the cardiovascular reflextests in type 2 diabetes

Doctoral thesis

Semmelweis University

Doctoral School of Basic Medicine

Supervisor: Péter Kempler, M.D., Ph.D., D.Sc.

Official opponents:

Pál Pánczél, M.D., PhD.

Tamás Várkonyi, MD., PhD.

Final exam chair: Rudolf De Chatel, M.D., PhD., D.Sc.

Final exam board members: László Gerő, M.D., Ph.D, D.Sc.

Gábor Pogátsa, M.D., Ph.D., D.Sc.

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INTRODUCTION

Diabetic neuropathy is the only microvascular complication of diabetes that affects the whole body. As a result, neuropathy is an interdisciplinary subject, comprising related fields from neurology and internal medicine in particular, as well as from urology, surgery, paediatrics and rehabilitation. In internal medicine, neuropathy is important for diabetologists, cardiologists, hepato-gastroenterologists and endocrinologists primarily. Thus the diagnosis and treatment of this complication requires a broad, interdisciplinary collaboration. Nowadays, one-third of polyneuropathies is attributed to diabetes altogether, one-third is attributed to chronic alcoholism and the remaining causes of neuropathy consists of several hundreds of diseases.

Both cardiovascular autonomic neuropathy and hypertension are associated with an increased risk of cardiovascular disease and death, but the nature of any relationship between the two is far from clear. This thesis highlights on the possible relationship between hypertension and cardiovascular autonomic neuropathy, since both are associated with an increased risk of cardiovascular disease and death, and the combination of the two further deteriorates the mortality of diabetic patients.

Ewing's standard cardiovascular reflex tests have been used for over 30 years for the assessment of cardiovascular autonomic neuropathy. Although new techniques have become available, the results of these tests still form the core of diagnosis. In order to make a proper estimate of the prevalence of cardiovascular autonomic neuropathy, it is necessary to know those factors that possibly influence the results of these tests. Data in literature are controversial regarding the age specificity of these tests and it has not been studied up to now, whether or not initial blood pressure values have an influence on the results of the blood pressure tests.

Similar to sensory neuropathy, cardiovascular autonomic neuropathy also belongs to the progrediating forms of neuropathy and its clinical and prognostic significance have been revealed over the past 30 years: follow-up studies have justified that the presence of cardiovascular autonomic neuropathy carries at least a five-fold risk of mortality to the patient. Despite the intensive researches of the past years, the precise explanation of this high mortality rate is still not fully elucidated. The increased mortality may be related to resting tachycardia, silent myocardial ischaemia and infarction, sudden cardiorespiratory arrest,

corrected QT interval prolongation, cardiac arrhythmias and cardiac dysfunction at rest or exercise even in the absence of ischaemic heart disease. The sympatho-vagal imbalance leads to the lack of physiological decrease in heart rate and blood pressure during night, which plays an important role in the development of left ventricular hypertrophy and thus increases mortality. Nowadays, attention has been focused on heart rate variability as well, since it has turned out that diminished heart rate variability (a sign of autonomic neuropathy) is considered to have a bad prognostic value. According to recent studies, hypertension also plays an important role in the increased mortality.

Both hypertension and autonomic neuropathy are associated with an increased risk of cardiovascular disease and death. Both are common occurrences in subjects with diabetes, but the nature of any relationship between the two is far from clear. It is well known that relative sympathetic overactivity plays an important role in the development of essential hypertension, especially in the early, hyperkinetic phase. Relative sympathetic overactivity due to early parasympathetic dysfunction may lead to the elevation of heart rate, even before the appearance of hypertension. The role of autonomic impairment in the pathogenesis of hypertension has been justified by using heart rate variability measurement, a more sensitive method, compared to the standard cardiovascular reflex tests. During the 9 year follow-up of the ARIC (Atherosclerosis Risk in Communities) study, diminished heart rate variability has been proved to be a reliable prognostic marker of later hypertension. The role of autonomic impairment in the pathogenesis of hypertension is supported by another study that has shown diminished heart rate variability in normotensive patients genetically predisposed to hypertension. These facts arise the question, whether or not there is a relationship between diminished heart rate variability and hypertension in hypertensive type 2 diabetic patients.

Former studies have shown a definite correlation between autonomic dysfunction and hypertension among diabetic patients, which may be caused by the altered renal haemodynamics and following nephropathy, due to the lack of blood pressure fall during night caused by autonomic dysfunction. This brings forward the question, whether this association can be shown in type 2 diabetic patients with normalbuminuria and no prior history of hypertension.

AIMS

Based on data detailed in the introduction, I have been looking for answers for the following questions:

1. Are the Ewing's standard cardiovascular reflex tests influenced by the subject's age?

2. Do initial systolic blood pressure values influence systolic blood pressure changes after standing up in diabetic patients and healthy controls?

3. Do initial diastolic blood pressure values influence diastolic blood pressure changes during the sustained handgrip test in diabetic patients and healthy controls?

4. Is there a relationship between diminished heart rate variability and hypertension in hypertensive type 2 diabetic patients?

5. Is there a relationship between hypertension and cardiovascular autonomic neuropathy in normotensive, normalbuminuric type 2 diabetic patients?

6. What is the prevalence of unrecognized hypertension in normotensive, normalbuminuric type 2 diabetic patients with or without cardiovascular autonomic neuropathy?

PATIENTS AND METHODS

The records of 125 diabetic patients (58 T1DM, 67 T2DM, mean age: 44,2 ±1,3 years) and 112 healthy control subjects (mean age: 39,4 ±1,2) years were analyzed retrospectively in the study, which aimed at evaluating the possible factors influencing the results of the standard cardiovascular reflex tests. Only those patients were recruited into the study from the several hundreds of patients attending a neuropathy examination between 1999 and 2004 in the Neuropathy Laboratory of the Semmelweis University, I.st Department of Medicine, who had no prior history of hypertension or any other disease that potentially influence autonomic function, who had normalbuminuria and whose laboratory parameters (fasting glucose, serum total cholesterol, serum triglyceride, HbA1c) were available.

Fourty type 2 diabetic patients (mean age: 58,9±8,6 years) were recruited into the study evaluating the correlation between diminished heart rate variability and hypertension. All of the patients suffered from hypertension, based on systolic blood pressure load over 20% measured by 24-hour ambulatory blood pressure monitoring. Since the majority of the antihypertensive agents affect the autonomic function, the measurements were made in an antihypertensive drug-free state.

Seventy patients with Type 2 diabetes and normalbuminuria were examined in the study evaluating the relationship between autonomic neuropathy and hypertension. All subjects had normal office blood pressure and had no prior history of hypertension. The patients were divided into two groups according to the presence of autonomic neuropathy. Thus there were 31 patients (mean age: 51,0±7,5 years) in the group without cardiovascular autonomic neuropathy, while the group with autonomic dysfunction consisted of 39 patients (mean age: 53,5±7,6 years). There were no significant differences regarding the age, the average duration of diabetes and HbA1c between the two groups.

Autonomic status was assessed by the five standard cardiovascular reflex tests using the Ewing protocol: heart rate responses to deep breathing, standing and Valsalva maneouvre assess mainly parasympathetic function, and blood pressure responses to standing and sustained handgrip assess mainly sympathetic function. The severity of autonomic neuropathy was assessed by a composite score with the results of each test scored as 0 (normal), 1 (borderline) or 2 (abnormal). Autonomic neuropathy was defined as the presence of at least one abnormal or two borderline tests. The measurement of heart rate variability and 24-hour

ambulatory blood pressure monitoring was performed using Meditech Cardiotens 01 device with a combined monitoring function (ABPM and ECG). Blood pressure was measured every 20 minutes during daytime and every 30 minutes during nighttime.

Heart rate variability (HRV) was characterized by time- and frequency domain analysis. The time domain parameters are gained by a statistical or geometrical processing of the normal-to-normal intervals (intervals between consecutive QRS complexes originating from the sinus node): The statistical measure consists of the SDNN (estimate of overall HRV), the SDANN (estimate of long term HRV), the SDNNindex (estimate of changes in heart rate due to cycles shorter than 5 minutes), the rMSSD and pNN50 parameters (both estimates of short-term components of HRV). The most important component of the geometric measures is the heart rate variability triangular index (HRVti, estimate of overall HRV). Frequency domain analysis examines the periodic oscillations of the normal-to-normal intervals using Fourier transformation. The total power (TP, estimate of overall HRV) of heart rate variability consists of the high frequency component (HF: 0,15-0,4Hz, estimate of parasympathetic tone) and the low frequency component (LF: 0,04-0,15Hz, influenced by both sympathetic and parasympathetic tone)

All analyses were performed using statistica software. In the study evaluating the possible factors influencing the cardiovascular reflex tests, unpaired t-tests were used to compare the diabetic and control group. The age-dependency of the tests was examined by correlation coefficient calculation. Adjustment to gender, BMI, HbA1c, duration of diabetes and smoking was carried out by multiple regression analysis. Pearson correlation was used to assess the association between initial blood pressure values and blood pressure changes. In order to take “regression to the mean” phenomenon into consideration, the mean of initial and end blood pressure values were correlated with the maximal changes. The correlation between the ABPM and HRV parameters in the hypertensive, type 2 diabetic group was carried out by Spearman correlation calculation. In the study involving normotensive, type 2 diabetic patients with and without autonomic neuropathy, Student’s t-test, analysis of variance (Kruskall Wallis ANOVA) with post hoc Tukey tests and Chi square tests were used to compare groups as appropriate. Evaluation of the relationship between autonomic neuropathy and the ABPM parameters and adjustment for age, gender, BMI HbA1c, duration of diabetes and smoking was carried out by Pearson’s partial correlation calculation. The $p<0,05$ was considered statistically significant.

RESULTS

1. The age-dependency of the cardiovascular reflex tests in type 1 and type 2 diabetic patients and healthy controls.

Age correlated significantly negatively with heart rate changes to deep breathing ($p<0,001$), to the Valsalva maneouvre (Valsalva ratio, $p<0,001$), to standing up (30/15 ratio, $p<0,001$) and diastolic blood pressure changes during sustained handgrip in diabetic patients. However, adjustment for gender, BMI, smoking, and HbA1c abolished correlation of age to the Valsalva ratio and 30/15 ratio. Heart rate changes to deep breathing ($r=-0,387$, $p<0,001$) and standing up ($r=-0,336$, $p<0,001$), and diastolic blood pressure changes during sustained hangrip ($r=-0,23$, $p<0,05$) correlated significantly negatively with age in the control group as well and remained significant after adjustment for the above mentioned parameters. There was no correlation between age and orthostatic hypotension in neither of the two groups

2. Correlation between initial systolic blood pressure values and orthostatic hypotension in diabetic patients and healthy controls.

There was a positive correlation between initial blood pressure values and blood pressure changes after standing up ($r=0,326$, $p<0,001$) in the diabetic group, which means that higher initial values were associated with smaller decrease in systolic blood pressure. This correlation was independent of age, gender, BMI, smoking, HbA1c, serum triglyceride and total cholesterol parameters. In order to avoid the possible influence of sympathetic autonomic neuropathy on the results, the correlation was calculated in patients suffering from exclusively parasympathetic autonomic neuropathy ($n=34$). Thus the correlation was even more convincing ($r=0,6027$, $p<0,0001$), but it disappeared when analyzing patients without autonomic neuropathy ($n=84$, $p=0,244$). There was no correlation in the control group either, since almost every healthy subjects had a blood pressure fall of zero mmHg.

3. Correlation between initial diastolic blood pressure values and diastolic blood pressure changes during sustained handgrip in diabetic patients and healthy controls.

Diastolic blood pressure changes during sustained handgrip did not correlate with initial values in the diabetic group and it remained unaltered when analyzing it among patients with only parasympathetic neuropathy (n=34) or with normal autonomic function (n=84). There was a significant positive correlation between initial diastolic blood pressure and blood pressure changes in the control group (r=0,306, p=0,001), independent of age, gender, BMI and smoking.

4. Correlation between diminished heart rate variability and hypertension in hypertensive, type 2 diabetic patients.

Analyzing the time-domain measures in hypertensive, type 2 diabetic patients, 24-hour mean systolic blood pressure values correlated significantly negatively with the triangular index (r=-0,38, p<0,05) and the SDNN (r=-0,40, p<0,01). The systolic blood pressure load also correlated significantly negatively with the triangular index (r=-0,37, p<0,05) and the SDNN (r=-0,40, p<0,01). There was a significant positive correlation between systolic diurnal indices and the rMSSD (r=0,42, p<0,01), the SDNN index (r=0,45, p<0,01), the triangular index (r=0,35, p<0,05) and the pNN50 (r=0,34, p<0,05). Diastolic diurnal indices correlated significantly positively with the rMSSD (r=0,36, p<0,05), the SDNNindex (r=0,37, p<0,05) and the triangular index (r=0,37, p<0,05).

Analyzing the frequency domain measures of heart rate variability, diminished heart rate variability correlated significantly negatively with 24 hour mean systolic blood pressure (total power: r=-0,35, p<0,05, low frequency component: r=-0,36, p<0,05), just as with systolic blood pressure load (total power: r=-0,35, p<0,05, low frequency component: r=-0,37, p<0,05) and systolic hyperbaric impact values (low frequency component: r=-0,37, p<0,05), while there was a significant positive correlation with the systolic diurnal index (total power: r=0,44, p<0,01, low frequency component: r=0,46, p<0,01, high frequency component: r=0,41, p<0,01) and the diurnal index (total power: r=0,37, p<0,05, low frequency component: r=0,35, p<0,05, high frequency component: r=0,40, p<0,01).

5. **Relationship between autonomic neuropathy and ABPM parameters in normotensive, normalbuminuric type 2 diabetic patients**.

24-hour mean systolic blood pressure (RRS) and systolic blood pressure load (BPLS) showed a significant negative correlation with heart rate responses to deep breathing and the Valsalva maneouvre (Vals), i.e. higher blood pressure values were associated with lower heart rate variability. Correlation between Valsalva ratio and the ABPM parameters were independent of age, gender, BMI, HbA1c, duration of diabtes, and smoking (*Vals. vs. RRS*: r=-0.28, p<0.05, *Vals. vs. BPLS:* r=-0.29, p<0.05), however, correlations between beat-to-beat variation and the ABPM parameters were abolished after adjustment for these parameters. Beat-to-beat variation during deep breathing was associated with systolic diurnal indices, i.e. diminished circadian rhythm of blood pressure was associated with lower heart rate variability. This correlation was independent of age, sex, BMI, HbA1c, duration of diabetes and smoking (r=0.28, p<0.05)

Diastolic blood pressure changes during sustained handgrip (*hand*) and postural systolic blood pressure changes (*orth*) correlated negatively with 24 hour mean systolic blood pressure (*RRS*), systolic and diastolic blood pressure load (*BPLS, BPLD*) and hyperbaric impact values (*HBIS, HBID*), i.e. higher ABPM parameters were associated with smaller blood pressure changes during sustained handgrip and greater blood pressure falls on standing up. These associations remained significant after adjustment for age, sex, BMI, HbA1c, duration of diabetes and smoking. (*hand vs. RRS*: r=-0.32, p<0.05, *hand vs. BPLS:* r=-0.31, p<0.05, *hand vs. BPLD*: r=-0.36, p<0.01, *hand vs. HBIS*: r=-0.35, p<0.01, *hand vs. HBID*: r=-0.37, p<0.01, *orth vs. RRS*: r=-0.51, p<0.001, *orth vs. BPLS:* r=-0.49, p<0.001, *orth vs. BPLD*: r=-0.33, p<0.05, *orth vs. HBIS*: r=-0.53, p<0.001, *orth vs. HBID*: r=-0.32, p<0.05).

The autonomic score showed a positive correlation with 24 hour mean systolic blood pressure (r=0,4203, p<0,001), systolic blood pressure load (r= 0,4361, p<0,001) and systolic hyperbaric impact values (r=0,49, p <0,001), independently of age, sex, BMI, HbA1c, duration of diabetes and smoking.

6. The prevalence of unrecognized hypertension in normotensive, normalbuminuric Type 2 diabetic patients with or without cardiovascular autonomic neuropathy

24-hour mean systolic and diastolic blood pressure values were normal in all subjects without cardiovascular autonomic neuropathy, whereas 7 (18%) subjects with cardiovascular autonomic neuropathy had values exceeding the normal range (24-hour mean systolic BP >135mmHg). In spite of no history of hypertension and normal clinic blood pressure values, hypertension (defined as systolic blood pressure load>20%) was present in 9 (29%) subjects in the diabetes group without cardiovascular autonomic neuropathy and in 21 (54%) subjects in the group with cardiovascular autonomic neuropathy ($p<0.05$). 24-hour mean systolic blood pressure, systolic blood pressure load and hyperbaric impact values were significantly higher in diabetes subjects with cardiovascular autonomic neuropathy compared to control subjects and to diabetes subjects without cardiovascular autonomic neuropathy. These results were independent of age, sex, BMI, HbA1c, duration of diabetes and smoking.

CONCLUSIONS

1. The subject's age should be taken into consideration in the evaluation of heart rate changes to deep breathing and to diastolic blood pressure changes during sustained handgrip. The other three cardiovascular reflex tests do not seem to be influenced by age.

2. Our data suggest that orthostatic hypotension is not independent of the initial systolic blood pressure values. In the presence of a dominantly parasympathetic autonomic neuropathy, higher initial systolic blood pressure values were associated with a smaller decrease in systolic blood pressure after standing up. We suppose that the relative sympathetic overactivity due to dominantly parasympathetic nerve dysfunction may be the reason for this phenomenon. A significant drop in postural systolic blood pressure is one of the core tests used in the diagnosis of cardiovascular autonomic neuropathy. It is the easiest test to perform and therefore frequently used in isolation as a screening tool in clinical practice. Our results suggest this approach is likely to under-estimate the prevalence of early cardiovascular autonomic neuropathy and therefore should not be relied on isolation.

3. Higher initial diastolic blood pressure values were associated with higher blood pressure changes during sustained handgrip in healthy subjects. This reflects the physiological situation. Similar correlation was not found in the diabetic group, which may be due to the underlying autonomic dysfunction itself.

4. There is a significant correlation between diminished heart rate variability and hypertension in type 2 diabetes. Presumably, the relative sympathetic overactivity due to the imbalance of the autonomic regulation may lead to hypertension among these patients.

5. There is a significant correlation between the cardiovascular reflex tests and the elevated ABPM parameters even in normalbuminuric Type 2 diabetic patients who have no history of hypertension and have normal clinic blood pressure values. Our data suggest that

the relative sympathetic overactivity due to the dominantly parasympathetic dysfunction may lead to hypertension in this group as well.

6. In normalbuminuric type 2 diabetic patients with no history of hypertension, the prevalence of unrecognized hypertension diagnosed by 24-hour ambulatory blood pressure monitoring is twice as many in those with autonomic dysfunction compared to those with normal autonomic function. Our data suggest that type 2 diabetic subjects with autonomic neuropathy should be screened for hypertension using 24 hour ambulatory blood pressure monitoring and vice versa, hypertensive, type 2 diabetic patients should be screened for autonomic dysfunction as well.

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