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Postural Blood Pressure Changes and Associated Factors in Long-Term Type 1 Diabetes: Wisconsin Epidemiologic Study of Diabetic Retinopathy

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Abstract

Purpose—To describe the frequency of orthostatic hypotension and hypertension and associations with risk factors in a cohort of persons with long term type 1 diabetes (n=440) participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).

Methods—Evaluations included detailed medical history, electrocardiography (ECG), and laboratory tests. Blood pressure (BP) was measured in supine and standing positions. Standing decrease in systolic (SBP) or diastolic (DBP) BP of at least 20 mmHg or 10 mmHg, respectively, was defined as orthostatic hypotension; increase of SBP from <140 to $\geq$ 140mmHg or DBP from < 90 to $\geq$ 90mmHg was defined as orthostatic hypertension.

Results—Prevalence of orthostatic hypotension and orthostatic hypertension was 16.1% and 15.2%, respectively. Some ECG measurements of cardiac autonomic dysfunction were significantly associated with orthostatic hypotension. Association between SBP and orthostatic hypotension and orthostatic hypertension were significant (Odds Ratio (95% CI), 1.02 (1.01–1.05) and 1.02 (1.01–1.04), respectively) after adjusting for confounders. Interaction between SBP and age was observed. SBP was significantly associated with orthostatic hypotension and orthostatic hypertension in people $\leq$ 40 years old (1.35 (1.02–1.78) and 1.12 (1.05–1.18), respectively).

Conclusions—Results showed that measurements derived from the ECG can help describe an individual at increased risk of having postural BP changes. Moreover, SBP was associated with postural BP changes among individuals who were < 40 years of age with long-term type 1 diabetes.

Keywords

diabetes complications; hypertension; hypotension; prevalence; risk

Control of the arterial blood pressure (BP) variation is important for the maintenance of homeostasis when changing from a supine to standing position. Among the various mechanisms involved in maintaining the BP within normal levels, the autonomic nervous system plays an important role in regulating responses of postural (orthostatic) changes in BP

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(Mukai & Lipsitz, 2002). In assuming a standing position, blood pools in the peripheral venous system causing a decrease in venous return and cardiac output. As a response, the autonomic nervous system triggers a series of events, including increase in heart rate and peripheral vasoconstriction to maintain blood pressure (Nardo, Chambless, Light, Rosamond, Sharrett, Tell, & Heiss, 1999).

In individuals with type 1 diabetes, risk factors for cardiac autonomic neuropathy, a manifestation of the autonomic nervous system impairment, include older age, higher glycosylated hemoglobin and systolic blood pressure (SBP), and the presence of neuropathy and retinopathy (Witte, Tesfaye, Chaturvedi, Eaton, Kempler, & Fuller, 2005). It is believed that the damage caused by chronic hyperglycemia in the neural and vascular systems or by autoimmune mechanisms may be responsible for changes in the sympathetic and parasympathetic pathways resulting in impaired BP response to standing in people with diabetes. If the BP control response fails when an individual assumes a standing position, BP decreases below certain ranges and orthostatic hypotension may occur. On the other hand, response to decreased cardiac output may generate an excessive sympathetic activation leading to a significant increase in BP causing orthostatic hypertension (Fessel & Robertson, 2006).

While a number of studies have shown a higher prevalence of orthostatic hypotension in persons with both type 1 and 2 diabetes, there are fewer studies that have examined the frequency and risk factors for orthostatic hypertension in persons with or without diabetes (Sapru, Sleight, Anand, Sambhi, Lopez, & Chhuttani, 1979; Streeten, Auchincloss, Jr., Anderson, Jr., Richardson, Thomas, & Miller, 1985; Wu, Lu, Yang, & Chang, 1999; Yoshinari, Wakisaka, Nakamura, Yoshioka, Uchizono, & Iwase, 2001). The purpose of this study is to describe the frequency of these complications and their association with risk factors in a cohort of persons with long term type 1 diabetes.

Methods

Study Population

This study is a cross-sectional analysis of the population seen in the last examination (2000–2001) of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). The WESDR is an ongoing prospective population-based cohort study initiated in 1980–1982 of persons with type 1 and 2 diabetes mellitus living in 11 counties of Wisconsin. The analyses in this report are limited to those with type 1 diabetes ($n=996$ at baseline). Participants were examined at baseline and every 4–6 years. In 2000–2001, 652 persons with type 1 diabetes participated; detailed protocols used in this period were published elsewhere (Klein, Klein, McBride, Cruickshanks, Palta, Knudtson, Moss, & Reinke, 2004; Klein, Klein, McBride, Moss, Prineas, & Reinke, 2005). Briefly, evaluations included detailed medical history, history of neuropathy, nephropathy, smoking and alcohol consumption, measurements of blood pressure in supine and standing positions, electrocardiography (ECG), body measurements, and fundus photography for diabetic retinopathy grading. Fasting blood samples were drawn for laboratory tests which included measurements of glycosylated hemoglobin, serum triglycerides, and high serum (HDL) and low (LDL) density lipoprotein cholesterol.

Definitions

Blood pressure was measured using a standard mercury sphygmomanometer using a cuff of appropriate size. First, measurements were taken in supine position and repeated within 3 minutes after participants were asked to stand up. Three different groups were defined according to changes in BP measurements after standing. Participants who had a decrease in systolic BP (SBP) or diastolic BP (DBP) of at least 20 mmHg or 10 mmHg, respectively, were defined as having orthostatic hypotension; participants who had an increase of SBP from <140

to ≥ 140 mmHg or increase of DBP from < 90 to ≥ 90 mmHg were defined as having orthostatic hypertension; those who did not have any of the changes described previously were classified as normotensive after standing.

ECG readings were used to define three measurements of cardiac autonomic neuropathy: QT index (QTI), standard deviation of successive RR intervals, and square root of the mean of squared differences of successive RR intervals (Klein, Klein, McBride, Moss, Prineas, & Reinke, 2005; Rautaharju, Park, Chaitman, Rautaharju, & Zhang, 1998). QT interval is a measurement reflecting ventricular polarization activity and QTI is a QT index adjusted for heart rate. A prolonged QTI may be an indication of cardiac autonomic neuropathy (Oka, Mochio, Sato, Sato, & Katayama, 1996). The standard deviation of successive RR intervals and the square root of the mean of squared differences of successive RR intervals are time domain heart rate variability indices derived from measurements of RR intervals. The standard deviation of successive RR intervals reflects total variability being influenced by both sympathetic and parasympathetic nervous systems. The square root of the mean of squared differences of successive RR intervals reflects high frequency variations in heart rate being more influenced by the parasympathetic nervous system. Both measurements are correlated and lower values mean reduced heart rate variation (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Due to this correlation, the standard deviation of successive RR intervals and the square root of the mean of squared differences of successive RR intervals were not analyzed together in our multivariable models and only results from the standard deviation of successive RR intervals are presented in the current study.

Hypertension was defined as SBP > 140 mmHg and DBP > 90 mmHg or use of any anti-hypertensive medication. Persons were defined as having a positive history of cardiovascular disease if they answered positively for questions regarding myocardial infarction, angina, stroke, coronary bypass surgery, angioplasty, transient ischemic attack, carotid endarterectomy or congestive heart failure. Neuropathy was defined by positive history of tingling or numbness in the hands, loss of tactile sensation, or loss of temperature sensitivity. Nephropathy was diagnosed if the participant had been under renal dialysis, a history of renal transplantation, or gross proteinuria. Diabetic retinopathy was assessed by fundus photographs and classified according to a modified Early Treatment Diabetic Retinopathy Study protocol (Early Treatment Diabetic Retinopathy Study Research Group, 1991). It was categorized into three groups: none to mild non-proliferative, moderate to severe non-proliferative, and proliferative retinopathy.

Data analysis

Statistical analysis consisted of comparisons among three groups using analysis of variance (ANOVA) with Bonferroni's test for multiple comparisons in continuous variables and χ^2 statistic for categorical variables. Multivariate analysis using logistic regression was performed to evaluate the presence of any independent factor related to orthostatic hypotension or orthostatic hypertension, adjusted for several confounders and to test for interactions. For both outcomes, the normotensive after standing group was used as reference. Odds ratios (OR) with 95% confidence intervals (CI) were estimated and p values less than 0.05 were considered significant. Analyses were performed in SAS (SAS Institute, Cary, NC, USA).

The Institutional Review Board approved the study and consent forms were obtained from all participants. This research was conducted in accordance to the principles of the Declaration of Helsinki.

Results

A total of 440 individuals with complete data were included in this study. The mean age ($\pm$ SD) of this population was 45.4 ± 10.0 years, and 48.9% were female. Table 1 shows comparisons of baseline characteristics between the group with complete data included in the current analysis ($n=440$) and those who died since the beginning of the study ($n=273$). Another comparison was done with those who participated in the last examination but were excluded from the current analysis ($n=212$). People who died were older, had longer diabetes duration, higher levels of glycosylated hemoglobin, more likely to be smokers, and had higher prevalence of hypertension, cardiovascular disease, nephropathy, neuropathy, and diabetic retinopathy at baseline than those included in the current analysis. Those who participated in the last follow-up examination but were excluded from this analysis had longer diabetes duration, lower HbA1c levels, serum HDL cholesterol levels, and QT index.

Table 2 shows the demographic characteristics of the population included in the current analyses according to postural BP status. Seventy one (16.1%) persons had orthostatic hypotension and 67 (15.2%) had orthostatic hypertension. Statistically significant differences were found between those with orthostatic hypotension compared to those with orthostatic hypertension and those normotensive after standing.

The orthostatic hypotension group had a significantly higher mean value of QTI when compared to the two other groups and a lower mean value for the square root of the mean of squared differences of successive RR intervals and standard deviation of successive RR intervals when compared to the normotensive after standing group. In the orthostatic hypotension group, the mean values of the square root of the mean of squared differences of successive RR intervals and standard deviation of successive RR intervals were slightly but not significantly lower compared to the normotensive after standing group. The value for QTI was very similar in both groups. The use of antihypertensive medications and diuretics was more common in the orthostatic hypotension group compared to the normotensive after standing group. The proportion of people taking other medications such as beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers was not different among groups. There were no differences in the frequency of hypertension, cardiovascular disease, and long term complications of diabetes (nephropathy, retinopathy, and history of neuropathy).

Using logistic regression analyses adjusting for age, gender, and body mass index (BMI), there were statistically significant associations of all the ECG autonomic measures, SBP and DBP, the presence of proliferative retinopathy, smoking status, and the use of alcohol and diuretics with orthostatic hypotension (Table 3). Systolic blood pressure was the only variable significantly associated with orthostatic hypertension.

In further multivariable analysis (Table 4), after including SBP, QTI, standard deviation of successive RR intervals, alcohol consumption, smoking status, diabetic retinopathy, and use of antihypertensive medication, in addition to age, gender, and BMI in the models, we observed that the association of SBP with orthostatic hypotension and orthostatic hypertension remained significant. Standard deviation of successive RR intervals was associated with reduced odds of having orthostatic hypotension (Odds Ratio (95% CI), 0.95 (0.91–0.99)).

Effect modification was tested and an interaction of age with SBP was significant for both orthostatic hypotension and orthostatic hypertension ($p<0.05$). To further explore this finding, we dichotomized the population by age (≤ 40 and > 40 years). Systolic blood pressure was significantly associated with orthostatic hypotension and orthostatic hypertension in people ≤ 40 years old (1.35 (1.02–1.78) and 1.12 (1.05–1.18), respectively); the relationships were

diminished in those who were older than 40 years of age (1.02 (0.99–1.04) and 1.00 (0.98–1.02), for those with orthostatic hypotension and orthostatic hypertension, respectively).

Conclusions

A prevalence of 16.1% for orthostatic hypotension and 15.2% for orthostatic hypertension was found in persons with long-term type 1 diabetes. This was consistent with the prevalence found in previous studies involving both type 1 and 2 diabetes (Krolewski, Warram, Cupples, Gorman, Szabo, & Christlieb, 1985; Wu, Lu, Yang, & Chang, 1999).

We focused on identifying factors that were associated with postural changes in BP in this cohort. One factor of interest was the potential role of ECG measurements of cardiac autonomic neuropathy. In a previous investigation in this population, Klein et al. (Klein, Klein, McBride, Moss, Prineas, & Reinke, 2005) reported on the associations of QTI, standard deviation of successive RR intervals, and the square root of the mean of squared differences of successive RR intervals (all showing evidences of cardiac autonomic neuropathy) with many of the chronic complications of long-term type 1 diabetes. In the current study, we found that standard deviation of successive RR intervals and the square root of the mean of squared differences of successive RR intervals (data not shown) were associated with orthostatic hypotension but not with orthostatic hypertension after controlling for relevant confounders. Oka et al. (Oka, Mochio, Sato, Sato, & Katayama, 1996) showed a significant relationship between orthostatic hypotension and QT interval prolongation in persons with type 2 diabetes. Although we observed that the QT index was not independently associated with orthostatic hypotension in our study, these findings suggest that individuals with lower heart rate variability, shown by the ECG measurements, possibly had worse autonomic neuropathy and increased chance of developing orthostatic hypotension.

Another relevant finding was that SBP was significantly associated with both orthostatic hypotension and orthostatic hypertension, after adjusting for several confounders with special consideration given to its interaction with age in our study. We found a substantial increase in risk of orthostatic hypotension and orthostatic hypertension after dichotomizing the population into two age groups, particularly in persons less than 40 years of age. This finding was unexpected as older age is one of the main risk factors for postural BP change and therefore, the older group was expected to be more affected (Hajjar, 2005; Heseltine & Bramble, 1988; Kario, Eguchi, Hoshide, Hoshide, Umeda, Mitsuhashi, & Shimada, 2002; Lipsitz, 1989; Luukinen, Koski, Laippala, & Airaksinen, 2004; Luukinen, Koski, Laippala, & Kivela, 1999; Masaki, Schatz, Burchfiel, Sharp, Chiu, Foley, & Curb, 1998; Ooi, Hossain, & Lipsitz, 2000). However, it is believed that high BP influences postural changes in BP as a result of baroreceptor sensitivity and cardiac filling impairment, independent of age (Lakatta, 1987). Harris et al. (Harris, Lipsitz, Kleinman, & Cornoni-Huntley, 1991), using data from the National Health and Nutrition Examination Survey II (NHANES II), showed that the prevalence of postural change in BP was associated with increasing levels of SBP in a representative sample of the general U.S. population. In that study, 10 mmHg increase in SBP was associated with a 1.6 times increased odds of developing postural BP change in non-diabetic individuals not medicated for hypertension, independent of age, sex, and health status. Thus, supine BP measurement, a common non-invasive procedure in regular patient care, might be an important tool to identify people at increased risk of developing either orthostatic hypotension or orthostatic hypertension.

While there are many strengths in the current study, especially its population-based design and use of standardized protocols, there are some limitations. First, this study involves follow-up of a cohort first defined in 1978–79. If postural BP changes were associated with death, it may have led to an underestimation of the frequency of orthostatic hypotension or orthostatic

hypertension and possibly altered risk factor relationships. Second, use of certain types of medications not assessed in our study (e.g., antipsychotic drugs) may have influenced some measurements (e.g., ECG measurement) and, therefore, residual confounding might have been an issue. Third, ECG and BP measurements in supine and standing positions were obtained only in this examination phase (2000–2001), which for a cross-sectional analysis, limited us from determining antecedent-consequent relationships. Finally, BP varies within individuals and we had to rely only on measurements taken during the examination.

In conclusion, the results found in this cohort of type 1 diabetic persons showed that heart rate variability derived from the ECG describes an individual at increased risk of developing postural BP changes. In addition, our study also showed that SBP was associated with postural BP abnormalities among individuals who were less than 40 years of age with long-term type 1 diabetes. If borne out in other studies, further emphasis of tight blood pressure control might be important in preventing these postural changes.

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References

- Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology* 1991;98:786–806. [PubMed: 2062513]
- Fessel J, Robertson D. Orthostatic hypertension: when pressor reflexes overcompensate. *Nat Clin Pract Nephrol* 2006;2:424–431. [PubMed: 16932477]
- Hajjar I. Postural blood pressure changes and orthostatic hypotension in the elderly patient: impact of antihypertensive medications. *Drugs Aging* 2005;22:55–68. [PubMed: 15663349]
- Harris T, Lipsitz LA, Kleinman JC, Cornoni-Huntley J. Postural change in blood pressure associated with age and systolic blood pressure. The National Health and Nutrition Examination Survey II. *J Gerontol* 1991;46:M159–M163. [PubMed: 1890281]
- Heseltine D, Bramble MG. Loop diuretics cause less postural hypotension than thiazide diuretics in the frail elderly. *Curr Med Res Opin* 1988;11:232–235. [PubMed: 3215040]
- Kario K, Eguchi K, Hoshida S, Hoshida Y, Umeda Y, Mitsuhashi T, Shimada K. U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: orthostatic hypertension as a new cardiovascular risk factor. *J Am Coll Cardiol* 2002;40:133–141. [PubMed: 12103267]
- Klein BE, Klein R, McBride PE, Cruickshanks KJ, Palta M, Knudtson MD, Moss SE, Reinke JO. Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. *Arch Intern Med* 2004;164:1917–1924. [PubMed: 15451768]
- Klein BE, Klein R, McBride PE, Moss SE, Prineas RJ, Reinke JO. Electrocardiographic abnormalities in individuals with long-duration type 1 diabetes. *Diabetes Care* 2005;28:145–147. [PubMed: 15616248]
- Krolewski AS, Warram JH, Cupples A, Gorman CK, Szabo AJ, Christlieb AR. Hypertension, orthostatic hypotension and the microvascular complications of diabetes. *J Chronic Dis* 1985;38:319–326. [PubMed: 3998049]
- Lakatta EG. Do hypertension and aging have a similar effect on the myocardium? *Circulation* 1987;75:169–177. [PubMed: 3791621]
- Lipsitz LA. Orthostatic hypotension in the elderly. *N Engl J Med* 1989;321:952–957. [PubMed: 2674714]
- Luukinen H, Koski K, Laippala P, Airaksinen KE. Orthostatic hypotension and the risk of myocardial infarction in the home-dwelling elderly. *J Intern Med* 2004;255:486–493. [PubMed: 15049883]

- Luukinen H, Koski K, Laippala P, Kivela SL. Prognosis of diastolic and systolic orthostatic hypotension in older persons. *Arch Intern Med* 1999;159:273–280. [PubMed: 9989539]
- Masaki KH, Schatz IJ, Burchfiel CM, Sharp DS, Chiu D, Foley D, Curb JD. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. *Circulation* 1998;98:2290–2295. [PubMed: 9826316]
- Mukai S, Lipsitz LA. Orthostatic hypotension. *Clin Geriatr Med* 2002;18:253–268. [PubMed: 12180246]
- Nardo CJ, Chambless LE, Light KC, Rosamond WD, Sharrett AR, Tell GS, Heiss G. Descriptive epidemiology of blood pressure response to change in body position. The ARIC study. *Hypertension* 1999;33:1123–1129. [PubMed: 10334798]
- Oka H, Mochio S, Sato K, Sato H, Katayama K. Prolongation of QTc interval and autonomic nervous dysfunction in diabetic patients. *Diabetes Res Clin Pract* 1996;31:63–70. [PubMed: 8792103]
- Ooi WL, Hossain M, Lipsitz LA. The association between orthostatic hypotension and recurrent falls in nursing home residents. *Am J Med* 2000;108:106–111. [PubMed: 11126303]
- Rautaharju PM, Park LP, Chaitman BR, Rautaharju F, Zhang ZM. The Novacode criteria for classification of ECG abnormalities and their clinically significant progression and regression. *J Electrocardiol* 1998;31:157–187. [PubMed: 9682893]
- Sapru RP, Sleight P, Anand IS, Sambhi MP, Lopez R, Chhuttani PN. Orthostatic hypertension. *Am J Med* 1979;66:177–182. [PubMed: 420246]
- Streeten DH, Auchincloss JH Jr, Anderson GH Jr, Richardson RL, Thomas FD, Miller JW. Orthostatic hypertension. Pathogenetic studies. *Hypertension* 1985;7:196–203. [PubMed: 3980066]
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J* 1996;17:354–381. [PubMed: 8737210]
- Witte DR, Tesfaye S, Chaturvedi N, Eaton SE, Kempler P, Fuller JH. Risk factors for cardiac autonomic neuropathy in type 1 diabetes mellitus. *Diabetologia* 2005;48:164–171. [PubMed: 15619072]
- Wu JS, Lu FH, Yang YC, Chang CJ. Postural hypotension and postural dizziness in patients with non-insulin-dependent diabetes. *Arch Intern Med* 1999;159:1350–1356. [PubMed: 10386511]
- Yoshinari M, Wakisaka M, Nakamura U, Yoshioka M, Uchizono Y, Iwase M. Orthostatic hypertension in patients with type 2 diabetes. *Diabetes Care* 2001;24:1783–1786. [PubMed: 11574442]

Table 1

Baseline Characteristics (1980–82) Between Individuals Included in the Current Study vs. Deceased and Comparison Between Individuals Included vs. Excluded in the Current Study (2000–2001). Data are Mean $\pm$ SD or %.

	Included [*] (n=440)	Deceased [*] (n=273)	Included [†] (n=440)	Excluded [†] (n=212)
Age (years)	25.8 $\pm$ 10.1	38.8 $\pm$ 14.4 [‡]	45.4 $\pm$ 10.0	43.7 $\pm$ 10.3
Gender (female)	49.1	42.5	48.9	50.4
Diabetes duration (years)	11.2 $\pm$ 7.9	22.4 $\pm$ 11.3 [‡]	30.8 $\pm$ 7.8	32.9 $\pm$ 8.6 [‡]
HbA1c (%)	10.6 $\pm$ 2.0	11.2 $\pm$ 2.2 [‡]	7.9 $\pm$ 1.4	7.4 $\pm$ 1.4 [‡]
Pulse rate (/30s)	41.2 $\pm$ 6.3	43.2 $\pm$ 6.9 [‡]	38.8 $\pm$ 5.5	40.5 $\pm$ 6.7
Systolic blood pressure (mmHg)	118.3 $\pm$ 13.2	138.5 $\pm$ 26.5 [‡]	128.1 $\pm$ 17.6	135.3 $\pm$ 21.6
Diastolic blood pressure (mmHg)	76.7 $\pm$ 10.1	82.9 $\pm$ 13.3 [‡]	76.4 $\pm$ 10.4	74.3 $\pm$ 12.9
HDL (mmol/l) [§]	-	-	1.48 $\pm$ 0.42	1.38 $\pm$ 0.38 [§]
QT index (%) [§]	-	-	99.7 $\pm$ 5.3	97.9 $\pm$ 5.8 [‡]
Smoking (packyears)	3.2 $\pm$ 8.9	13.2 $\pm$ 22.6 [‡]	7.6 $\pm$ 20.5	9.2 $\pm$ 17.6
Smoking status (current)	19.0	34.1 [‡]	14.5	14.2
Hypertension (yes)	10.9	44.4 [‡]	53.4	50.9
Cardiovascular disease (yes)	0.9	14.0 [‡]	37.9	46.4
Neuropathy (yes)	16.2	47.5 [‡]	44.4	52.7
Nephropathy (yes)	9.9	43.8 [‡]	25.4	22.8
Retinopathy (yes)	65.3	76.8 [‡]	91.6	100.0

Abbreviations: SD=standard deviation; HbA1c=glycosylated hemoglobin; HDL=high density lipoprotein

^{*} Comparison of characteristics between those included in the current analysis vs. deceased at baseline (1980–82)

[†] Comparison between those included vs. excluded in the last WESDR examination (2000–01)

[‡] p<0.01

[§] Values not available at baseline

Table 2

Demographic Characteristics of the Wisconsin Epidemiologic Study of Diabetic Retinopathy Cohort According to Postural BP Status, 2000–2001. Data are Mean $\pm$ SD or %.

	Normotensive After Standing (n=302)	Orthostatic Hypotensive (n=71)	Orthostatic Hypertensive (n=67)
Gender, female	51.3	46.5	40.3
Age (years)	44.9 $\pm$ 9.7	49.5 $\pm$ 11.1 [*]	43.1 $\pm$ 9.0 [†]
Body mass index (kg/m ²)	27.5 $\pm$ 4.8	27.8 $\pm$ 5.5	28.7 $\pm$ 4.7
Diabetes duration (years)	30.3 $\pm$ 7.5	33.3 $\pm$ 9.6 [*]	30.3 $\pm$ 6.5
HbA1c (%)	7.9 $\pm$ 1.4	8.1 $\pm$ 1.3	7.8 $\pm$ 1.5
Triglycerides (mmol/l)	1.08 $\pm$ 0.76	1.31 $\pm$ 0.89	1.06 $\pm$ 0.74
HDL (mmol/l)	1.47 $\pm$ 0.41	1.46 $\pm$ 0.41	1.52 $\pm$ 0.46
LDL (mmol/l)	2.67 $\pm$ 0.80	2.65 $\pm$ 0.97	2.61 $\pm$ 0.58
Pulse rate (/30s)	38.9 $\pm$ 5.5	38.9 $\pm$ 5.8	38.2 $\pm$ 5.4
QT index (%)	99.3 $\pm$ 5.0	101.6 $\pm$ 5.6 [*]	99.3 $\pm$ 5.9 [†]
RMSSD (ms)	17.6 $\pm$ 22.3	9.5 $\pm$ 8.5 [*]	15.8 $\pm$ 14.7
SDNN (ms)	18.2 $\pm$ 20.2	9.8 $\pm$ 7.8 [*]	15.2 $\pm$ 12.1
Supine systolic blood pressure (mmHg)	125.3 $\pm$ 17.2	137.7 $\pm$ 21.2 [*]	130.3 $\pm$ 10.5 [†]
Standing systolic blood pressure (mmHg)	126.1 $\pm$ 16.7	117.4 $\pm$ 24.5 [*]	140.4 $\pm$ 12.2 [†]
Supine diastolic blood pressure (mmHg)	75.0 $\pm$ 9.8	80.2 $\pm$ 12.7 [*]	78.8 $\pm$ 9.3 [†]
Standing diastolic blood pressure (mmHg)	78.1 $\pm$ 9.2	69.8 $\pm$ 12.8 [*]	87.1 $\pm$ 9.4 [†]
Smoking (pack years)	6.0 $\pm$ 13.3	16.9 $\pm$ 39.5 [*]	5.1 $\pm$ 14.8 [†]
Alcohol consumption (oz/day)	0.13 $\pm$ 0.28	0.23 $\pm$ 0.67	0.20 $\pm$ 0.42
Hypertension (%)	50.4	65.3	59.3
Cardiovascular disease (%)	36.7	49.3	31.3
Neuropathy (%)	41.4	56.3	45.4
Nephropathy (%)	23.5	35.2	23.9
Retinopathy			
None-mild non-proliferative (%)	47.3	32.7	41.9
Moderate-severe non-proliferative (%)	20.1	14.5	19.3
Proliferative (%)	32.6	52.8	38.8
Diuretics use (%)	23.5	39.4 [‡]	29.8

Abbreviations: HbA1c=glycosylated hemoglobin; HDL=high density lipoprotein; LDL=low density lipoprotein; RMSSD=square root of the mean of squared differences of successive RR intervals; SDNN=standard deviation of successive RR intervals

* p<0.05 when comparing orthostatic hypotension to normotensive after standing

[†] p<0.05 when comparing orthostatic hypertensive to orthostatic hypotensive

[‡] p<0.05 for χ^2 statistic comparing all three groups

Table 3

Odds Ratios (OR) and 95% Confidence Intervals (CI) for Different Factors, Adjusted by Age, Gender, and Body Mass Index.

	Orthostatic Hypotensive (n=71) OR (95% CI)	Orthostatic Hypertensive (n=67) OR (95% CI)
HbA1c, 1%	1.07 (0.88–1.31)	0.96 (0.80–1.15)
QT index, 1%	1.06 (1.01–1.11)*	1.03 (0.97–1.08)
RMSSD, 1ms	0.95 (0.92–0.98)*	0.99 (0.97–1.01)
SDNN, 1ms	0.95 (0.92–0.98)*	0.98 (0.96–1.01)
Systolic blood pressure, 1 mmHg	1.04 (1.02–1.06)*	1.02 (1.01–1.04)*
Diastolic blood pressure, 1 mmHg	1.07 (1.04–1.10)*	1.03 (0.99–1.06)
Smoking, 1 packyear	1.02 (1.01–1.03)*	0.99 (0.97–1.02)
Alcohol consumption, 1oz/day	1.95 (1.01–3.82)*	1.65 (0.77–3.50)
Hypertension, present	1.38 (0.68–2.80)	1.20 (0.65–2.22)
Cardiovascular disease, present	1.52 (0.87–2.65)	0.81 (0.45–1.45)
Neuropathy, present	1.63 (0.93–2.83)	1.26 (0.72–2.20)
Nephropathy, present	1.47 (0.81–2.69)	0.98 (0.52–1.85)
NPDR, present		
Moderate-severe NPDR vs. none-mild NPDR	1.13 (0.44–2.91)	0.90 (0.41–1.98)
Proliferative vs. none-mild NPDR	2.21 (1.11–4.41)*	1.21 (0.64–2.30)
Use of antihypertensive medication, current	1.38 (0.76–2.50)	1.40 (0.78–2.53)
Use of diuretics, current	1.84 (1.01–3.38)*	1.41 (0.75–2.65)

Abbreviations: HbA1c=glycosylated hemoglobin; RMSSD=square root of the mean of squared differences of successive RR intervals; SDNN=standard deviation of successive RR intervals; NPDR=nonproliferative diabetic retinopathy

*
p<0.05

Table 4

Odds Ratios (OR) and 95% Confidence Intervals (CI) in Multivariable Analysis.

	Orthostatic Hypotensive (n=71) * OR (95% CI)	Orthostatic Hypertensive (n=67) * OR (95% CI)
Gender, male	0.87 (0.43–1.77)	1.31 (0.69–2.46)
Age, 1 year	1.01 (0.98–1.05)	0.96 (0.92–0.99) *
Systolic blood pressure, 1 mmHg	1.02 (1.01–1.05) *	1.02 (1.01–1.04) *
Body mass index, 1kg/m ²	1.05 (0.98–1.12)	1.07 (1.00–1.14)
SDNN, 1 ms	0.95 (0.91–0.99) *	0.99 (0.97–1.01)
QT index, 1%	1.01 (0.95–1.08)	1.01 (0.94–1.07)
Alcohol consumption, 1oz/day	2.29 (0.98–5.40)	1.68 (0.75–3.78)
Smoking, 1 pack/year	1.02 (0.99–1.05)	1.01 (0.97–1.03)
NPDR, present		
Moderate-severe NPDR vs. none-mild NPDR	0.57 (0.18–1.77)	0.72 (0.31–1.69)
Proliferative vs. none-mild NPDR	1.69 (0.75–3.80)	0.91 (0.44–1.86)
Use of antihypertensive medication, current	0.76 (0.36–1.60)	1.22 (0.62–2.40)

Abbreviations: SDNN=standard deviation of successive RR intervals; NPDR=nonproliferative diabetic retinopathy

*
p<0.05