Pulse Pressure and Diurnal Blood Pressure Variation: Association With Micro- and Macrovascular Complications in Type 2 Diabetes

Søren Tang Knudsen, Per Løgstrup Poulsen, Klavs Würgler Hansen, Eva Ebbehøj, Toke Bek, and Carl Erik Mogensen

Background: In nondiabetic subjects pulse pressure (PP) is an independent predictor of cardiovascular disease and microalbuminuria. Reduced circadian blood pressure (BP) variation is a potential risk factor for the development of diabetic complications. We investigated the association between retinopathy, nephropathy, macrovascular disease, PP, and diurnal BP variation in a group of type 2 diabetic patients.

Methods: In 80 type 2 diabetic patients we performed 24-h ambulatory BP (AMBP) and fundus photographs. Urinary albumin excretion was evaluated by urinary albumin/creatinine ratio. Presence or absence of macrovascular disease was assessed by an independent physician.

Results: Forty-nine patients had no detectable retinal changes (grade 1), 13 had grade 2 retinopathy, and 18 had more advanced retinopathy (grades 3–6). Compared to patients without retinopathy (grade 1), patients with grades 2 and 3–6 had higher PP and blunted diurnal BP variation: night PP 55 ± 10 mm Hg, 64 ± 10 mm Hg, 61 ± 15 mm Hg, P < .05 and systolic night/day ratio 89.3% ± 7%, 94.6% ± 8%, and 92.0% ± 6%, P < .05 (grade 1, 2, and 3–6, respectively). Comparing nephropathy groups (45 normo-, 19 micro-, and 15 macroalbuminuric patients) results were similar: night PP 54 ± 9 mm Hg, 57 ± 10 mm Hg, and 70 ± 15 mm Hg, P < .001 and systolic night/day ratio 88.9% ± 7%, 92.0% ± 7%, and 94.9% ± 7%, P < .02. Likewise, compared to patients without macrovascular disease (n = 55), patients with this complication (n = 25) had higher AMBP values: night PP 57 ± 12 mm Hg v 63 ± 11 mm Hg, P < .05 and systolic night/day ratio 89.2% ± 6% v 94.1% ± 9%, P < .01.


Key Words: Diabetic retinopathy, diabetic nephropathy, macrovascular disease, circadian blood pressure variation, pulse pressure, type 2 diabetes.

Elevated blood pressure (BP) is a key risk factor for the development of diabetic complications. In nondiabetic, hypertensive subjects 24-h ambulatory BP measurement (AMBP) has been shown to be superior to conventional BP measurement in predicting cardiovascular disease and death. Recently, focus has been directed toward pulse pressure (PP) as a predictor of cardiovascular risk in nondiabetic subjects. Moreover, increased PP has recently been associated with microalbuminuria in nondiabetic subjects. At present there are no published studies concerning the role of PP in diabetes and associated complications.

There is an increasing amount of evidence that not only the average level of BP, but particularly an abnormal circadian BP rhythm with a decreased fall in night BP (nondipping), determines the development of diabetic complications. An association between disturbed diurnal BP variation and diabetic complications has been found in both type 1 (retinopathy and nephropathy) and in type 2 diabetes (nephropathy and macrovascular disease). The aim of the present study was to evaluate the association between diabetic micro- and macrovascular complications and PP, as well as circadian BP variation, in patients with type 2 diabetes.
Methods

Patients

Eighty type 2 diabetic patients were identified from our diabetes clinic, according to the following criteria: age at diagnosis >30 years, no need for insulin treatment for at least 1 year after the diagnosis of diabetes, and no history of ketoacidosis. Retinal examination was performed within 1 month from an assessment of 24-h AMBP. Hemoglobin $A_{1c}$ ($HbA_{1c}$) was determined by high-performance liquid chromatography (nondiabetic range 4.4% to 6.4%). The patients were classified as nonsmokers (without daily use of tobacco for the preceding year) or smokers (daily use of tobacco).

Twenty-Four-Hour BP Measurements

The AMBP was measured by an oscillometric technique (Spacelabs 90202 and 90207 [Redmond, Washington], validated by the British Hypertension Society18). Spacelabs 90202 obtained readings every 20 min between 6 AM and 12 PM and once hourly between 12 PM and 6 AM, whereas Spacelabs 90207 measured at 20-min intervals throughout 24 h. Measurements were performed during a day with normal activities at home or at work. Individually reported sleeping times were used in the calculation of day and night BP. If more than 3 h were missing, the patient was excluded (four patients).

Retinopathy Grading

In each eye a standard photograph of 60 degrees was taken. The number of each type of pathologic lesions: hemorrhages or microaneurysms, hard exudates, or cotton wool spots was counted (truncated at 99), and the presence of laser scars or vascular abnormalities such as intraretinal microvascular abnormalities (IRMA vessels), venous beading, or neovascularizations was noted. Each photograph was evaluated independently by two experienced graders. When the two evaluations of a photograph were discrepant it was reassessed by the two graders together. In case there was still discrepancy, the opinion of the most senior grader was used.

On the basis of the grading of all lesions on a photograph each eye was assigned an overall retinopathy grade on a scale from 1 to 6 according to the principles used in the Wisconsin Epidemiologic Study of Diabetic Retinopathy19 with a modification to ensure that lesions implying the same risk of progression to proliferative diabetic retinopathy resulted in the same retinopathy level (ETDRS Report 1220): 1 = no retinopathy; 2a = less than 20 hemorrhages or microaneurysms, or 2b = cotton wool spots alone; 3a = 20 or more hemorrhages or microaneurysms, or 3b = hard exudates combined with any number of hemorrhages or microaneurysms, or 3c = less than 5 cotton wool spots combined with hemorrhages or microaneurysms or hard exudates; 4 = 5 or more cotton wool spots or IRMA vessels combined with hemorrhages or microaneurysms with or without hard exudates; 5 = venous beading combined with hemorrhages or microaneurysms with or without hard exudates. IRMA vessels, or cotton wool spots; 6 = proliferative diabetic retinopathy, or scars of photocoagulation known to have been directed at new vessels.

In each patient the retinopathy grade on the worst eye was used for the analysis. The ophthalmologists had no knowledge of AMBP values.

Nephropathy Classification

The urinary albumin excretion (UAE) was evaluated by albumin/creatinine ratios in three samples of morning urine. Patients were classified as normoalbuminuric, when at least two of three urinary albumin/creatinine ratios were <2.5 mg/mmol (men) and <3.5 mg/mmol (women), microalbuminuric (between 2.5 and 25 mg/mmol (men) and between 3.5 and 35 mg/mmol (women)), or macroalbuminuric (>25 mg/mmol (men) and >35 mg/mmol (women)) or dip stick positive proteinuria in at least two of three samples.21

Macrovascular Disease Classification

A subject was classified as having macrovascular disease if one or more of the following was present: symptoms of angina pectoris, history of myocardial infarction, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, symptoms of or operation for intermittent claudication, amputations, or history of transient ischemic attack or stroke. The physician who performed the classification of macrovascular disease status had no knowledge of AMBP values.

The study was approved by the local ethics committee.

Statistical Analysis

When analysis of variance (ANOVA) indicated significant differences between groups, pairwise comparisons were assessed with significance levels appropriately modified using the method of Dunnett (two-sided). For noncontinuous variables the $\chi^2$ test with Yates’ correction was used. Multiple regression analysis was performed by stepwise linear regression analysis. A two-tailed $P$ value of less than .05 was considered significant. Results are expressed as mean ± SD.

Results

Retinopathy

Forty-nine patients had no detectable retinal changes (grade 1), 13 had grade 2 retinopathy, and 18 had more advanced retinopathy (grades 3–6). The latter were grouped together due to the small numbers in each group. The AMBP values and clinical characteristics of the patients when grouped according to severity of complications are given in Table 1. The AMBP was consistently higher in patients with retinopathy (grades 2 and 3–6)
Table 1. Clinical characteristics and ambulatory blood pressure of patients grouped according to severity of complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>n (♂/♀)</th>
<th>Age (y)</th>
<th>Duration (y)</th>
<th>AHT (%)</th>
<th>HbA1c (%)</th>
<th>Systolic AMBP (mm Hg)</th>
<th>Diastolic AMBP (mm Hg)</th>
<th>Pulse Pressure (mm Hg)</th>
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<tr>
<td></td>
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<td>Day Night N/D ratio (%)</td>
<td>Day Night N/D ratio (%)</td>
<td>Day Night N/D ratio (%)</td>
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<tr>
<td>Retinopathy grade</td>
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<tr>
<td>1</td>
<td>49 (25/24)</td>
<td>55 ± 11</td>
<td>3.4 ± 4.4</td>
<td>55</td>
<td>8.8 ± 1.8</td>
<td>144 ± 14 128 ± 14</td>
<td>89.3 ± 7 86 ± 9 73 ± 8</td>
<td>85.1 ± 9 57 ± 11 55 ± 10</td>
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<tr>
<td>2</td>
<td>13 (10/3)</td>
<td>59 ± 10</td>
<td>2.4 ± 3.0</td>
<td>54</td>
<td>8.3 ± 2.2</td>
<td>154 ± 19 145 ± 16</td>
<td>94.6 ± 8 90 ± 15 81 ± 14</td>
<td>90.8 ± 10 64 ± 11 64 ± 10</td>
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<td>3-6</td>
<td>18 (14/4)</td>
<td>58 ± 9</td>
<td>8.8 ± 7.5</td>
<td>78</td>
<td>8.3 ± 2.0</td>
<td>154 ± 21 142 ± 23</td>
<td>92.0 ± 6 91 ± 9 82 ± 11</td>
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<td><em>P</em></td>
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<tr>
<td>Normo</td>
<td>45 (23/22)</td>
<td>55 ± 9</td>
<td>3.5 ± 4.1</td>
<td>53</td>
<td>8.9 ± 2.1</td>
<td>143 ± 13 127 ± 13</td>
<td>88.9 ± 7 86 ± 9 73 ± 8</td>
<td>84.8 ± 9 57 ± 9 54 ± 9</td>
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<tr>
<td>Micro</td>
<td>19 (13/6)</td>
<td>53 ± 11</td>
<td>3.9 ± 5.5</td>
<td>68</td>
<td>8.5 ± 1.7</td>
<td>147 ± 15 136 ± 16</td>
<td>92.0 ± 7 89 ± 10 79 ± 11</td>
<td>88.9 ± 7 59 ± 11 57 ± 10</td>
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<tr>
<td>Macro</td>
<td>15 (12/3)</td>
<td>62 ± 10</td>
<td>8.2 ± 8.0</td>
<td>73</td>
<td>8.1 ± 1.5</td>
<td>162 ± 22 153 ± 20</td>
<td>94.9 ± 7 93 ± 12 84 ± 12</td>
<td>91.0 ± 10 70 ± 16 70 ± 15</td>
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<tr>
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<tr>
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<td>55 (30/25)</td>
<td>54 ± 9</td>
<td>3.8 ± 5.4</td>
<td>53</td>
<td>8.8 ± 2.1</td>
<td>147 ± 17 131 ± 19</td>
<td>89.2 ± 6 89 ± 10 76 ± 11</td>
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<tr>
<td>Yes</td>
<td>25 (19/6)</td>
<td>60 ± 11</td>
<td>5.8 ± 5.9</td>
<td>76</td>
<td>8.3 ± 1.5</td>
<td>149 ± 17 140 ± 16</td>
<td>94.1 ± 9 86 ± 11 78 ± 11</td>
<td>91.0 ± 11 63 ± 12 63 ± 11</td>
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<tr>
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<td>NS</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
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</table>

AMBP = ambulatory blood pressure; AHT = receiving antihypertensive treatment; HbA1c = hemoglobin A1c; N/D = night/day; NS = not significant; Normo = normoalbuminuria; Micro = microalbuminuria; Macro = macroalbuminuria.

Data are mean ± SD.
compared to the group with no detectable retinal changes (grade 1), whereas AMBP values in patients with retinopathy grades 2 and 3–6 were similar. Diurnal BP variation was blunted in the patients with retinopathy as indicated by higher night/day ratios of systolic ($P < .05$) as well as diastolic BP ($P = .07$).

Mean values of systolic and diastolic night BP and night PP for the three groups are depicted in Fig. 1. As apparent from the figure particularly systolic ($P < .01$ for grades 2 and 3–6 vs grade 1) but also diastolic night BP ($P < .05$ for grades 2 and 3–6 vs grade 1) were higher in patients with retinopathy compared to patients without retinopathy, whereas there was no difference between grades 2 and 3–6. As the increase in BP with increasing severity of retinopathy was more pronounced in systolic than in diastolic night BP, night PP was higher in the groups with retinopathy compared to the group without retinopathy (grade 2 vs grade 1, $P < .05$, grade 3–6 vs grade 1, $P =$ not significant).

Most patients with no retinopathy (grade 1) had normal UAE (19% were micro- and 11% macroalbuminuric), whereas this was not the case in patients with grade 2 (50% micro- and 25% macroalbuminuric) and 3–6 retinopathy (22% micro- and 39% macroalbuminuric), $P < .05$ for grades 2 and 3–6 vs grade 1. Duration of diabetes was significantly longer in patients with grade 3–6 compared to patients in the other two groups. There were no significant differences regarding age, sex, tobacco consumption, antihypertensive or antidiabetic treatment, body mass index (BMI), HbA1c, or lipids between the groups (data not shown).

There was a weak, nonsignificant association between duration of diabetes and AMBP parameters, age correlated significantly with some AMBP parameters (night/day ratios, systolic night BP and night PP), whereas albuminuria status correlated strongly with almost all AMBP parameters (as described in detail in the next paragraph). When albuminuria status, age, and duration were entered as covariates in the ANOVA, there was still a significant effect of retinal grade on diastolic night BP ($P = .03$), whereas the effect of retinopathy grade on the rest of the AMBP parameters barely reached statistical significance (eg, $P = .06$ for systolic night BP).

**Nephropathy**

Forty-five patients were normoalbuminuric (median urinary albumin/creatinine ratio 1.5 mg/mmol, mean plasma ([p]-creatinine) 77 µmol/L), 19 patients were microalbuminuric (median albumin/creatinine ratio 7.1 mg/mmol, mean p-creatinine 75 µmol/L), and 15 patients were macroalbuminuric (median albumin/creatinine ratio 124.2 mg/mmol, mean p-creatinine 95 µmol/L); in 1 patient it was not possible to obtain information on UAE. The AMBP values were consistently lowest in the group with normal UAE, somewhat higher in the microalbuminuric group, and highest in the group with macroalbuminuria (Table 1). This stepwise increment in BP with increasing degree of albuminuria was statistically significant for all AMBP parameters, except for diastolic day BP, as well as for all PP. Diurnal BP variation was increasingly blunted, with stepwise augmentation in night/day ratios of systolic ($P < .02$) and diastolic BP ($P < .05$), in the normo-, micro-, and macroalbuminuric groups.

Mean values of systolic and diastolic night BP and night PP for the patients divided according to albuminuria status are depicted in Fig. 1. As apparent from the figure particularly systolic ($P < .01$ for grades 2 and 3–6 vs grade 1) but also diastolic night BP ($P < .05$ for grades 2 and 3–6 vs grade 1) were higher in patients with retinopathy compared to patients without retinopathy, whereas there was no difference between grades 2 and 3–6. As the increase in BP with increasing severity of retinopathy was more pronounced in systolic than in diastolic night BP, night PP was higher in the groups with retinopathy compared to the group without retinopathy (grade 2 vs grade 1, $P < .05$, grade 3–6 vs grade 1, $P =$ not significant).

Most patients with no retinopathy (grade 1) had normal UAE (19% were micro- and 11% macroalbuminuric), whereas this was not the case in patients with grade 2 (50% micro- and 25% macroalbuminuric) and 3–6 retinopathy (22% micro- and 39% macroalbuminuric), $P < .05$ for grades 2 and 3–6 vs grade 1. Duration of diabetes was significantly longer in patients with grade 3–6 compared to patients in the other two groups. There were no significant differences regarding age, sex, tobacco consumption, antihypertensive or antidiabetic treatment, body mass index (BMI), HbA1c, or lipids between the groups (data not shown).

There was a weak, nonsignificant association between duration of diabetes and AMBP parameters, age correlated significantly with some AMBP parameters (night/day ratios, systolic night BP and night PP), whereas albuminuria status correlated strongly with almost all AMBP parameters (as described in detail in the next paragraph). When albuminuria status, age, and duration were entered as covariates in the ANOVA, there was still a significant effect of retinal grade on diastolic night BP ($P = .03$), whereas the effect of retinopathy grade on the rest of the AMBP parameters barely reached statistical significance (eg, $P = .06$ for systolic night BP).
are depicted in Fig. 1. Systolic and diastolic night BP tended to be higher in the micro- than in the normoalbuminuric group \( (P = .08 \text{ for both}) \) and was highest in the macroalbuminuric group \( (P < .001 \text{ for both}) \). Night PP was highest in the macroalbuminuric group \( (P < .001 \text{ for normoalbuminuric group}) \), whereas the difference between the micro- and normoalbuminuric groups was not statistically significant.

Patients with macroalbuminuria were older and had longer duration of diabetes than patients in the normo- and microalbuminuric groups. There were no significant differences regarding sex, tobacco consumption, antihypertensive or antidiabetic treatment, BMI, HbA1c, or lipids between the groups (data not shown). When age and duration were included as covariates in a multivariate analysis, the effect of albuminuria status on systolic day \( (P < .01) \) and night \( (P < .001) \), diastolic night BP \( (P < .01) \), systolic and diastolic night/day ratio \( (P < .05 \text{ for both}) \), and day and night PP \( (P < .05 \text{ and } P < .001, \text{ respectively}) \) was still statistically significant.

### Macrovascular Disease

Fifty-five patients had no history or symptoms of macrovascular disease, whereas the remaining 25 patients fulfilled at least one of the above-mentioned criteria for this condition (10 patients had symptoms of angina pectoris, 3 had previous myocardial infarction, 1 coronary artery bypass grafting, 5 intermittent claudication, 1 amputation, 1 transient ischemic attack, and 7 patients stroke). Systolic AMBP values were consistently higher in the group with macrovascular disease, reaching statistical significance for systolic night BP (Table 1). Conversely, diastolic day BP tended to be a little lower in the group with macrovascular disease, whereas diastolic night BP tended to be a little higher. Consequently, PP and night/day ratios were significantly higher in this group, compared to the group without macrovascular disease.

Mean values of systolic and diastolic night BP and night PP for the two groups are depicted in Fig. 1. It is apparent from the figure that systolic night BP and night PP \( (P < .05 \text{ for both}) \) were higher in the group with macrovascular disease than in the group without macrovascular disease, whereas there was no significant difference in diastolic night BP between the groups.

Patients with macrovascular disease were older and tended to have longer duration of diabetes than patients without this complication. Albuminuria tended to be higher in patients with macrovascular disease (24% were micro- and 28% macroalbuminuric) than in patients without macrovascular disease (23% micro- and 15% macroalbuminuric), but this difference was not statistically significant. There were no differences regarding sex, tobacco consumption, antihypertensive or antidiabetic treatment, BMI, HbA1c, or lipids between the groups (data not shown). When age or duration were introduced as covariates in the analysis, the effect of macrovascular disease group was still significant for systolic and diastolic night/day ratios \( (P < .05 \text{ for both}) \), but not for the rest of the AMBP parameters.

When entering retinopathy, albuminuria, and macrovascular disease groups together with age, sex, duration, antihypertensive treatment, BMI, and HbA1c into a multivariate analysis, predictors of systolic night BP were albuminuria \( (P < .001) \) and age \( (P < .01) \), whereas the effect of retinopathy grade was borderline significant \( (P = .06, \text{ for the total multivariate analysis: } r^2 = 0.33, P < .001) \). Predictors of systolic night/day ratio were age, albuminuria, and macrovascular disease group \( (P < .05 \text{ for all, total analysis } r^2 = 0.25, P < .001) \), and predictors of night PP were albuminuria group \( (P < .001) \) and age \( (P < .05, \text{ total analysis } r^2 = 0.28, P < .001) \). All other factors mentioned had no significant predictive value for these BP parameters.

### Discussion

We present data on the association between AMBP and three complications of type 2 diabetes: retinopathy, nephropathy, and macrovascular disease. The AMBP values correlated consistently with the severity of complications. Night BP were increased to a higher extent than day BP in patients with complications compared to patients without complications, reflecting a disturbed circadian BP variation in these patients. Likewise, increments in systolic were larger than in diastolic BP, resulting in higher PP in groups with compared to groups without complications.

We also found a strong association between the presence of retinopathy and nephropathy, whereas the association between these two microvascular complications and the presence of macrovascular disease was not statistically significant. However, as no invasive tests for macrovascular disease were performed, precision may be limited in the classification of individuals according to this complication, thus possibly introducing dilution bias, favoring the null hypothesis. Despite this potential lack of power we were able to demonstrate significant differences in AMBP values between subjects with and without clinically evident macrovascular disease.

The association between elevation in BP and diabetic complications is well known.\(^{22}\) A possible reason for the association between hypertension and retinopathy is proposed by Kohner and Patel.\(^{23,24}\) Blood pressure elevation leads to increased perfusion pressure, which causes hyperperfusion, especially in the presence of hyperglycemia, as this condition impairs autoregulation. The resulting increase in capillary shear stress leads to damage and closure of these small vessels with subsequent additional hyperperfusion, thus establishing a true circulus vitiosus. In the kidney these hemodynamic changes might result in glomerular hypertension and subsequent glomerular leakage of plasma proteins, forming the basis for the increase in albuminuria.\(^{25}\) In larger arteries increased shear stress might facilitate atherosclerosis and endothelial dysfunc-
tion, two pathophysiologic mechanisms in the development of macrovascular disease.

In accordance with this hypothesis our patients with complications had higher values of AMBP, than did those without complications. Furthermore, BP dropped significantly less during the nighttime in patients with complications. This association between disturbed diurnal BP variation (nondipping) and diabetic complications is in line with previous studies in both type 1 and type 2 diabetic patients. A blunted diurnal BP variation could be an indicator of autonomic dysfunction, a condition that has been related to the other diabetic complications. Dysfunction of autonomic nerves to resistance vessels might adversely affect their ability to prevent the propagation of an elevated systemic BP to the microcirculation, thus putting further strain on the autoregulation of capillary perfusion and aggravating the capillary hypertension and hyperperfusion, as mentioned previously. However, as we have no data on autonomic nervous function in these patients, this association remains speculative.

Until recently focus has been directed toward increments in diastolic rather than systolic BP. Systolic BP often increases with age, whereas diastolic BP remains unchanged or declines, causing a widening of the PP. These changes, thought to be due to the development of arteriosclerosis-induced stiffness of the arteries were, until recently thought to be physiologic and benign in nature. However, recent randomized trials have shown substantial benefits of treating isolated systolic hypertension in elderly patients, and lately several studies have shown PP to be a major, independent predictor of cardiovascular events in nondiabetic subjects. Moreover, in middle-aged, nondiabetic subjects PP and isolated systolic hypertension has recently been shown to be associated with microalbuminuria.

Our study is the first to report an association between increments in PP and diabetic complications. If an augmented PP to some extent is an epiphennomenon, reflecting a decreased elasticity of large- and middle-sized arteries, one might imagine that the capability of these vessels to absorb changes in BP is decreased, and consequently, these vessels would be more likely to allow the propagation of an increased BP to the microcirculation. The resulting increased BP amplitude imposes a steep increase in shear stress on the microvasculature, especially if resistance vessel innervation and autoregulation is impaired as described above, resulting in capillary/glomerular hypertension and development of micro- and macrovascular complications.

In conclusion, our data show that in type 2 diabetic patients the presence of retinopathy, nephropathy, and macrovascular disease is consistently associated with increased PP and decreased fall in night BP. These hemodynamic abnormalities might be a result of or a contributor to the development of diabetic complications. Prospective studies are needed to further evaluate these associations and to establish the putative feasibility of initiating antihypertensive therapy on the basis of abnormalities in PP or diurnal BP variation.

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References


