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High Pulse Pressure Associated With Cardiovascular Events in Patients With Type 2 Diabetes Undergoing Hemodialysis

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Background: The aims of this study were to examine systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and pulse pressure (PP) in patients with type 2 diabetes undergoing hemodialysis (HD), and to assess the relationships between these parameters and cardiovascular (CV) events such as coronary heart disease and congestive cardiac failure.

Methods: A total of 80 Afro-Caribbean type 2 diabetic patients undergoing hemodialysis in three centers in Guadeloupe, French West Indies, were included in this cross-sectional study. Pre- and postdialysis BP were recorded. Logistic regression methods and areas under the receiver operating characteristic curves were used.

Results: The mean age (± standard deviation) was 62.2 years (±10.2 years). A total of 24 subjects (30%) had one or more CV events. Sixteen (20%) had coronary disease, 15 (18.8%) cardiac failure, and seven (8.8%) had both. The medians [interquartile ranges] for predialysis PP was higher in patients with CV comorbidity than in patients without a history of CV at 84.5 mm Hg [74.5 to 92.3]*v* 69.5 mm Hg [61.0 to 79.5], $P = .003$. Areas under the ROC curves (95% confidence intervals) predialysis were significant only for SBP and PP at 0.70 (0.58 to 0.82) *v* 0.71 (0.59 to 0.83) without statistical differences. After adjustment for gender, age, body mass index, antihypertensive use, time on hemodialysis (≥2 years), and hemoglobin rate, the odds ratio was significant only predialysis, and a higher odds ratio was found for PP at 2.25 (1.22 to 4.18), $P = .01$, than for SBP 1.97 (1.12 to 3.49), $P = .02$.

Conclusions: Our results suggest that the strongest association of PP with CV morbidities should be considered in therapeutic strategies. These results show the necessity of targeting antihypertensive treatment to patients' predialysis blood pressure values. Am J Hypertens 2005; 18:1457–1462 © 2005 American Journal of Hypertension, Ltd.

Key Words: Pulse pressure, cardiovascular events, type 2 diabetes, hemodialysis.

Diabetes mellitus and end-stage renal disease are associated with increased cardiovascular (CV) risk. In Guadeloupe, a French West Indies island of 443,000 inhabitants, the reported prevalence of diabetes is 5.8%.[1] reached that observed in Afro-American population. Among patients starting hemodialysis (HD) between 1978 and 1997, 22% were diabetic.[2] In a survey conducted in 1995 in French overseas territories, the respective prevalence and incidence of diabetes in renal replacement therapy were respectively 25.7% and 35.6%, and reached the US levels during the same period.[3] Cardiovascular diseases as coronary disease, cardiac failure and hypertension are highly prevalent in patients with chronic kidney disease[4] and are associated with high mortality rates.[5]

Pulse pressure (PP) is an indicator of arterial stiffness. Recently prospective data suggested that PP, which appears to be a more sensitive measure of risk than other indexes of blood pressure (BP), may improve the Framingham risk prediction among individuals of middle age and older.[6] Pulse pressure was also demonstrated to increase CV risk in diabetic and HD patients.[7] This BP component was found to be a better predictive parameter of mortality than systolic BP (SBP) and diastolic BP (DBP).[8]

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The aims of the present study were to assess the prevalence of CV comorbidities such as coronary heart disease and congestive cardiac failure in Afro-Caribbean individuals with type 2 diabetes who were undergoing HD, and to determine more precisely the association among the four BP components: SBP, DBP, PP, and mean arterial pressure (MAP), and CV comorbidity in this population.

Methods

A cross-sectional study was conducted in patients with type 2 diabetes who were undergoing HD in three dialysis centers of Guadeloupe. We collected data of 80 patients who had initiated HD >1 month before. This sample represented 85% of the patients with type 2 diabetes who were undergoing HD in Guadeloupe. The remaining 15% underwent dialysis at home or in secondary facilitating centers. Patient age ranged from 33 to 80 years, and diabetic status was either a comorbid condition or the etiology of chronic kidney disease.

Data Collection

Demographic, clinical, and laboratory data were collected for all HD patients between December 2003 and March 2004. Age, sex, height, weight, time on HD before December 2003, history of a CV event, and current therapy for diabetes and hypertension were recorded. Body mass index (BMI) was calculated as weight/height^2(in kg/m^2).

Measurement of BP

Both SBP and DBP were recorded by trained professionals with automated monitors 5 min before and 15 min after HD for every dialysis session during the study. Average SBP and DBP over a 1-month period were calculated.

Laboratory Data

A single measurement of the hemoglobin rate (in g/dL) was performed for the purpose of this study.

Clinical Factors

Pulse pressure was calculated as SBP − DBP (in mm Hg) and mean arterial pressure (MAP) as (SBP + 2 DBP)/3 (in mm Hg).

Hypertension was defined on the basis of SBP ≥140, or a DBP ≥90 mm Hg, or a history of hypertension, and current use of antihypertensive medication.

Obesity was defined as BMI ≥30 kg /m^2.

Cardiovascular comorbidity included cardiac events occurring before December 2003. These included coronary artery disease (defined on the basis of a history of angina pectoris, acute myocardial infarction, coronary bypass surgery, or coronary angioplasty) and congestive cardiac failure.

Statistical Analysis

Data were expressed as medians [interquartile ranges, IQR] for the continuous variables and by numbers (percentages) for the categorical variables. For comparisons, patients were categorized into two groups, according to the presence of one or more CV comorbidities (group 1) or the absence of a history of cardiovascular events (group 2). The χ^2 test and Mann-Whitney nonparametric test were used to compare ratios and values between patients groups. We used the receiver operating characteristic (ROC) curves to study the value of the four BP components in discriminating patients with and without CV history. By varying the cut points of SBP, DBP, MAP, and PP, we used sensitivity and specificity of different cut points in determining the presence or absence of CV comorbidity. Sensitivity, or true-positive rate, was plotted against 1-specificity or false-positive rate for each cut point to constitute the ROC curves. The areas under ROC curves and their 95% confidence intervals (CI) were computed and compared. We used logistic regression analysis to study the association of BP components (10 mm Hg–increase in SBP, DBP, MAP, or PP) and other covariates with CV events. Odds ratios and 95% CI) were calculated. The variables studied included age (10-year increase), gender, BMI, antihypertensive drug use, time on dialysis (≥2 years or <2 years), and hemoglobin rate. Adjustment was performed for each BP component with all significant covariates at the level of $P \leq .2$ in the univariate analysis. The SPSS version 12.0 statistical software package (SPSS Inc., Chicago, IL) and Stata 7.0 (Stata Corp., College Station, TX) were used for data analysis. All P values were two-sided and were considered to be significant at a level of $P < .05$.

Results

Demographic and Clinical Characteristics

A total of 80 individuals with type 2 diabetes who were undergoing HD were enrolled in the study. The sample comprised 33 (41.3%) men. Demographic and clinical characteristics of the population under study are shown in Table 1. Of the subjects, 73 (91.3%) had hypertension, and among them 62 (84.9%) received antihypertensive treatment. There was no significant difference in mean PP between patients who were untreated and those who were not treated with antihypertensive therapy.

In 24 patients (30%), one or more CV events were recorded (group 1). Among them, 13 (54.2%) had occurred before the onset of HD and 11 (44.8%) later. In 16 (20%) of the subjects with type 2 diabetes who were on HD, coronary artery disease was recorded; in 15 (18.8%), congestive heart failure; and in seven (8.8%), both of these conditions. Among those patients with coronary heart disease we noted 11 (68.7%) with angina (two had undergone coronary angioplasty) and five (31.3%) with acute myocardial infarction.

Table 1. Characteristics of patients with type 2 diabetes undergoing hemodialysis, Guadeloupe, 2003

Characteristic	Overall diabetic subjects (*N* = 80)	One or more cardiovascular comorbidities: Yes : group 1 (*N* = 24)	One or more cardiovascular comorbidities: No : group 2 (*N* = 56)	*P* value
Age (ys)	62.0 [55.0–70.0]	63.5 [56.2–71.5]	62.0 [54.2–69.0]	.36
Body mass index (kg/m^2)	26.2 [23.4–29.8]	25.7 [21.5–28.9]	25.7 [21.5–28.9]	.07
Hemoglobin rate (g/dL)	11.8 [10.4–12.8]	11.9 [10.7–12.6]	11.8 [10.0–12.8]	.75
Time on hemodialysis (ys)	2 [1–4]	3 [1–4.7]	2 [1–4]	.36
Male sex (%)	33 (41.3)	13 (54.2)	20 (37.5)	.10
Hypertension (%)	73 (91.3)	24 (100)	49 (87.5)	.09
Coronary heart disease (%)	16 (20.0)	16 (67)	—	
Cardiac insufficiency (%)	15 (18.8)	15 (66.6)	—	
Antihypertensive drugs (%)	64 (80.0)	23 (95.8)	41 (73.2)	.02
Antihyperlipemic drugs (%)	9 (11.3)	3 (12.5)	6 (10.7)	
Antidiabetic drugs (%)	60 (75)	18 (75)	42 (75)	
Antiplatelet drugs (%)	52 (65)	21 (87.5)	31 (55.3)	

Data are expressed as, medians [interquartile ranges] or as numbers (%).

Mean predialysis PP in the whole population was 74.7 mm Hg (standard deviation, 15.2 mm Hg). The prevalence of hypertension was similar between both groups, at 100% in group 1 and 87.5% in group 2 without CV comorbidity ($P = .09$). Median [IQR] predialysis PP was higher in group 1 than in group 2 (84.5 mm Hg [74.5 to 92.2] *v* 69.5 mm Hg [61.0 to 79.5], $P = .003$).

As shown in Table 2, in the whole population, all BP components were found lower after dialysis compared with predialysis values. Significant differences were found between both groups for median SBP and median PP, both predialysis ($P = .004$ and $P = .003$, respectively) and postdialysis ($P = .009$ and $P = .02$, respectively). No significant differences were found for DBP and MAP.

Areas Under the ROC Curves

Table 3 shows the area under the ROC curve for pre- and postdialysis BP components in identifying subjects with type 2 diabetes who were undergoing HD and had CV comorbidity. For DBP and MAP, the 95% CI of the areas included 0.5 and these areas were not significant, whereas they were both significantly greater than 0.5 pre- and postdialysis for SBP. These areas (95% CI) were as follows: for SBP 0.70 (0.58 to 0.82); 0.68 (0.54 to 0.82) and for PP (0.71 (0.59 to 0.83)); 0.66 (0.51 to 0.80). No significant differences were found between the areas under the curves for SBP and PP pre- and postdialysis. Figure 1 shows the ROC curves for predialysis SBP and PP.

Regression Analysis of History of CV Comorbidity

Table 4 shows the unadjusted odds ratios (OR) for experiencing a CV event in the presence of each 10–mm Hg increment in SBP, DBP, MAP, PP, and other variables.

In the univariate analysis of CV comorbidity, for every 10–mm Hg increment in SBP, the OR (95% CI) were

Table 2. Median values of blood pressure (BP) components in predialysis and postdialysis for type 2 diabetic patients

BP component	Overall diabetic subjects (*N* = 80)	One or more cardiovascular comorbidities: Yes : group 1 (*n* = 24)	One or more cardiovascular comorbidities: No : group 2 (*n* = 56)	*P* value
Predialysis				
SBP	151.5 [141.2–166.5]	162.0 [151.7–170.5]	147.0 [138.0–160.7]	.004
DBP	78.0 [70.0–85.7]	79.0 [70.0–83.7]	77.5 [70.2–88.7]	.97
PP	73.5 [62.0–86.7]	84.5 [74.5–92.2]	69.5 [61.0–79.5]	.003
MAP	102.3 [96.7–109.0]	105.2 [98.7–112.7]	101.2 [96.0–107.7]	.09
Postdialysis				
SBP	137.0 [124.2–150.7]	149.0 [128.7–158.7]	133.5 [123.2–143.0]	.009
DBP	73.0 [67.0–81.0]	75.0 [67.0–83.5]	73.0 [67.0–80.0]	.51
PP	62.0 [51.0–73.7]	70.5 [55.2–80.5]	58.0 [51.0–68.7]	.02
MAP	94.3 [88.3–102.9]	99.5 [89.8–108.5]	93.7 [86.5–99.7]	.08

DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; SBP = systolic blood pressure.
Data are expressed as medians [interquartile ratios].

Table 3. Areas under the receiver operating characteristic (ROC) curves of blood pressure (BP) components, pre- and postdialysis, in identifying patients with type 2 diabetes undergoing hemodialysis with one or more cardiovacular comorbidities

BP component	Areas (95% CI) under the curves		*P* value (difference between curves)*
	Predialysis	Postdialysis	
SBP	0.70 (0.58–0.82)	0.68 (0.54–0.82)	.75
DBP	0.50 (0.36–0.65)†	0.55 (0.40–0.69)*	.54
MAP	0.62 (0.48–0.75)†	0.62 (0.48–077)*	.95
PP	0.71 (0.59–0.83)	0.66 (0.51–0.80)	.44

CI = confidence interval; other abbreviations as in Table 2.

* *P* values of differences between areas of ROC curve for predialysis and postdialysis blood pressure. Confidence intervals that excluded 0.5 were considered to indicate consistent results.

† For DBP and MAP, the 95% CI of the areas included 0.5 and were not significant.

statistically significant: 1.93 (1.17 to 3.21), $P = .01$ predialysis and 1.50 (1.06 to 2.13), $P = .02$ postdialysis). The OR were also significant for every 10–mm Hg increment in PP: 2.29 (1.33 to 3.94), $P = .003$ predialysis and 1.56 (1.06 to 2.29), $P = .02$ postdialysis).

Multivariate analysis of CV comorbidity was performed for 10–mm Hg increment in each of the four blood pressure components adjusted for gender, age (per 10-year increase), BMI, antihypertensive drug use, time undergoing dialysis (≥2 years or <2 years), and hemoglobin rate. Adjusted OR were not significant for DBP and MAP either pre- or postdialysis (data not shown) or for SBP and PP postdialysis. For SBP and PP predialysis, the adjusted OR were still significant: 1.97 (1.12 to 3.49), $P = .02$, and 2.25 (1.22 to 4.18), $P = .01$ (Table 5).

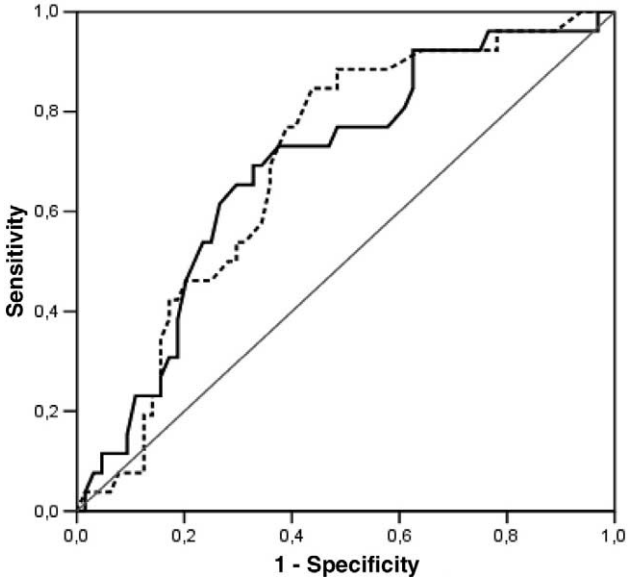

FIG. 1. Receiver operating characteristic curves for identifying individuals with one or more form of cardiovascular comorbidity. Curves are plotted for predialysis systolic blood pressure (**dotted line**) and pulse pressure (**heavy solid line**) in individuals with type 2 diabetes undergoing hemodialysis.

Discussion

This is the first study that has aimed to determine the association between PP and CV events in an Afro-Caribbean population of patients with type 2 diabetes who are undergoing HD. On the island of Guadeloupe about 400 individuals are receiving renal replacement therapy and 30% are diabetic, the majority of whom have type 2 diabetes. This high prevalence is similar to that observed in countries with similar mixed-blood populations (Afro-Caribbeans, Asians, Indians, and individuals of mixed ethnicity).[3] In our sample including 85% of the overall population of patients with type 2 diabetes who are undergoing HD on the island, analysis by areas under the

Table 4. Unadjusted regression analysis of cardiovascular comorbidities (coronary disease, cardiac insufficiency) in patients with type 2 diabetes undergoing hemodialysis

Characteristic	OR	95% CI	*P* value
Sex (male *v* female)	1.92	0.76–4.82	.16
Age/10 years	1.28	0.79–2.05	.31
Body mass index (kg/m^2)	0.92	0.84–1.01	.07
Antihypertensive drug use	9.57	1.21–75.9	.03
Time on hemodialysis >2 years	1.91	0.70–5.19	.20
Hemoglobin (g/dL)	1.21	0.92–1.59	.17
Blood pressure			
Predialysis			
SBP	1.93	1.17–3.21	.01
DBP	1.14	0.69–1.88	.61
PP	2.29	1.33–3.94	.003
MAP	1.56	0.89–2.71	.12
Postdialysis			
SBP	1.50	1.06–2.13	.02
DBP	1.24	0.78–1.98	.36
PP	1.56	1.06–2.29	.02
MAP	1.56	0.89–2.71	.12

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 2.

Table 5. Adjusted regression analysis of history of at least one form of cardiac disease such as coronary disease or cardiac insufficiency

	SBP			PP		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Predialysis BPc*/10 mm Hg	1.97	1.12–3.49	.02	2.25	1.22–4.18	.01
Postdialysis BPc*/10 mm Hg	1.40	0.96–2.04	.08	1.53	0.98–2.39	.06

Abbreviations as in Tables 2 and 4.

The adjusted parameters were sex (male *v* female), age/10 years, body mass index (kg/m^2), antihypertensive use, time on hemodialysis >2 years, hemoglobin (g/dL) the Corresponding adjusted OR were all nonsignificant.

* BPc: Blood pressure component

ROC curves indicates that of the four BP components, only SBP and PP can discriminate patients with significant CV history. Furthermore regression analysis pointed out a stronger association of CV morbidity with PP than with SBP predialysis.

Our results show that 30% of the subjects had had coronary disease or cardiac insufficiency, and that 9% had both. Of these comorbidities, 54% were present before the onset of dialysis. In a study in 180 subjects in renal failure predialysis, 27% had CV disease.[9]

Ischemic heart disease and cardiac failure, which are inter-related and share risk factors, are also both associated with higher mortality rates in HD patients.[4,5,10]

Epidemiologic studies have found that patients starting HD often had histories of CV events occurring in end-stage chronic renal failure. Patients with diabetic nephropathy also experienced a higher frequency of cumulative risk factors, compared with other groups of patients with renal failure,[10] and therefore had a higher mortality rate in dialysis. The median survival time was previously evaluated in a Guadeloupean cohort of HD patients and was significantly impaired in diabetic patients compared with nondiabetic patients.[2]

Previous studies reported that PP in HD patients was higher than in normal control subjects.[11,12] In the present study, PP was significantly higher in patients with CV comorbidity than in patients without a history of CV. The PP values in patients undergoing HD were shown to be a reflection of myocardial function, vascular compliance, and volume overload.[13]

Moreover, diabetes mellitus may accelerate the decrease in compliance of the vessels,[14] and increased arterial stiffening can result in elevated PP.[15] Pulse pressure was previously recognized as a crucial risk factor in CV events and mortality in the general population[16,17] and in patients undergoing chronic HD.[8,18] In our whole population of patients 62 years of median age with type 2 diabetes, we found values for mean PP (74,7 mm Hg) similar to those in the population of HD patients (including diabetic patients) aged 55 years reported in the study by Tozawa et al (PP, 75 mm Hg).[12] Age and diabetes have been reported as significant predictors of elevated PP in both normal subjects and HD patients.[12]

Hypertension has also been involved in the pathogenesis of CV morbidity and mortality in HD patients. In our study group, hypertension was found in 91% of diabetic subjects and in all of those who experienced CV comorbidity. The majority of patients with moderate or even mild renal failure are hypertensive, and it has been shown that the prevalence of hypertension increases as renal function is declining.[19]

The analysis by the areas under the ROC curves suggested in our study the accuracy of pre- and postdialysis SBP and PP to discriminate subjects with and without CV comorbidity, but no significant difference between SBP and PP was found. The multivariate regression analysis showed a significant association between SBP and CV comorbidity and also a strong association between PP and CV events.

In a cross-sectional study performed in chronic HD patients followed for 9 years, it was found that PP was an independent predictor of total mortality with a higher predicting ability than that of SBP or DBP. However, SBP was found superior to either PP or DBP[8] for predicting CV events, indicating that PP pressure was rather associated with the risk of death in HD patients. Our data in which PP was strongly associated with previous history of CV disease might partly explain the better power of PP for predicting overall mortality.

Study Limitations and Strengths

One limitation of our investigation is the fact that this study is cross-sectional and therefore cannot determine whether the increase in PP preceded the occurrence of CV event. It is also clear that additional laboratory measures might have modified the strength of the associations. Results might be also different if the sample size were larger. Nonetheless, the strength of the study lies in the fact that this sample represented about 85% of the patients with type 2 diabetes undergoing HD in Guadeloupe, allowing application of these results in this population. Multiple BP

measures were also used, which minimized the outlying BP values. In addition, this is the first study focusing on an analysis of PP on patients with type 2 diabetes who are undergoing HD. In fact, this group is generally taken into account as a covariate or a parameter of adjustment.

Therapeutic Implications

Our findings suggest that it will be of interest to focus on predialysis BP to define therapeutic strategies. In addition to adequate SBP and DBP control recommended in the management of HD patients, PP, which is associated with CV comorbidity, should be calculated and carefully taken into account. Angiotensin-converting enzyme inhibitors and calcium channel blockers reduce aortic pulse wave velocity and therefore may reduce pulse pressure.[20–22,23] These properties are of great interest in diabetic patients undergoing HD, in whom it was previously demonstrated that increased aortic stiffness, identified by increased aortic pulse wave velocity, might contribute to higher CV mortality rates.[24] Moreover, as shown in the Heart Outcomes Prevention Evaluation (HOPE) study, these two classes of drugs were associated with a better prognosis in patients at high risk of CV events than were other antihypertensive drugs.[25]

In conclusion, our study confirmed data from different previous investigations showing that PP values may be important in the management of patients undergoing HD. Further prospective studies are in progress in this population that aim to confirm the prognostic value of PP as an indicator of CV morbidity and mortality and to evaluate the potentially protective effect of therapeutic interventions targeting high PP values in diabetic patients.

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