Pulse Pressure Predicts Cardiovascular Risk in Patients With Type 2 Diabetes Mellitus

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Background: Pulse pressure (PP), a marker of arterial stiffness, is a better predictor of coronary heart disease (CHD) risk than systolic blood pressure (SBP) or diastolic blood pressure (DBP) in older adults. Whether this is also true in subjects with type 2 diabetes, who are at increased risk for cardiovascular disease, is unknown.

Methods: Data on 2911 type 2 diabetic subjects relating to blood pressure (BP), other risk factors, and cardiovascular events were abstracted from The Cardiff Diabetes Database. Logistic regression was used to assess the relationship among BP components and the risk of CHD, cerebrovascular (CVD), and peripheral vascular (PVD) events after correction for age, gender, cholesterol, and smoking status.

Results: In the 4-year follow-up period there were 574 CHD, 168 CVD, and 157 PVD events. Both PP and SBP, but not DBP, were positively associated with the risk of all event types. However, PP emerged as the best predictor of CHD events, and SBP as the best predictor of CVD and PVD events. Total and HDL-cholesterol were the most important variables associated with PP after age.

Conclusions: In summary, PP is a better predictor of CHD events than SBP in persons with type 2 diabetes, but the converse is true for CVD and PVD. Am J Hypertens 2005;18: 1463–1467 © 2005 American Journal of Hypertension, Ltd.

Key Words: Cardiovascular risk, diabetes, pulse pressure.

The importance of arterial blood pressure (BP) as a determinant of cardiovascular risk, and the benefits of treatment have been well established in a number of large randomized controlled trials. More recently, the pre-eminence of diastolic blood pressure (DBP) in predicting coronary heart disease (CHD) risk has been challenged, and attention has been focused on systolic (SBP) and pulse (PP) pressure, especially in older individuals. Indeed, the latest data from Framingham Heart Study demonstrate that PP is the strongest predictor of CHD risk in the individuals >50 years of age.[1,2] Although this view is supported by data from several other studies,[3,4] it is at variance with a recent meta-analysis suggesting that SBP may be more predictive.[5] Nevertheless, PP is a surrogate marker of large artery stiffness, which itself is an independent predictor of cardiovascular risk.[6,7]

Individuals with type 2 diabetes are at greatly increased risk for cardiovascular disease,[8] and the results of the United Kingdom Prospective Diabetes Study (UKPDS) have confirmed the importance of systolic BP as a risk factor for cardiovascular events.[9] Moreover, tight BP control reduces the risk of stroke and cardiovascular mortality.[10] Pulse pressure is associated with both the micro- and macrovascular complications of type 2 diabetes.[11] Although PP is important in predicting mortality among individuals with impaired glucose tolerance,[12] only one previous study has investigate the predictive value of PP in persons with diabetes mellitus. This was as part of a larger study and included only 208 diabetic subjects.[13]

We hypothesized that pulse pressure would be a better predictor of cardiovascular events in type 2 diabetes because this condition occurs predominantly in older subjects and is associated with premature arterial stiffening.[14] Moreover, recent data indicate that aortic stiffness is an independent predictor of mortality in patients with diabetes.[15] Therefore we examined the relationship between the

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various components of BP and the incidence of cardiovascular disease using The Cardiff Diabetes Database.

Methods

Patients

The Cardiff Diabetes Database is a register of 10,004 individuals with both type 1 and type 2 diabetes mellitus and has previously been described in detail.[16,17] This data set was originally derived from a population of 434,398 individuals in 1996, whose demographic characteristics reflected those of the United Kingdom as a whole. Data concerning age, sex, duration of diabetes, SBP, DBP, height, weight, cholesterol (total, LDL, and HDL), triglycerides, HbA_{1c}, and smoking status were abstracted from the register for the baseline year (1996). The distinction between type 1 and type 2 diabetes was made on the basis of clinical diagnosis recorded in the general practitioners' or hospitals' medical records. Of the complete database of 10,004 diabetic individuals, 8,503 (85%) had type 2 diabetes mellitus. However, only 2,911 of these patients could be included in the analysis, as the other potentially available patients did not have complete data on important associated risk factors. Blood pressure values were those recorded at hospital outpatient appointments in the index year. Individuals known to have type 1 diabetes were excluded from the analysis. The incidence of both fatal and nonfatal cardiovascular events for the entire study population over the next 4 years (1996 to 2000) was then obtained from the register. The definitions and methods of identification of CHD, cerebrovascular disease (CVD), and peripheral vascular disease (PVD) events used in this study have been previously described in detail.[16–18] Subjects with known hypertension or previous cardiovascular events were not excluded from the analysis.

Data Analysis

Pulse pressure was calculated as SBP minus DBP, and body mass index (BMI) was measured as weight/height^2. Baseline data are reported as means (standard deviations). Associations between cardiovascular events and individual risk factors were identified using standard logistic regression after adjusting for age and gender. The relationship between cardiovascular events and single BP components (SBP, DBP, and PP) was assessed using multivariate logistic regression. Logistic regression models were also developed to assess the dual influence of SBP and DBP and of PP, with either SBP or DBP on CHD events because of the pre-existing data concerning PP and CHD risk and the anticipated higher number of CHD events compared with other cardiovascular endpoints. All models were adjusted for age, gender, smoking status, and total/HDL cholesterol ratio (all treated as continuous variables except gender and smoking, which were included as binary variables). The odds ratios presented represent the risk associated with a 10–mm Hg increase evaluated at the mean age of the study population (66 years). Significance levels represent those obtained from likelihood ratio test statistics.

The interaction between PP and other cardiovascular risk factors was assessed using binary recursive partitioning[19] after converting PP into a binary variable (high PP $\geq$60 mm Hg; low PP $<$60 mm Hg). The cut-off of 60 mm Hg was chosen because this was mean PP of the population. Variables from this nonparametric technique were ranked according to their predictive capability.

Results

Data on 2911 subjects with type 2 diabetes were available for analysis. The baseline characteristics of the study population are presented in Table 1. During the 4-year follow-up period there were 574 CHD events, 168 CVD events and 157 PVD events. Greater age and male sex were associated with the occurrence of CHD and PVD events, and age alone with CVD events. After adjustment for these factors, SBP, PP, total:HDL cholesterol ratio, triglycerides, and smoking, but not DBP, were all associated with CHD, CVD, and PVD events. Duration of diabetes was also correlated with CHD and PVD but not with CVD.

There was a significant correlation between SBP and PP ($r = 0.88$; $P < .001$) and between SBP and DBP ($r = 0.53$; $P < .001$). The DBP and PP were significantly but weakly correlated ($r = 0.05$; $P = .008$).

Single BP Components

After adjustment for other risk factors, SBP and PP were both predictive of CHD, CVD, and PVD events (Table 2). However, PP emerged as the strongest predictor of CHD events, and SBP of CVD and PVD events. Conversely,

Table 1. Baseline characteristics of the study population

Variable (units)	Men	Women
Number	1564	1347
Age (y)	65 (11)	67 (11)
Duration of diabetes (y)	8.8 (6.7)	8.7 (7.0)
BMI (kg/m^2)	29.5 (9.6)	30.6 (10.0)
SBP (mm Hg)	143 (19)	148 (21)
DBP (mm Hg)	82 (11)	82 (10)
HbA_{1c} (%)	9.1 (2.3)	9.3 (2.4)
Cholesterol (mmol/L)	5.1 (1.2)	5.9 (1.2)
HDL cholesterol (mmol/L)	1.14 (0.30)	1.3 (0.34)
LDL cholesterol (mmol/L)	3.4 (0.9)	3.6 (0.9)
Triglycerides (mmol/L)	2.3 (1.8)	2.6 (1.7)
Smoker (%)	14.2	24.0

BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Data represent means with standard deviations in parentheses.

Table 2. Logistic regression models relating cardiovascular risk to single blood pressure components

	Coefficient*	Odds ratio*	χ^2	Significance
CHD				
PP	0.57	1.69	12.6	.002
SBP	0.39	1.43	11.8	.003
DBP	0.05	1.00	2.4	NS
CVD				
PP	0.37	1.42	6.1	.047
SBP	0.49	1.58	8.4	.015
DBP	0.91	2.34	4.5	NS
PVD				
PP	0.23	1.25	7.8	.022
SBP	0.43	1.51	9.4	.009
DBP	1.05	2.58	5.1	.078

PP = pulse pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, CHD = coronary heart disease, CVD = cerebrovascular disease, PVD = peripheral vascular disease.

Data are adjusted for age, sex, smoking history, and total:HDL cholesterol ratio.

* Per 10 mmHg increment in blood pressure, evaluated at age 66 years.

there was no association between DBP and any cardiovascular outcome.

Dual BP Components and Risk Prediction

The combination of SBP (positive) and DBP (negative) showed no increase in the prediction of CHD or PVD events beyond that obtained from SBP alone. Similarly, the combination of SBP and PP or DBP and PP produced no increase in the prediction of CHD or PVD once PP was included. The risk of CHD by SBP and DBP is shown graphically in Fig. 1.

For CVD events the combination of SBP (positive) and DBP (negative) in model 1 showed no increase in the predictive value beyond that obtained from SBP alone. However, the addition of PP to either SBP or DBP just failed to increase significantly the prediction of CVD events ($P = .05$).

Factors Relating to PP

Logistic regression identified age, gender, duration, total cholesterol, and HDL cholesterol as factors associated with pulse pressure. Binary recursive partitioning identified age, HDL cholesterol, and total cholesterol as the three most important factors for the classification of pulse pressure as high or low (>60 or <60 mm Hg).

Discussion

Arterial BP is firmly established as an important determinant of cardiovascular risk. However, there has been considerable debate recently regarding the precise BP component that best predicts cardiovascular risk.[20] Indeed, the latest data from the Framingham Heart Study suggest that PP, a surrogate measure of arterial stiffness, is a better predictor of CHD risk that either SBP or DBP, at least in individuals >50 years of age,[1] whereas the converse seems to apply in younger subjects.[2] These observations are supported by several other epidemiologic and intervention studies.[3,4,21] The predictive value of the different BP components among diabetic individuals is of importance because type 2 diabetes mellitus is associated with considerably increased risk of cardiovascular disease, and because arterial stiffness, a key factor in determining PP, independently predicts mortality among diabetic subjects.[15]

To our knowledge, only one previous study has investigated the predictive value of PP in diabetic subjects.[13] Although PP was associated with increased cardiovascular and total mortality in this study, data came from only 208 type 2 diabetic individuals who formed part of a much larger cohort. Moreover, data concerning the relationship between PP and CHD, CVD, or PVD risk were not reported. Therefore, the aim of the present study was to investigate the relationship between the various BP components and cardiovascular risk in a large, community-based cohort of subjects with type 2 diabetes. The main novel findings were that PP was an independent predictor of CHD, CVD, and PVD risk, and that PP was a better predictor of CHD events than SBP. In addition, when

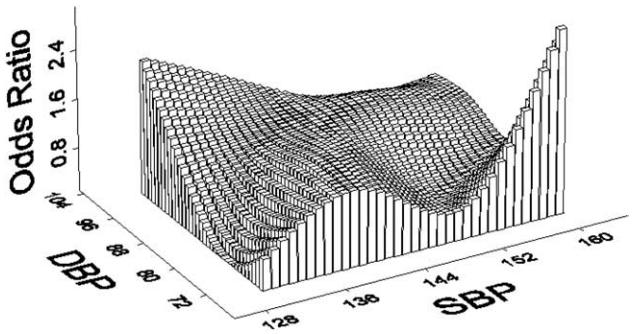

FIG. 1. Coronary heart disease risk and blood pressure. The relationship between risk of coronary heart disease (CHD), and systolic and diastolic pressure in patients with type 2 diabetes (blood pressure measured in millimeters of mercury [mm Hg]).

considered alone, DBP was not predictive of any cardiovascular endpoints.

The finding that PP was a better predictor of CHD risk than either SBP or DBP in type 2 diabetic subjects is in agreement with data from both normotensive[1,21,22] and hypertensive[3,22] nondiabetic populations with mean ages similar to that in the present study. This observation, however, is at variance with data from a recent meta-analysis[5] in nearly 1 million subjects, although the investigators did not provide separate data concerning the diabetic subgroup.

In addition, we have demonstrated that neither SBP nor DBP contributes additional value in defining CHD risk beyond that provided by PP alone. However, given the relatively small number of subjects <50 years of age (12%), we were unable to investigate whether the age of "transition" from DBP or SBP to PP, the best predictor of CHD risk, is influenced by the presence of diabetes. Indeed, as type 2 diabetes is associated with premature arterial stiffening, one might expect PP to become relatively more important earlier in life (ie, before the age of 50 years).

The lack of any relationship between DBP and CHD risk in the present study may be considered somewhat surprising. However, previous studies have also failed to find any association between DBP and both cardiovascular[21] and CHD[2] risk in individuals >60 years of age. This is likely to be caused by the increasing importance of arterial stiffness as a determinant of cardiovascular risk with aging. With age the large arteries stiffen,[23,24] and as a consequence SBP increases; but DBP actually falls, that is, PP widens. Therefore, the positive association between CHD risk and DBP will be reduced and ultimately become negative.[2] Conversely the relative importance of SBP and PP will increase.

We also elected to investigate the relationship between PVD and CVD the various components of BP separately because of the high rate of these complications among subjects with type 2 diabetes. Although PP was predictive of both events, it was slightly less valuable than SBP alone. Once again, DBP was not associated with either CVD or PVD risk. Few data concerning PVD and PP have been previously reported. Moreover, the relationship between CVD risk and PP in nondiabetic subjects is unclear. Franklin et al did not report data concerning CVD risk,[1] but Benetos et al found that PP predicts CVD risk in French men but not women.[22] In contrast Madhavan et al reported that PP predicts CVD but not CHD risk among hypertensive individuals.[3]

We have extended the current study by examining the factors related to a widened PP. Using standard statistical techniques age, gender, duration of diabetes, total cholesterol, and HDL cholesterol were positively associated with PP. However, we also used recursive partitioning, a well-described technique[19] that sequentially partitions patient data to arrive at a homogeneous population, to investigate the most important factors relating to a widened PP. This revealed that age, followed by HDL and total cholesterol, were the three most predictive factors of PP. Interestingly, serum cholesterol is positively associated with arterial stiffness,[25,26] and decreased HDL cholesterol is predictive of increased intima-media thickness in both diabetic[27] and nondiabetic individuals.[28] Because PP provides and index of large artery stiffness, this may explain why subjects with low HDL cholesterol and high total cholesterol have widened PP. Moreover, the association between age and PP is well described.[29]

The one potential limitation of the current study is the nonstandardized method of BP measurement. Although the study staff did not receive specific training in measuring BP, the BP values were recorded in the setting of a hospital clinic after 5 min of seated rest, which may make the highly significant associations between the various BP components and cardiovascular events observed in the present study more applicable to everyday clinical practice. Similarly, although a high proportion of patients were receiving antihypertensive medication in keeping with the high cardiovascular risk and prevalence of hypertension associated with type 2 diabetes, this is more likely to accurately reflect the situation in most diabetes clinics. Indeed, this is supported by the similarity of baseline characteristics between the subjects in this study and those in the UKPDS. Moreover, a number of previously studies confirming the importance of PP in the prediction of cardiovascular risk have also included cohorts of treated and untreated patients.[3,22] In addition, no data on previous cardiovascular events were available. However, the major objective of the current study was to quantify the association between the components of BP and CV events rather than the ability of PP to predict new CV events.

In summary, PP is the best predictor of CHD risk in older subjects with type 2 diabetes mellitus. Both SBP and PP predict the risk of CVD and PVD, but SBP is slightly superior. In contrast, DBP does not predict CHD, CVD, or PVD risk. These data suggest that large artery stiffness is a key determinant of risk in subjects with type 2 diabetes, and that assessment of PP or arterial stiffness or both may assist in risk stratification and monitoring therapeutic response. However, confirmation of this awaits further investigation with more direct measures of arterial stiffness. Indeed, data from the FIELD Study, which is assessing the impact of insulin therapy in type 2 diabetes, relating to central BP and arterial stiffness may address this important issue.

References

1. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D: Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. Circulation 1999;100:354–360.
2. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Levy D: Does the relation of blood pressure to coronary heart disease risk change with aging: the Framingham Heart Study. Circulation 2001; 103:1245–1249.

3. Madhavan S, Ooi WL, Cohen H, Alderman MH: Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. Hypertension 1994;23:395–401.
4. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard J-L, Ducimetiere P, Guize L. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. Hypertension 1997; 30:1410–1415.
5. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–1913.
6. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar M, London G: Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999;99:2434–2439.
7. Blacher J, Asmar R, Djane S, London GM, Safar ME: Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 1999;33:1111–1117.
8. Haffner S, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234.
9. Turner RC, Millins H, Neil HAW, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in noninsulin dependent diabetes mellitus; United Kingdom Prospective Diabetes Study (UKPDS:23). Br Med J 1998;316:823–828.
10. United Kingdom Prospective Diabetes Study (UKPDS) Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type II diabetes: UKPDS 38. Br Med J 1998;317:703–712.
11. Knudsen ST, Poulsen PL, Hansen KW, Ebbehoj E, Bek T, Mogensen CE: Pulse pressure and diurnal blood pressure variation: association with micro- and macrovascular complications in type 2 diabetes. Am J Hypertens 2002;15:244–250.
12. van Dijk RA, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD: Brachial artery pulse pressure and common carotid artery diameter: mutually independent associations with mortality in subjects with a recent history of impaired glucose tolerance. Eur J Clin Invest 2001;31:756–763.
13. Schram MT, Kostense PJ, van Dijk RA, Dekker JM, Nijpels G, Bouter LM, Heine RJ, Stehouwer CD: Diabetes, pulse pressure and cardiovascular mortality: the Hoorn Study. J Hypertens 2002;20: 1743–1751.
14. Wahlqvist M, Lo C, Myers K, Simpson R, Simpson J: Putative determinants of arterial wall compliance in NIDDM. Diabetes Care 1988;11:787–790.
15. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG: Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 2002;106:2085–2090.
16. Currie CJ, Morgan CL, Peters JR: Patterns and costs of hospital care for coronary heart disease related and not related to diabetes. Heart 1997;78:544–549.
17. Currie CJ, Morgan CL, Gill L, Stott NC, Peters JR: Epidemiology and costs of acute hospital care for cerebrovascular disease in diabetic and nondiabetic populations. Stroke 1997;28:1142–1146.
18. Currie CJ, Morgan CL, Peters JR: The epidemiology and cost of inpatient care for peripheral vascular disease, infection, neuropathy, and ulceration in diabetes. Diabetes Care 1998;21:42–48.
19. Zhang HP: Classification trees for multiple binary responses. J Am Stat Assoc 1998;93:180–193.
20. O'Rourke MF, Frohlich ED. Pulse pressure: is this a clinically useful risk factor? Hypertension 1999;34:372–374.
21. Sesso HD, Stampfer MJ, Rosner B, Hennekens CH, Gaziano JM, Manson JE, Glynn RJ: Systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure as predictors of cardiovascular disease risk in men. Hypertension 2000;36:801–807.
22. Benetos A, Rudnichi A, Safar M, Guize L: Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. Hypertension 1998;32:560–564.
23. Bramwell JC, Hill AV: Velocity of transmission of the pulse-wave and elasticity of the arteries. Lancet 1922;i:891–892.
24. Avolio AP, Fa-Quan D, Wei-Qiang L, Yao-Fei L, Zhen-Dong H, Lian-Fen X, O'Rourke MF: Effects of ageing on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. Circulation 1985;71:202–210.
25. Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ, Cockcroft JR: Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. J Am Coll Cardiol 2002;39:1005–1011.
26. Dart AM, Lancombe F, Yeoh JK, Cameron JD, Jennings GL, Laufer E, Esmore DS: Aortic distensibility in patients with isolated hypercholesterolaemia, coronary artery disease, or cardiac transplantation. Lancet 1991;338:270–273.
27. Matsumoto K, Sera Y, Nakamura H, Ueki Y, Miyake S: Correlation between common carotid arterial wall thickness and ischemic stroke in patients with type 2 diabetes mellitus. Metabolism 2002;51:244–247.
28. Davis PH, Dawson JD, Riley WA, Lauer RM: Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. Circulation 2001;104:2815–2819.
29. Franklin SS, Gustin IVW, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D: Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. Circulation 1997; 96:308–315.