Pulse Pressure and Risk of Cardiovascular Events and Mortality in Patients on Haemodialysis

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Abstract
Over the years, diastolic- (DBP), systolic- (SBP) and pulse (PP) pressures have successively been entered into the equation for cardiovascular (CVS) risk. In recent studies PP has been shown as a risk factor for CVS events or total mortality.
In this study we analysed 94 patients (52 men and 42 women) of average age 57.84 ± 11.62 years, who were on chronic haemodialysis in our Centre during a period of 7 years. Comorbid conditions were indexed using IDS (index of disease severity) and cardiovascular components of this index were also included in the analysis [ischaemic heart disease, congestive heart failure, arrhythmia, other cardiovascular diseases (OTH) mainly dependent of left ventricular hypertrophy (LVH), hypertension (HTA) and total CVS morbidity]. We analysed the correlation between average values of blood pressure components: diastolic-, systolic-, mean arterial- (MAP) and pulse pressure and these individual comorbid CVS components as well as total CVS morbidity, index of disease severity (IDS), haemoglobin (Hb), serum calcium (Ca), phosphate (PO_4), albumin, body mass index (BMI), Kt/V (Daurgidas), age and mortality. The analysis revealed: significant positive correlation between PP (0.021) and SBP (0.012) and total CVS morbidity, PP (0.009) and SBP (0.051) and OTH with LVH, PP (0.022) and SBP (0.041) and total IDS, all blood pressure components and HTA, all blood pressure components and serum PO4; significant negative correlation between PP (0.049) and Hb, MAP (0.029) and age. Cox proportional hazard model did not reveal PP, SBP, DBP and MAP as mortality risk factors in this group of haemodialysis patients. So, we can conclude that PP was a good predictor of total CVS morbidity, LVH, total IDS and anaemia (Hb), but it was not a predictor of mortality in our analysed patients.

Introduction

Over the years, diastolic-, systolic-, median- and pulse pressures have successively been entered into the equation for cardiovascular (CVS) risk. First it was diastolic blood pressure (DBP) (1), then systolic blood pressure (SBP) and mean arterial pressure (MAP) (2-4). From this contraposition between systolic and diastolic blood pressure the notion of pulse pressure (PP) as a risk factor appeared as a logical consequence, the more so because it represents the most straightforward expression of pathological arterial wall rigidity (3-5).
Blood pressure components and CVS risk were the object of many experimental, clinical and epidemiological studies, which analysed various groups of patients. From these studies we can conclude that SBP and DBP are the best markers for CVS risk in the young, but PP is the best marker for CVS risk in the middle aged and elderly (6). Pulse pressure is a better marker for CVS morbidity than MAP (7).
The aim of this study was to analyse the correlation between blood pressure components and CVS comorbid components, laboratory parameters, clinical parameters and mortality in patients on haemodialysis.

Patients and methods

The study included 94 patients (52 men and 42 women) aged between 23 and 84 years, who were on chronic haemodialysis in our Centre during a period of 7 years.

Inclusion criteria: All patients in our Centre who were more than two years on haemodialysis on January 1st 1996. It was a 7-year prospective single cohort study, which consisted of: two years of baseline measurements (1996-1997) and 5 years of follow-up (1998-2002). *Comorbid conditions* were indexed using the index of disease severity (IDS), as it was done in HEMO study as a part of the index of coexistent diseases (ICED), and cardiovascular components of this index which were also included in the analysis, such as the following: hypertension (HTA) as comorbid condition, ischaemic heart disease (IHD), congestive heart failure (CHF), arrhythmia (ARR), other cardiovascular diseases (OTH) mainly dependent on left ventricular hypertrophy (LVH) and total CVS morbidity (8). Example of indexing for hypertension: 0 – no hypertension; 1 – moderate hypertension without therapy; 2 – mild hypertension on antihypertensive therapy; 3 – severe hypertension on antihypertensive therapy. We analysed the correlation between average values of blood pressure components: diastolic, systolic-, mean arterial- and pulse pressures and individual comorbid CVS components as well as total CVS morbidity, IDS, haemoglobin (Hb), serum calcium (Ca), phosphate (PO_4), albumin, body mass index (BMI), Kt/V (Daurgidas), age, mortality. Cox proportional hazard model was used for analysing blood pressure components as mortality risk factors in haemodialysis patients.

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Results

Blood pressure components of the analysed patients, which are represented as their minimal, maximal and mean values as well as standard deviation can be seen in Table 1.

Table 1. Blood pressure parameters in analyzed patients

	N	Min	Max	Mean	SD
SBP	94	82	171	140	17
DBP	94	45	102	80	7
MAP	94	46	119	100	10
PP	94	17	81	60	12

Legend: SBP – systolic blood pressure; DBP diastolic blood pressure; MAP – mean arterial pressure; PP – pulse pressure; N – number of patients.

In Table 2 various degrees of severity of comorbid conditions are represented in terms of percentage. There were about 40% of patients without hypertension. Most of patients on antihypertensive therapy had mild hypertension. It is also interesting that all of the analysed patients had some comorbid condition, and that the majority of them had index 2.

Table 2. Various degrees of severity of comorbid conditions in percentage

Score	0	1	2	3
Hypertension	39.4	24.4	35.1	1.1
Ishaemic heart disease	57.4	27.7	13.8	1.1
Congestive heart failure	57.4	26.6	16.0	0
Arrhytmia	63.8	14.9	21.3	0
Others with left ventr. hypertrophy	32.9	66.0	0	1.1
Total cardiovascular morbidity	9.6	27.7	59.6	3.2
Index of disease severity	0	19.1	54.3	26.6

The correlations between blood pressure components and CVS comorbid components are presented in Table 3. There are significant positive correlations between all blood pressure components and HTA as comorbid condition (p<0,01), PP and SBP and OTH with LVH (p<0,01; p<0,05), total CVS morbidity (p<0,05; p<0,05) and total IDS (p<0,05; p<0,05).

Table 3. Correlation between blood pressure components and CVS comorbid components

		SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	PP (mmHg)
HTA	r	0.627	0.397	0.541	0.606
	p	0.001*	0.001*	0.001*	0.001*
IHD	r	-0.041	-0.113	-0.080	0.047
	p	0.698	0.277	0.441	0.651
CHF	r	-0.032	-0.100	-0.035	-0.063
	p	0.756	0.337	0.735	0.549
ARR	r	-0.180	-0.152	-0.173	-0.170
	p	0.082	0.140	0.095	0.101
OTH	r	0.202	0.039	0.133	0.270
	p	0.051**	0.711	0.202	0.009*
TCVM	r	0.257	0.145	0.232	0.238
	p	0.012**	0.165	0.024	0.021**
IDS	r	0.212	0.078	0.176	0.235
	p	0.041**	0.457	0.089	0.022**

Legend: SBP – systolic blood pressure; DBP diastolic blood pressure; MAP – mean arterial pressure; PP – pulse pressure; HTA – hypertensia; IHD – ishaemic heart disease; CHF – congestive heart failure; ARR – arrhythmia; OTH – others with left ventricular hypertrophy; TCVM – total cardiovascular morbidity; IDS – Index of disease severity. *p<0.001; **p<0.05

Table 4. Correlation between blood pressure components and laboratory parameters

		SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	PP (mmHg)
Hb	r	-0.131	0,035	-0.056	-0.204
	p	0.209	0.741	0.591	0.049**
Ca	r	-0.053	0.099	0.049	-0.350
	p	0.615	0.341	0.641	0.195
PO_4	r	0.240	0.247	0.269	0.242
	p	0.020**	0.016**	0.009*	0.019**
Alb	r	0.087	0.122	0.114	0.009
	p	0.403	0.240	0.275	0.934

Legend: SBP – systolic blood pressure; DBP diastolic blood pressure; MAP – mean arterial pressure; PP – pulse pressure; Hb – haemoglobin; Ca – calcium; PO_4 – phosphate; Alb – albumin. *p<0.001; **p<0.05

The correlations between blood pressure components and laboratory parameters are expressed in Table 4. There are significant positive correlations between all blood pressure components and serum phosphorous (p<0,05; p<0,05; p<0,05; p<0,01), and significant negative correlation between PP and Hb (p<0,05).

Table 5. Correlation between blood pressure components and clinical parameters

		SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	PP (mmHg)
BMI	r	-0.027	-0.034	-0.034	-0.032
	p	0.800	0.749	0.748	0.766
Kt/V	r	-0.193	-0.156	-0.188	-0.132
	p	0.063	0.132	0.070	0.205
Age	r	-0.084	-0,226	-0.161	-0.062
	p	0.423	0.029**	0.120	0.553

Legend: – systolic blood pressure; DBP diastolic blood pressure; MAP – mean arterial pressure; PP – pulse pressure; BMI – body mass index; Kt/V – dialysis adequacy. **p<0.05

Table 6. Univariant Cox proportional hazard model

	B	SE (B)	p	Risk ratio	CI↓	CI↑
SBP (mmHg)	0.006	0.009	n.s.	-	-	-
DBP (mmHg)	0.009	0.019	n.s.	-	-	-
MAP (mmHg)	0.002	0.014	n.s.	-	-	-
PP (mmHg)	0.000	0.014	n.s.	-	-	-
HTA	0.878	0.167	0.000	2.407	1.734	3.341
IHD	0.328	0.161	0.041	1.388	1.013	1.902
CHF	0.775	0.172	0.000	2.171	1.551	3.039
ARR	-0.083	0.172	n.s.	-	-	-
OTH	0.488	0.221	0.028	1.628	1.055	2.513
TCVS	0.770	0.220	0.001	2.160	1.395	3.344
IDS	0.910	0.230	0.000	2.484	1.582	3.902

Legend: SBP – systolic blood pressure; DBP diastolic blood pressure; MAP – mean arterial pressure; PP – pulse pressure; HTA – hypertensia; IHD – ishaemic heart disease; CHF – congestive heart failure; ARR – arrhythmia; OTH – others with left ventricular hypertrophy; TCVM – total cardiovascular morbidity; IDS – Index of disease severity. B – regression coefficient; SE – standard error of coefficient B; CI – confidence interval; n.s. – not significantly.

Table 5 represents the correlations between blood pressure components and clinical parameters such as BMI, Kt/V and age. There is a significant negative correlation only between MAP and age (p<0,05).

We used univariant Cox proportional hazard model which did not reveal PP, SBP, DBP and MAP as mortality risk factors in this group of haemodialysis patients (Table 6).

Discussion

Hypertension is an important contributor to a poor prognosis (9), and a significant predictor of cardiovascular mortality (10) and stroke (11) in patients on chronic haemodialysis. High SBP has been shown to predict poor prognosis in this group of patients (12). Iseki et al previously reported that low DBP was a significant risk factor of total mortality in chronic haemodialysis patients (13). These results lead to the hypothesis that high SBP and low DBP may be significant predictors of cardiovascular events or mortality in chronic haemodialysis patients (14).

Blood pressure propagates through the arterial tree as a repetitive continuous wave and is more accurately described as consisting of a pulsatile component and a steady component. The pulsatile component is PP, which depends on ventricular ejection, arterial stiffness and timing of wave reflections. The steady component is MAP, which is determined mainly by cardiac output and vascular resistance. PP has been shown as an independent risk factor for cardiovascular events or mortality in several studies in screened populations (4, 15-17), hypertensive subjects (3, 18-20), the elderly cohort (21) and patients with significant left ventricular dysfunction after myocardial infarction (22). The high prevalence of atherosclerosis-related complications and marked abnormalities of arterial compliance have been well documented in haemodialysis patients (23, 24). It is also known that prolonged uraemia has a deleterious effect on stiffening of the artery wall (25). However, the impact of PP on prognosis in a relatively large cohort of chronic haemodialysis patients has been sufficiently studied.

The major findings of this seven-year follow-up study were that in our haemodialysis patients, baseline PP significantly correlates with total CVS morbidity, total IDS and LVH. That indicated a significant influence of PP on the development of CVS changes in haemodialysis patients which had a negative influence on patients' outcome. On the other hand, the significant correlation between PP and serum phosphorus proved the well known role of calcium-phosphorus metabolic disorders in pathogenesis of vascular lesions (Table 3, Table 4). The significant negative correlation found between PP and anaemia indicated yet one factor influencing PP (Table 4). So, our analysis of parameters correlating with PP revealed two different sides of coin: factors influencing PP and consequences of increased PP.

Our results are in accordance with the previous showing that pulse pressure is an independent CVS risk factor for: all ages, both sexes (26), all races, all values of blood pressure, even in normotensive patients and pregnant women (20, 27). Also, PP is an independent predictor of: left ventricular hypertrophy (Table 3), myocardial infarction, congestive heart failure, CVS mortality (27), coronary artery disease (28), total mortality (14) and stroke (29).

It is important to emphasise that CVS risk is higher with: PP over 60 - 65 mmHg for ambulatory blood pressure and PP

over 56 mmHg for median 24h blood pressure (26). For every 10 mmHg growth in PP the following are also raised: total CVS risk for 10-20% (5); risk of stroke for 24%; risk of myocardial infarction for 32% (3).

Lower body mass index or serum albumin is an independent predictor of a wide PP in diabetic or non-diabetic patients on haemodialysis (14) which we did not find in the analysed patients (Table 4, Table 5).

Tozawa and coll. (14) found that PP was an independent predictor of total mortality in non-diabetic patients on chronic haemodialysis. PP was a more potent predictor of total mortality than SBP or DBP. However, we used univariant Cox proportional hazard model which did not reveal PP, SBP, DBP and MAP as mortality risk factors in this group of haemodialysis patients (Table 6). Duratini et al. also found no significant difference in survival between normotension and hypertension in dialysis patients (30).

Conclusion

The presented results led to the conclusion that pulse pressure was a good predictor of LVH, total CVS morbidity, total IDS, but it was not a predictor of mortality in the analysed patients on chronic haemodialysis. But, PP correlated significantly with comorbid conditions known as the predictors of mortality.

References

1. Kannel WB, Dawber TR, McGee DL. Perspectives on systolic hypertension. The Framingham Study. Circulation 1980;61:1179-1182.
2. Birkenhager WH, De Leeuw PW. The Older Hypertensive. Blood Pressure 2001;10: 299-310.
3. Blacher J, Staessen JA, Girerd X et al. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. Arch Intern Med 2000;160(8):1085-1089.
4. 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.
5. Stolarz K, Staessen JA. Prognostic significance of pulse pressure. 9th European Meeting on Cardionephrology, Italy, Editoriale Bios 2002;257-260.
6. Franklin SS. Cardiovascular risks related to increased diastolic, systolic and pulse pressure. An epidemiologist's point of view. Pathol Biol 1999;47(6):594-603.
7. Domanski M, Mitchell G, Pfeffer M et al. MRFIT Research Group. Pulse pressure and cardiovascular disease-related mortality: follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 2002;287(20):2677-2683.
8. Miskulin DC, Athienites NV, Yan G et al: Comorbidity assessment using the Index of Coexistent Diseases in a multicenter clinical trial. Kidney Int 2001;60(4):1498-1510.
9. Charra B, Calemard E, Ruffet M et al. Survival as an index of adequacy of dialysis. Kidney Int 1992;41:1286-1291.
10. Foley RN, Parfrey PS, Harnett JD et al. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. Kidney Int 1996;49:1379-1385.
11. Iseki K, Fukiyama K. Predictors of stroke in patients receiving chronic hemodialysis. Kidney Int 1996;50:1672-1675.
12. Tomita J, Kimura G, Inoue T et al. Role of systolic blood pressure in determining prognosis of hemodialyzed patients. Am J Kidney Dis 1995;25:405-412.
13. Iseki K, Miyasato F, Tokuyama K et al. Low diastolic blood pressure, hypoalbuminemia, and risk of death in a cohort of chronic hemodialysis patients. Kidney Int 1997;51:1212-1217.
14. Tozawa M, Iseki K, Iseki C, Takishita S. Pulse pressure and risk of total mortality and cardiovascular events in patients on chronic hemodialysis. Kidney Int 2002;61(2): 717-726.
15. Benetos A, Safar M, Rudnichi A et al. Pulse pressure: A predictor of long-term cardiovascular mortality in French male population. Hypertension 1997;30:1410-1415.
16. Fang J, Madhavan S, Cohen H, Alderman MH. Measures of blood pressure and myocardial infarction in treated hypertensive patients. J Hypertens 1995;13:413-419.
17. Scuteri A, Cacciafesta M, Di Bernardo MG et al. Pulsatile versus steady-state component of blood pressure in elderly females: an independent risk factor for cardiovascular disease? J Hypertens 1995;13:185-191.
18. Benetos A, Rudnichi A, Safar M. Guize: Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. Hypertension 1998;32:560-564.
19. Millar JA, Lever AF, Burke V. Pulse pressure as a risk factor for cardiovascular events in the MRC Mild Hypertension Trial. J Hypertens 1999;17:1065-1072.
20. Domanski MJ, Davis BR, Pfeffer MA, Kastantin M, Mitchell GF. Isolated systolic hypertension: prognostic information provided by pulse pressure. Hypertension 1999;34 (3):375-380
21. Chae CU, Pfeffer MA, Glynn RJ et al. Increased pulse pressure and risk of heart failure in the elderly. JAMA 1999;281:634-639.
22. Mitchell GF, Moye LA, Braunwald E et al. Sphygmomanometrically determinated pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impared left ventricular function. SAVE investigators. Survival and Ventricular enlargement. Circulation 1997;96:4254-4260.

23. Linder A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med 1974;290:697-701.
24. London GM. Increased arterial stiffnes in end-stage renal failure: Why is it of interest to the clinical nephrologist? Nephrol Dial Transplant 1994;9:1709-1712.
25. Luik AJ, Spek JJ, Charra B et al. Arterial compliance in patients on long-treatment-time dialysis. Nephrol Dial Transplant 1997;12:2629-2632.
26. Bonner G. Risk evaluation and therapeutical implications of pulse pressure in primary arterial hypertension. Dtsch Med Wochenschr 2002;127(45):2396-2399.
27. Benetos A. Pulse pressure and cardiovascular risk. J Hypertens 1999;17(Suppl 5): S21-S24.
28. Mourad JJ. Arterial pulse pressure. Presse Med 2002;31(30):1423-1427.
29. Safar ME. Systolic blood pressure, pulse pressure and arterial stiffness as cardiovascular risk factors. Curr Opin Nephrol Hypertens 2001;10(2):257-261.
30. Duranti E, Imperiali P, Sasdelli M. In hypertension a mortality risk factor in dialysis? Kidney Int 1996;55:S173-S174.