available at http://health.elsevier.com/tcmj

Tzu Chi Medical Journal

Original Article

Arterial Stiffness in Hemodialysis Patients

*Wen-Tien Wu[1], Ru-Ping Lee[2], Chih-Hsien Wang[3], Te-Chao Fang[3,4], Bang-Gee Hsu[3,4]**

[1]Department of Orthopedics, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
[2]Department of Nursing, Tzu Chi University, Hualien, Taiwan
[3]Department of Nephrology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
[4]Department of Medicine, Tzu Chi University, Hualien, Taiwan

Article info

Article history:
Received: February 26, 2007
Revised: March 16, 2007
Accepted: March 29, 2007

Keywords:
Arterial stiffness
Hemodialysis
Pulse wave velocity

Abstract

Objectives: Increased arterial stiffness is an independent predictor of death from cardiovascular disease, and cardiovascular disease is the leading cause of death among patients with end-stage renal disease. The aim of this study was to compare arterial stiffness in hemodialysis patients.

Patients and Methods: Serum samples were taken from 42 hemodialysis patients with the same high flux artificial kidney. Brachial-ankle pulse wave velocity (baPWV) was measured in the right or left brachial artery to the ankle segments that did not have arteriovenous fistula using an automatic pulse wave analyzer. Plasma adiponectin levels were measured using a commercial enzyme-linked immunosorbent assay kit. Body fat mass was determined using bioelectrical impedance analysis.

Results: Arterial stiffness was higher in hemodialysis patients (85.7%). Age ($p=0.018$), systolic blood pressure ($p<0.001$) and fasting glucose ($p=0.007$) were higher, and hematocrit ($p=0.016$) was lower in hemodialysis patients with arterial stiffness. Plasma homocystine ($p=0.899$), adiponectin ($p=0.204$), C-reactive protein ($p=0.276$), body fat mass ($p=0.756$), total cholesterol ($p=0.607$), triglyceride ($p=0.737$), calcium ($p=0.698$) and phosphorous ($p=0.629$) metabolism were not associated with arterial stiffness in hemodialysis patients. Multivariate forward stepwise linear regression analysis of arterial stiffness showed that systolic blood pressure and age were independent predictors of arterial stiffness in hemodialysis patients and explained 45.8% of the variance in patients with arterial stiffness ($R^2=0.458$).

Conclusion: The incidence of arterial stiffness was higher in hemodialysis patients. Systolic blood pressure and age were independent predictors of arterial stiffness in hemodialysis patients. {*Tzu Chi Med J* 2007;19(3): 139–144}

*Corresponding author. Department of Nephrology, Buddhist Tzu Chi General Hospital, 707, Chung Yang Road, Section 3, Hualien, Taiwan.
E-mail address: geelily@mail.tcu.edu.tw

© 2007 Buddhist Compassion Relief Tzu Chi Foundation

1. Introduction

Cardiovascular disease is the leading cause of death among patients with end-stage renal disease (ESRD) [1]. Moreover, arterial stiffness has been associated with a high incidence of cardiovascular events and death in patients with ESRD [2,3]. The high incidence of cardiovascular disease in ESRD has been ascribed to an excess of traditional risk factors including hypertension, dyslipidemia, smoking, old age, diabetes and non-traditional risk factors including hyperhomocysteinemia, increased C-reactive protein (CRP), abnormal calcium and/or phosphorous metabolism [4]. Clinical studies have shown that damage of arteries is a major contributory factor to death in patients with uremia [5,6]. Brachial-ankle pulse wave velocity (baPWV) is a noninvasive method for analyzing vascular stiffness in the assessment of vascular damage [7,8]. The validity and reproducibility of baPWV measurements are considerably high, and this method seems to be an acceptable marker reflecting arteriosclerosis [8,9]. High baPWV is also found to be a risk factor for carotid atherosclerosis in patients with ESRD [10]. The aim of this study was to investigate the risk factors of arterial stiffness among hemodialysis patients in eastern Taiwan.

2. Patients and methods

2.1. Patients

Forty-two hemodialysis patients with the same high flux disposable artificial kidney (Fx class; Fresenius, Bad Homburg, Germany), including 27 men and 15 women aged from 26 to 87 years, were studied in April 2005 in a medical center in Hualien, eastern Taiwan. Hemodialysis was performed three times a week (4 hours/day) using standard bicarbonate dialysate. The Protection of Human Subjects Institutional Review Board at Tzu Chi University and Hospital approved this study. Anthropometric measurements included height and weight measurements. The Kt/V and urea reduction ratio (URR) were measured before dialysis, and immediately after dialysis blood urea nitrogen (BUN) levels were measured using a formal single-compartment dialysis urea kinetic model.

2.2. Bioimpedance analysis

Impedance measurements were performed at the bedside according to the standard, tetrapolar, whole body (hand-foot) technique, using a single-frequency (50-kHz) analyzer (Biodynamic-450; Biodynamics Corporation, Seattle, WA, USA). Measurements were carried out by the same operator 20 minutes before dialysis began. Fat mass was collected and analyzed using the specific formulae offered by the manufacturer.

2.3. Evaluation of baPWV

Arterial stiffness was assessed using baPWV in the right or left brachial artery at the ankle segments that did not have arteriovenous fistula. The device measures baPWV using an oscillometric method [11]. Complete measurement of all baPWV was usually finished in less than 5 minutes. The baPWV was automatically calculated using a waveform analyzer (VP-1000; Colin Corporation, Komaki, Japan). The baPWV value of 13.5 m/s was defined as the threshold value for arterial stiffness according to the manufacturer's definition.

2.4. Biochemical investigations

Fasting serum samples taken before dialysis from each subject were immediately centrifuged for biochemical study. Blood samples of approximately 0.5 mL for complete blood count (CBC) (Vitros 750; Johnson & Johnson, USA) and others were immediately centrifuged at 3000 rpm for 10 minutes. The plasma was stored at 4°C for biochemical examinations within 1 hour after collection. Plasma levels of BUN, creatinine, fasting glucose, total cholesterol, triglyceride, calcium, phosphorus, albumin, homocysteine and CRP were measured using an autoanalyzer (Hitachi 747; Hitachi, Tokyo, Japan) to evaluate various biochemical data. The serum hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV) were detected using commercially available enzyme immunoassays (Abbott Laboratories, Abbott Park, IL, USA). Plasma adiponectin levels were measured using a commercial enzyme-linked immunosorbent assay kit (Linco Research Inc., St Charles, MO, USA).

2.5. Statistical analysis

Data are expressed as case numbers and analyzed using the χ^2 test. Other data are expressed as mean ± standard deviation and compared using the Student t test. A p value less than 0.05 was considered statistically significant. All statistically significant variables ($p<0.05$) were put into a multiple linear regression model as independent variables and we used baPWV as a dependent variable. Data were analyzed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) for Windows.

3. Results

The basic clinical characteristics of hemodialysis patients are presented in Table 1. Twenty-seven men and 15 women were enrolled in this study. Thirty patients were aged below 65 years. The causes of uremia varied. Eighteen patients suffered from uremia

due to diabetes mellitus, 10 of them were due to hypertension and 10 were due to chronic glomerulonephritis. The percentage of patients who had been on hemodialysis for less than 5 years was 57%, whereas 14% had been on hemodialysis for more than 10 years.

Patients were divided into arterial stiffness and non-arterial stiffness groups based on the results of baPWV. The characteristics of each group are presented in Table 2 and Table 3. Thirty-six patients (85.7%) had arterial stiffness and six patients (14.3%) did not have arterial stiffness. Age ($p=0.018$), systolic blood pressure ($p<0.001$) and fasting glucose ($p=0.007$) were higher, and hematocrit ($p=0.016$) was lower in hemodialysis patients with arterial stiffness. There were no statistically significant differences in height, weight, smoking, betel nut chewing,

Table 1 — Baseline clinical characteristics of hemodialysis patients in the study

	%
Sex	
Male	64
Female	36
Age (yr)	
<65	71
≥65	29
Cause of end-stage renal disease	
Diabetes	43
Hypertension	24
Glomerulonephritis	24
Other	9
Duration of hemodialysis	
<5yr	57
≥5yr and <10yr	29
≥10yr	14

Table 2 — Comparisons of clinical background of hemodialysis patients with and without arterial stiffness

	Non-arterial stiffness *n* (%)	Arterial stiffness *n* (%)	*p*
HBsAg			0.150
Negative	6 (100)	30 (83.3)	
Positive	0 (0)	6 (16.7)	
Anti-HCV			0.150
Negative	6 (100)	30 (83.3)	
Positive	0 (0)	6 (16.7)	
Gender			0.438
Male	3 (50.0)	24 (66.7)	
Female	3 (50.0)	12 (33.3)	
Smoking			0.097
No	6 (100)	28 (77.8)	
Yes	0 (0)	8 (22.2)	
Alcohol consumption			0.383
No	5 (83.3)	34 (94.4)	
Yes	1 (16.7)	2 (5.6)	
Betel nut chewing			0.383
No	5 (83.3)	34 (94.4)	
Yes	1 (16.7)	2 (5.6)	
Diabetes mellitus			0.410
No	5 (83)	19 (53)	
Yes	1 (17)	17 (47)	

Table 3 — Comparisons of laboratory parameters of hemodialysis patients with and without arterial stiffness*

	Non-arterial stiffness ($n=6$)	Arterial stiffness ($n=36$)	*p*
Age (yr)	43.00±10.60	57.39±13.49	0.018†
Duration of HD (mo)	73.00±64.33	49.81±45.54	0.283
Body weight (kg), pre-HD	61.77±13.21	65.87±12.98	0.484
Body weight (kg), post-HD	58.22±12.31	62.72±12.07	0.410
Height (cm)	163.15±7.59	161.77±9.28	0.734
Body fat mass, pre-HD	26.76±6.88	27.78±7.37	0.756
SBP (mmHg)	113.50±13.58	154.80±23.49	0.000†
DBP (mmHg)	71.67±7.84	82.11±15.18	0.110
WBC (×1000/μL)	6.33±2.59	6.29±1.89	0.962
Hct (%)	33.13±4.34	29.76±2.83	0.016†
CRP (mg/dL)	0.896±0.911	0.438±0.325	0.276
Homocysteine (μmol/L)	22.07±7.44	22.52±7.90	0.899
Adiponectin (ng/mL)	264.15±25.74	277.204±22.493	0.204
Triglyceride (mg/dL)	209.83±197.30	180.75±96.81	0.737
Cholesterol (mg/dL)	185.0±49.7	174.89±43.41	0.607
Fasting glucose (mg/dL)	115.67±20.49	167.22±95.45	0.007†
Creatinine (mg/dL)	12.75±1.8	11.16±2.25	0.109
Collected calcium (mg/dL)	9.1967±0.428	9.33±0.78	0.698
Phosphorus (mg/dL)	5.5±2.2	5.15±1.53	0.629
Calcium × phosphorus	50.28±18.99	48.15±15.72	0.766
IPH (pg/mL)	314.15±239.60	206.76±136.95	0.174
URR	0.67±0.168	0.698±0.074	0.695
Kt/V (Gotch)	1.208±0.474	1.232±0.261	0.910

*Data are expressed as mean±standard deviation; †$p<0.05$, malnourished *vs.* well-nourished patients, Student *t* test. HD = hemodialysis; SBP = systolic blood pressure; DBP = diastolic blood pressure; WBC = white blood cell count; Hct = hematocrit; CRP = C-reactive protein; IPH = intact parathyroid hormone; URR = urea reduction ratio; Kt/V = fractional clearance index for urea.

Table 4 — Multivariate stepwise linear regression analysis of arterial stiffness*

Items	β	R^2	R^2 change	*p*
SBP	0.008	0.307	0.307	<0.001
Age (yr)	0.010	0.458	0.151	0.002

*Dependent variable: brachial-ankle pulse wave velocity; independent variable: age, hematocrit, systolic blood pressure (SBP) and fasting glucose.

alcohol consumption, gender distribution, duration of hemodialysis, pre-hemodialysis body fat mass, white blood cell count, serum homocystine, adiponectin, CRP, total cholesterol, triglyceride, calcium, phosphorous, calcium-phosphorous deposition, URR and Kt/V urea between patients with and without arterial stiffness.

Multivariate forward stepwise linear regression analysis of arterial stiffness showed that systolic blood pressure and age were independent predictors of arterial stiffness in hemodialysis patients (R^2=0.458); the results are presented in Table 4.

4. Discussion

The results of our study showed that age and systolic blood pressure were independent predictors of arterial stiffness in hemodialysis patients and the incidence of arterial stiffness was high in hemodialysis patients. The results were the same as age and systolic blood pressure were significant factors associated with increased PWV in patients with diabetes with arterial stiffness [12].

The principal pathophysiological consequences of vascular alterations in ESRD include increased intima-media thickness, decreased arterial distensibility and increased PWV that increase systolic blood pressure, left ventricular hypertrophy and altered coronary circulation [13]. These changes induce high cardiovascular mortality rate in individuals on dialysis [14]. After stratification for age, gender, race, and the presence or absence of diabetes, cardiovascular death in dialysis patients is 10–20 times higher than in the general population [1]. Traditional cardiovascular risk factors identified in the general population include hypertension, diabetes mellitus, hyperlipidemia, tobacco use, and physical activity. In addition, some uremia-related risk factors, such as anemia, abnormalities in calcium phosphate balance, hyperhomocysteinemia, increased oxidative stress, and inflammatory vascular response, also contribute to the high incidence of cardiovascular disease in patients with uremia [4,15]. In addition to correlations between PWV and cardiovascular risk factors in patients with uremia, our results showed that age, systolic blood pressure, fasting glucose and anemia were associated with arterial stiffness in uremia. Increased CRP is a significant risk factor for cardiovascular events and death in the ESRD population [16]. Adiponectin enhances insulin sensitivity and is inversely related to metabolic risk factors like glucose, triglyceride, and insulin in uremic patients, suggesting that this cytokine is a protective factor for atherosclerosis in patients with uremia [17]. Our results did not show a relationship between CRP and adiponectin with arterial stiffness in hemodialysis patients. This may be due to the small number of cases in this study, and further randomized studies are needed.

Aging is a risk factor for the development of arterial stiffness and vascular disease [18], and it is related to the upregulation of matrix metalloproteinase-2 in the aorta of humans [19]. The changes induced vessel luminal dilation, medial thickening, elastic membrane fragmentation, thickening of vascular intima and increased arterial stiffness [19]. Increased systolic blood pressure and loss of elasticity in large arteries in the elderly are considered a normative aging process of the arterial wall [20]. Elevated blood pressure over time can also lead to vascular remodeling, hypertrophy, and hyperplasia that produce intrinsic arterial stiffening [20]. Annual rates of progression in PWV were higher in subjects treated for hypertension than in normotensive subjects, suggesting accelerated progression of arterial stiffness among the hypertensive subjects [21]. Systolic blood pressure rises as a result of arterial stiffness and early pulse wave reflection which is a major problem in hemodialysis patients [22]. Systolic blood pressure is a significant independent predictor of survival in hemodialysis patients [22]. Arterial stiffness is also more closely associated with ischemic heart disease in patients with type 2 diabetes mellitus [23]. Arterial stiffness was increased in patients who had diabetes and was increased further in a stepwise manner with the advanced stage of chronic renal failure or uremia [12,24]. Uncorrected anemia will result in sympathetic nervous system activation and decreases in systemic vascular resistance, contributing to the development of left ventricular hypertrophy, heart failure and increased arterial stiffness [25,26]. Epidemiologic studies have confirmed anemia to be a highly significant and independent risk factor for death and hospitalization in hemodialysis patients. Complementary cohort studies in dialysis patients demonstrated clear associations between anemia and cardiovascular disease [27]. However, the results of our study showed that after multivariate forward stepwise linear regression analysis, systolic blood pressure and age were the major independent factors associated with increased PWV in uremia patients.

Recent studies have revealed that patients with chronic renal failure show stepwise increases in the risk for cardiovascular disease and increased regional PWV in a stepwise manner at different stages of chronic renal failure (28,29). Arterial stiffness is a strong independent predictor of cardiovascular disease death in uremia patients and is an excellent predictor of survival in ESRD patients (2,3). Early diagnosis of arterial stiffness with noninvasive techniques before the development of cardiovascular complications is important in patients with uremia (10). Guerin et al showed that ACE inhibitors (perindopril) decreased PWV and improved the survival rates of patients with uremia (30). Fluvastatin reduced PWV and prevented further worsening of arterial biomechanics in diabetic uremic patients (31). Further studies with large numbers of patients and long observation periods are needed to confirm the beneficial effects of ACE inhibitors or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors on arterial stiffness in uremic patients.

There were some limitations to our study. First, this was a cross-sectional study. Therefore, the conclusions must await further exploration of outcome studies and attempts at modifying PWV. Second, the case number was small. Third, history of drug use in this study is pending and the affects of the drugs on arterial stiffness is unknown. Thus, further studies with larger numbers of patients and long follow-up periods are required to elucidate this complex relationship.

In conclusion, the results of our study showed that arterial stiffness was higher in hemodialysis patients. Systolic blood pressure and age were independent predictors of arterial stiffness in hemodialysis patients.

References

1. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol* 1999;10:1606–15.
2. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end stage renal disease. *Circulation* 1999;99:2434–9.
3. Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int* 2003;63:1852–60.
4. Chade AR, Lerman A, Lerman LO. Kidney in early atherosclerosis. *Hypertension* 2005;45:1042–9.
5. Lindner A, Charra B, Sherrard D, Scribner BM. Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 1974;290:697–702.
6. London GM, Drüeke TB. Atherosclerosis and arteriosclerosis in chronic renal failure. *Kidney Int* 1997;51:1678–95.
7. Kubo T, Miyata M, Minagoe S, Setoyama S, Maruyama I, Tei C. Simple oscillometric technique for determining new indices of arterial distensibility. *Hypertens Res* 2002; 25:351–8.
8. Yamashina A, Tomiyama H, Takeda K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002;25:359–64.
9. Yufu K, Takahashi N, Anan F, Hara M, Yoshimatsu H, Saikawa T. Brachial arterial stiffness predicts coronary atherosclerosis in patients at risk for cardiovascular diseases. *Jpn Heart J* 2004;45:231–42.
10. Munakata M, Sakuraba J, Tayama J, et al. Higher brachial-ankle pulse wave velocity is associated with more advanced carotid atherosclerosis in end-stage renal disease. *Hypertens Res* 2005;28:9–14.
11. Kitahara T, Ono K, Tsuchida A, et al. Impact of brachial-ankle pulse wave velocity and ankle-brachial blood pressure index on mortality in hemodialysis patients. *Am J Kidney Dis* 2005;46:688–96.
12. Kimoto E, Shoji T, Shinohara K, et al. Regional arterial stiffness in patients with type 2 diabetes and chronic kidney disease. *J Am Soc Nephrol* 2006;17:2245–52.
13. Guerin AP, Marchais SJ, Metivier F, London GM. Arterial structural and functional alterations in uraemia. *Eur J Clin Invest* 2005;35(Suppl 3):S85–8.
14. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;32(Suppl 3):S112–9.
15. Parfrey PS. Cardiac disease in dialysis patients: diagnosis, burden of disease, prognosis, risk factors and management. *Nephrol Dial Transplant* 2000;15(Suppl 5): S58–68.
16. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 2001;38:938–42.
17. Zoccali C, Mallamaci F, Tripepi G. Adipose tissue as a source of inflammatory cytokines in health and disease: focus on end-stage renal disease. *Kidney Int* 2003; 63(Suppl 63):S65–8.
18. Wang M, Lakatta EG. Altered regulation of matrix metalloproteinase-2 in aortic remodeling during aging. *Hypertension* 2002;39:865–73.
19. McNulty M, Spiers P, McGovern E, Feely J. Aging is associated with increased matrix metalloproteinase-2 activity in the human aorta. *Am J Hypertens* 2005;18:504–9.
20. Franklin SS, Gustin W, 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;96:308–15.
21. Benetos A, Adamopouolos C, Bureau J-M, et al. Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period. *Circulation* 2002;105:1202–7.
22. Lynn KL. Hypertension and survival in hemodialysis patients. *Semin Dial* 2004;17:270–4.
23. Hatsuda S, Shoji T, Shinohara K, et al. Regional arterial stiffness associated with ischemic heart disease in type 2 diabetes mellitus. *J Atheroscler Thromb* 2006;13: 114–21.
24. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes: the ARIC Study. *Circulation* 1995;91: 1432–43.
25. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999;34:125–34.

26. Collins AJ, Li S, St Peter W, Ebben J, Roberts T, Ma JZ, Manning W. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephro*l 2001; 12:2465–73.
27. McMahon LP. Hemodynamic cardiovascular risk factors in chronic kidney disease: what are the effects of intervention? *Semin Dial* 2003;16:128–39.
28. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296–305.
29. Wang MC, Tsai WC, Chen JY, Huang JJ. Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease. *Am J Kidney Dis* 2005;45: 494–501.
30. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001;103:987–92.
31. Ichihara A, Hayashi M, Ryuzaki M, Handa M, Furukawa T, Saruta T. Fluvastatin prevents development of arterial stiffness in haemodialysis patients with type 2 diabetes mellitus. *Nephrol Dial Transplant* 2002;17:1513–7.