ISSN 2278-7690

ARTERIAL STIFFNESS EVALUATION BY PULSE WAVE VELOCITY IN HYPERTENSION AND DIABETES MELLITUS SUBJECTS

Jiyun Wang [a, *], Jinbo Liu [b,*],Yingyan Zhou [b], Huan Liu [b], Hongyu Wang [b,#]

Cardiovascular Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, P.R. of China
trjiyunwang@126.com

[b] Department of Vascular Medicine; Peking University Shougang Hospital, Beijing 100144, P. R. of China.
lijinbo114@aliyun.com

[b] Department of Vascular Medicine; Peking University Shougang Hospital, Beijing 100144, P. R. of China
bazhongfengcai@163.com

[b] Department of Vascular Medicine; Peking University Shougang Hospital, Beijing 100144, P. R. of China.
sgliuhuan@163.com

[b] Department of Vascular Medicine; Peking University Shougang Hospital, Beijing 100144, P. R. of China.
hongyuwang@188.com

[*] Equal contributors

[#]Corresponding Author: Hongyu Wang, Department of Vascular Medicine; Peking University Shougang Hospital; Beijing 100144, P. R. of China.

Tel (Fax): +8610-57830226; +8610-57830077

hongyuwang@188.com

Abstract

Background: Arterial stiffness is an independent predictor for vascular diseases. Carotid-femoral pulse wave velocity (CFPWV) is a reliable index of arterial stiffness. In the present study, we investigated the possible risk factors involving CFPWV in hypertension and diabetes mellitus (DM) subjects.

Methods: 425 subjects (M/F 168/257) from Shougang Corporation Examination Center were divided into four groups: healthy group (n=185), hypertension group (n=135), DM group (n=32), hypertension with DM group (n=73). CFPWV was measured by Complior apparatus.

Keywords: Carotid-femoral pulse wave velocity; Hypertension; Diabetes mellitus

ISSN 2278-7690

Results: Our results showed that CFPWV was significantly higher in hypertension subjects with DM than in healthy and hypertension group, respectively (12.00+2.57 vs 10.12+2.28 m/s; 12.00+2.57 vs 10.78+2.07 m/s, both $p<0.05$). CFPWV was positively correlated with age, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), fasting plasma glucose (FBG), HbA1c, uric acid, Log NT-proBNP and Log Urine Albumin (microalbumin) Excretion [Log UAE] in the entire group(r=0.437, 0.410, 0.206, 0.423, 0.210, 0.275, 0.130, 0.135, 0.166, all $p<0.05$, respectively). Multivariate analysis showed that age, body mass index, SBP, PP, FBG were independent associating factors of CFPWV in all subjects (β=0.287, $p<0.001$; β= -0.194, $p=0.003$; β=0.223, $p=0.001$; β=0.293, $p<0.001$; β=0.161, $p=0.008$; respectively).

Conclusions: Our present study suggested that CFPWV was significantly higher in hypertension subjects with DM compared to healthy and hypertension groups.

1. Introduction

Hypertension and diabetes mellitus (DM) are the mostly risk factors of vascular-related diseases such as coronary artery diseases, stroke, and peripheral vascular diseases. And arteriosclerosis is the basic path-physiological change of hypertension and DM. Both hypertension and DM could cause macro- and micro- vascular complications, such as aortic atherosclerosis and retinal artery arteriosclerosis, leading to an increase of arterial wall thickness, endothelial dysfunction and calcification, finally leading to an increase of arterial stiffness [1]. Arterial stiffness is a strong predictor of future cardiovascular events and all-cause mortality. And it is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall [2]. Pulse wave velocity (PWV) is considered as the gold standard method of arterial stiffness suggested by European Society of Hypertension/European Society of Cardiology guidelines [3]. And our previous studies showed that arterial stiffness was positively correlated with pulse pressure and it was increased in hypertension patients with left ventricular hypertrophy [4, 5]. Recently, a meta-analysis showed that PWV is a strong predictor of future cardiovascular events and all-cause mortality, which revealed that an increase in aortic PWV by 100 cm/s corresponded to an age-, sex, and risk factor-adjusted risk increase of 14%, 15%, and 15% in total cardiovascular events, cardiovascular mortality, and all-cause mortality, respectively [6].

Biomarkers of vascular-related diseases such as homocysteine (Hcy), N-Terminal pro-brain natriuretic peptide (NT-proBNP), and urine albumin(microalbumin) excretion have involved the pathophysiological development of arteriosclerosis. However, there was little research about CFPWV and biomarkers in hypertension subjects with DM. So our present study was to investigate the possible relationship between CFPWV and biomarkers in hypertension subjects with DM.

2. Materials and methods

2.1 Subjects

425 subjects (M/F 168/257) from Shougang Corporation Examination Center from January 2012 to December 2013 were enrolled into our study. Subjects with coronary artery diseases, heart failure, stroke, renal function impairment, liver function impairment, systemic inflammatory diseases, infectious disease or cancer were excluded. They were divided into four groups: healthy group (n=185), hypertension group (n=135), DM group (n=32), hypertension with DM group (n=73).

Hypertension was defined as blood pressure measurement ≥140/90mmHg in three occasions at rest. DM was defined according to the 75 g oral glucose tolerance test (OGTT). All participants gave their written informed consent.

2.2 The assessment of CFPWV

Arterial stiffness was evaluated by measuring automatic PWV using the Complior apparatus which was used for the measurement of PWV widely around the world with great accuracy and reproducibility. The basic principle of PWV assessment is that pressure pulse generated by ventricular ejection is propagated along the arterial system at a speed determined by elasticity of the arterial wall. Knowing the distance and pulse transit time, the velocity can be calculated.

Patients were placed in recumbent position and, after a 10-minute rest, underwent PWV measurement and carotid-femoral PWV (CF-PWV) was obtained automatically. Estimation of the distance travelled by the pulse is based on measuring the distance between the common carotid artery and the right femoral artery according to previous study.

2.3 Laboratory measurements

Blood samples were drawn from an antecubital vein in the morning after overnight fasting and collected into vacuum tubes containing EDTA for the measurement of plasma lipid and lipoprotein levels. Fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), homocysteine, and hs-C reactive protein (hs-CRP) were analyzed by colorimetric enzymatic assays with the use of an autoanalyzer (HITACHI-7170, Hitachi, Tokyo, Japan) at the central chemistry laboratory of the Peking University Shougang Hospital. Low-density lipoprotein cholesterol (LDL-C) levels were calculated. Urine Albumin(microalbumin) Excretion (UAE) was determined on the 12 hours overnight urine samples calculated from the urine albumin concentration, urine volume and collection time at the central chemistry laboratory of the Peking University Shougang Hospital. The level of NT-proBNP was measured using the method of Bio-directional lateral flow immunoassay (ReLIA) according to the procedure.

2.4 Statistical analysis

The differences between groups were analyzed by one-way ANOVA and least-significant difference (LSD). Correlation coefficient was done to find linear relation between different variables using Spearman correlation coefficient. Multiple linear regressions were used to estimate the coefficients of the linear equation, involving independent variables that affected the value of the dependent variables. The values of NT-proBNP and UAE were not in normal distribution, so we made log transformation of NT-proBNP and urinary-microalbumin in the present study. Values were shown as mean± SD unless stand otherwise. $p < 0.05$ (2-tailed) was considered statistically significant.

3. Results

3.1 Clinical characteristics of the study participants

The clinical characteristics of study participants are shown in Table 1. Our results showed that the CFPWV was significantly higher in hypertension subjects with DM than in healthy and hypertension group, respectively (12.00+2.57 vs 10.12+2.28 m/s; 12.00+2.57 vs 10.78+2.07 m/s, both p<0.05). And there was significant difference in age, BMI, blood pressure, Hcy and Log UAE between these four groups.

3.2 Pearson correlations between CFPWV and metabolic markers

Next, we investigated the Pearson correlations between CFPWV and metabolic markers and other variables in the entire group. As shown in Table 2, our results showed that CFPWV was positively correlated with age, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), fasting plasma glucose (FBG), HbA1c, uric acid, Log NT-proBNP and Log UAE in the entire group(r=0.437, 0.410, 0.206, 0.423, 0.210, 0.275, 0.130, 0.135, 0.166, all p<0.05, respectively). And there was significant correlation between CFPWV and FBG, uric acid and Log UAE in non-healthy subjects (r=0.212, 0.186, 0.200, all p<0.05, respectively).

3.3 Multiple linear regression analysis

Multiple linear regressions were used to estimate the coefficients of the linear equation, involving independent variables that affected the value of CAVI. As shown in Table 3, our results showed that age, body mass index (BMI), SBP, PP, FBG were independent associating factors of CFPWV in all subjects (β=0.287, p<0.001; β= -0.194, p=0.003; β=0.223, p=0.001; β=0.293, p<0.001; β=0.161, p=0.008; respectively). BMI and PP were independent associating factors of CFPWV in healthy subjects (β= -0.216, p=0.020; β= 0.623, p<0.001; respectively). Age, BMI, SBP, FBG and UA were independent associating factors of CFPWV in non-healthy subjects (β=0.251, p=0.002; β= -0.187, p=0.031; β=0.362, p<0.001; β=0.193,

p=0.015; β=0.260, *p*=0.001; respectively).

4. Discussion

Our present study showed that CFPWV was significantly higher in hypertension subjects with DM compared to healthy and hypertension groups. There was positive correlation between CFPWV and biomarkers.

An increase of arterial stiffness is not only a pathological status of hypertension and diabetes mellitus (DM) but also a strong predictor for the cardiovascular morbidity and mortality caused by these diseases. Pulse wave velocity (PWV) has been considered as the golden method of arterial stiffness suggested by European Society of Hypertension/European Society of Cardiology guidelines [3]. And many studies have showed the value of PWV in the prediction of vascular-related accidents. Kingwell et al reported that large artery stiffness was a major determinant for myocardial ischemic threshold in patients with coronary artery disease [7]. In the Rotterdam Study [8], they reported their results that aortic PWV was an independent predictor of coronary heart disease and stroke in apparently health subjects, aortic PWV also provided additional predictive value above cardiovascular risk factors. Hansen found that PWV was a useful predictor for cardiovascular outcomes above and beyond traditional cardiovascular risk factors such as 24-hour mean blood pressure in a prospective study of general Danish population [9]. Another prospective study showed that carotid and femoral stiffness indices were independently associated with incident cardiovascular events and all-cause mortality [10]. Aortic PWV was increasing in patients with diabetes mellitus or end-stage renal disease, indicating a higher arterial stiffness compared with health persons [11]. Recent study showed that the level of CFPWV was higher in DM subjects with higher HbA1c [12]. A recent review showed that PWV was a marker of cognitive impairment in the elderly subjects [13]. Above research suggest that CFPWV is a reliable evaluation index of arterial stiffness. However, these studies focused on research about CFPWV in single disease such as DM or coronary artery disease or hypertension, and there was little research about CFPWV in hypertension subjects with DM simultaneously and hyperglycemia might exacerbate vascular function in hypertension patients. And our present study showed that CFPWV was significantly higher in hypertension subjects with DM compared to healthy and hypertension groups.

Hypertension and DM were important risk factors causing macrovascular or microvascular lesions contributing to an increase of PWV. Microalbuminuria is one of the most common complications of hypertension and DM. NT-proBNP is a controregulatory hormone associated with cardiac remodeling. Recent study showed that NT-proBNP was correlated with pulse wave velocity and ankle-brachial index in patients with DM indicating NT-proBNP could be a marker of subclinical atherosclerosis [14]. Microalbuminuria is an early indicator of impaired renal function caused by hypertension and The UAE increased significantly with the severity of hypertension [15]. And our present study showed that CFPWV was positively correlated with Log NT-proBNP and Log UAE in the entire group, and there was significant correlation between CFPWV and Log UAE in non-healthy subjects. Baena found that uric acid was significantly associated to CFPWV in an apparently healthy population, the similar result to our present study [16]. Another study showed that circulating levels of uridine, phenylacetylglutamine, and serine appear strongly correlated with PWV in women [17]. And recent study showed that high normal albuminuria was associated with aortic stiffness in DM patients [18]. These results suggested the relationship between CFPWV and complications caused by hypertension and DM, similar results to our present study. However, a major limitation of our study is its cross-sectional design; another limitation is that the subjects' numbers of each group were not balanced, so large sample and prospective study need to be investigated in future.

In conclusion, our present study suggested that CFPWV was significantly higher in hypertension subjects with DM compared to healthy and hypertension groups. And there was correlation between CFPWV and biomarkers in these subjects, more studies should be investigated in future.

Acknowledgments

This work was supported by grants from The Capital Health Research and Development of Special to HY Wang (No.

2011-4026-02), and the hospital fund of Peking University Shougang Hospital to Hongyu Wang (No. 2010-Y002 and 2014-Hospital-Clinical-02) and Jinbo Liu (No. 2012Y04) , and Shougang Keji Fund (2013 Keguan 20-1), and the Seeding Grant for Medicine and Engineering Sciences of Peking University(2014-ME-07).

References

[1] Dernellis J, Panaretou M. 2005. Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. Hypertension 2005; 45: 426-31.

[2] Cavalcante JL, Lima JAC, Redheuil A, er al. 2011.Aortic stiffness. J Am Coll Cardiol 2011; 57:1511-22.

[3] ESH/ESC Task Force for the Management of Arterial Hypertension.2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension.J Hypertens. 2013 Oct;31(10):1925-38.

[4] Ni Y, Wang H, Hu D, Zhang W. 2003.The Relationship between Pulse Wave Velocity and Pulse Pressure in Chinese Patients with Essential Hypertension. Hypertens Res 2003;26:871-874.

[5] Wang H, Zhang W, Gong L, et al. 2000.Study of relationship between large artery distensibility and left ventricular hypertrophy in patients with essential Hypertension. Chin J Cardiol, 2000;28:177-180.

[6] Vlachopoulos C, Aznaouridis K, Stefanadis C. 2010.Prediction of cardiovascular events and all-cause mortality with arterial stiffness a systematic review and meta-analysis. J Am Coll Cardiol 2010; 55:1318–27.

[7] Kingwell BA, Waddell TK, Medley TL, et al.2002. Large artery stiffness predicts ischemic threshold in patients with coronary artery disease. J. Am. Coll. Cardiol. 2002; 40;773-779.

[8] Mattace-Raso F, van der Cammen T, Hofman A, et al.2006.Arterial stiffness and risk of coronary heart disease and stroke the Rotterdam Study. Circulation 2006;113:657-663.

[9] Hansen TW, Staessen JA, Torp-Pedersen C , Rasmussen S, Thijs L, Ibsen H, et al. 2006.Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. Circulation. 2006;113:664-670.

[10] van Sloten TT, Schram MT, van den Hurk K, Dekker JM, Nijpels G, Henry RM, Stehouwer CD. Local stiffness of the carotid and femoral artery is associated with incident cardiovascular events and all-cause mortality: the Hoorn study. 2014.J Am Coll Cardiol. 2014 May 6;63(17):1739-47. doi: 10.1016/j.jacc.2013.12.041. Epub 2014 Feb 26.

[11] Aoun S, Blacher J, Safar ME, Mourad JJ. 2001.Diabetes mellitus and renal failure:effects on large artery stiffness. Journal of Human Hypertension 2001; 15:693-700.

[12] Ferreira MT, Leite NC, Cardoso CR, Salles GF. 2015.Correlates of Aortic Stiffness Progression in Patients With Type 2 Diabetes: Importance of Glycemic Control: The Rio de Janeiro Type 2 Diabetes Cohort Study. Diabetes Care. 2015 Feb 12. pii: dc142791. [Epub ahead of print]

[13]Scuteri A, Wang H. 2014.Pulse wave velocity as a marker of cognitive impairment in the elderly. J Alzheimers Dis. 2014;42 Suppl 4:S401-10. doi: 10.3233/JAD-141416.

[14] Senmaru T, Fukui M, Tanaka M, Sakabe K, Ushigome E, Asano M, et al. 2013.N-terminal pro-brain natriuretic peptide could be a marker of subclinical atherosclerosis in patients with type 2 diabetes. Heart Vessels. 2013 Mar;28(2):151-6. doi: 10.1007/s00380-011-0227-0. Epub 2012 Jan 11.

[15] Oluwatowoju IO, Ajuluchukwu JN, Afonja OA. 2014.Clinical usefulness of a timed overnight (8 hours) Urine Albumin (microalbumin) excretion in monitor-ing treatment in benign essential hypertension. Niger Postgrad Med J. 2014 Jun;21(2):177-80.

[16] Baena CP, Lotufo PA, Mill JG, Cunha RS, Benseñor IJ. 2015.Serum Uric Acid and Pulse Wave Velocity Among Healthy Adults: Baseline Data From the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Am J Hypertens. 2015 Jan 21. pii: hpu298. [Epub ahead of print]

[17] Menni C, Mangino M, Cecelja M, Psatha M, Brosnan MJ, Trimmer J, et al. 2014.Metabolomic study of carotid-femoral pulse-wave velocity in women. J Hypertens. 2014 Dec 8. [Epub ahead of print]

[18] Liu JJ, Tavintharan S, Yeoh LY, et a; 2014. SMART2D study. High normal albuminuria is independently associated with aortic stiffness in patients with Type 2 diabetes. Diabet Med. 2014 Oct;31(10):1199-204. doi: 10.1111/dme.12461.

Table 1 Clinical characteristics in different groups.

Characterisitics	Healthy (N=185)	Hypertension (N=135)	DM (N=32)	Hypertension + DM (N=73)	*p*
Age (year）	55.95+10.47	59.01+10.58	61.22+9.46*	61.44+10.85*	<0.001
Male/Famale	74/111	54/81	12/30	28/45	0.988
BMI	24.35+3.43	25.93+3.08	24.89+4.25	25.97+3.38*	<0.001
CFPWV	10.12+2.28	10.78+2.07	11.04+2.47	12.00+2.57*#	<0.001
SBP (mmHg）	128.7+16.2	143.0+19.4*&	130.8+15.8	147.4+18.5*&	<0.001
DBP (mmHg）	80.6+9.6	87.5+11.4*&	80.3+10.3	88.6+10.3*&	<0.001
PP (mmHg）	48.1+10.5	55.4+13.9*	50.7+12.2	58.8+16.0*&	<0.001
FPG (mmol/L)	5.50+0.85	5.54+0.88	7.15+1.72*#	6.60+2.00*#	<0.001
HbA1c %	5.54+0.61	5.55+0.84	6.46+1.00*#	6.71+1.26*#	<0.001
UA	298.17+72.0	314.70+81.60	288.68+68.06	309.01+80.0	0.160
TC (mmol/L)	5.17+1.10	5.07+1.15	4.82+1.09	4.64+1.30*	0.008
HDL-C (mmol/L)	1.33+0.35	1.27+0.33	1.26+0.31	1.18+0.26*	0.012
LDL-C (mmol/L)	3.24+0.89	3.21+0.88	3.00+0.92	2.68+0.94*	<0.001
TG (mmol/L)	1.71+1.39	1.84+1.59	1.76+1.02	1.75+1.17	0.894
HCY	11.54+5.92	14.31+9.00*	10.09+3.93#	13.98+6.59	0.001
Log NT-proBNP	2.03+0.40	2.08+0.46	2.14+0.51	2.20+0.27	0.085
Log UAE	0.57+0.39	0.75+0.55*	0.80+0.59	0.84+0.60*	0.004

Note: * vs Normal p<0.05; # vs Hypertension p<0.05; & vs DM p<0.05. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; FPG: fasting plasma glucose; UA: uric acid; TC: cholesterol; LDL-C: low-density lipoprotein cholesterol. HDL-C: high-density lipoprotein cholesterol. TG: triglycerides. UAE: Urine Albumin (microalbumin) Excretion , CF-PWV:Carotid-femoral pulse wave velocity. The differences between groups were

analyzed by one-way ANOVA and least-significant difference (LSD). Proportions were analyzed by χ^2 -test.

Table 2 Spearman correlations between CFPWV and study variables among entire study group, healthy group and non-healthy group

	Entire group (N=425)		Healthy group (N=185)		Non-healthy group (N=240)	
	r	P value	r	P value	r	P value
Age (year）	0.437	<0.001	0.451	<0.001	0.384	<0.001
BMI	-0.014	0.774	-0.109	0.148	-0.029	0.653
SBP (mmHg）	0.410	<0.001	0.364	<0.001	0.363	<0.001
DBP (mmHg）	0.206	<0.001	0.122	0.098	0.173	0.008
PP (mmHg）	0.423	<0.001	0.448	<0.001	0.355	<0.001
FPG (mmol/L)	0.210	<0.001	0.091	0.221	0.212	0.001
HbA1c %	0.275	<0.001	0.087	0.307	0.203	<0.001
UA	0.130	0.008	0.017	0.817	0.186	0.004
HCY	0.088	0.078	-0.032	0.675	0.105	0.117
Log NT-proBNP	0.135	0.014	0.160	0.050	0.081	0.282
Log UAE	0.166	0.004	-0.032	0.736	0.200	0.007

Note: BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; FPG: fasting plasma glucose; UA: uric acid; UAE: Urine Albumin (microalbumin) Excretion , CF-PWV:Carotid-femoral pulse wave velocity.

ISSN 2278-7690

Table 3 Multiple linear regression analysis for the relationship between CFPWV and study variables among entire study group, healthy group and non-healthy group

	Entire group (N=425)		Healthy group (N=185)		Non-healthy group (N=240)	
	β	P value	β	P value	β	P value
Age (year）	0.287	<0.001	0.178	0.065	0.251	0.002
BMI	-0.194	0.003	-0.216	0.020	-0.187	0.031
SBP (mmHg）	0.223	0.001	0.050	0.753	0.362	<0.001
DBP (mmHg）	-0.051	0.406	0.029	0.753	0.197	0.114
PP (mmHg）	0.293	<0.001	0.623	<0.001	-0.267	0.127
FPG (mmol/L)	0.161	0.008	0.102	0.279	0.193	0.015
HbA1c %	-0.040	0.613	0.033	0.732	-0.005	0.959
UA	0.139	0.019	0.025	0.788	0.260	0.001
HCY	-0.051	0.406	-0.054	0.547	-0.044	0.592
Log NT-proBNP	-0.074	0.237	-0.020	0.824	-0.099	0.251
Log UAE	0.072	0.252	0.082	0.417	0.070	0.395

Note: BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; FPG: fasting plasma glucose; UA: uric acid; UAE: Urine Albumin (microalbumin) Excretion , CF-PWV:Carotid-femoral pulse wave velocity.