Evaluation of the Associations between Vascular Endothelial Function and Coronary Artery Stenosis in Patients with Elevated Blood Pressure during Coronary Angiography

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ABSTRACT

Objectives: The aim of the present study is to explore the correlation between vascular endothelial function and coronary artery stenosis in non-hypertensive patients with elevated blood pressure under stress.

Methods: This study included 1141 patients suspected of having coronary artery disease (CAD) without hypertension. Coronary arteriography and ultrasonic detection were used to measure the flow-mediated dilatation (FMD) function in the brachial artery. Patients were divided into 2 groups according to coronary angiography: experiment group, patients with blood pressure ≥ 140/90 mm Hg; control group, patients with blood pressure <140/90 mm Hg. The correlation between vascular endothelial function and coronary artery stenosis was observed.

Results: The majority of the patients in the control group were found to have either normal coronary arteries or stenosis <50%. Patients in the experiment group (those with invasive blood pressure [IBP] >140/90) were more likely to have some degree of coronary artery stenosis. Specifically, there were significantly more patients with >50% stenosis in the experiment when compared with the control group ($P < .05$). The FMD in the experiment group was significantly lower than that in the control group ($P < .05$).

Conclusion: The non-hypertensive patients with elevated blood pressure under stress had coronary artery stenosis, which was associated with vascular endothelial dysfunction.

INTRODUCTION

Coronary vascular endothelial function plays a pivotal role in the development, progression, and clinical manifestations of coronary artery disease (CAD) [Ludmer 1986]. CAD has multiple classic risk factors, including aging, hypertension, diabetes mellitus, smoking, and hyperlipidemia [Modan 1985; DeFronzo 1991]. The presence of multiple metabolic derangements in certain subjects has also been associated with a threefold increased risk of coronary heart disease, myocardial infarction, and stroke, and a three- to five-fold increased risk of cardiovascular death [Hurst 2003; Isomaa 2001; Olijhoek 2004].

One defining characteristic of non-diseased vascular tissue is endothelial release of nitric oxide (NO), which inhibits platelet aggregation, attenuates inflammation, decreases cellular proliferation, and induces local vascular smooth muscle vasodilation [Deanfield 2007]. Functional changes in coronary arteries precede lesion formation and become more pronounced with disease progression [Luscher 1995; Ludmer 1986; Schachinger 1995]. Endothelial dysfunction occurs as a response to injury to oxidized low-density lipoproteins [Deanfield 2007; Tanner 1991], hypertension [Luscher 1987; Linder 1990; Panza 1990], increased blood glucose [Cosentino 1997; Johnstone 1993], and oxygen-derived free radicals [Mugge 1991]. Endothelial dysfunction is a key process in atherosclerosis and has been reported in chronic mild fasting hyperhomocysteinemia in subjects free of vascular disease [Cosentino 1997; Johnstone 1993].

There is a strong and frequent association between arterial hypertension and CAD. Hypertension induces endothelial dysfunction, exacerbates the atherosclerotic process, and contributes to making the atherosclerotic plaque more unstable. People with hypertension have a 3-4 times higher risk of coronary disease than those with normal blood pressure. Thus, early control of blood pressure is very important for delaying the occurrence of coronary artery atherosclerosis in patients. In our clinical work, coronary artery stenosis was found in non-hypertensive patients with elevated blood pressure under stress such as tension, fear, or irritation, especially in patients with a significant rise in blood pressure because of tension in coronary angiogram. Thus, the purpose of the present study is to evaluate the correlations between vascular endothelial function and coronary artery stenosis in non-hypertensive patients with elevated blood pressure under stress.

METHODS

Study Population

Between October 2004 and October 2011, 1141 consecutive patients (age 56.7 ± 11.3; 589 male, 552 female) who were admitted to our hospital for coronary angiography were studied. Vasoactive medications including calcium-channel blockers, ACE inhibitors, and long-acting nitrates were withheld for over 24 hours before the start of the study. The protocol of this study was approved by the institutional Human Investigation Review Committee, and written informed consent was obtained from all patients before enrollment into the study. We excluded patients with a history of hypertension, acute myocardial infarction or old myocardial infarction, and coronary stent implantation or coronary artery bypass surgery.

Table 1. Baseline Characteristics of the Study Population*

	IBP <140/90 mm Hg (n = 507)	IBP ≥140/90 mm Hg (n = 634)	P value
Age, y	55±12	56±11	.45
Male sex, n	291	298	.24
Height, cm	174.2±11.7	172.4±10.3	.19
Weight, kg	75.2±14.3	77.5±16.2	.21
BMI, kg/m2	28.4±3.2	26.3±4.1	.18
Smoking, n	56	72	.11
Heart rate, bpm	67±10	66±10	.32
LDL-C, mg/dL	131±35	128±32	.16
HDL-C, mg/dL	47±12	45±10	.25
Triglycerides, mg/dL	158±51	161±47	.18
Systolic BP, mm Hg†	133±16	132±16	.32
Diastolic BP, mm Hg†	73±9	72±9	.21

*Data are expressed as mean ± SD of the patients. BMI indicates body mass index; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; BP: blood pressure.
†Blood pressure was taken at 1 hour before coronary angiography.

Study Design

The blood pressure of the patients was taken during angiography. Patients with invasive blood pressure (IBP) ≥140/90 mm Hg were assigned to the experiment group, and patients with IBP >140/90 mm Hg were assigned to the control group. Coronary angiography results were divided into three grades: normal (coronary artery stenosis was not detected), stenosis <50%, and stenosis >50%.

Coronary Angiography

Coronary angiography was performed by appointed cardiologists and angiograms were analyzed at a core lab. Left and right coronary angiography was performed via the femoral and radial artery. Readers were blinded to patients' identity and the severity of coronary artery stenosis was expressed by diameter method. Identification of CAD and assessment of its extent and severity were the indications for cardiac catheterization.

Measurements of Flow-Mediated Dilatation in the Brachial Artery

Patients were studied under quiet conditions in a temperature-controlled room after 30 minutes of supine rest. Flow-mediated dilatation (FMD) was measured by use of Doppler high-resolution ultrasound and electrocardiogram (ECG) was recorded at the same time. Briefly, optimal brachial artery images were obtained approximately 2 and 3 cm above the antecubital fossa. This location was marked, and all subsequent images were obtained at the same location. The exact distance of the measured point on the skin surface from the antecubital fossa was recorded in each patient to ensure that

Table 2. Coronary Arteriography of Patients in Experiment and Control Group

Group	Normal	Stenosis <50%	Stenosis >50%
IBP <140/90 (n = 507)	224 (44%)	198 (39%)	85 (17%)
IBP ≥140/90 (n = 634)	136 (22%)*	286 (45%)	212 (33%)*

IBP indicates invasive blood pressure.
*$P < .05$.

the same segment of the brachial artery was measured at each time point during follow-up. A forearm blood-pressure cuff was placed distal to the antecubital fossa and inflated to 300 mm Hg for 4 minutes. End-diastolic diameter was measured at baseline and at approximately 60-90 seconds after cuff deflation. Endothelium-dependent vasomotion was determined by the maximal brachial artery diameter after exactly 60 seconds of reactive hyperemia compared with the baseline vessel diameter, and was expressed as percent FMD: $(\text{diameter}_{max} - \text{diameter}_{baseline})/\text{diameter baseline} \times 100\%$.

Statistical Analysis

All measurements and analysis of all measures were done in a blinded fashion. Data were entered into Excel and analyzed with SPSS 15.0 (SPSS, Chicago, IL, USA). Data are expressed as mean ± SE. Comparisons between the experiment and control group were performed with an unpaired t test or Pearson's χ^2 test to demonstrate potential associations with FMD. $P < .05$ was considered statistically significant.

RESULTS

Patient Characteristics

A total of 1141 patients (589 male, 552 female) with a mean age of 56.7 ± 11.3 were enrolled and assigned to the experiment group (n = 634) or the control group (n = 507) according to their IBP (Table 1).

Result of Coronary Arteriography

Coronary arteriography was performed in order to determine whether elevated blood pressure under stress would have an effect on CAD. As shown in Table 2, the majority of the patients in the control group were found to have either normal coronary arteries or stenosis <50%. Patients in the experiment group (those with IBP >140/90) were more likely to have some degree of coronary stenosis. Specifically, there were significantly more patients with >50% stenosis in the experiment when compared with the control group ($P < .05$).

Effect of Elevated Blood Pressure Under Stress on Vascular Endothelial Function

The effect of elevated blood pressure under stress on vascular endothelial function is shown in Table 3. There was

Table 3. Brachial Artery Ultrasound Measurements

	IBP <140/90 mm Hg (n = 507)	IBP ≥140/90 mm Hg (n = 634)
Baseline diameter, mm	4.14±0.15	4.16±0.21
FMD diameter, mm	4.65±0.40	4.42±0.15
% FMD	12.24±1.63	6.48±0.85*

IBP indicates invasive blood pressure; FMD: flow-mediated dilatation.
*$P < .05$.

no significant difference in baseline brachial artery dimensions between the control and experiment groups. FMD was significantly lower (4.42 ± 0.15) in the 634 subjects with IBP ≥140/90 mm Hg compared with the 507 subjects with IBP <140/90 mm Hg (4.65 ± 0.40).

DISCUSSION

Psychological pressure-induced temporal stress condition is common when patients receive coronary angiography. Stress is an organism's response to a stressor such as an environmental condition or a stimulus. Previous studies have demonstrated that stress can affect vascular endothelial function in spontaneously hypertensive rats. The stress state can affect multiple systems, such as blood pressure, arteriosclerosis, blood fat, blood sugar by changing the body's neuroendocrine, endothelial function, and behavior [Seeman 2001]. Therefore, stress has been recognized as a major risk factor for hypertension, coronary heart disease, diabetes, and hyperlipoidemia [Ducher 2006; Jiang 2008].

Previous reports have noted a correlation between abnormalities in FMD of the brachial artery and the presence of CAD by coronary angiography [Neunteufl 1997; Schroeder 1999]. In this study, we demonstrated for the first time that there are associations between coronary artery stenosis and FMD in patients with elevated blood pressure under stress, which includes tension and fear. The results show that patients with significantly increased blood pressure always have coronary artery stenosis and there were significantly more patients with stenosis >50% than with a normal coronary artery. In addition, FMD was significantly lower in individuals with coronary artery stenosis compared with those who had a normal coronary artery. Furthermore, FMD was an independent predictor of coronary artery stenosis.

The mechanism that hypertension leads to coronary atherosclerotic cardiopathy is unclear. It has been reported that vascular endothelial injury can cause endothelium-derived relaxing factors (EDRFs) to decrease and endothelium-derived contracting factors (EDCFs) to increase, thus leading to a decrease of endothelium-dependent dilatation and elevated blood pressure [Drexler 1999]. It has been recognized that endothelial dysfunction is closely related to initiation and progression of coronary atherosclerotic diseases and cardiac events [Bissinger 2011]. Therefore, FMD of patients in both groups was measured and the result suggests that endothelial function in patients with elevated blood pressure is significantly lower than in patients with normal blood pressure, demonstrating that there is endothelium dysfunction and coronary artery stenosis in non-hypertensive patients with elevated blood pressure under stress.

In conclusion, the current study shows that endothelium dysfunction can be found in the early period of hypertension. Non-hypertensive patients with elevated blood pressure under stress are in an early period of hypertension, which can lead to endothelium dysfunction and coronary artery stenosis. One limitation of this study is that the subjects were not evaluated to see if they were experiencing stress during the coronary angiography. However, further studies are needed to define the mechanisms and clinical implications of vascular effects.

REFERENCES

Bissinger A, Grycewicz T, Wlodzimierz G, et al. 2011. Endothelial function and left ventricular remodeling in diabetic and non-diabetic patients after acute coronary syndrome. Med Sci Monit 17:CR73-7.

Cosentino F, Hishikawa K, Katusic ZS, et al. 1997. High glucose increases nitric oxide synthase expression and superoxideanion generation in human aortic endothelial cells. Circulation 96:25-8.

Deanfield JE, Halcox JP, Rabelink TJ. 2007. Endothelial function and dysfunction: testing and clinical relevance. Circulation 115:1285-95.

DeFronzo RA, Ferrannini E. 1991. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 14:173-94.

Drexler H, Hornig B. 1999. Endothelial dysfunction in human disease. J Mol Cell Cardiol 31:51-60.

Ducher M, Cerutti C, Chatellier G, et al. 2006. Is high job strain associated with hypertension genesis? Am J Hypertens 19:694-700.

Hurst RT, Lee RW. 2003. Increased incidence of coronary atherosclerosis in type 2 diabetes mellitus: mechanisms and management. Ann Intern Med 139:824-34.

Isomaa B, Almgren P, Tuomi T, et al. 2001. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 24:683-9.

Jiang L, Beals J, Whitesell NR, et al. 2008. Stress burden and diabetes in two American Indian reservation communities. Diabetes Care 31:427-9.

Johnstone MT, Creager SJ, Scales KM, et al. 1993. Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. Circulation 88:2510-6.

Linder L, Kiowski W, Buhler FR, Luscher TF. 1990. Indirect evidence for release of endothelium-derived relaxing factor in human forearm circulation in vivo. Blunted response in essential hypertension. Circulation 81:1762-7.

Ludmer PL, Selwyn AP, Shook TL, et al. 1986. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 315:1046-51.

Luscher TF, Raij L, Vanhoutte PM. 1987. Endothelium-dependent vascular responses in normotensive and hypertensive Dahl rats. Hypertension 9:157-63.

Luscher TF, Noll G. 1995. The endothelium in coronary vascular control. In: Braunwald E ed. Heart Disease, Update 3, Philadelphia: Saunders, pp. 1-10.

Modan M, Halkin H, Almog S, et al. 1985. Hyperinsulinemia. A link between hypertension obesity and glucose intolerance. J Clin Invest 75:809-17.

Mugge A, Elwell JH, Peterson TE, et al. 1991. Chronic treatment with polyethylene-glycolated superoxide dismutase partially restores endothelium-dependent vascular relaxations in cholesterol-fed rabbits. Circ Res 69:1293–1300. Neunteufl T, Katzenschlager R, Hassan A, et al. 1997. Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. Atherosclerosis 129:111-8.

Olijhoek JK, Van Der Graaf Y, Banga JD, et al. 2004. The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm. Eur Heart J 25:342-8.

Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE. 1990. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 323:22-7.

Schachinger V, Zeiher AM. 1995. Quantitative assessment of coronary vasoreactivity in humans in vivo. Importance of baseline vasomotor tone in atherosclerosis. Circulation 92:2087-94.

Schroeder S, Enderle M, Ossen R, et al. 1999. Noninvasive determination of endothelium-mediated vasodilation as a screening test for coronary artery disease: pilot study to assess the predictive value in comparison with angina pectoris, electrocardiography, and myocardial perfusion imaging. Am Heart J 138:731–9.

Seeman TE, McEwen BS, Rowe JW, et al. 2001. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci USA 98:4770-5.

Tanner FC, Noll G, Boulanger CM, Luscher TF. 1991. Oxidized low density lipoproteins inhibit relaxation of porcine coronary arteries. Role of scavenger receptor and endothelium-derived nitric oxide. Circulation 83:2012-20.