CARDIOVASCULAR MEDICINE

Coronary flow reserve is preserved in white-coat hypertension

D Erdogan, H Gullu, M Caliskan, I Yildirim, D Tok, H Muderrisoglu

See end of article for
authors' affiliations

Heart 2006;92:1109–1112. doi: 10.1136/hrt.2005.074914

Correspondence to:

Dr Dogan Erdogan,
Cardiology Department,
Konya Teaching and
Medical Research Center,
Baskent University, Hoca
Cihan Mah, Saray Cad,
No 1, Selcuklu, Konya,
Turkey; aydoganer@
yahoo.com

Accepted 2 December
2005

Published Online First
30 December 2005

Objectives: To assess the possible influence of white-coat hypertension (WCH) on coronary flow reserve (CFR).

Methods: CFR was measured by means of transthoracic second harmonic Doppler echocardiography in 29 patients with WCH, 32 patients with sustained hypertension and 35 healthy volunteers.

Results: CFR was significantly lower in the sustained hypertension group than in the WCH and the control groups, but it was not different between the WCH and the control groups (2.40 (SD 0.54), 2.77 (0.41) and 2.83 (0.60), respectively).

Conclusion: CFR is preserved in patients with WCH.

White-coat hypertension (WCH) is defined as persistently raised office blood pressure (BP) in the absence of a rise in average daytime ambulatory BP.¹ About 25% of patients with high BP in the clinic have a normal BP on ambulatory BP monitoring (ABPM).^{2–3} Some recent studies, but not all, suggested that patients with WCH have a better prognosis than patients with sustained hypertension.^{4–6} Developed recently, transthoracic second harmonic Doppler echocardiography (TTDE) is a useful tool that produces highly reproducible results in evaluating coronary flow reserve (CFR) and several studies have validated its feasibility.^{7–9} Although substantial evidence supports the contention that WCH does not cause end-organ damage, to date no study has investigated CFR in these patients with the use of TTDE. In this study, we used TTDE to measure CFR in normotensive patients, in patients with WCH, and in patients with newly diagnosed and never treated sustained hypertension without excessive left ventricular hypertrophy.

METHODS

Study population

We consecutively selected 29 patients for the WCH group, 32 patients for the sustained hypertension group and 35 healthy volunteers for the control group from our cardiology outpatient clinic. Inclusion criteria were age 18–55 years, a regular menstrual cycle for women and office BP between 90–109 mm Hg diastolic or 140–179 mm Hg systolic (mild or moderate hypertension) for the WCH and sustained hypertensive participants. Exclusion criteria were any systemic disease such as haemolytic, hepatic and renal diseases or any disease that can cause CFR impairment (for example, diabetes mellitus or an impaired oral glucose tolerance test), family history of coronary artery disease, smoking, alcohol use and any history of antihypertension drug use for all groups.

Patients taking any vasoactive drug or with ECG changes specific for myocardial ischaemia, hyperlipidaemia, raised liver enzymes, body mass index > 30 kg/m² or excessive left

ventricular hypertrophy (left ventricular mass index > 125 g/m² in men and > 110 g/m² in women)¹⁰ were excluded from the study. Two patients (2.04%) were excluded because their left anterior descending coronary artery (LAD) was inadequately visualised. Written informed consent was obtained from each participant, and the institutional ethics committee approved the study protocol.

BP measurement

BP was measured with a mercury sphygmomanometer in the office setting. Non-invasive 24 h ambulatory BP was monitored with a portable recorder (Model 92512; Spacelabs Medical, Redmond, Virginia, USA) and analysed with the manufacturer's software (Model 90207; Spacelabs Medical). All participants wore an ABPM device for 24 h BP recording every 15 min during the daytime (between 07 00 and 23 00) and every 30 min during the night (between 23 00 and 07 00), which provided about 80 records over 24 h. When valid readings exceeded at least 80% of the total, the recording was considered satisfactory.

Diagnosis of WCH and sustained hypertension

Participants' BP was measured after they had been sitting comfortably for 15 min on three separate days and averaged. Then each participant undertook 24 h ABPM. WCH was defined in office setting as systolic BP ≥ 140 mm Hg and diastolic BP ≥ 90 mm Hg and in ABPM as an average daytime systolic BP < 135 mm Hg and diastolic BP < 85 mm Hg and an average night time systolic BP < 125 mm Hg and diastolic BP < 75 mm Hg. Office systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg and averaged ABPM daytime systolic BP ≥ 135 mm Hg or diastolic BP ≥ 85 mm Hg and night time systolic BP ≥ 125 mm Hg or diastolic BP ≥ 75 mm Hg led to a diagnosis of sustained

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CFR, coronary flow reserve; LAD, left anterior descending coronary artery; TTDE, transthoracic second harmonic Doppler echocardiography; WCH, white-coat hypertension

Table 1 Demographic and biochemical characteristics of the three groups

	White-coat hypertension (n = 29)	Sustained hypertension (n = 32)	Normotensive controls (n = 35)
Age (years)	46.6 (6.4)	45.1 (7.1)	44.5 (6.1)
Men/women	12/17	16/16	16/19
Body mass index (kg/m ²)	27.9 (2.1)	26.9 (2.6)	27.6 (1.7)
Office systolic BP (mm Hg)	144.5 (6.7)*	145.7 (7.5)*	115.5 (10.7)
Office diastolic BP (mm Hg)	92.6 (4.6)*	93.3 (3.4)*	72.5 (5.7)
Heart rate (beats/min)	68.5 (10.3)	70.5 (10.6)	73.2 (8.8)
Total cholesterol (mmol/l)	5.04 (0.66)	4.96 (0.72)	4.74 (0.68)
HDL cholesterol (mmol/l)	1.28 (0.33)	1.31 (0.30)	1.19 (0.28)
LDL cholesterol (mmol/l)	2.98 (0.56)	2.99 (0.54)	2.96 (0.63)
Triglyceride (mmol/l)	1.62 (0.58)	1.42 (0.64)	1.46 (0.63)
Haemoglobin (g/l)	141 (10)	143 (11)	142 (12)
hsCRP (mg/l)	2.8 (1.9)	2.9 (2.2)	2.1 (1.4)
Glucose (mmol/l)	5.17 (0.45)	5.20 (0.40)	5.08 (0.40)

Data are mean (SD) or number.

*p<0.001 versus control group.

BP, blood pressure; hsCRP, high-sensitivity C reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

hypertension. Control group participants had office systolic BP < 140 mm Hg or diastolic BP < 90 mm Hg and averaged ABPM daytime systolic BP < 135 mm Hg and diastolic BP < 85 mm Hg, and night time systolic BP < 125 mm Hg and diastolic BP < 75 mm Hg.

Echocardiographic examination and CFR measurement

Each participant was examined with an Acuson Sequoia C256 echocardiography system equipped with 3V2c and 5V2c broadband transducers (Acuson, Mountain View, California, USA). The distal LAD was visualised from a modified, foreshortened two-chamber view obtained by sliding the transducer on the upper part and medially from an apical two-chamber view. Coronary flow in the distal LAD was examined by colour Doppler flow mapping over the epicardial part of the anterior wall, with the colour Doppler velocity set in the range of 8.9–24.0 cm/s.¹¹ The left ventricle was imaged on the long-axis cross section, and the ultrasound beam was then inclined laterally. Next, coronary blood flow in the LAD (middle to distal) was searched by colour Doppler flow mapping. All participants had Doppler recordings of the LAD with a dipyridamole infusion at a rate of 0.56 mg/kg over 4 min. Placing the sample volume on the colour signal allowed spectral Doppler of the LAD to show the characteristic biphasic flow pattern with larger diastolic and smaller systolic components. Coronary diastolic peak velocities were measured at baseline and after dipyridamole infusion by averaging the highest three Doppler signals for each measurement. CFR was defined as the ratio of hyperaemic to baseline diastolic peak velocities.¹¹ CFR was successfully measured in 96 of the 98 participants (98%). To test the reproducibility of CFR measurement, in 20 participants the measurement was repeated two days later. The intraobserver intraclass correlation coefficient was 0.855 for coronary flow measurement and 0.834 for CFR.

Statistical analyses

Data were analysed with SPSS V.9.0 (SPSS, Chicago, Illinois, USA). Data are expressed as mean (SD). The three groups were compared by one-way analysis of variance followed by Tukey's test for multiple comparisons or Kruskal–Wallis test when appropriate. Pearson's correlation test was used to test possible associations. A value of p < 0.05 was considered significant.

Table 2 Ambulatory blood pressure (BP) monitoring data of the study subjects.

Blood pressure (mm Hg)	White-coat hypertension	Sustained hypertension	Normotensive controls
24 h systolic	112.3 (10.4)	135.8 (11.7)*	111.6 (7.2)
24 h diastolic	72.2 (11.7)	99.4 (9.9)*	69.0 (6.5)
Daytime systolic	113.9 (12.7)	138.4 (16.1)*	114.4 (7.6)
Daytime diastolic	74.7 (11.7)	92.6 (10.7)*	71.4 (6.9)
Night time systolic	107.2 (11.0)	128.4 (16.0)*	105.6 (7.1)
Night time diastolic	67.9 (11.2)	83.5 (12.2)*	62.9 (7.5)

Data are mean (SD).

*p<0.001 versus patients with white-coat hypertension and controls.

RESULTS

Demographic features and biochemical measurements were similar in the three groups. Office BP was similar between the WCH and the sustained hypertension groups but was significantly lower in the controls (table 1).

Average daytime and night time systolic and diastolic BP was significantly higher in the sustained hypertension group than in the other two groups. Average daytime and night time systolic and diastolic BP was not different between the WCH and the control groups (table 2).

Left ventricular mass index and end diastolic and end systolic diameters were significantly greater in the sustained hypertension group than in the WCH and the control groups (table 3).

Analysis of CFR measurements

Heart rate was similar in the three groups. Peak systolic and diastolic BP was higher in the sustained hypertension group than in the other two groups (table 3). Baseline diastolic peak flow velocity of LAD was similar between the WCH and the control groups but was significantly higher in the sustained hypertension group than in the control group and slightly higher than that in the WCH group (p = 0.09). Hyperaemic diastolic peak flow velocity of the LAD, however, was slightly lower in the sustained hypertension group than in the other two groups; accordingly, CFR was significantly lower in the sustained hypertension group than in the WCH (p = 0.005) and the control groups (p = 0.003) but was not different between the WCH and the control groups (table 3).

CFR inversely correlated with age (r = -0.318, p = 0.002). Mitral E velocity and mitral E:A ratio slightly correlated with CFR (r = 0.202, p = 0.04; r = 0.292, p = 0.004, respectively).

DISCUSSION

In this study, by using TTDE we evaluated CFR and thereby coronary microvascular functions in patients with WCH or sustained hypertension and in controls. We have found that CFR was significantly impaired in patients with sustained hypertension; however, CFR did not differ between patients with WCH and the control group. Hypertensive patients with no epicardial coronary artery disease are known to have reduced CFR and increased rest coronary flow velocity even in the absence of left ventricular hypertrophy and left ventricular diastolic dysfunction,^{12–14} as our results show.

Although WCH has been widely studied in recent years, it remains a matter of controversy. Some recent studies suggested that WCH may be a benign condition and does not cause end-organ damage, and thus pharmacological intervention may not be necessary.^{15–17} On the other hand, some reported results were contradictory.^{18,19} In line with the findings of Cardillo *et al*,¹⁹ we found that the left ventricular mass index differed significantly between the sustained hypertension and control groups, and that in patients with WCH left ventricular mass index was slightly greater than

Table 3 Data from echocardiographic examinations of the study participants

	White-coat hypertension	Sustained hypertension	Normotensive controls
Interventricular septum (cm)	1.08 (0.12)	1.14 (0.12)*†	1.07 (0.08)
Posterior wall (cm)	1.01 (0.11)	1.04 (0.11)	0.99 (0.07)
LVDD (cm)	4.52 (0.31)	4.63 (0.33)*	4.47 (0.31)
LVSD (cm)	2.84 (0.21)	2.90 (0.17)*	2.76 (0.20)
Left atrial diameter (cm)	3.25 (0.5)	3.35 (0.6)	3.17 (0.3)
Ejection fraction (%)	66.6 (1.4)	67.2 (2.3)	67.4 (1.9)
LVMI (g/m ²)	95.2 (18.0)	100.7 (16.9)*	91.0 (12.5)
Peak mitral E velocity (cm/s)	75.5 (15.0)	72.3 (16.2)	74.3 (14.2)
Peak mitral A velocity (cm/s)	70.8 (16.9)	70.3 (16.0)	68.2 (10.9)
E:A	1.10 (0.25)	1.07 (0.33)	1.11 (0.22)
Mitral E deceleration time (s)	203.6 (42.5)	205.2 (49.1)	188.0 (18.2)
Baseline heart rate (beats/min)	71.5 (11.2)	72.3 (11.7)	75.8 (9.9)
Baseline systolic BP (mm Hg)	146.7 (7.7)**	146.9 (6.7)**	118.2 (12.7)
Baseline diastolic BP (mm Hg)	93.4 (4.4)**	94.0 (4.1)**	75.5 (6.0)
Peak heart rate (beats/min)	94.3 (12.1)	94.2 (14.7)	98.5 (10.6)
Peak systolic BP (mm Hg)	135.3 (7.7)**	143.4 (9.3)**††	116.2 (13.0)
Peak diastolic BP (mm Hg)	87.7 (4.5)**	90.9 (3.9)**††	72.0 (6.7)
Baseline DPFV (cm/s)	24.7 (3.6)	26.1 (5.2)*	23.2 (3.7)
Hyperaemic DPFV (cm/s)	68.4 (13.3)	63.3 (19.4)	65.7 (15.9)
Coronary flow reserve	2.77 (0.41)	2.40 (0.54)**††	2.83 (0.60)

*p<0.05 versus controls; †p<0.05 versus white-coat hypertension; **p<0.01 versus controls; ††p<0.01 versus white-coat hypertension.

BP, blood pressure; DPFV, diastolic peak flow velocity of left anterior descending coronary artery; LVDD, left ventricular diastolic diameter; LVMI, left ventricular mass index; LVSD, left ventricular systolic diameter.

that of the controls and slightly lower than that of the sustained hypertension group, but these differences were not significant.

Recently, Pierdomenico *et al.*¹⁷ suggested that patients with WCH had significantly higher concentrations of nitrogen oxides than did patients with sustained hypertension, as well as significantly higher endothelium-dependent dilatation; however, they observed no significant difference in these parameters between their WCH and normotensive groups. Our findings regarding CFR and coronary microvascular functions support the result of Pierdomenico *et al.*¹⁷

Left ventricular hypertrophy and left ventricular diastolic dysfunction have been shown to cause CFR impairment and coronary microvascular dysfunction.^{13–20} In our study, to prevent the confounding effects of left ventricular hypertrophy on the study results, we excluded patients with excessive left ventricular hypertrophy. We have observed, however, that CFR directly correlated with peak mitral E velocity and mitral E:A ratio, and negatively correlated with peak mitral A velocity and mitral E wave deceleration time, although left ventricular diastolic function did not differ significantly between the groups.

Study limitations

In this study we excluded patients with confounding factors for CFR, which are commonly encountered in the normal population, such as left ventricular hypertrophy, diabetes mellitus and current smoking, to investigate the independent effects of WCH on CFR. In addition, there was a sex imbalance between the groups. Therefore, the study does not provide information about white-coat effects on CFR in the population overall.

Conclusion

WCH does not alter CFR, a reflection of endothelium-independent coronary vasodilator function and a marker of target-organ damage in hypertension. The results of the present study are important, as reduced CFR may be one of the earliest indicators of future coronary artery disease and a sensitive indicator of hypertensive target-organ damage. Even patients with borderline hypertension have impaired CFR. Accordingly, our results emphasise the importance of ABPM instead of merely measuring office BP.

Authors' affiliations

D Erdogan, H Gullu, M Caliskan, D Tok, H Muderrisoglu, Cardiology Department, Konya Teaching and Medical Research Center, Baskent University, Konya, Turkey

I Yildirim, Internal Medicine Department, Nephrology Division, Konya Teaching and Medical Research Center, Baskent University, Konya, Turkey

REFERENCES

- 1 Chobanian AV, Bakris GL, Black HR, *et al.* The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;**42**:1206–52.
- 2 Staessen JA, O'Brien ET, Atkins N, *et al.* Short report: ambulatory blood pressure in normotensive compared with hypertensive subjects. The Ad-Hoc Working Group. *J Hypertens* 1993;**11**:1289–97.
- 3 Mancia G, Zanchetti A. White-coat hypertension: misnomers, misconceptions and misunderstandings. What should we do next? *J Hypertens* 1996;**14**:1049–52.
- 4 Redon J, Campos C, Narciso ML, *et al.* Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. *Hypertension* 1998;**31**:712–8.
- 5 Khatrar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension: a 10-year follow-up study. *Circulation* 1998;**98**:1892–7.
- 6 European Society of Hypertension–European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;**21**:1011–53.
- 7 Caiati C, Zedda N, Montaldo C, *et al.* Contrast-enhanced transthoracic second harmonic echo Doppler with adenosine: a noninvasive, rapid and effective method for coronary flow reserve assessment. *J Am Coll Cardiol* 1999;**34**:122–30.
- 8 Hozumi T, Yoshida K, Akasaka T, *et al.* Noninvasive assessment of coronary flow velocity and coronary flow velocity reserve in the left anterior descending coronary artery by Doppler echocardiography: comparison with invasive technique. *J Am Coll Cardiol* 1998;**32**:1251–9.
- 9 Saraste M, Koskenvuo J, Knuuti J, *et al.* Coronary flow reserve: measurement with transthoracic Doppler echocardiography is reproducible and comparable with positron emission tomography. *Clin Physiol* 2001;**21**:114–22.
- 10 Marcus R, Krause L, Weder AB, *et al.* Sex-specific determinants of increased left ventricular mass in the Tecumseh blood pressure study. *Circulation* 1991;**90**:928–36.
- 11 Polese A, De Cesare N, Montorsi P, *et al.* Upward shift of the lower range of coronary flow autoregulation in hypertensive patients with hypertrophy of the left ventricle. *Circulation* 1991;**83**:845–53.
- 12 Antony I, Nitenberg A, Foul JM, *et al.* Coronary vasodilator reserve in untreated and treated hypertensive patients with and without left ventricular hypertrophy. *J Am Coll Cardiol* 1993;**22**:514–20.
- 13 Galdieri M, de Simone G, Cicala S, *et al.* Coronary flow reserve in hypertensive patients with appropriate or inappropriate left ventricular mass. *J Hypertens* 2003;**21**:2183–8.

- 14 **Kozakova M**, Palombo C, Pratali L, et al. Mechanisms of coronary flow reserve impairment in human hypertension: an integrated approach by transthoracic and transesophageal echocardiography. *Hypertension* 1997;**29**:551–9.
- 15 **Cavallini MC**, Roman MJ, Pickering TG, et al. Is white coat hypertension associated with arterial disease or left ventricular hypertrophy? *Hypertension* 1995;**26**:413–9.
- 16 **Pierdomenico SD**, Lapenna D, Guglielmi MD, et al. Target organ status and serum lipids in patients with white coat hypertension. *Hypertension* 1995;**26**:801–7.
- 17 **Pierdomenico SD**, Cipollone F, Lapenna D, et al. Endothelial function in sustained and white coat hypertension. *Am J Hypertens* 2002;**15**:946–52.
- 18 **Palatini P**, Mormino P, Santonastaso M, et al. Target-organ damage in stage I hypertensive subjects with white coat and sustained hypertension: results from the HARVEST study. *Hypertension* 1998;**31**:57–63.
- 19 **Cardillo C**, De Felice F, Campia U, et al. Psychophysiological reactivity and cardiac end-organ changes in white coat hypertension. *Hypertension* 1993;**21**:836–44.
- 20 **Galderisi M**, Cicala S, Caso P, et al. Coronary flow reserve and myocardial diastolic dysfunction in arterial hypertension. *Am J Cardiol* 2002;**90**:860–4.

IMAGES IN CARDIOLOGY

doi: 10.1136/hrt.2005.078998

Value of multidetector cardiac CT in calcified constrictive pericarditis for pericardial resection

A 58-year-old man presented with a one month history of progressive dyspnoea, orthopnoea, and abdominal distension. He had no previous pericarditis or pulmonary tuberculosis. The patient was in sinus rhythm with tachycardia. The chest x ray (lateral view) showed dense pericardial calcification (upper panel, left) which was more evident upon multidetector computed cardiac tomography (MCDT) (upper panel, right).

Echocardiographic features of constrictive pericarditis were present. The patient underwent cardiac catheterisation and showed equalisation of diastolic pressures between the left ventricle and right ventricle. Pericardiectomy was planned and an MDCT was performed which showed asymmetric degree of pericardial thickening and calcification. The maximal pericardial calcification in our patient was predominantly over the right atrium and ventricle, diaphragmatic surface, and atrioventricular grooves (lower panel). This case shows the advance that MDCT represents as a complementary technique in the imaging of calcified constrictive pericarditis. Three-dimensional reconstruction using volume rendering and reformatted techniques produced excellent visualisation of the distribution of calcium, morphology and adjacent structures.

Left: Chest x ray (lateral view) showing dense pericardial calcification (arrows), confirmed by the multidetector computed cardiac tomography reformatted short axis view (right). LV, left ventricle; RV, right ventricle.

Volume rendering reconstruction of cardiac structures showed dense pericardial calcification predominantly over the right atrium and ventricle and atrioventricular grooves (arrows). LA, left atrium; LV, left ventricle; PA, pulmonary trunk artery.

P Robles
A Rubio
P Olmedilla
 problesve@yahoo.es