Myocardial perfusion in hypertensive patients with normal coronary angiograms

Kalina Kawecka-Jaszcz[a], Danuta Czarnecka[a], Agnieszka Olszanecka[a], Artur Klecha[a], Agnieszka Kwiecień-Sobstel[a], Katarzyna Stolarz-Skrzypek[a], Dudley J. Pennell[b], Mieczysław Pasowicz[c], Piotr Klimeczek[c] and Robert P. Banyś[c]

Background **Pressure-induced left ventricular hypertrophy is one of the mechanisms responsible for an impaired coronary vasodilating capacity leading to myocardial ischemia and angina.**

The aim of the study was to investigate myocardial perfusion using cardiovascular magnetic resonance in patients with arterial hypertension and a history of chest pain and normal coronary angiography, and to estimate the influence of left ventricular hypertrophy on the parameters of myocardial perfusion.

Methods **The study included 102 patients (mean age 55.4 ± 7.7 years) with well controlled hypertension and 12 healthy volunteers. In 96 patients, myocardial first-pass perfusion cardiovascular magnetic resonance both at rest and during an infusion of adenosine 140 μg/kg/min was performed. Semiquantitative perfusion analysis was performed by using the upslope of myocardial signal enhancement to derive the myocardial perfusion index and the myocardial perfusion reserve index. The study group was divided according to the presence of left ventricular hypertrophy in the cardiovascular magnetic resonance examination: group with left ventricular hypertrophy ($n = 40$) and without left ventricular hypertrophy ($n = 56$).**

Results **Independent of the presence of left ventricular hypertrophy, there were significant differences in baseline myocardial perfusion index between hypertensive patients and controls (0.13 ± 0.07 vs. 0.04 ± 0.01; $P < 0.001$), and in stress myocardial perfusion index (hypertensive patients 0.21 ± 0.10 vs. controls 0.09 ± 0.03; $P < 0.001$). In hypertensive patients, the myocardial perfusion reserve index was reduced in the mid and apical portions of the left ventricle (1.71 ± 1.1 vs. 2.52 ± 0.83; $P < 0.02$). There was no significant correlation of myocardial perfusion reserve index with left ventricular mass or hypertrophy.**

Conclusion **In patients with mild or moderate hypertension and a history of chest pain with normal coronary angiography, there is regional myocardial perfusion reserve impairment that is independent of the presence of left ventricular hypertrophy and may be a reason for angina.**

Journal of Hypertension 2008, **26**:1686–1694

Keywords: cardiovascular magnetic resonance imaging, coronary microcirculation, hypertension, left ventricular hypertrophy

Abbreviations: ABPM, ambulatory blood pressure measurement; CFR, coronary flow reserve; CMR, cardiovascular magnetic resonance; FOV, field-of-view; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, left ventricular mass index; MPI, myocardial perfusion index; MPRI, myocardial perfusion reserve index; PET, positron emission tomography

[a]I Department of Cardiology and Hypertension, Jagiellonian University Medical College, Krakow, Poland, [b]Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital, London, United Kingdom and [c]Center for Diagnosis and Rehabilitation of Lung and Heart Disease, John Paul II Hospital, Krakow, Poland

Correspondence to Agnieszka Olszanecka, MD, PhD, I Department of Cardiology and Hypertension, Jagiellonian University Medical College, 17 Kopernika Str, 31-501 Krakow, Poland
Tel: + 48 12 424 73 00; fax: + 48 12 424 73 20; e-mail: olszanec@su.krakow.pl

Received 7 October 2007 **Revised** 18 March 2008
Accepted 8 April 2008

Introduction

Arterial hypertension is well established risk factor responsible for cardiovascular morbidity and mortality. The relationship between blood pressure and coronary events is linear and continuous, starting from the levels of blood pressure between 115–100 mmHg for systolic and 75–70 mmHg for diastolic [1]. Chronically elevated blood pressure causes changes in the coronary circulation characterized by a reduction of coronary vascular reserve and acceleration of the atherosclerotic process. However, a number of hypertensive patients complain of angina despite no obstructive coronary heart disease [2–4]. Although in these patients, multiple mechanisms may be involved in coronary flow reserve (CFR) reduction, it still remains controversial whether this reduction occurs as a consequence of increased afterload itself or because of the development of left ventricular hypertrophy (LVH).

Cardiovascular magnetic resonance (CMR) offers the possibility to study noninvasively myocardial perfusion [5,6]. Recently, several interesting CMR studies [7–9] examined the myocardial blood flow and flow reserve in patients with cardiac X syndrome. Although some data about microvascular dysfunction in patients with normal

0263-6352

coronary angiograms are available, this issue has not been examined in the specific group of patients with arterial hypertension.

Thus, the aim of our study was to assess myocardial perfusion in patients with essential hypertension, a history of chest pain and normal coronary angiography. Moreover, we investigated the relationship between myocardial perfusion and left ventricular mass (LVM) and hypertrophy.

Patients and methods

Study population

We studied 114 individuals: 102 patients with essential arterial hypertension (35–65 years old) and 12 healthy volunteers. The hypertensive group consisted of consecutive patients with the history of chest pain, referred for the elective coronary angiography to the I Department of Cardiology and Hypertension between November 2003 and July 2006. Sixty-nine patients referred for coronary angiography had positive results of electrocardiographic exercise tests, 22 positive thalium-201 perfusion scintigraphy, five positive dobutamine stress echocardiography and six were admitted to the coronary care unit with the history of chest pain at rest (on the basis of repeated blood tests, consecutive electrocardiographical examinations and negative coronary angiography; in all of them acute coronary syndromes were excluded). Controlled mild and moderate hypertension, normal coronary angiograms and preserved left ventricular systolic function comprised the inclusion criteria. Patients with diabetes mellitus, valvular heart diseases, primary myocardial diseases, contraindications to the magnetic resonance imaging (claustrophobia, electrically, magnetically or mechanically activated implants), contraindications to adenosine infusion (asthma, carotid arteries atherosclerosis, arrhythmias and conduction disturbances) were excluded from the study. In patients treated with angiotensin-converting enzyme inhibitors and calcium channel blockers, therapy was withdrawn and replaced with β-blockers and/or diuretics 6–8 weeks before the study procedures.

The myocardial-perfusion CMR was performed in 97 patients (five patients were excluded because of the newly diagnosed claustrophobia) and, in one patient, the image analysis was not possible because of low quality of CMR. Thus, finally after the study procedures, data from 96 patients were analyzed. The control group consisted of 12 individuals with no cardiovascular risk factors, with optimal blood pressure values. All individuals were included in the study after providing their written informed consent. The study protocol was approved by the Bioethics Committee of the Jagiellonian University (KBET/506/2003).

Procedures

The following procedures were performed: clinical assessment with detailed history taking, office blood pressure measurements according to European Society of Hypertension–European Society of Cardiology (ESH-ESC) guidelines [10]), anthropometric measurements, 24-h ambulatory blood pressure monitoring (ABPM) and electrocardiograph (ECG) monitoring. After the assessment of blood pressure control with ABPM and exclusion of heart rhythm disturbances (ECG monitoring), myocardial-perfusion CMR with adenosine infusion was performed.

Twenty-four-hour ambulatory blood pressure monitoring

ABPM was done with use of validated oscillometric SpaceLabs 90207 monitors (Redmond, Washington, USA) fitted with the same cuff size as for conventional measurements. Blood pressure readings were obtained every 15 min from 08:00 to 22:00 h and every 30 min from 22:00 to 08:00 h. The mean systolic and diastolic blood pressure was calculated over the entire 24 h and separately in the night and in the day, and the circadian pattern was analyzed.

Twenty-four-hour continuous ECG recording

ECG recording was performed using analogue tape recorders (Marquette Medical Systems, GE Healthcare Clinical Systems, Milwaukee, Wisconsin, USA). Analysis was done using a computer and original DRG software (DRG International Inc., Mountainside, New Jersey, USA). The following parameters were assessed: maximal, mean and minimal heart rate, and presence and type of cardiac arrhythmia.

Myocardial-perfusion cardiovascular magnetic resonance

The patients were instructed to avoid any caffeine-containing beverages 24 h before CMR and to be preprandial on the day of the test. Before testing, an intravenous line was positioned in the antecubal veins in both arms. We used a single cannula for administration of contrast and a separate cannula for the administration of adenosine. Imaging was performed with a 1.5-T whole body magnetic resonance scanner (Magnetom Sonata, Siemens, Erlangen, Germany) using a two-element and later six-element phased array cardiac receiver coil, and with the patient in a supine position. CMR consisted of localization sequences, adenosine stress and rest perfusion tests and LV mass examination. The following multislice localizers T1 SE were performed: three coronal, three sagittal, three transversal. Retrospective triggered segmented cine steady state free recession (SSFP): two-chamber, four-chamber cine-views, LV outflow tract. Parameters are as follows: slice 10 mm, gap 0, base resolution 192, phase resolution 72, 25 phases, average 14 segments with arrhythmia detection as appropriate. To obtain the first-pass contrast-enhanced images, a saturation prepared single shot SSFP was applied.

For stress and rest perfusion imaging, the nonselective saturation recovery SSFP sequence was performed. The

image acquisition was performed in three slices: short-axis orientation, positioned in the aid of the localizers (basal, medial, periapical), distance factor optimized to the size of heart, slice thickness 8 mm, minimum possible repetition time 172 ms, echo time 1.06 ms, flip angle 50°, receiver bandwidth 1370 Hz/pixel, minimal image matrix 192×144.

Preaquisition with 10 measurements was performed during inspiration. Images were inspected to verify slice positioning, field of view, and to check for presence of wrap around artifacts. Acquisitions were repeated with modified field-of-view, if necessary. Adenosine was injected with dose of 140 μg/min/kg for 4 min. During adenosine perfusion, heart rate was monitored continuously and blood pressure was obtained every 1 min. The perfusion imaging started after 3 min of adenosine injection. Using the same protocol as that used at baseline with setting measurements 50–60, images were acquired on inspiration. Ten to fifteen minutes after the end of the stress infusion, the rest perfusion examination was performed using the same protocol. The analysis of first pass perfusion study was based on the 16-segment heart model, dividing the left ventricle into six basal, six mid-ventricular and four distal segments. Analysis of the MR images was done both visually and semiquantitatively. The observer of the CMR was blinded for the results of other diagnostic procedures. First-pass perfusion contrast-enhanced MR images were assessed for the presence or absence of regions of reduced contrast uptake. The perfusion and data were postprocessed and were assessed manually using CMR tools software (CVIS Ltd, London, UK). The endocardial and epicardial contours on perfusion images were traced and corrected manually for cardiac motion. Each slice was divided respectively into six (basal, medial) or four (periapical) equiangular segments, starting from the inferior septal insertion of the right ventricle. To obtain information about the input function, an additional region was drawn in the left ventricular cavity. For each of the defined regions, a curve was generated showing relative signal intensity plotted against time. The maximum upslopes of the myocardium and the left ventricular blood pool were determined using five-point slopes. The results for the myocardial regions were corrected for differences in the arterial input function of the contrast agent bolus by dividing the myocardial upslope with the left ventricular blood pool upslope. A myocardial perfusion reserve index (MPRI) was calculated by dividing the values at maximal vasodilatation by the values at rest. Global cardiac function and mass were assessed by calculating left ventricular end-diastolic and end-systolic volumes using planimetry of all short-axis images in each patient. Normal LVM and left ventricular mass index (LVMI) ranges in CMR examination already established in other studies were used to categorize patients [11]. These normal ranges expressed over a range of 2 SD from the mean equated with 85–181 g or 46–83 g/m^2 for men and 66–114 g or 37–67 g/m^2 for women, respectively [11]. LVH was defined as more than 2 SD above the normal range; thus, these ranges were used to categorize the hypertensive group into subgroups with and without LVH.

Statistical analysis

We used the Statistica 6 PL software package, version 6.12 (StatSoft Inc, Tulsa Oklahoma, USA) for database management and statistical analysis. The Shapiro–Wilks *W*-test was used in testing for normality of distribution. Comparisons of means and proportions involved the standard normal *t*-test and the chi-square statistics, respectively. Differences and interactions between study groups were evaluated by two-way analysis of variance (ANOVA) and a posthoc Tukey test, for unequal sample sizes (Spjotvoll–Stoline test). Univariate correlations were tested by Pearson's method. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the examined groups

The study group consisted of 67 women and 29 men with mild or moderate essential hypertension and history of chest pain with normal coronary angiographies. The control group consisted of 12 healthy volunteers (seven women and five men) without cardiovascular risk factors and with negative family history concerning cardiovascular disorders. Detailed characteristics of the study group are shown in Table 1. The two groups did not differ according to sex. Controls were younger than those in the study group; thus, in further analyses, data were adjusted to age. Hypertensive patients had significantly higher BMI. Patients with arterial hypertension, (despite reaching blood pressure control targets), had higher blood pressure values from 24-h blood pressure monitoring compared with normotensive healthy volunteers.

The hypertensive group was divided on the basis of the presence of LVH according to CMR examination. Patients with LVH ($n = 40$) were compared with those without LVH ($n = 56$). Subgroups did not differ according to age, duration of hypertension, BMI, or blood pressure values. Data are summarized in Table 2.

Myocardial perfusion assessment

There were significantly higher values of baseline myocardial perfusion index (MPI) in the hypertensive patients compared with those in the controls in all of the 16 analyzed segments (both in subendocardial and subepicardial areas) of left ventricle (mean for 16 segments for hypertensive patients vs. controls was 0.13 ± 0.07 vs. 0.04 ± 0.01; $P < 0.001$). In both hypertensive and normotensive groups, a significant increase in MPI was observed after adenosine infusion (in hypertensive patients, mean increase in MPI was 0.076 ± 0.05; $P < 0.001$ vs. controls 0.051 ± 0.01; $P < 0.001$).

Table 1 Characteristics of the hypertensive patients and control group

Variable	Hypertensive patients ($n=96$)	Controls ($n=12$)	P
Age (years)	55.4 ± 7.7	48.3 ± 6.6	0.002
Sex, (Men/Women; (*n*, %W)	29/67 (69)	7/5 (41)	0.06
BMI (kg/m^2)	27.9 ± 8.3	25.4 ± 2.3	0.04
Hypercholesterolemia [*n*, (%)]	68 (71)	0	0.00001
Current smokers [*n*, (%)]	4 (4)	0	0.33
24-h SBP (mmHg)	118.5 ± 14.3	108.2 ± 7.8	0.01
24-h DBP (mmHg)	72.3 ± 9.5	65.4 ± 6.6	0.02
Daytime SBP (mmHg)	121.6 ± 15.1	112.9 ± 7.9	0.05
Daytime DBP (mmHg)	76.2 ± 11.9	71.0 ± 7.3	0.14
Nighttime SBP (mmHg)	111.9 ± 16.5	102.4 ± 8.6	0.06
Nighttime DBP (mmHg)	66.9 ± 10.7	58.5 ± 7.0	0.01
24-h SBP SD	12.1 ± 3.7	10.6 ± 2.0	0.17
24-h DBP SD	9.8 ± 2.6	10.4 ± 1.6	0.44
Daytime SBP SD	10.9 ± 3.0	8.9 ± 2.5	0.04
Daytime DBP SD	8.7 ± 2.3	8.2 ± 2.3	0.50
Nighttime SBP SD	8.9 ± 3.0	8.8 ± 2.1	0.01
Nighttime DBP SD	7.3 ± 2.3	7.9 ± 1.3	0.39
24-h HR (bpm)	67.0 ± 13.1	72 ± 8	0.13
Daytime HR (bpm)	69 ± 12.5	78.5 ± 10.4	0.02
Nighttime HR (bpm)	60 ± 12.3	65.9 ± 8.7	0.16
CMR LVM (g)	121.2 ± 22.3	104.1 ± 4.8	0.02
CMR LVMI (g/m^2)	66.7 ± 11.6	56.5 ± 3.9	0.03
Ejection fraction (%)	66.5 ± 5.5	67.2 ± 5.9	0.68

Data in table are shown as mean (±) SD. CMR, cardiovascular magnetic resonance; DBP, diastolic blood pressure; HR, heart rate; LVM, left ventricular mass; LVMI, left ventricular mass index; SBP, systolic blood pressure.

Differences between groups in MPI in all 16 analyzed segments remained significant after adenosine infusion (mean MPI for 16 segments for hypertensive patients was 0.21 ± 0.10 vs. controls 0.09 ± 0.03; $P<0.001$). The values of MPI at rest and after adenosine infusion separately for endocardial and epicardial areas (means for 16 segments) are shown in Fig. 1. The differences in MPI both at rest and after adenosine infusion between hypertensive patients and controls remained significant after normalization for LVM and double product (systolic blood pressure multiplied by heart rate) both and separately (Table 3).

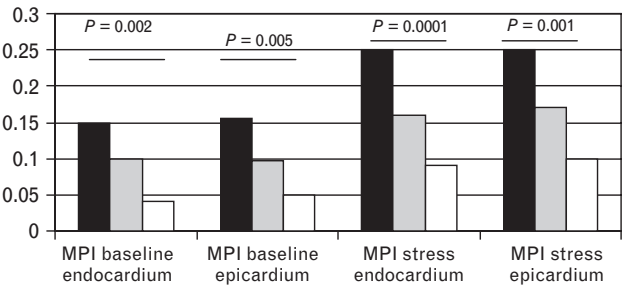
Table 2 Characteristics of hypertensive patients with and without left ventricular hypertrophy

	Hypertension		
Variable	LVH ($n=40$)	Without LVH ($n=56$)	P
Age (years)	55.5.3 ± 6.9	5.5 ± 6.2	0.44
Duration of hypertension	10.1 ± 5.4	9.8 ± 6.9	0.55
Sex, (Men/Women; *n*, %W)	12/28 (70)	17/39 (69)	0.97
BMI (kg/m^2)	28.0 ± 3.0	26.6 ± 5.0	0.16
24-h SBP (mmHg)	119.9 ± 12.4	119.8 ± 15.5	0.97
24-h DBP (mmHg)	72.6 ± 8.5	74.1 ± 10.1	0.54
Daytime SBP (mmHg)	123.0 ± 15.7	123.0 ± 13.9	0.99
Daytime DBP (mmHg)	75.7 ± 10.4	78.9 ± 12.5	0.34
Nighttime SBP (mmHg)	115.4 ± 14.8	111.3 ± 19.0	0.26
Nighttime DBP (mmHg)	68.5 ± 11.0	68.1 ± 10.2	0.89
24-h SBP SD	11.3 ± 2.7	12.6 ± 4.3	0.27
24-h DBP SD	9.1 ± 2.5	10.0 ± 2.5	0.65
Daytime SBP SD	8.4 ± 2.1	8.7 ± 2.2	0.60
Daytime DBP SD	8.4 ± 2.1	8.7 ± 2.2	0.60
Nighttime SBP SD	8.1 ± 2.5	9.0 ± 3.4	0.31
Nighttime DBP SD	6.3 ± 1.9	7.4 ± 2.2	0.10
CMR LVM (g)	137.7 ± 16.6	114.2 ± 20.5	0.0001
CMR LVMI (g/m^2)	79.5 ± 8.3	61.3 ± 8.0	0.0001
Ejection fraction (%)	67.1 ± 5.5	66.0 ± 5.5	0.46

Data in table are shown as mean (±) SD. CMR, cardiovascular magnetic resonance; DBP, diastolic blood pressure; LVM, left ventricular mass; LVMI, left ventricular mass index; SBP, systolic blood pressure.

An index for myocardial perfusion reserve was calculated as the ratio of the MPI during stress to the MPI at rest. The MPRI for the entire transmural extent of the myocardium in hypertensive patients was 1.85 ± 0.75 and in controls, 2.30 ± 0.34 ($P=0.04$). There was no significant difference between the MPRI in the subendocardium and the subepicardium in hypertensive patients (1.75 ± 0.73 vs. 1.89 ± 0.79, $P=0.14$) and controls (2.07 ± 0.67 vs. 2.34 ± 0.66, $P=0.11$). The mean subendocardial : subepicardial MPRI ratio in the examined population was 1.06 + 0.36. None of the patients had a subendocardial : subepicardial

Fig. 1



Myocardial perfusion indices at baseline and after adenosine infusion in subendocardium and subepicardium in hypertensive patients with and without left ventricular hypertrophy and in normotensive controls. [*P* for analysis of variance (ANOVA)]. LVH, left ventricular hypertrophy; MPI, myocardial perfusion index. ■, LVH; ▒, without LVH; □, controls.

Table 3 Myocardial perfusion index at rest and after adenosine infusion, values normalized to age, left ventricular mass and double product

	Hypertensive patients	Controls	*P*
Values normalized to left ventricular mass			
Rest myocardial perfusion index	0.11 ± 0.07	0.4 ± 0.01	$P < 0.001$
Stress myocardial perfusion index	0.18 ± 0.09	0.09 ± 0.03	$P = 0.005$
Values normalized to double product			
Rest myocardial perfusion index	0.18 ± 0.10	0.07 ± 0.01	$P < 0.001$
Stress myocardial perfusion index	0.27 ± 0.14	0.11 ± 0.03	$P < 0.001$
Values normalized to both left ventricular mass and double product			
Rest myocardial perfusion index	0.14 ± 0.080	0.04 ± 0.01	$P = 0.001$
Stress myocardial perfusion index	0.23 ± 0.12	0.10 ± 0.04	$P = 0.005$

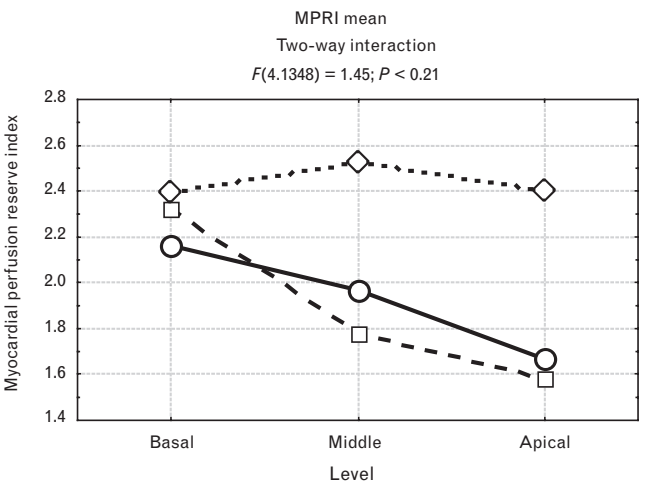
MPRI ratio less than 0.72, which has been proposed as the optimal cut-off for distinguishing between normal controls and subendocardial hypoperfusion in patients with syndrome X [7].

The MPRI was significantly different between hypertensive patients and controls in eight from analyzed 16 segments of left ventricle (segments 8–10: hypertensive patients vs. controls, 1.81 ± 1.2 vs. 2.62 ± 0.86; $P = 0.023$; and segments 12–16: hypertensive patients vs. controls, 1.62 ± 0.94 vs. 2.43 ± 0.80; $P < 0.01$). After calculation of global MPRI (mean for all 16 segments), the higher values in hypertensive patients failed to reach significance (hypertensive patients vs. controls, 1.87 ± 0.89 vs. 2.3 ± 0.34; $P = 0.10$). However, analyzing the differences in MPRI between study groups (controls, hypertensive patients with LVH and without LVH) and the segment position (basal: 1–6, middle: 7–12, and apical: 13–16), we found significant influence of both hypertensive status (*P* for ANOVA = 0.02) and segment position (*P* for AVOVA = 0.01) on MPRI. Independent of LVH, hypertensive patients had significantly lower MPRI in middle and apical segments of left ventricle (Fig. 2). In the two-way AVOVA (influence of both hypertensive group and segment position), we did not show significance of this interaction ($P = 0.21$).

Analyzing groups with and without LVH, higher values of MPI (both in subendocardium and subepicardium) were found in patients with LVH, although this difference was at borderline level of significance (Fig. 2). Groups with and without LVH did not differ according to MPRI in any of analyzed segments of left ventricle. Analyzing left ventricular mass as a continuous variable, there was no correlation between LVMI and MPRI (Fig. 3).

The MPRI was further analyzed in categories using a median of MPRI: 1.8 as a cut-off value to stratify patients into two groups. The duration of hypertension was not significantly higher in the group with lower MPRI. There were no differences between groups with respect to BMI and LVMI. There was, however, a significantly higher nighttime blood pressure in patients with MPRI less than 1.8 (Table 4).

Fig. 2



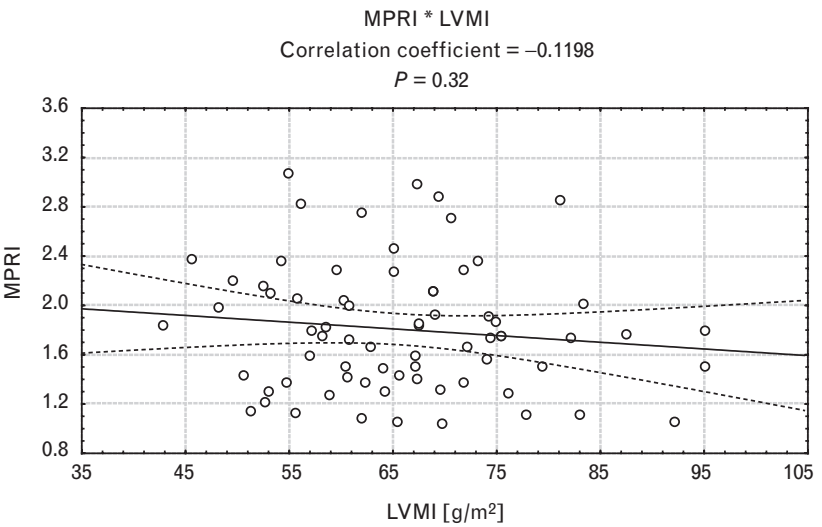
Myocardial perfusion reserve index in hypertensive group with left ventricular hypertrophy, without left ventricular hypertrophy and in controls by segment position (basal, middle, apical). LVH, left ventricular hypertrophy; MPRI, myocardial perfusion reserve index. ○, group: LVH(−); □, group: LVH(+); ◇, group: controls.

Discussion

The main finding of our study is that, in mild and moderate hypertensive patients, with a history of chest pain and normal coronary angiograms, and despite blood pressure control, both rest and stress MPIs are increased and this is neither explained by increased myocardial demand nor by LVH. Moreover, in hypertensive patients, MPRI in middle and apical segments is decreased compared with normotensive controls.

CMR is a relatively new tool for the assessment of myocardial perfusion, but its place in the detection of myocardial ischemia and CFR is well established [5]. Studies [6,12,13] show that the sensitivity of CMR in myocardial perfusion assessment is similar to the positron emission tomography, which is considered to be a gold standard for perfusion investigations. However, the use of this technique is limited by its reduced availability. CMR is widely used for assessment of myocardial perfusion in patients with obstructive coronary heart disease [5,14]. But its utility has been shown also in patients with chest pain and no obstructive coronary artery disease in coronary angiography [7]. Panting *et al.* [7] has shown that, in 20 patients with cardiac syndrome X, CMR demonstrated subendocardial hypoperfusion during intravenous administration of adenosine. These data were confirmed by most recent results of Lanza *et al.* [8]. In the group of 18 patients with cardiac syndrome X, CFR impairment (measured by transthoracic Doppler echocardiography in left anterior descending artery during adenosine infusion) was accompanied by dobutamine-induced perfusion defects observed in CMR [8]. However, both of these studies are at variance with the results of study by

Fig. 3



Correlation between myocardial perfusion reserve index (mean from 16 segments) and left ventricular mass index in the study group. LVMI, left ventricular mass index; MPRI, myocardial perfusion reserve index.

Vermeltfoort *et al.* [9]. In 20 patients with chest pain and normal coronary angiograms, significant perfusion responses to adenosine in both the subendocardium and subepicardium were documented. Thus, no evidence for subendocardial hypoperfusion was found, although visual findings of perfusion defects were present, but labeled as artifactual. The above-mentioned studies differ with respect to studied population. Although all included patients had chest pain and normal coronary angiography, Vermeltfoort *et al.* [9] examined patients with abnormal perfusion in single photon emission computed tomography (hypertension excluded), Lanza patients with effort angina and exercise-induced ST-segment depression (61% had hypertension) [8] and Panting patients having ST-segment depression with exercise but with excluded hypertension, diabetes and LVH [7]. As patients with chest pain and normal coronary angiograms are a heterogenous population, there are difficulties in making direct comparisons between cited studies. Our study group consisted of well phenotyped patients with clearly defined and mild and moderate arterial hypertension. Studies with CMR have not been used to analyze the myocardial perfusion in this specific group of patients. This issue, however, was addressed in the studies using other methods for coronary microcirculation investigations, both invasive and noninvasive, and the results obtained are inconsistent.

Table 4 Clinical characteristics of hypertensive patients within two categories of myocardial perfusion reserve index

Variable	MPRI>1.8 ($n=48$)	MPRI<1.8 ($n=48$)	P
Age (years)	54.5 ± 7.9	55.3 ± 8.0	0.61
Duration of hypertension (years)	8.8 ± 4.9	9.5 ± 5.3	0.07
BMI (kg/m^2)	26.8 ± 3.3	28.2 ± 4.3	0.13
CMR LVM (g)	117.7 ± 21.4	121.2 ± 21.3	0.49
CMR LVMI (g/m^2)	63.9 ± 11.2	67.3 ± 11.5	0.23
24-h SBP (mmHg)	118.0 ± 13.3	118.6 ± 11.3	0.88
24-h DBP (mmHg)	72.8 ± 9.2	73.0 ± 8.8	0.94
Daytime SBP (mmHg)	119.2 ± 11.6	122.4 ± 13.9	0.14
Daytime DBP (mmHg)	75.5 ± 9.7	76.4 ± 11.9	0.75
Nighttime SBP (mmHg)	107.9 ± 13.3	112.9 ± 15.2	0.04
Nighttime DBP (mmHg)	64.2 ± 10.2	66.6 ± 9.9	0.31

Data in table are shown as mean (±) SD. CMR, cardiovascular magnetic resonance; DBP, diastolic blood pressure; LVM, left ventricular mass; LVMI, left ventricular mass index; MPRI, myocardial perfusion reserve index; SBP, systolic blood pressure.

An important finding in our study is the substantial difference in MPI between hypertensive patients and controls, at rest and during adenosine infusion. Resting myocardial blood flow, commonly referred to as autoregulated blood flow, correlates with myocardial oxygen consumption and is determined primarily by left ventricular wall stress, myocardial contractility and heart rate [15] Thus, increased baseline perfusion in our study group may reflect an adaptive mechanism, compensating increased oxygen demand of the heart working under increased afterload. On the contrary, even after normalization of the MPI to both double product and LVM, the differences between hypertensive patients and normotensive individuals remained significant. The mechanisms responsible for this observation are not clear, but it seems that, in the presence of long lasting systemic hypertension, simple relation between autoregulated flow and rate–pressure product and LVM is altered by interplay of other factors such as wall stress and left ventricular inotropic function, which may contribute to a variable extend to changes in resting oxygen demand.

Our observation of increased rest myocardial blood flow in hypertensive patients is in agreement with the results

obtained by Kjaer *et al.* [16]. Comparing myocardial perfusion with positron emission tomography in elite athletes with LVH, hypertensive patients with LVH and normotensive age-matched controls, they found that hypertensive patients have 25% higher baseline myocardial perfusion. After vasodilatation with dipyridamole, the perfusion index did not differ among groups. Thus, decreased flow reserve in hypertensive patients with LVH resulted mostly from higher baseline perfusion. Similar data are reported by Kozakova *et al.* [17]. In 33 hypertensive patients with and without LVH, rest coronary flow measured by transesophageal Doppler echocardiography in left anterior descending artery was significantly higher than that measured in 10 normotensive controls. Hypertensive patients also showed blunted response to low-dose dipyridamol with subsequent decrease in CFR, which was independent of LVM.

Our results are interesting in light of studies with invasive measurements of CFR [18]. Hypertensive patients with LVH had higher coronary flow at rest compared with both hypertensive patients without LVH and normotensive controls. Consequently, the decrease in CFR compared with the control group was significant only for patients with hypertension complicated with LVH.

As per our data, patients with LVH had higher MPIs than those without LVH, both at rest and during adenosine-induced vasodilation. However, both groups reacted with significant increase in perfusion during adenosine infusion, which resulted in no differences in MPRI.

In hypertensive patients (independent of LVH), significant reduction in MPRI was found for middle and apical portions of left ventricle. Taking into account that the differences observed in MPRI between hypertensive patients and controls in our study do not refer to territories of coronary arteries and affect the mid and apical portions of the left ventricle, it indicates the diffused microcirculation disturbances in these areas, independent of LVM. Heterogeneity of microvascular dysfunction has already been described in untreated hypertensive patients with normal coronary angiograms and increased LVM [19] and in patients with chest pain not attributable to coronary artery disease [20].

Several possible mechanisms could explain a reduced myocardial perfusion reserve in hypertensive individuals. They include structural remodeling of the coronary microvasculature, inadequate neoangiogenesis and accumulation of fibrillar collagen in the myocardium [21,22]. Vascular remodeling increases coronary resistance as it is associated with the reduction in arteriolar lumen and eventually leads to the reduction in the density of arterioles and capillaries in the vascular bed [23].

A second mechanism is related to LVH, in which resting myocardial blood flow may be increased to supply the hypertrophied myocardium. But even in hypertensive patients without LVH, an increase in baseline myocardial flow may occur to compensate increased oxygen demand due to increased left ventricular loading conditions. In the present study, we observed a significant increase in baseline global MPIs in hypertensive patients compared with normotensive controls only partially explained by increased LVM.

The lack of correlation of LVH with myocardial perfusion during adenosine-induced hyperemia observed in our study and other cited works, suggests that decreased perfusion reserve in hypertension results mostly from primarily increased vascular tone and/or impaired vasodilation capacity, independent of LVH.

The endothelium has been recognized to be a major regulator of vascular tone and growth. Both experimental and clinical studies [24–26] have demonstrated the relationship between arterial hypertension and endothelium-dependent relaxation impairment. Adenosine dilates coronary arteries through both specific endothelial receptors linked to the release of nitric oxide and direct vasodilatation via receptors in vascular smooth muscle cells, leading to activation of adenylate cyclase and membrane hyperpolarization [27,28]. Thus, the lower MPRIs observed in hypertensive patients in our study might be related to decreased vasodilation via both endothelium dependent and independent pathways, although a clinical study such as ours cannot clearly identify the mechanisms responsible for the reduced coronary vasodilation response for adenosine infusion. It is of note that endothelial function impairment in hypertension detected by flow-mediated dilation of the brachial artery correlates with coronary perfusion disorders [26,29]. An interesting observation was found in patients with cardiac syndrome X, in whom microcirculatory response to cold (i.e. reflecting the endothelium function) was normal suggesting preserved microcirculatory endothelial function [30]. However, a markedly attenuated hyperemic flow and flow reserve suggested a dysfunction of the adenosine-mediated endothelium-independent vasodilatation at the microcirculatory level in these patients.

Independent of the mechanism of coronary microvascular dysfunction, it has been shown that myocardial perfusion impairment in patients without obstructive coronary artery disease negatively influences patient's prognosis (higher rates of angina hospitalizations, repeated angiographies) and therapeutic costs [25,31,32].

Limitations

In the present study, parameters of myocardial perfusion were analyzed in the group of hypertensive patients with a history of chest pain, and our results should not be

extended to the whole hypertensive population. However, there are data available concerning CFR impairment in the asymptomatic, untreated patients with borderline hypertension [33]. A possible limitation of this study is the inclusion of treated hypertensive patients. Only patients with blood pressure control, achieved with therapy based on β-blockers and/or diuretics, entered the study. Data on the influence of different therapy regimen on myocardial perfusion and CFR are limited to a number of human and animal studies with inconsistent results. However, the angiotensin-converting enzyme inhibitors, angiotensin receptor blockers as well as calcium channel blockers are known to increase flow reserve [34–36]. Diuretic therapy does not significantly affect either coronary flow or flow reserve, but there have been a very few studies conducted on the long-term effects of diuretic therapy on the microcirculation. Hydrochlorothiazide therapy was reported to have no beneficial effect on structural changes in precapillary resistance vessels in hypertensive patients [37]. Critically analyzing our data, the influence of treatment with β-blockers has to be taken into account as a factor limiting study results. However, there is little evidence that β-blockers exert a marked beneficial action on microvessel structure. Treatment with propranolol had no effect on the cross-sectional area of the vessel wall or the external diameter of maximally dilated arterioles in spontaneously hypertensive rats [38]. In hypertensive patients, treatment with atenolol for 1 year produced no significant improvement in the media-to-lumen ratio of small peripheral arteries [39]. On the contrary, more recent studies [40] employing selective β-1 adrenergic receptor blockade with metoprolol showed that it may modulate both resting and hyperemic flow. In 10 healthy volunteers, examination by positron emission tomography during dipiridamol vasodilatation showed that β-1 receptor blockade reduced resting blood flow and increased myocardial flow reserve. The influence of metoprolol on CFR was shown to result from its influence on the rate–pressure product. As we adjusted our results of myocardial perfusion for rate–pressure product, it is unlikely that β-blocker therapy significantly influenced our results and conclusions.

For ethical reasons, invasive assessment of coronary arteries in normotensive controls was not possible. The clinical data (no cardiovascular risk factors, negative family history of cardiac diseases) and additional examinations performed minimize the probability of significant coronary atherosclerosis in the controls.

Conclusion

In patients with mild or moderate hypertension and a history of chest pain with normal coronary angiography, there is regional myocardial perfusion reserve impairment, which is independent of the presence of LVH and may be a reason for angina.

References

1 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**:1903–1913.

2 Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS Registry study. *J Am Coll Cardiol* 1986; **7**:479–483.

3 Cannon RO III. Epstein SE 'microvascular angina' as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol* 1988; **61**:1338–1343.

4 Kaski JC. Pathophysiology and management of patients with chest pain and normal coronary arteriograms (cardiac syndrome X). *Circulation* 2004; **109**:568–572.

5 Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE, *et al.*, Society for Cardiovascular Magnetic Resonance; Working Group on Cardiovascular Magnetic Resonance of the European Society of Cardiology. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel Report. *Eur Heart J* 2004; **25**:1940–1965.

6 Parkka JP, Niemi P, Saraste A, Koskenvuo JW, Komu M, Oikonen V, *et al.* Comparison of MRI and positron emission tomography for measuring myocardial perfusion reserve in healthy humans. *Magn Reson Med* 2006; **55**:772–779.

7 Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, Pennell DJ. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002; **346**:1948–1953.

8 Lanza GA, Buffon A, Sestito A, Natale L, Sgueglia GA, Galiuto L, *et al.* Relation between stress-induced myocardial perfusion defects on cardiovascular magnetic resonance and coronary microvascular dysfunction in patients with cardiac syndrome X. *J Am Coll Cardiol* 2008; **51**:466–472.

9 Vermeltfoort IA, Bondarenko O, Raijmakers PG, Odekerken DA, Kuijper AF, Zwijnenburg A, *et al.* Is subendocardial ischaemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study. *Eur Heart J* 2007; **28**:1554–1558.

10 2003 European Society of Hypertension–European Society of Cardiology. Guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**:1011–1053.

11 Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU. Normal human left and right dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequence. *J Magn Reson Imaging* 2003; **17**:323–329.

12 Schwitter J, DeMarco T, Kneifel S, von Schulthess GK, Jorg MC, Arheden H, *et al.* Magnetic resonance-based assessment of global coronary flow and flow reserve and its relation to left ventricular functional parameters: a comparison with positron emission tomography. *Circulation* 2000; **101**:2696–2702.

13 Koskenvuo JW, Sakuma H, Niemi P, Toikka JO, Knuuti J, Laine H, *et al.* Global myocardial blood flow reserve measurements by MRI and PET are comparable. *J Magn Reson Imaging* 2001; **13**:361–366.

14 Nagel E, Klein C, Paetsch I, Hettwer S, Schnackenburg B, Wegscheider K, Fleck E. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. *Circulation* 2003; **108**:432–437.

15 Camici PG, Crea F. Coronary microcirculation dysfunction. *N Engl J Med* 2007; **356**:830–840.

16 Kjaer A, Meyer C, Wachtell K, Olsen MH, Ibsen H, Opie L, *et al.* Positron emission tomographic evaluation of regulation of myocardial perfusion in physiological (elite athletes) and pathological (systemic hypertension) left ventricular hypertrophy. *Am J Cardiol* 2005; **96**:1692–1698.

17 Kozakova M, Palombo C, Pratali L, Pittella G, Galetta F, L'Abbate A. Mechanisms of coronary flow reserve impairment in human hypertension. An integrated approach by transthoracic and transesophageal echocardiography. *Hypertension* 1997; **29**:551–559.

18 Hamasaki S, Al Suwaidi J, Higano ST, Miyauchi K, Holmes DR Jr, Lerman A. Attenuated coronary flow reserve and vascular remodeling in patients with hypertension and left ventricular hypertrophy. *J Am Coll Cardiol* 2000; **35**:1654–1660.

19 Gimelli A, Schneider-Eicke J, Neglia D, Sambuceti G, Giorgetti A, Bigalli G, *et al.* Homogeneously reduced versus regionally impaired myocardial blood flow in hypertensive patients: two different patterns of myocardial perfusion associated with degree of hypertrophy. *J Am Coll Cardiol* 1998; **31**:366–373.

20 Marroquin OC, Holubkov R, Edmundowicz D, Rickens C, Pohost G, Buchthal S, *et al.* Heterogenity of microvascular dysfunction in women with chest pain not attributable to coronary artery disease: implications for clinical practice. *Am Heart J* 2003; **145**:628–635.

21 Levy BI, Ambrosio G, Preis AR, Struijker-Boudier HAJ. Microcirculation in hypertension. A new target for treatment? *Circulation* 2001; **104**:735–740.
22 Chilian WM. Coronary microcirculation in health and disease. Summary of an NHLBI workshop. *Circulation* 1997; **95**:522–528.
23 Li XY, Li R, Yu W, Shi HY, Wei LX. Differences in coronary microvascular lesions in coronary heart disease and hypertension: an autopsy study of elderly patients. *Chin Med J* 2004; **111**:207–212.
24 Perticone F, Ceravolo R, Pujia A, Ventura G, Iacopino S, Scozzafava A, *et al.* Prognostic significance of endothelial dysfunction in hypertensive patients. *Circulation* 2001; **104**:191–196.
25 Halcox JP, Schenke WH, Zalos G, Mincemoyer R, Prasad A, Waclawiw MA, *et al.* Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002; **106**:653–658.
26 Hasdai D, Gibbons RJ, Holmes DR Jr, Higano ST, Lerman A. Coronary endothelial dysfunction in humans is associated with myocardial perfusion defects. *Circulation* 1997; **96**:3390–3395.
27 Wang J, Whitt SP, Rubin LJ, Huxley VH. Differential coronary microvascular exchange responses to adenosine: roles of receptor and microvessel subtypes. *Microcirculation* 2005; **12**:313–326.
28 Sato A, Terata K, Miura H, Toyama K, Loberiza FR Jr, Hatoum OA, *et al.* Mechanism of vasodilation to adenosine in coronary arterioles from patients with heart disease. *Am J Physiol Heart Circ Physiol* 2005; **288**:1633–1640.
29 Palmieri V, Storto G, Arezzi E, Pellegrino T, Mancini M, Di Minno G, *et al.* Relations of left ventricular mass and systolic function to endothelial function and coronary flow reserve in healthy, new discovered hypertensive subjects. *J Hum Hypertens* 2005; **19**:941–950.
30 Bøttcher M, Botker HE, Sonne H, Nielsen TT, Czernin J. Endothelium dependent and -independent perfusion reserve and the effect of l-arginine on myocardial perfusion in patients with syndrome X. *Circulation* 1999; **99**:1795–1801.
31 Johnson BD, Shaw LJ, Buchthal SD, Bairey Merz CN, Kim HW, Scott KN, *et al.*, National Institutes of Health-National Heart, Lung, and Blood Institute. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004; **109**:2993–2999.
32 Britten MB, Zeiher AM, Schachinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome. *Coron Artery Dis* 2004; **15**:259–264.
33 Palombo C, Kozakova M, Magagna A, Bigalli G, Morizzo C, Ghiadoni L, *et al.* Early impairment of coronary flow reserve and increase in minimum coronary resistance in borderline hypertensive patients. *J Hypertens* 2000; **18**:453–459.
34 Levy BI, Duriez M, Samuel JL. Coronary microvasculature alteration in hypertensive rats: effect of treatment with diuretic and an ACE inhibitor. *Am J Hypertens* 2001; **14**:7–13.
35 Schwartzkopff B, Brehm M, Mundhenke M, Strauer BE. Repair of coronary arerioles after treatment with perindopril in hypertensive heart disease. *Hypertension* 2000; **36**:220–225.
36 Rakusan K, Cicutti N, Kazda S, Turek Z. Effect of nifedipine on coronary capillary geometry in normotensive and hypertensive rats. *Hypertension* 1994; **24**:205–211.
37 Dalhof B, Hansson L. The influence of antihypertensive therapy on the structural changes in essential hypertension: different effects of enalapril and hydrochrorothiazide. *J Intern Med* 1993; **234**:271–279.
38 Chillion JC, Baumbach GL. Effects of an angiotensin-converting enzyme inhibitor and beta blocker on cerebral arterioles in rats. *Hypertension* 1999; **33**:856–861.
39 Buus NH, Bøttcher M, Jørgensen CG, Christensen KL, Thygesen K, Nielsen TT, Mulvany MJ. Myocardial perfusion during long-term angiotensin-converting enzyme inhibition or beta-blockade in patients with essential hypertension. *Hypertension* 2004; **44**:465–470.
40 Bøttcher M, Czernin J, Sun K, Phelps ME, Schelbert HR. Effect of beta 1 adrenergic receptor blockade on myocardial blood flow and vasodilatory capacity. *J Nucl Med* 1997; **38**:442–446.