Journal of Human Hypertension (2016) **30,** 690–696

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ORIGINAL ARTICLE

Positive effects of aggressive vasodilator treatment of well-treated essential hypertensive patients

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Increased systemic vascular resistance and coronary microvascular dysfunction are well-documented in essential hypertension (EH). We investigated the effect of additional vasodilating treatment on coronary and peripheral resistance circulation in EH patients with high systemic vascular resistance index (SVRI) despite well-treated blood pressure (BP). We enroled patients on stable antihypertensive treatment that were given intensified vasodilating therapy (ACE inhibitor, angiotensin II receptor blocker or calcium channel blocker). Before and following 6 months of intensified therapy, coronary resting and maximal artery flow were measured by transthoracic Doppler echocardiography to calculate coronary flow reserve (CFR) and minimum vascular resistance (C-R_{min}). Cardiac output was estimated by inert gas rebreathing to calculate SVRI. Maximal forearm blood flow was determined by venous occlusion plethysmography to calculate minimum vascular resistance (F-R_{min}). Patients were assigned into two groups: high-SVRI and low-SVRI subgroups, based on a median split at baseline. Following additional treatment SVRI decreased more in the high-SVRI group than in the low-SVRI group (14.4 vs − 2.2%: $P = 0.003$), despite similar baseline ambulatory BP (132/81 mm Hg) and BP reduction (6.5 and 4.6%: $P = 0.19$). F-R_{min} remained unchanged (6.5 vs − 2.0%: $P = 0.30$), while C-R_{min} decreased by 22 and 24% ($P = 0.80$) and CFR increased by 23 and 17% ($P = 0.16$). Thus, intensified vasodilating therapy improved SVRI more in patients with high SVRI than in those with low SVRI. Regardless of SVRI status, the treatment improved cardiac but not forearm dilatation capacity. The substantial improvement of the hypertensive cardiac microvascular dysfunction was not related to the reduction in SVRI.

Journal of Human Hypertension (2016) **30,** 690–696; doi:10.1038/jhh.2016.13; published online 10 March 2016

INTRODUCTION

Microvascular impairment is considered a pathophysiological hallmark in essential hypertension (EH). The lumen diameter of the small arteries and arterioles is reduced and the media-to-lumen ratio increased but with no change in the total amount of wall material, a process termed eutrophic inward remodelling.[1] The structural alterations of the microvasculature lead to a systemic increase in minimum vascular resistance[2] and a reduced vasodilator capacity[3] that may compromise the ability of the local circulation to respond to an increase in tissue oxygen demand and thus to demand-related organ dysfunction.[4] Remodelling of resistance arteries occurs early in the development of hypertension[5] and has been demonstrated in numerous vascular beds including the forearm circulation[6] and in the heart,[7] where the coronary flow reserve (CFR) is reduced due to both remodelling and fibrosis.[8] This may lead to reduced exercise capacity and microvascular angina and eventually to hypertensive heart failure. In addition, abnormal resistance artery structure has been found to predict cardiovascular events independently of blood pressure (BP) and of the degree of large artery disease progression[9] in individuals with EH[10,11] even during ongoing therapy[12] suggesting that correction of the vascular structure could serve as a supplemental treatment goal in addition to BP reduction.

A central issue is the effect of various antihypertensive drugs on the ability to correct vascular structure. Microvascular structure adapts to vasodilation rather than BP.[13] In agreement, vasodilating therapy with ACE inhibitors (ACEI),[14] angiotensin II receptor blockers (ARB)[15] and calcium channel blockers (CCB)[16] have been found superior to non-vasodilating β-blockers with regard to normalising media-to-lumen ratio of resistance arteries,[14–16] despite similar reductions in BP. Comparative findings exist from the myocardial circulation, where ACEI increase CFR and cause regression of hypertensive resistance artery structure when compared with β-blockers.[17]

Many recent studies have focused on the effects of vasodilating treatment in previously untreated patients with EH; however, despite a sizeable residual cardiovascular risk in patients receiving antihypertensive treatment,[18] little prospective information exists on correction of microvascular structure and systemic vascular resistance by vasodilating treatment in these patients.

The primary aim of the present study was to improve the understanding of how structural changes in the microvasculature are corrected in hypertensive patients during antihypertensive treatment. First, we aimed to investigate whether patients with high systemic vascular resistance index (SVRI), despite well-treated BP, would benefit from additional vasodilator therapy in terms of a reduction in systemic vascular resistance. Second, we investigated whether changes in SVRI could predict correction of vascular structure, assessed indirectly by CFR, minimum coronary resistance (C-R_{min}) and minimum forearm vascular resistance (F-R_{min}). The study was designed as a prospective cohort study as the purpose was not to investigate the effect of specific

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Received 6 September 2015; revised 11 January 2016; accepted 1 February 2016; published online 10 March 2016

antihypertensive drugs, but rather the association between changes in the hemodynamic parameters. Patients were stratified into two subgroups according to baseline SVRI: those with SVRI above median (group 1), and those with SVRI below median (group 2).

MATERIALS AND METHODS

The study was approved by the locally appointed Ethics Committee and the Danish Medicines Agency and conducted in accordance with the Helsinki II Declaration and Title 45, US Code of Federal Regulations, part 46, Protection of Human Subjects, revised 13 November 2001, effective 13 December 2001. Written informed consent was obtained from all participating subjects and the study was conducted according to good clinical practice guidelines (ICH-GCP Guideline (CPMP/ICH/135/95, Directive 2001/20/EC)), registered at www.clinicaltrials.gov (NCT01180413) and monitored by the Good Clinical Practice unit at Aarhus University Hospital, Denmark.

Essential hypertensive patients (age 25–80 years), on antihypertensive treatment, were recruited from the Hypertension Outpatient Clinic or by advertising in the local newspaper. Clinical characteristics are listed in Table 1. Subjects were eligible for inclusion if they had received unaltered antihypertensive medication for a minimum of 3 months and if daytime ambulatory BP (ABP) was above 120/75 mm Hg on current treatment (to prevent symptomatic hypotension). Patients underwent a clinical examination, electrocardiogram, blood and urine analyses. Twenty-four-hour ABP was then determined and baseline recordings were performed if patients met the inclusion criteria. Main exclusion criteria were secondary forms of hypertension, body mass index >35 kg m^{-2}, signs or a history of ischaemic heart disease, valvular heart disease, atrial fibrillation/flutter, diabetes, renal disease, neurological disease, ejection fraction $\leqslant 45\%$ by echocardiography or ongoing antihypertensive treatment with a combination of either a CCB+ACEI or a CCB+ARB.

Experimental protocol

The investigation was designed as a single centre open-label prospective cohort study. Six months of intensive vasodilating therapy was given as add-on to the ongoing antihypertensive treatment. Patients who received neither CBB nor ACEI had 5 mg amlodipine and 5 mg ramipril added to their treatment. If the ongoing treatment included a CCB, only 5 mg ramipril was added, and if treatment included an ACEI/ARB and no CCB, 5 mg amlodipine was added. One month following inclusion, office BP was measured. Patients who had ramipril added to their ongoing treatment and who did not show signs or symptoms of hypotension had the dose of ramipril increased to 10 mg. In the case of dry cough, 5 or 10 mg ramipril was substituted with 50 or 100 mg losartan. Amlodipine was substituted with 10 mg lercanidipine in the case of ankle oedema.

BP measurements

24-h ABP monitoring was performed with validated and calibrated monitors (Spacelab 90217; Spacelabs Healthcare, Issaquah, Washington, USA). Daytime (0700–2300 hours) ABP measurements were performed automatically at 20 min intervals and every 30 min during the night (2300–0700 hours). Patients were asked to perform normal activities of daily living except physical training.

Echocardiography

Two-dimensional and Doppler echocardiograms were recorded with the Vivid 7 Dimension Ultrasound System (General Electric Healthcare, Buckinghamshire, UK) with a standard adult probe (4 S GE ultrasound probe 1.7/3 MHz) according to the recommendations of the American Society of Echocardiography guidelines.[19]

Coronary flow reserve

CFR is the ratio between blood flow velocity during rest and during maximal dilation. Doppler echocardiography was used to assess beat-to-beat coronary flow velocity in left anterior descending artery (LAD) under basal resting conditions and during pharmacologically induced coronary vasodilation with adenosine (140 μg min^{-1} kg^{-1}, Adenosine Life Medical Sweden AB). The distal part of LAD was visualised from a modified apical long axis view and maximum resting flow velocity measured with a 7 MHz broadband probe (7 S GE Healthcare 3–8 MHz).[20] A two-dimensional view of LAD during rest and hyperaemia was stored and used for measurement of LAD cross-sectional area (CSA). Two flow velocities were measured during rest and hyperaemia and the mean values were used for calculation of CFR. CFR was successfully determined in 45 patients, but could not be determined in three individuals because of suboptimal image quality.

Forearm plethysmography

With the patient in supine position, forearm blood flow was measured by strain gauge venous occlusion plethysmography (Hokanson EC6; Bellevue, WA, USA) on the non-dominant arm.[21] The brachial cuff was inflated to 50 mm Hg above systolic BP or at least 200 mm Hg for 10 min to induce

Table 1. Patient characteristics and blood pressure

	Group 1			*Group 2*		
	Baseline	*Follow-up*	*Δ*	*Baseline*	*Follow-up*	*Δ*
N	24			24		
Sex (male/female)	11/13			10/14		
Non-smoker/smoker	23/1			23/1		
Age	60.4 ± 1.8	61.1 ± 1.8		60.2 ± 1.7	60.7 ± 1.7	
BMI (kg m^{-2})	27.3 ± 0.6	27.3 ± 0.6	0.0 ± 0.1	25.4 ± 0.7†	25.3 ± 0.6	0.0 ± 0.1
Total cholesterol (mmol l^{-1})	5.4 ± 0.2	5.5 ± 0.2	0.1 ± 0.1	5.4 ± 0.1	5.3 ± 0.1	−0.1 ± 0.1
LDL cholesterol (mmol l^{-1})	3.3 ± 0.2	3.3 ± 0.2	0.0 ± 0.1	3.1 ± 0.1	3.0 ± 0.1	−0.1 ± 0.1
HDL cholesterol (mmol l^{-1})	1.5 ± 0.1	1.5 ± 0.1	0.0 ± 0.0	1.8 ± 0.1†	1.8 ± 0.1	0.0 ± 0.0
Triglyceride (mmol l^{-1})	1.3 ± 0.1	1.3 ± 0.2	0.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.0 ± 0.1
Glucose (mmol l^{-1})	5.8 ± 0.1	5.8 ± 0.1	−0.1 ± 0.1	5.7 ± 0.1	5.7 ± 0.2	0.0 ± 0.1
U-albumin/creatine (mg g^{-1})	9.2 ± 2.4	9.5 ± 2.0	0.3 ± 2.0	8.7 ± 3.4	8.9 ± 2.8	0.2 ± 1.5
Estimated GFR (ml min^{-1} per 1.73 m^2)	75.7 ± 2.0	74.5 ± 2.3	−1.2 ± 1.2	82.0 ± 1.8†	82.8 ± 1.8	0.8 ± 1.0
24-h MAP (mm Hg)	99 ± 1	92 ± 1**	−6.6 ± 1.2	97 ± 1	92 ± 1**	−4.6 ± 1.0
24-h SBP (mm Hg)	132 ± 2	122 ± 2**	−9.7 ± 1.9	131 ± 2	125 ± 2*	−6.0 ± 1.6
24-h DBP (mm Hg)	82 ± 1	77 ± 1**	−5.7 ± 1.1	79 ± 1	76 ± 1*	−3.9 ± 0.8
24-h HR (beats per min)	69 ± 2	69 ± 2	−0.5 ± 1.4	68 ± 2	68 ± 1	−0.2 ± 1.1
Office SBP (mm Hg)	146 ± 3	129 ± 3**	−17.0 ± 2.7	145 ± 4	131 ± 3**	−13.7 ± 3.1
Office DBP (mm Hg)	92 ± 2	82 ± 2**	−10.0 ± 2.0	89 ± 2	83 ± 2*	−5.9 ± 1.8

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filteration rate: HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; MAP, mean arterial pressure; SBP, systolic blood pressure. Patients were assigned into two groups based on baseline systemic vascular resistance index (SVRI): group 1, high baseline SVRI (above median); group 2, low baseline SVRI (below median). Values are mean ± s.e.m. Baseline vs baseline, †$P < 0.05$. Baseline vs follow-up, *$P < 0.05$, **$P < 0.001$. Δgroup 1 vs Δgroup 2, non-significant.

ischaemia. Hand circulation was simultaneously interrupted by inflating a wrist cuff to 220 mm Hg. After 5 min of ischaemia, 10 handgrips were performed to maximise the oxygen consumption in the forearm.[22] Five venous occlusion measurements were performed in a rapid sequence with the brachial cuff deflated to 40 mm Hg. Concurrently, BP was measured on the contralateral arm. The percentage rise in forearm volume at each occlusive sequence was measured by a circumference adapted mercury-in-silastic strain gauge positioned at the widest part of the forearm.

Cardiac output

Noninvasive measurements of cardiac output (CO) were performed with a validated inert gas rebreathing method (Innocor; Innovision, Odense, Denmark).[23] Patients were asked to avoid physical activity and food consumption for 1 h. Before starting, patients were instructed on correct breathing technique and three test rounds with atmospheric air were performed to accustom patients to the system.[5] Patients then rebreathed an oxygen-enriched gas mixture containing an inert soluble gas (0.5% N_2O) and an inert insoluble gas (0.1% SF_6) at a respiration rate of 15–20 l min^{-1}. N_2O concentration decreases during rebreathing with a rate proportional to pulmonary blood flow, which in the absence of pulmonary shunts (defined as arterial O_2 saturation >98%) equals CO.[24] Respiration of insoluble SF_6 allowed for determination of lung volume from which the soluble gas disappeared. Brachial cuff BP measurements were performed simultaneously and SVR calculated from (mean arterial pressure (MAP) – 4.6 mm Hg)/CO, where 4.6 mm Hg is the estimated venous pressure.

Calculations and statistical analysis

The study population was stratified into two groups according to baseline SVRI (median SVRI 37.5 ± 1.4 mm Hg min l^{-1} m^{-2} at baseline). Baseline SVRI above median (group 1) and baseline SVRI below median (group 2; Figure 1). Quantile–quantile plots were used to test for normal distribution. In the absence of Gaussian distribution, the variable was log-transformed. Between-group differences were analysed with unpaired two-tailed student's *t*-test, while within-group differences were analysed with paired *t*-test. Student's *t*-test was performed with GraphPad Prism 5.0 (GraphPad Software Inc., CA, USA). The relationship between changes in the hemodynamic indices was analysed with a simple linear regression analysis. SPSS 19.0 (SPSS, IL, USA) was used for Multivariate analysis to adjust for change in BP. All data are presented as means ± s.e.m. Statistical significance was defined as $P < 0.05$.

Left ventricular mass (LVM) and LVM index (LVMI) were calculated according to international guidelines.[19] CSA of LAD was calculated from the diameter (*d*) assuming a circular model: $CSA = \pi d^2/4$.[25] Maximal coronary volume flow was calculated as maximal coronary flow velocity × CSA. $C\text{-}R_{min}$ pr. 100 g LVM was calculated as: MAP during adenosine infusion/(maximal coronary volume flow) × (LVM/100 g). Glomerular filtration rate (GFR) was estimated with the Cockcroft-Gault formula:[26] GFR = ((140–age) × body mass, kg × constant)/serum creatinine, μmol l^{-1}, where the constant is 1.23 for men and 1.04 for women.

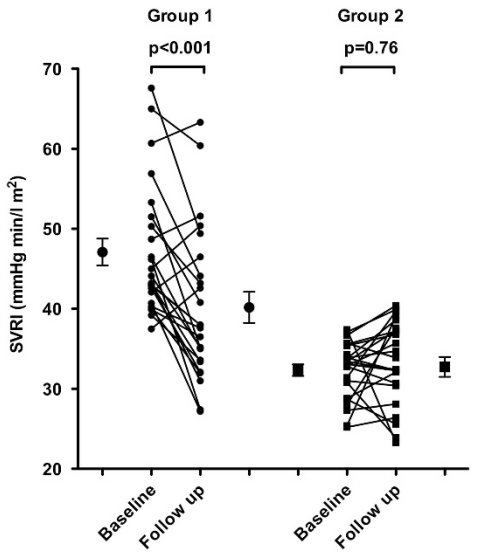

Figure 1. Individual measurements of SVRI in well-treated patients with essential hypertension before and after 6 months of intensified vasodilation therapy. Group 1 (high-SVRI): baseline SVRI above median. Group 2 (low-SVRI): Baseline SVRI below median. Data given as mean ± s.e.m.

RESULTS

Fifty-one patients were enroled and 48 patients completed the study (44% male and 56% female). One patient was excluded because of newly diagnosed diabetes, one because of moderate aortic regurgitation and one withdrew his informed consent. No severe adverse events occurred during the study.

Clinical characteristics and BP reduction

At inclusion, 28 patients received monotherapy and 20 patients received dual antihypertensive therapy. Taken together, 12 patients received treatment with CCB, 19 received thiazides, 5 received β-blockers, 18 ACEIs and 14 received ARBs as monotherapy or in combination. The majority of patients were non-smokers (96%). Biochemical parameters, body mass index and GFR were unaltered following treatment (Table 1).

Patients were on average well regulated with respect to baseline 24-h ABP: 132 ± 1/81 ± 1 mm Hg systolic and diastolic, respectively, with no significant difference between groups 1 and 2 ($P = 0.71$). Following additional vasodilating treatment, 24-h MAP decreased significantly ($P < 0.001$, Table 1) by 6.5 ± 1.1% (group 1) and 4.6 ± 0.9% (group 2; group 1 vs 2: $P = 0.19$). Ambulatory systolic BP and diastolic BP decreased by the same proportion, with no significant change in HR ($P = 0.93$).

Systemic hemodynamic responses to intensified vasodilation

Table 2a summarizes systemic cardiovascular parameters at baseline and following intensified treatment. Baseline SVRI was significantly higher in group 1 ($P < 0.001$) and decreased by 14.4 ± 3.1% ($P < 0.001$) compared with −2.2 ± 4.1% ($P = 0.76$) in group 2 (group 1 vs group 2: $P = 0.003$, Figure 1). Heart rate did not change significantly during cardiac output measurement.

Coronary and forearm microcirculation

Coronary minimum vascular resistance ($C\text{-}R_{min}$) decreased by 22 ± 8% (group 1, $P = 0.02$) and 24 ± 4% (group 2, $P < 0.001$) during the 6 months of additional treatment (group 1 vs 2: $P = 0.80$, Figure 2). CFR increased by 23 ± 3% (group 1, $P < 0.001$) and 17 ± 3% (group 2, $P < 0.001$; group 1 vs 2: $P = 0.16$). This was caused by a combination of decreased resting coronary flow velocity and increased flow velocity during adenosine-induced hyperaemia. No significant change was observed in forearm minimum vascular resistance; 6.5 ± 6.3% (group 1, $P = 0.79$) vs −2.0 ± 4.8% (group 2, $P = 0.38$; group 1 vs 2: $P = 0.30$), see Figure 2, Table 2b.

Echocardiography

LVMI decreased significantly ($P < 0.001$) by 9.9 ± 2.0% (group 1) and 8.4 ± 1.9% (group 2) during treatment (group 1 vs group 2: $P = 0.60$, Table 3). Indices of left ventricular systolic and diastolic function were unchanged (EF, TEI-index, E/A-ratio and E/E'; Supplementary Echocardiographic Data). Likewise, atrial size was unchanged.

Correlations

There was a significant but weak correlation between changes in CFR and SVRI ($r^2 = 0.12$, $P = 0.02$; data not shown). No significant correlation was found between CFR and MAP ($r^2 = 0.03$, $P = 0.24$).

Table 2a. Systemic hemodynamics, rebreathing technique (Innocor)

	Group 1			*Group 2*		
	Baseline	*Follow-up*	*Δ*	*Baseline*	*Follow-up*	*Δ*
Cardiac index (l min^{-1} m^{-2})	2.1 ± 0.1	2.2 ± 0.1	0.1 ± 0.1	2.8 ± 0.1††	2.6 ± 0.1	−0.2 ± 0.1
Stroke volume (ml)	56.7 ± 2.2	58.1 ± 2.1	1.4 ± 2.2	70.2 ± 2.2††	66.6 ± 3.0	−3.6 ± 3.3
Heart rate (beats per min)	72.4 ± 2.3	73.5 ± 2.6	1.2 ± 2.8	73.3 ± 2.0	72.2 ± 1.3	−1.1 ± 1.4
MAP—Innocor (mm Hg)	101.4 ± 2.2	89.5 ± 2.0**	−12.0 ± 2.0	93.2 ± 2.0††	87.0 ± 1.8**	−6.2 ± 1.4‡
SVRI (mm Hg min l^{-1} m^{-2})	47.1 ± 1.7	40.2 ± 1.9**	−6.9 ± 1.5	32.3 ± 0.7††	32.8 ± 1.2	0.4 ± 1.3‡‡

Abbreviations: MAP, mean arterial pressure; SVRI, systemic vascular resistance index. Group assignment as in Table 1. Values are mean ± s.e.m. Baseline vs follow-up, *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Baseline vs baseline, †$P < 0.05$, ††$P < 0.01$. Δgroup 1 vs Δgroup 2, ‡$P < 0.05$, ‡‡$P < 0.01$.

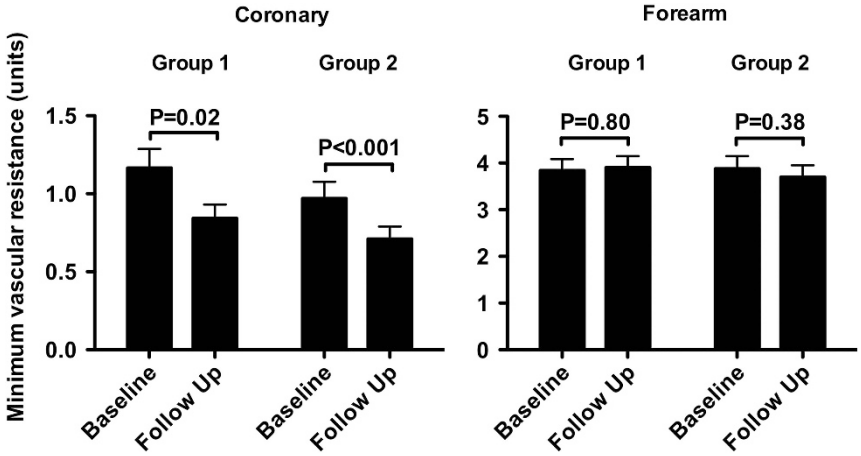

Figure 2. Measurements of minimum vascular resistance in the coronary and forearm vascular beds. Patients were assigned into two groups: group 1 (high-SVRI) and group 2 (low-SVRI) based on a median split at baseline. Data given as mean ± s.e.m. (Units: mm Hg min ml^{-1} pr. 100 g).

Changes in SVRI did not correlate to changes in either C-R_{min} ($r^2 = 0.02$, $P = 0.41$) or F-R_{min} ($r^2 = 0.002$, $P = 0.83$).

DISCUSSION

The present study shows that for patients already well treated for EH but with high SVRI, aggressive vasodilator treatment causes reduction in SVRI that was greater than that seen in patients with lower SVRI. Regardless of SVRI status, treatment caused lower coronary minimum vascular resistance and greater maximum vasodilator capacity in the heart. Unexpectedly, this occurred independently of SVRI and of BP. No changes were seen in the forearm circulation. Although several previous studies have demonstrated that antihypertensive treatment improves coronary microvascular dysfunction in EH, to our knowledge there are no previous data on the impact of additional vasodilating treatment in patients with mild hypertension and well-regulated BP. Thus, the present study is the first to demonstrate that coronary, but not forearm, microvascular dysfunction can be further improved despite BP control and that this may not be predicted from changes in SVRI.

Systemic response to intensified vasodilator treatment

The main aim of the current study was to evaluate whether mildly hypertensive patients with high SVRI despite well-regulated BP, would have a more pronounced improvement in coronary and peripheral microcirculation as a response to intensified vasodilator therapy compared with patients with low SVRI. This was based on the fact that systemic vascular resistance is increased in EH and previous observations that antihypertensive therapy did not reduce peripheral vascular resistance (F-R_{min}) in all EH patients despite reduced BP.[13] Hence, determination of SVRI and secondary identification of high-SVRI individuals could be of potential clinical interest, in order to target treatment specifically to reduce SVRI using additional vasodilating therapy. However, despite our current finding that SVRI is significantly more reduced in the high-SVRI group than in the low SVRI group, we observed comparable improvements in the coronary and peripheral microcirculation and no clinical relevant correlations between SVRI and microvascular structure. Only a weak linear correlation between changes in SVRI and CFR was found, that was non-significant following subdivision per SVRI group. We have previously reported similar findings in untreated patients with mild hypertension following initiation of antihypertensive treatment ($r = -0.30$, $P = 0.04$ vs $r = -0.35$, $P = 0.02$).[22] Thus, current results are in agreement with previous findings and supports a lack of clinical important association between SVRI and non-invasive indices of vascular structure. Although a large-scale prospective clinical study is needed for final conclusions regarding the correlation between changes in SVRI and CFR, current and previous findings, does not support assessment of SVRI to be helpful in determining cardiac microvascular dysfunction in EH.

Mechanisms for the improvement in CFR and decrease in minimal coronary resistance

Coronary microvascular dysfunction is documented in EH and even in patients with prehypertension. In the present study, coronary microvascular function was improved following intensified long-term vasodilator therapy in patients with both high and lower SVRI. The reduction in C-R_{min} and increase in maximal

Table 2b. Coronary and forearm hemodynamics

	Group 1			*Group 2*		
	Baseline	*Follow-up*	*Δ*	*Baseline*	*Follow-up*	*Δ*
Coronary hemodynamic measurements						
CFR	2.6 ± 0.1	3.1 ± 0.1***	0.5 ± 0.1	2.8 ± 0.1	3.3 ± 0.1***	0.5 ± 0.1
Resting Vd (m s^{-1})	0.21 ± 0.01	0.18 ± 0.01**	− 0.03 ± 0.01	0.20 ± 0.01	0.19 ± 0.01**	− 0.01 ± 0.01
Hyperaemic Vd (m s^{-1})	0.53 ± 0.02	0.56 ± 0.02	0.02 ± 0.01	0.57 ± 0.02	0.61 ± 0.02**	0.05 ± 0.01
LAD CSA (mm^2)	6.7 ± 0.2	7.3 ± 0.5	0.6 ± 0.5	6.7 ± 0.3	7.4 ± 0.4	0.7 ± 0.4
Resting volumetric flow rate (ml min^{-1})	54.0 ± 5.8	50.2 ± 5.2	− 3.8 ± 5.9	47.3 ± 4.4	47.4 ± 4.0	0.1 ± 5.3
Hyperaemic volumetric flow (ml min^{-1})	216.5 ± 11.5	243.7 ± 19.5	27.2 ± 18.3	229.6 ± 12.6	273.1 ± 18.0*	43.5 ± 16.5
Coronary R_{min} (mm Hg min ml^{-1} pr. 100 g LVM)	1.2 ± 0.1	0.8 ± 0.1*	− 0.3 ± 0.1	1.0 ± 0.1	0.7 ± 0.1**	− 0.3 ± 0.1
MAP baseline (mm Hg)	109.2 ± 1.7	99.2 ± 1.7***	− 9.9 ± 1.8	104.5 ± 1.5†	99.3 ± 1.3***	− 5.2 ± 1.2‡
MAP during adenosine (mm Hg)	105.3 ± 2.7	92.8 ± 2.4***	− 12.5 ± 2.4	98.5 ± 2.3	93.7 ± 2.0*	− 4.8 ± 2.0‡
Forearm hemodynamic measurements						
Hyperaemic forearm flow (ml pr. 100 ml tissue per min)	29.8 ± 1.8	27.0 ± 1.5	− 2.8 ± 1.7	29.0 ± 1.8	28.4 ± 1.9	− 0.5 ± 1.3
Forearm R_{min} (mm Hg min ml^{-1} pr. 100 ml tissue)	3.8 ± 0.2	3.9 ± 0.2	0.1 ± 0.2	3.9 ± 0.3	3.7 ± 0.3	− 0.2 ± 0.2
MAP during hyperaemia (mm Hg)	104.8 ± 2.0	97.6 ± 2.1***	− 7.2 ± 1.9	101.3 ± 1.4	95.2 ± 1.4***	− 6.1 ± 1.1

Abbreviations: CFR, coronary flow reserve (max flow velocity/resting flow velocity); HR, heart rate; LAD CSA, cross-sectional area of left anterior descending coronary artery; LVM, left ventricular mass; Vd, diastolic coronary flow velocity. Group assignment as in Figure 1. Values are mean ± s.e.m. Baseline vs follow-up, *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Baseline vs baseline, †$P < 0.05$. Δgroup 1 vs Δgroup 2, ‡$P < 0.05$.

Table 3. Left ventricular structure and function

	Group 1			*Group 2*		
	Baseline	*Follow-up*	*Δ*	*Baseline*	*Follow-up*	*Δ*
LVDd (mm)	46.3 ± 0.7	46.7 ± 0.7	0.4 ± 0.3	46.4 ± 0.8	46.5 ± 0.8	0.1 ± 0.3
LVMI (g m^{-2})	109.9 ± 4.3	98.5 ± 4.1***	− 11.4 ± 2.2	111.3 ± 2.9	101.7 ± 3.1**	− 9.5 ± 2.0
LA-volume (ml)	45.4 ± 2.2	43.2 ± 2.1	− 2.2 ± 2.0	41.3 ± 2.0	43.3 ± 1.6	3.7 ± 1.9‡
E/E′	7.1 ± 0.3	7.1 ± 0.3	0.01 ± 0.2	7.2 ± 0.3	7.3 ± 0.4	0.04 ±0.2

Abbreviations: LA, left atrium; LVDd, left ventricle diastolic diameter; LVMI, left ventricle mass index. Group assignment as in Figure 1. Values are mean ± s.e.m. Baseline vs follow-up, **$P < 0.01$, ***$P < 0.001$. Δgroup 1 vs Δgroup 2, ‡$P < 0.05$

coronary flow velocity combined with decreased left ventricular mass index indicate this is caused by a combination of functional and structural improvements of the coronary microcirculation. First, the lowering of resting coronary flow velocity contributed significantly to the substantial improvement in CFR following vasodilator therapy. As resting coronary flow velocity primarily relates to the myocardial oxygen consumption,[27] the reduction in resting flow velocity observed in this study may be associated with the lowering of mean arterial pressure and hence afterload. This is consistent with previous findings by Rossen *et al.*,[28] who showed that changes in heart rate or BP are accompanied by changes in resting coronary perfusion. Second, intensified vasodilator therapy has been shown to improve coronary perfusion by correction of structural alterations of intramyocardial arterioles in hypertensive rodents,[29] which is consistent with the increase in maximal coronary flow velocity in the current study. In addition, improvements in diastolic function may have contributed since myocardial perfusion manly occurs in diastole (Supplementary Echocardiographic Data). Although, no linear correlation was found between changes in MAP and CFR, the multifactorial mechanisms of impaired CFR in EH (increased resting flow due to LV hypertrophy and impaired hyperaemic response due to remodelling and diastolic dysfunction) suggests some degree of relation. However, the improvement of coronary reserve could not be predicted from changes in SVRI and no significant correlation between MAP and coronary reserve was found in the current study, supporting a dissociation between microvascular structure and arterial pressure.[4]

Forearm and coronary vascular structure

Previous cross-sectional studies have indicated that the structure of the peripheral vasculature is correlated with the vascular resistance in the coronary microcirculation.[30] This is further supported by a recent prospective study, which demonstrated that structural changes in the forearm and coronary microcirculation occur in parallel during initiation of antihypertensive treatment.[22] Surprisingly our data showed no change in F-R_{min} despite marked improvements in the coronary perfusion, indicating that changes in F-R_{min} do not predict changes in CFR in well-treated patients with hypertension during intensive vasodilating treatment. This suggests that there may be a limit to the reduction in F-R_{min} that can be obtained by vasodilator treatment.

Clinical implications of improved coronary microcirculation

Although the additional treatment reduced MAP and improved CFR, these two parameters were not correlated. Thus, reduction in MAP could not be taken to imply an improvement in coronary reserve, and *vice versa*. Moreover, despite the gain in coronary perfusion with today's first-choice antihypertensive drug classes,[17] the data indicate that even though the recommended treatment goals for BP have already been attained, further improvements in the coronary perfusion may still be achieved with intensified vasodilator treatment. This was found in spite of the fact that the majority (92%) of the included patients already received at least one vasodilator drug at baseline. The current study indicates that improved coronary perfusion can be obtained with intensified

vasodilator therapy, but prognostic data are needed to establish whether this improves exercise capacity and cardiovascular outcome. Currently such data are lacking in relation to CFR in uncomplicated EH, but reduced CFR is a sensitive predictor of target-organ damage[31] and has been associated with adverse clinical outcome in patients with chest pain,[9] hypertrophic cardiomyopathy[32] and LAD stenosis[33] suggesting a prognostic role of CFR. In addition, CFR closely correlates with maximal exercise capacity,[34] and exercise capacity is a strong predictor of subsequent cardiac events.[35] So to the extent that an improvement in CFR is advantageous, there is a potential to improve outcome with intensified vasodilating treatment, but certainly also to improve angina in symptomatic microvascular disease.

Limitations

Although the study has provided a clear result, there are limitations. First, CFR and C-R_{min} were determined non-invasively and no direct measurements of the coronary microvascular structure were made. The improved coronary vasodilator reserve could thus be related to mechanisms other than correction of vascular structure. In addition, CFR is a surrogate marker of global coronary perfusion and cannot fully reveal the distribution of blood flow in the entire myocardium, although there were no clinical indications of coronary artery disease in these mildly hypertensive patients. The investigated population was exclusively Caucasian and limitations exist when extrapolating the results to humans of different ethnic-origin.[36] Arterial stiffness was not determined. Although, arterial stiffness is predominantly related to ageing of conduit arteries some influence may exist on the microvasculature that may affect the current results. BP was measured in the brachial artery, not centrally. Antihypertensive agents have been reported to have varying effects on peripheral and central arteries.[37]

In conclusion, the current study demonstrates that for patients with high SVRI, additional vasodilating treatment can cause a decrease in SVRI. Furthermore, regardless of SVRI status, hypertensive coronary microvascular dysfunction can be improved by additional vasodilating treatment, even in mildly hypertensive patients with well-regulated BP. Moreover, coronary microvascular changes occurred independently of the change in BP and SVRI. In contrast, no changes in forearm microvascular dysfunction were seen. We conclude that, the status of the coronary microvasculature should be assessed directly rather than using information on BP and SVRI to assess the need for further treatment.

What is known about this topic?

- Increased systemic vascular resistance and microvascular dysfunction are well-documented in essential hypertension (EH) and contributes to hypertension-related cardiovascular organ damage.
- Pharmacological therapy with vasodilating antihypertensive drugs (ACE inhibitors/angiotensin II receptor blocker, calcium channel blocker) have been found to, at least partly, reverse microvascular dysfunction in EH, in contrast to the non-vasodilating β-blockers.

What this study adds?

- This study investigated the vascular effects of aggressive vasodilator therapy on coronary and peripheral resistance circulation in EH patients with well-regulated blood pressure (BP).
- Intensified vasodilating therapy improved systemic vascular resistance index (SVRI) more in patients with high SVRI than in those with low SVRI, and improved cardiac dilatation capacity. This occurred independently of the change in BP and SVRI.
- Coronary microvasculature should thus be assessed directly rather than using information on BP and SVRI to predict coronary dysfunction in EH.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The project was funded by a grant from the Danish Council for Independent Research

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