

ORIGINAL ARTICLE

High blood pressure is inversely related with the presence and extent of coronary collaterals

J Koerselman¹, PPTH de Jaegere^{2,4}, MC Verhaar³, Y van der Graaf¹ and DE Grobbee¹ for the SMART Study Group⁵

¹Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; ²Department of Cardiology, Heart Lung Center Utrecht, University Medical Center Utrecht, Utrecht, The Netherlands; ³Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

Patients with hypertension have an increased case fatality during acute myocardial infarction (MI). Coronary collateral (CC) circulation has been proposed to reduce the risk of death during acute ischaemia. We determined whether and to which degree high blood pressure (BP) affects the presence and extent of CC circulation. A cross-sectional study in 237 patients (84% males), admitted for elective coronary angioplasty between January 1998 and July 2002, was conducted. Collaterals were graded with Rentrop's classification (grade 0–3). CC presence was defined as Rentrop-grade ≥ 1 . BP was measured twice with an inflatable cuff manometer in seated position. Pulse pressure was calculated by systolic blood pressure (SBP)–diastolic blood pressure (DBP). Mean arterial pressure was calculated by $DBP + 1/3 \times (SBP - DBP)$. Systolic hyper-

tension was defined by a reading ≥ 140 mmHg. We used logistic regression with adjustment for putative confounders. SBP (odds ratio (OR) 0.86 per 10 mmHg; 95% confidence interval (CI) 0.73–1.00), DBP (OR 0.67 per 10 mmHg; 95% CI 0.49–0.93), mean arterial pressure (OR 0.73 per 10 mmHg; 95% CI 0.56–0.94), systolic hypertension (OR 0.49; 95% CI 0.26–0.94), and antihypertensive treatment (OR 0.53; 95% CI 0.27–1.02), each were inversely associated with the presence of CCs. Also, among patients with CCs, there was a graded, significant inverse relation between levels of SBP, levels of pulse pressure, and collateral extent. There is an inverse relationship between BP and the presence and extent of CC circulation in patients with ischaemic heart disease. *Journal of Human Hypertension* (2005) 19, 809–817. doi:10.1038/sj.jhh.1001917; published online 18 August 2005

Keywords: collateral circulation; coronary artery disease; blood pressure; epidemiology; cross-sectional studies

Introduction

Preinfarction systolic blood pressure (SBP) strongly relates to death and increased case-fatality in patients with an acute myocardial infarction (MI).¹ In a prospective analysis from the Finnmark Study, in which 46% of the 760 patients with MI died during follow-up, Njolstad and Arnesen¹ found SBP at baseline to lead to a relative risk of 1.22 (95% confidence interval (CI) 1.13–1.31) per 15 mmHg. The prognosis of patients with an acute MI may be beneficially affected by the presence of coronary collateral (CC) circulation.^{2,3} CCs, or 'natural

bypasses', are anastomotic connections without an intervening capillary bed between portions of the same coronary artery and between different coronary arteries.⁴ Well-developed CCs may minimize the infarct area and predict the presence of viable myocardium in patients with a history of antero-septal MI.⁵ Moreover, CCs may increase the number of 'golden hours' from the onset of an acute MI to successful coronary reperfusion. There appears, however, to be marked interindividual variability in the extent of collateral circulation.²

High blood pressure (BP) has been suggested to influence the development of CCs, but conflicting results remain, and the exact mechanism is still unknown at present.^{6–11} In the present study, we sought to determine whether high BP is related to the presence and extent of CC circulation.

Materials and methods

The study was approved by the Medical Ethics Review Committee of the University Medical Center

Correspondence: Professor DE Grobbee, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (UMC Utrecht) HP Str 6.131, Heidelberglaan 100, PO Box 85500, 3508 GA Utrecht, The Netherlands.

E-mail: D.E.Grobbee@umcutrecht.nl. URL: www.juliuscenter.nl

⁴Current address: Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands.

⁵Members listed in the Appendix.

Received 18 February 2005; revised 28 April 2005; accepted 11 May 2005; published online 18 August 2005

Utrecht (UMC Utrecht). Written informed consent was obtained from all patients.

Study population

A cross-sectional study was performed as part of the 'Second Manifestations of ARterial disease (SMART)' study. The SMART study¹² is an ongoing prospective cohort study conducted at the UMC Utrecht. For the purpose of the present analyses, the baseline diagnostic coronary angiograms of 237 patients, who were referred for elective percutaneous transluminal coronary angioplasty (PTCA) and took part in the SMART study between 1 January 1998 and 8 July 2002, were reviewed. At enrollment, medical history was recorded with a standardized questionnaire, and height, weight, and BP were measured. Blood and urine samples were taken.

CC circulation

The presence of CCs on each baseline coronary angiogram (CAG) was defined and visually assessed with Rentrop's¹³ classification (grade 0—no filling of collateral vessels; grade 1—filling of collateral vessels without any epicardial filling of the recipient artery; grade 2—partial epicardial filling by collateral vessels of the recipient artery; grade 3—complete epicardial filling by collateral vessels of the recipient artery). Grading was carried out independently by a trained research physician (JK) and a cardiologist (PPTHdJ), who were blinded to the clinical data. If an angiogram was graded differently, consensus was obtained. The pre-PTCA angiograms were graded in random order. To assess the interobserver variability of the grading, 100 randomly selected coronary angiograms were scored by another cardiologist, not involved in the study and unaware of the results of the reading of the two other observers and of the clinical data, during a separate session. The strength of agreement between the two observers (JK and PPTHdJ) and the other cardiologist was good (κ 0.65, 95% CI 0.51–0.79). The reproducibility of Rentrop's score has already been described as high previously (κ 0.85, 95% CI 0.77–0.93).¹⁴

Measures of BP

At enrollment in the SMART study, BP was measured by trained observers at each arm with an inflatable cuff manometer (Omron M5-1, Intelli Sense, Omron Matsusaka Co., Ltd, Japan; cuff size Type M or L depending on the patient's arm circumference), according to a standardized protocol. The patients were seated on a chair with their arms lying on a table. Prior to the first measurement, patients were made comfortable and at ease. In addition, patients were seated for at least 10 min

before this first BP measurement was carried out. BP was measured twice about 15 min apart. The mean value of these two BP readings at each arm was used. If, however, the two BP levels obtained 15 min apart were very different, a third BP measurement was carried out, at least 10 min after the second measurement. This third BP reading then replaced the second BP reading. Pulse pressure was calculated by systolic BP–diastolic BP. Mean arterial pressure was calculated by diastolic BP + $1/3 \times$ (systolic BP – diastolic BP).¹⁵ Systolic hypertension was defined as systolic BP ≥ 140 mmHg and diastolic hypertension as diastolic BP ≥ 95 mmHg. A history of hypertension and use of antihypertensive treatment was derived from the self-administrated, standardized questionnaires.

Data analysis

The primary outcome of interest was the presence of CCs, defined as a Rentrop-grade ≥ 1 .^{16–18} Unless specified otherwise, data are presented as count with percentage, or mean \pm standard deviation. The association between the presence and absence of CCs and each separate measure of BP was quantified with binary logistic regression analysis with adjustment for gender, age, history of MI, time-interval since MI (if previous), and diabetes mellitus. A history of MI and diabetes mellitus was entered into the model to adjust for potential confounding of the relation between BP and the presence of CC circulation.^{7,8} Subsequently, the analyses were repeated with additional adjustment for other putative confounders namely number of types of antihypertensive medication, time interval since diagnosis of hypertension, hyperlipidaemia, use of statins, current smoking, number of packyears, duration of anginal complaints, presence of coronary occlusion, degree of most severe coronary obstruction, and multivessel coronary disease.

The relation between the extent of CC circulation and measures of BP (as a continuous variable, notably systolic BP, diastolic BP, pulse pressure, and mean arterial pressure) was quantified with linear logistic regression analysis with adjustment for gender, age, a history of MI, and diabetes mellitus. Then, the analyses were repeated with further adjustment for the same, putative confounders, mentioned above. Odds ratios (ORs), betas, and 95% confidence interval are presented. A two-sided (multivariate) *P*-value < 0.05 was considered significant. The statistical package used was SPSS for Windows, release 12.0.1 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Baseline- and clinical characteristics of the study population are presented in Table 1. CCs were present

Table 1 Baseline- and clinical characteristics of the study population (n = 237)

Characteristic	All patients (n = 237) n (valid %) or mean ± s.d.	Collaterals present (n = 88) Rentrop = 1, 2, or 3 n (valid %) or mean ± s.d.	Collaterals absent (n = 149) Rentrop = 0 n (valid %) or mean ± s.d.	P-value
<i>Demographics</i>				
Male gender	198 (84)	77 (88)	121 (81)	0.21
Age at index-PTCA (years)	57.9 ± 9.2	57.6 ± 9.5	58.1 ± 9.1	0.64
<i>Cardiovascular risk factors</i>				
Current smoking	68 (29)	36 (41)	32 (22)	<0.01
Current alcohol consumption	181 (77)	68 (77)	113 (76)	0.87
Hypertension	90 (38)	26 (30)	64 (43)	0.04
Diabetes mellitus	47 (20)	24 (27)	23 (15)	0.03
Hyperlipidaemia	196 (83)	72 (82)	124 (84)	0.70
Obesity (BMI ≥ 30 kg/m ²)	41 (17)	14 (16)	27 (18)	0.68
<i>Blood pressure (BP)</i>				
Systolic BP (mmHg)	135 ± 21	132 ± 18	137 ± 22	0.04
Diastolic BP (mmHg)	77 ± 10	76 ± 9	78 ± 10	0.06
Pulse pressure (mmHg) ^a	58 ± 17	56 ± 14	59 ± 18	0.16
Mean arterial pressure (mmHg) ^b	97 ± 12	94 ± 11	98 ± 12	0.03
Mean number of types of antihypertensive drugs	1.5 ± 0.8	1.5 ± 0.8	1.5 ± 0.9	0.82
Duration since diagnosis hypertension (years)	11.0 ± 12.5	9.0 ± 10.1	12.0 ± 13.5	0.28
<i>Previous conditions</i>				
Prior angina pectoris	219 (92)	82 (93)	137 (92)	0.73
Previous myocardial infarction	102 (43)	44 (50)	58 (39)	0.11
Previous PTCA or CABG	74 (31)	28 (31)	46 (31)	0.88
Previous TIA or stroke	24 (10)	5 (6)	19 (13)	0.08
Previous non-cardiac vascular surgery	19 (8)	9 (10)	10 (7)	0.34
<i>Angiographic characteristics</i>				
Degree of coronary stenosis:				
50–90% ^c	149 (63)	20 (23)	129 (87)	—
90–99%	39 (17)	30 (34)	9 (6)	<0.01
100%	49 (21)	38 (43)	11 (7)	<0.01
Coronary occlusion	49 (21)	38 (43)	11 (7)	<0.01
Multivessel coronary disease	98 (41)	50 (57)	48 (32)	<0.01
Impaired left-ventricle function ^d	87 (41)	34 (43)	53 (41)	0.71
1-vessel coronary disease ^e	139 (59)	38 (43)	101 (68)	—
2-vessel coronary disease	77 (33)	38 (43)	39 (26)	<0.01
3-vessel coronary disease	21 (9)	12 (14)	9 (6)	<0.01
<i>Type of antihypertensive drugs used</i>				
Beta-adrenergic receptor antagonists	184 (78)	70 (80)	114 (77)	0.59
Diuretics	20 (8)	5 (6)	15 (10)	0.24
ACE-inhibitors	44 (19)	17 (19)	27 (18)	0.82
Calcium channel-blockers	96 (41)	34 (39)	64 (42)	0.65
Alpha-1 receptor antagonists	1	—	1	— ^e
Combined prescription medicines	4	4	—	— ^e
Selective imidazoline receptor agonists	1	—	1	— ^e
Angiotensin II receptor blockers	3	—	3	— ^e
Other type of antihypertensive drugs	1	—	1	— ^e
<i>Statins</i>				
Use of statins	130 (55)	52 (59)	78 (52)	0.31

n = number of patients (valid %) or mean ± s.d.

^aPulse pressure = systolic BP – diastolic BP.

^bMean arterial pressure = diastolic BP + 1/3 × (systolic BP – diastolic BP).

^cReference category.

^dIn 27 patients the ventriculogram turned out not to be performed.

^eToo few data.

BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation; TIA = transient ischemic attack.

in 88 patients (37%): 13 patients (15%) had grade 1 (no epicardial filling), 31 patients (35%) had grade 2 (partial epicardial filling), and 44 patients (50%) had grade 3 collaterals (complete epicardial filling).

BP and presence of CCs

Table 2 summarizes the results of the analyses regarding measures of BP and the presence of CC

Table 2 Measures of blood pressure and their association with the presence of coronary collaterals

Measures of blood pressure (BP)	Collaterals present (n = 88) Rentrop = 1, 2, or 3 n (valid %) or mean ± s.e.m.	Collaterals absent (n = 149) Rentrop = 0 n (valid %) or mean ± s.e.m.	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)	P-value after adjustment ^a
Systolic BP (mmHg)	132 ± 1.9	137 ± 1.8	0.87 (0.76–1.00) ^d	0.86 (0.73–1.00) ^d	0.05
Diastolic BP (mmHg)	76 ± 1.0	78 ± 0.8	0.76 (0.57–1.01) ^d	0.67 (0.49–0.93) ^d	0.02
Pulse pressure (mmHg) ^b	56 ± 1.5	59 ± 1.5	0.89 (0.75–1.05) ^d	0.91 (0.75–1.11) ^d	0.34
Mean arterial pressure (mmHg) ^c	94 ± 1.1	98 ± 1.0	0.77 (0.61–0.97) ^d	0.73 (0.56–0.94) ^d	0.02
Systolic hypertension (SBP ≥ 140 mmHg)	26 (29.5)	64 (43.0)	0.56 (0.32–0.98)	0.49 (0.26–0.94)	0.03
Diastolic hypertension (DBP ≥ 95 mmHg)	2 (2.3)	9 (6.0)	0.36 (0.08–1.71)	0.33 (0.07–1.59)	0.17
Antihypertensive treatment	22 (25.6)	52 (37.4)	0.58 (0.32–1.04)	0.53 (0.27–1.02)	0.06

^aOdds ratios and 95% confidence intervals adjusted for gender, age, history of myocardial infarction (MI), time interval since MI, and diabetes mellitus.

^bPulse pressure = systolic BP – diastolic BP.

^cMean arterial pressure = diastolic BP + 1/3 × (systolic BP – diastolic BP).

^dOdds ratio and 95% confidence interval expressed per 10 mmHg.

BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; OR = odds ratio; SBP = systolic blood pressure; s.e.m. = standard error of the mean.

Table 3 Blood pressure and its relation with the extent of coronary collateral (CC) circulation

Measures of blood pressure (BP)	CC-grade 1 (n = 13) Rentrop = 1 reference-category Mean ± s.e.m.	CC-grade 2 (n = 31) Rentrop = 2 Mean ± s.e.m.	CC-grade 3 (n = 44) Rentrop = 3 Mean ± s.e.m.	Unadjusted beta ^a (95% CI)	Adjusted beta ^{a,b} (95% CI)	P-value after adjustment ^b
Systolic BP (mmHg)	141 ± 6.5	133 ± 3.4	128 ± 2.0	–0.11 (–0.19; –0.02)	–0.11 (–0.20; –0.01)	0.03
Diastolic BP (mmHg)	76 ± 2.7	75 ± 1.8	76 ± 1.3	0.04 (–0.13; 0.21)	–0.01 (–0.20; 0.18)	0.94
Pulse pressure (mmHg) ^c	65 ± 5.0	58 ± 2.6	51 ± 1.7	–0.18 (–0.28; –0.07)	–0.17 (–0.29; –0.05)	<0.01
Mean arterial pressure (mmHg) ^d	97 ± 3.6	95 ± 2.1	94 ± 1.4	–0.08 (–0.23; 0.07)	–0.10 (–0.26; 0.06)	0.21

^aBetas and 95% confidence intervals expressed per 10 mmHg.

^bBetas and 95% confidence intervals adjusted for gender, age, history of myocardial infarction (MI), time interval since MI, and diabetes mellitus.

^cPulse pressure = systolic BP – diastolic BP.

^dMean arterial pressure = diastolic BP + 1/3 × (systolic BP – diastolic BP).

BP = blood pressure; CC = coronary collateral; CI = confidence interval; s.e.m. = standard error of the mean.

circulation, both unadjusted and adjusted for gender, age, history of MI, and diabetes mellitus. Systolic BP, diastolic BP, mean arterial pressure, systolic hypertension, and antihypertensive treatment were each inversely associated with the presence of CCs. Pulse pressure and diastolic hypertension were not associated with CC presence. Further adjustment for number of types of antihypertensive medication, time-interval since diagnosis of hypertension, hyperlipidemia, use of statins, current smoking, number of packyears, duration of anginal complaints, presence of coronary occlusion, degree of most severe coronary obstruction, and multivessel coronary disease left the relations essentially unchanged. However, in this full model, antihypertensive treatment (OR 0.85; 95% CI 0.32–2.27) was no longer associated with collateral presence.

BP and extent of CC circulation

Among patients with CCs, there was a graded and significant inverse relation between levels of systolic BP, levels of pulse pressure, and the extent of CCs (see Table 3). Diastolic BP and mean arterial pressure were not associated with CC extent. Additional adjustment for number of types of antihypertensive medication, time interval since diagnosis of hypertension, hyperlipidaemia, use of statins, current smoking, number of packyears, duration of anginal complaints, presence of coronary occlusion, degree of most severe coronary obstruction, and multivessel coronary disease did not materially change the findings. Bar graphs are presented, displaying the relation between each continuous measure of BP and each degree of CC circulation (see Figures 1–4).

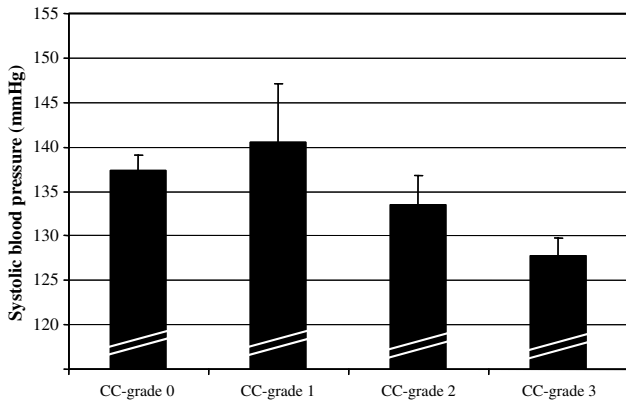


Figure 1 Systolic blood pressure across degrees of coronary collateral circulation. Mean value and standard error of the mean are displayed for each measure of blood pressure. CC=coronary collateral; grade 0=no filling of collateral vessels; grade 1=filling of collateral vessels without any epicardial filling of the recipient artery; grade 2=partial epicardial filling by collateral vessels of the recipient artery; grade 3=complete epicardial filling by collateral vessels of the recipient artery.

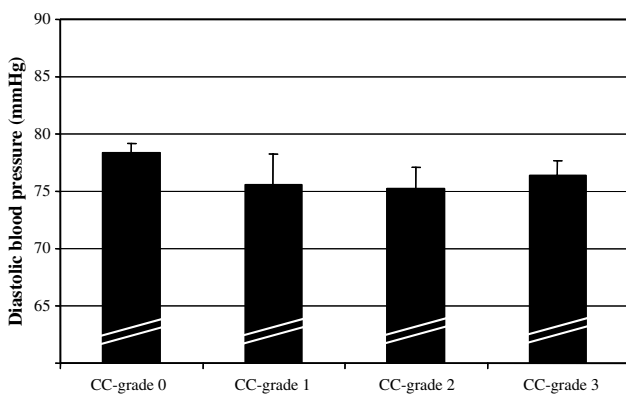


Figure 2 Diastolic blood pressure across degrees of coronary collateral circulation. Mean value and standard error of the mean are displayed for each measure of blood pressure. CC=coronary collateral; grade 0=no filling of collateral vessels; grade 1=filling of collateral vessels without any epicardial filling of the recipient artery; grade 2=partial epicardial filling by collateral vessels of the recipient artery; grade 3=complete epicardial filling by collateral vessels of the recipient artery.

Discussion

In the present study among 237 patients referred for elective PTCA, we found that high levels of BP were inversely related with the presence and extent of CCs. This was particularly pronounced for systolic BP and pulse pressure.

To appreciate these results, some aspects of this study need to be addressed. First, we investigated the presence or absence of CC circulation cross-sectionally, but not the development of collaterals over time. This makes causal inference regarding the role of high BP in reducing development of collaterals preliminary.

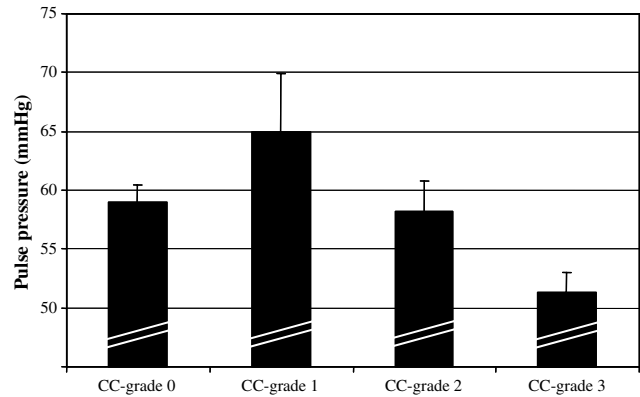


Figure 3 Pulse pressure across degrees of coronary collateral circulation. Mean value and standard error of the mean are displayed for each measure of blood pressure. CC=coronary collateral; grade 0=no filling of collateral vessels; grade 1=filling of collateral vessels without any epicardial filling of the recipient artery; grade 2=partial epicardial filling by collateral vessels of the recipient artery; grade 3=complete epicardial filling by collateral vessels of the recipient artery.

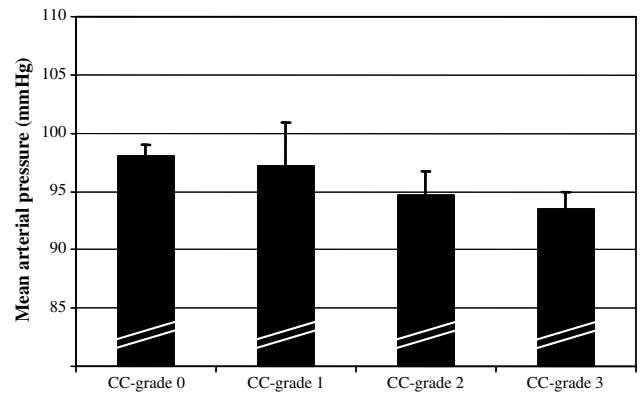


Figure 4 Mean arterial pressure across degrees of coronary collateral circulation. Mean value and standard error of the mean are displayed for each measure of blood pressure. CC=coronary collateral; grade 0=no filling of collateral vessels; grade 1=filling of collateral vessels without any epicardial filling of the recipient artery; grade 2=partial epicardial filling by collateral vessels of the recipient artery; grade 3=complete epicardial filling by collateral vessels of the recipient artery.

Second, the use of angiography to define and assess CCs may have influenced our observations. Coronary angiography, although the most frequently used diagnostic technique for the assessment of collateral vessels, can only identify vessels >100 μ m in diameter, whereas most collateral vessels are smaller.¹⁹ Furthermore, even though the overlap between quantitative measures and qualitative angiographic degrees of collateral flow has been demonstrated to be quite large,²⁰ quantitative indices of collateral circulation may be better markers of the functional significance of collateral vessels, in particular in recruitable (Rentrop-grade 1) collaterals.^{14,21,22} A recent study,²³ nonetheless, reported

good correlation between a novel angiographic method of assessment and function. This is to be expected considering the fundamental physical law describing that vessel radius is related to the fourth power of flow.²⁴ It is, thus, likely that the morphologic degree of collaterals used in this study is closely related with the functional degree of CC circulation. In addition, spontaneously visible CCs were found to be most adequate in preventing cardiac ischaemia during coronary occlusion, when compared with patients with recruitable collaterals or no collaterals.¹⁴

Finally, a last source of unquantifiable bias could have been introduced by the selection of patients admitted for elective coronary angioplasty. This selection is highly restrictive even within the domain of patients with known coronary artery disease. It must be acknowledged that patients with sufficient collaterals may not undergo diagnostic catheterization or angioplasty. At the other extreme, patients with extensive coronary artery disease with or without collaterals may be referred for coronary surgery and not angioplasty.

The mechanism of the formation of CCs is subject to intense preclinical and clinical research. In addition to high BP as explored in the present study, genetic factors and a number of other patient characteristics including age, myocardial ischaemia, physical exercise, smoking, body mass index, hyperlipidaemia, hyperhomocysteinaemia, diabetes mellitus, and use of various cardiovascular drugs have been proposed.^{6–9,16,25–35} Yet, results of these studies are conflicting and the pathophysiologic role and importance of these patient characteristics is still unclear.^{2,3,36}

To our knowledge, this is the first study to show an inverse association between (high) BP

and the presence and extent of CCs. This inverse relation continued to exist even after additional adjustment for, among other things, the duration of hypertension, number of types of antihypertensive drugs, duration of anginal complaints, coronary lesion severity, and the presence of coronary occlusion.

Two studies, in patients with carotid artery disease,³⁷ also reported a lower prevalence of cerebral collateral circulation among the patients with hypertension. Yet, three other studies⁹ found hypertension to be positively associated with the presence of CCs. Kyriakides *et al*⁹ compared 61 hypertensive patients with total or subtotal occlusion of a single coronary artery, with 252 normotensive patients with similar angiographic findings, and found that the CC circulation was more extensive in the hypertensive group. Karpanou *et al*¹⁰ studied 433 male patients with angiographically documented coronary artery disease, and found that CCs were more frequently present in patients with arterial hypertension, especially high-grade CCs. Finally, in a series of 200 patients with an occlusion of a single coronary artery, Kilian *et al*⁷ found a positive relation between hypertension and the number of collaterals with Rentrop-grade 3. Yet, this was only the case in univariate analysis.

In three other studies,⁶ no association between hypertension and CC presence was found.^{8,11} In a consecutive group of 112 patients with a chronic total coronary occlusion,⁶ hypertension was equally distributed among the patients, independent of CC presence or grade. Fujita *et al*⁸ studied 248 patients undergoing coronary angiography within 12 h after the onset of a first acute MI, and found hypertension to be equally present among the patients with and

Table 4 What is known on this topic/what this study adds

What is known on this topic

- Coronary collaterals, or 'natural bypasses', are anastomotic connections without an intervening capillary bed between portions of the same coronary artery and between different coronary arteries.
- Patients with hypertension have an increased case fatality during acute myocardial infarction.
- Well-developed coronary collaterals may minimize the infarct area and predict the presence of viable myocardium in patients with a history of anteroseptal myocardial infarction.
- Coronary collaterals may increase the number of 'golden hours' from the onset of an acute myocardial infarction to successful coronary reperfusion.
- There appears to be marked interindividual variability in the extent of collateral circulation.
- High blood pressure has been suggested to influence the development of coronary collaterals, but conflicting results remain, and the exact mechanism is still unknown, at present.

What this study adds

- This is the first study to show an inverse association between (high) blood pressure and the presence and extent of coronary collaterals. This was particularly pronounced for the systolic blood pressure and pulse pressure.
- This inverse relation may be explained by functional and structural remodeling of the coronary arterioles and microvasculature and venules in response to increased blood pressure.
- This arteriolar remodeling has been referred to as *microvascular rarefaction* (or rarification or rarefaction) and ultimately involves the obliteration of pre-existing blood vessels.
- The ensuing reduction in blood vessels not only may contribute to hypertensive lesions of target organs, but may also maintain or even amplify the increased blood pressure by augmenting the peripheral vascular resistance, thus creating a vicious circle.
- We postulate that the increased case fatality in hypertensive patients with an acute myocardial infarction may be related to these findings.

without well-developed CCs (defined as Rentrop-grade 2 or 3). Finally, Heinle *et al*¹¹ studied 248 patients undergoing selective coronary angiography, and found no difference in the occurrence of hypertension among the patients with and without CCs.

The controversy regarding the role of BP or hypertension in determining the presence and extent of CCs may in part be explained by differences in the patients studied and the methods used. A positive relation between BP or hypertension and the presence of CCs may be explained by an increased myocardial oxygen demand, which may trigger the formation or development of collaterals,¹⁰ or enlargement of collateral arteries.⁹

Another potential explanation for this controversy may be in the vasculature under study. We examined functional collateral vessels that were spontaneously visible with contrast angiography, thus vessels of at least 100 μm . The inverse relation, currently found between (high) BP and CC presence, may also be explained by functional and structural remodelling of the coronary arterioles and microvasculature and venules in response to increased BP, as proposed by Boudier,³⁸ Boudier³⁹ and Vicaut.⁴⁰ This arteriolar remodelling has been referred to as *microvascular rarefaction* (or rarification or rarefaction) and ultimately involves the obliteration of pre-existing blood vessels.⁴⁰ This destructive process affects the microvascular network, in particular the arteriolar vessels that are 100–150 μm in diameter, where a large part of the systemic pressure gradient takes place.^{39,40} Microvascular rarefaction is completely different from angiogenesis (the proliferation of capillaries in ischaemic areas) or arteriogenesis (the maturation of pre-existing collateral vessels into functional muscular collateral arteries), that generally involves vessels less than 100 μm in diameter.²⁷

Microvascular rarefaction has been observed even in very early stages of the development of hypertension. The ensuing reduction in blood vessels not only may contribute to hypertensive lesions of target organs, but may also maintain or even amplify the increased BP by augmenting the peripheral vascular resistance, thus creating a vicious circle. Microvascular changes in hypertension may also lead to an increase in pulse pressure, which may subsequently induce lesions of the vessel walls, and of the endothelium of the large arteries.³⁸ Both genetic and fetal mechanisms have been proposed to be involved.³⁹

Recently, in a large prospective cohort study with 2451 normotensive people and 10 years follow-up,⁴¹ the potentially important role of the narrowing of the small blood vessels in the pathogenesis of hypertension was clearly determined. Wong *et al*⁴¹ showed that people with smaller retinal arteriolar diameters were more likely to develop hypertension over a 10-year-period than people with larger arteriolar diameters, independent of known risk factors for hypertension. They also found that

the combined exposure to higher pre-existing BP at baseline and narrowed arterioles was associated with a higher risk of hypertension than the effect of either alone. This finding supports the theory of microvascular rarefaction described above, that higher BP may cause arteriolar vasoconstriction, vascular remodelling, and higher peripheral vascular resistance, leading to further increases in BP and the maintenance of the hypertensive state.^{38,41}

In conclusion, the results of this study show that high BP, and notably elevated systolic BP and increased pulse pressure, is inversely associated with the presence and extent of CC (arteriolar) circulation. Microvascular rarefaction in response to increased BP may explain our findings. We postulate that the increased case fatality in hypertensive patients with an acute MI¹ may be related to these findings (Table 4).

Acknowledgements

These data were presented previously in part as a poster, entitled 'High blood pressure is inversely related with presence and extent of coronary collaterals', at the 14th European Meeting on Hypertension of the European Society of Hypertension 2004 (Paris, France). We gratefully acknowledge Koos (J) Plomp, Cardiologist, Department of Cardiology, Heart Lung Center Utrecht, UMC Utrecht, Utrecht, The Netherlands, for scoring the 100 coronary angiograms to assess interobserver variability of the collateral grading. We thank Michael Edlinger for his accurate handling of the SMART-data. We thank Prof Harry AJ Struijker Boudier, PhD, for critical revision of the manuscript. We thank Christine AE Broeders for her excellent secretarial assistance. The work presented in this paper is part of a program grant from the Netherlands Organisation for Health Research and Development (ZonMw, project number 904-65-095). This funding source had no involvement in the writing of this paper or its submission. MCV is supported by the Netherlands Organisation for Scientific Research (NWO, Grant number 016-036-041).

Conflict of interest statement: None.

References

- 1 Njolstad I, Arnesen E. Preinfarction blood pressure and smoking are determinants for a fatal outcome of myocardial infarction: a prospective analysis from the Finnmark Study. *Arch Intern Med* 1998; **158**: 1326–1332.
- 2 Koerselman J, van der Graaf Y, de Jaegere PP, Grobbee DE. Coronary collaterals: an important and underexposed aspect of coronary artery disease. *Circulation* 2003; **107**: 2507–2511.
- 3 Seiler C. The human coronary collateral circulation. *Heart* 2003; **89**: 1352–1357.

- 4 Popma JJ, Bittl J. Coronary angiography and intravascular ultrasonography. In: Braunwald E, Zipes DP, Libby P (eds). *Heart Disease: A Textbook of Cardiovascular Medicine*. WB Saunders Company: Philadelphia, 2001, pp 387–418.
- 5 Fukai M *et al*. Angiographically demonstrated coronary collaterals predict residual viable myocardium in patients with chronic myocardial infarction: a regional metabolic study. *J Cardiol* 2000; **35**: 103–111.
- 6 Kornowski R. Collateral formation and clinical variables in obstructive coronary artery disease: the influence of hypercholesterolemia and diabetes mellitus. *Coron Artery Dis* 2003; **14**: 61–64.
- 7 Kilian JG, Keech A, Adams MR, Celermajer DS. Coronary collateralization: determinants of adequate distal vessel filling after arterial occlusion. *Coron Artery Dis* 2002; **13**: 155–159.
- 8 Fujita M *et al*. Determinants of collateral development in patients with acute myocardial infarction. *Clin Cardiol* 1999; **22**: 595–599.
- 9 Kyriakides ZS *et al*. Coronary collateral circulation in coronary artery disease and systemic hypertension. *Am J Cardiol* 1991; **67**: 687–690.
- 10 Karpanou EA *et al*. Significance of arterial hypertension on coronary collateral circulation development and left ventricular function in coronary artery disease. *J Hypertens* 1988; (Suppl 6): S151–S153.
- 11 Heinle RA, Levy RI, Gorlin R. Effects of factors predisposing to atherosclerosis on formation of coronary collateral vessels. *Am J Cardiol* 1974; **33**: 12–16.
- 12 Simons PC *et al*. Second manifestations of ARterial disease (SMART) study: rationale and design. *Eur J Epidemiol* 1999; **15**: 773–781.
- 13 Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985; **5**: 587–592.
- 14 van Liebergen RA *et al*. Quantification of collateral flow in humans: a comparison of angiographic, electrocardiographic and hemodynamic variables. *J Am Coll Cardiol* 1999; **33**: 670–677.
- 15 Rogers G, Oosthuyse T. A comparison of the indirect estimate of mean arterial pressure calculated by the conventional equation and calculated to compensate for a change in heart rate. *Int J Sports Med* 2000; **21**: 90–95.
- 16 Kurotobi T *et al*. Reduced collateral circulation to the infarct-related artery in elderly patients with acute myocardial infarction. *J Am Coll Cardiol* 2004; **44**: 28–34.
- 17 Habib GB *et al*. Influence of coronary collateral vessels on myocardial infarct size in humans. Results of phase I thrombolysis in myocardial infarction (TIMI) trial. The TIMI Investigators. *Circulation* 1991; **83**: 739–746.
- 18 Rentrop KP, Thornton JC, Feit F, Van Buskirk M. Determinants and protective potential of coronary arterial collaterals as assessed by an angioplasty model. *Am J Cardiol* 1988; **61**: 677–684.
- 19 Sabia PJ *et al*. An association between collateral blood flow and myocardial viability in patients with recent myocardial infarction. *N Engl J Med* 1992; **327**: 1825–1831.
- 20 Seiler C, Fleisch M, Garachemani A, Meier B. Coronary collateral quantitation in patients with coronary artery disease using intravascular flow velocity or pressure measurements. *J Am Coll Cardiol* 1998; **32**: 1272–1279.
- 21 Kyriakidis MK *et al*. Relation between changes in blood flow of the contralateral coronary artery and the angiographic extent and function of recruitable collateral vessels arising from this artery during balloon coronary occlusion. *J Am Coll Cardiol* 1994; **23**: 869–878.
- 22 Meier B *et al*. Coronary wedge pressure in relation to spontaneously visible and recruitable collaterals. *Circulation* 1987; **75**: 906–913.
- 23 Werner GS *et al*. Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions. *Circulation* 2003; **107**: 1972–1977.
- 24 Buschmann I, Schaper W. The pathophysiology of the collateral circulation (arteriogenesis). *J Pathol* 2000; **190**: 338–342.
- 25 Yilmaz MB *et al*. Obesity is associated with impaired coronary collateral vessel development. *Int J Obes Relat Metab Disord* 2003; **27**: 1541–1545.
- 26 Lee CW *et al*. Temporal patterns of gene expression after acute hindlimb ischemia in mice: insights into the genomic program for collateral vessel development. *J Am Coll Cardiol* 2004; **43**: 474–482.
- 27 Fujita M, Tambara K. Recent insights into human coronary collateral development. *Heart* 2004; **90**: 246–250.
- 28 Miura S *et al*. Angiotensin-converting enzyme inhibitor promotes coronary collateral circulation in patients with coronary artery disease. *Circ J* 2003; **67**: 535–538.
- 29 Heeschen C, Weis M, Cooke JP. Nicotine promotes arteriogenesis. *J Am Coll Cardiol* 2003; **41**: 489–496.
- 30 Hochberg I *et al*. Haptoglobin phenotype and coronary artery collaterals in diabetic patients. *Atherosclerosis* 2002; **161**: 441–446.
- 31 Nishikawa H *et al*. Pravastatin promotes coronary collateral circulation in patients with coronary artery disease. *Coron Artery Dis* 2002; **13**: 377–381.
- 32 Nagai Y *et al*. Plasma level of homocysteine is inversely-associated with the development of collateral circulation in patients with single-vessel coronary artery disease. *Circ J* 2002; **66**: 158–162.
- 33 Duan J *et al*. Hyperhomocysteinemia impairs angiogenesis in response to hindlimb ischemia. *Arterioscler Thromb Vasc Biol* 2000; **20**: 2579–2585.
- 34 Piek JJ *et al*. Clinical, angiographic and hemodynamic predictors of recruitable collateral flow assessed during balloon angioplasty coronary occlusion. *J Am Coll Cardiol* 1997; **29**: 275–282.
- 35 Newman PE. The coronary collateral circulation: determinants and functional significance in ischemic heart disease. *Am Heart J* 1981; **102**: 431–445.
- 36 Sasayama S, Fujita M. Recent insights into coronary collateral circulation. *Circulation* 1992; **85**: 1197–1204.
- 37 Henderson RD *et al*. Angiographically defined collateral circulation and risk of stroke in patients with severe carotid artery stenosis. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. *Stroke* 2000; **31**: 128–132.
- 38 Boudier HA. Hypertension and microcirculation. *Arch Mal Coeur Vaiss* 2002; **95**(Spec No 6): 17–22.
- 39 Boudier HA. Arteriolar and capillary remodelling in hypertension. *Drugs* 1999; **58**(Spec No 1): 37–40.
- 40 Vicaut E. Microcirculation and arterial hypertension. *Drugs* 1999; **58**(Spec No 1): 1–10.
- 41 Wong TY *et al*. Prospective cohort study of retinal vessel diameters and risk of hypertension. *BMJ* 2004; **329**: 79.

Appendix

The SMART Study Group consists of A Algra, MD, PhD, Y van der Graaf, MD, PhD, DE Grobbee, MD, PhD, GEHM Rutten, MD, PhD, Julius Center for Health Sciences and Primary Care, JD Banga, MD, PhD, FLJ Visseren, MD, PhD, Department of Internal Medicine, BC Eikelboom, MD, PhD, FL

Moll, MD, PhD, Department of Vascular Surgery, LJ Kappelle, MD, PhD, Department of Neurology, HA Koomans, MD, PhD, Department of Nephrology, WPTHM Mali, MD, PhD, Department of Radiology, PAFM Doevendans, MD, PhD, and PPTH de Jaegere, MD, PhD, Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands.