Collateral and collateral-adjacent hyperemic vascular resistance changes and the ipsilateral coronary flow reserve: Documentation of a mechanism causing coronary steal in patients with coronary artery disease

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Abstract

Objectives: The goal of this clinical study was to assess the influence of hyperemic ipsilateral, collateral and contralateral vascular resistance changes on the coronary flow velocity reserve (CFVR) of the collateral-receiving (i.e. ipsilateral) artery, and to test the validity of a model describing the development of collateral steal. **Methods:** In 20 patients with one- to two-vessel coronary artery disease (CAD) undergoing angioplasty of one stenotic lesion, adenosine induced intracoronary (i.c.) CFVR during vessel *patency* was measured using a Doppler guidewire. During stenosis *occlusion*, simultaneous i.c. distal ipsilateral flow velocity and pressure (P_{occl}, using a pressure guidewire) as well as contralateral flow velocity measurements via a third i.c. wire were performed before and during intravenous adenosine. From those measurements and simultaneous mean aortic pressure (P_{ao}), a collateral flow index (CFI), and the ipsilateral, collateral, and contralateral vascular resistance index (R_{ipsi}, R_{coll}, R_{contra}) were calculated. The study population was subdivided into groups with CFI<0.15 and with CFI≥0.15. **Results:** The percentage-diameter coronary artery stenosis (%-S) to be dilated was similar in the two groups: 78±10% versus 82±12% (NS). CFVR was not associated with %-S. In the group with CFI≥0.15 but not with CFI<0.15, CFVR was directly and inversely associated with R_{coll} and R_{contra}, respectively. **Conclusions:** A hemodynamic interaction between adjacent vascular territories can be documented in patients with CAD and well developed collaterals among those regions. The CFVR of a collateralized region may, thus, be more dependent on hyperemic vascular resistance changes of the collateral and collateral-supplying area than on the ipsilateral stenosis severity, and may even fall below 1. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Coronary disease; Coronary circulation; Regional blood flow; Collateral circulation

1. Introduction

Well developed collateral blood flow to an occluded coronary artery seems to be sufficient to maintain myocardial viability, and to protect against large infarcts, left ventricular (LV) aneurysm formation, impaired systolic LV function, and even increased mortality [1,2]. Conversely, the presence of extensive collaterals has been associated with disadvantages, such as more frequent restenosis after percutaneous transluminal coronary angioplasty (PTCA) [3,4], and the occurrence of coronary steal [5]. Coronary steal is defined as hyperemia induced blood flow reduction instead of augmentation to a vascular region of interest (i.e. coronary flow reserve, CFR <1) [5,6]. Coronary steal, or more generally, the CFR in a collateral-receiving area has been hypothesized to be influenced not only by the stenosis severity in the vascular region of interest (determining the ipsilateral vascular resistance, R_{ipsi}; Fig. 1), but also by the interaction via collaterals between adjacent vascular resistances, i.e. the hyperemia-induced resistance

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changes of the collateral circulation itself (R_{coll}), and that of the contralateral, collateral-supplying region (R_{contra}) [7–10]. The interaction of adjacent vascular resistances may not exist in patients with poorly developed collaterals [10].

So far, the illustrated hemodynamic interactions during hyperemia of the mentioned vascular resistances and their effect on CFR have only been validated experimentally or in an electrical analogue model [7,8,11]. The lack of such investigations in patients with CAD may be due to the fact that at least three simultaneous intracoronary pressure and blood flow velocity measurements are required at rest and during hyperemia (Fig. 1) for the calculation of the circulatory parameters involved. Therefore, the goal of this clinical study was to assess the influence of hyperemic ipsilateral, collateral and contralateral vascular resistance changes on the coronary flow velocity reserve (CFVR) of the collateral-receiving (i.e. ipsilateral) artery, and to test the validity of a model describing the development of collateral steal.

2. Methods

2.1. Patients

Twenty patients with one- to two-vessel CAD were included into the study. All underwent PTCA of one stenotic lesion because of symptoms related to CAD. Patients were prospectively selected as follows: (1) any angiographic degree of coronary collaterals, (2) identifiable vessel supplying the collaterals (i.e. contralateral artery), (3) no auto-collaterals (i.e. no regional anastomoses within the vessel undergoing PTCA as seen by angiography), (4) no previous infarction in the myocardial area undergoing PTCA (i.e. the ipsilateral area; Fig. 1), (5) no previous infarction in the myocardial area supplying collaterals (i.e. the contralateral area; Fig. 1), (6) no baseline ECG ST-segment abnormalities.

The present investigation was approved by the institutional ethics committee, and the patients gave informed consent to participate in the study.

The study population was divided into two similarly sized groups with fewer and more extensive collaterals according to the intracoronary (i.c.) pressure-derived collateral flow index (CFI) being <0.15 (group CFI<0.15) or ≥0.15 (group CFI≥0.15).

2.2. Cardiac catheterization and coronary angiography

Patients underwent left heart catheterization. Aortic pressure was measured using the PTCA guiding catheter. Biplane left ventriculography was performed followed by coronary angiography. Coronary artery stenoses were
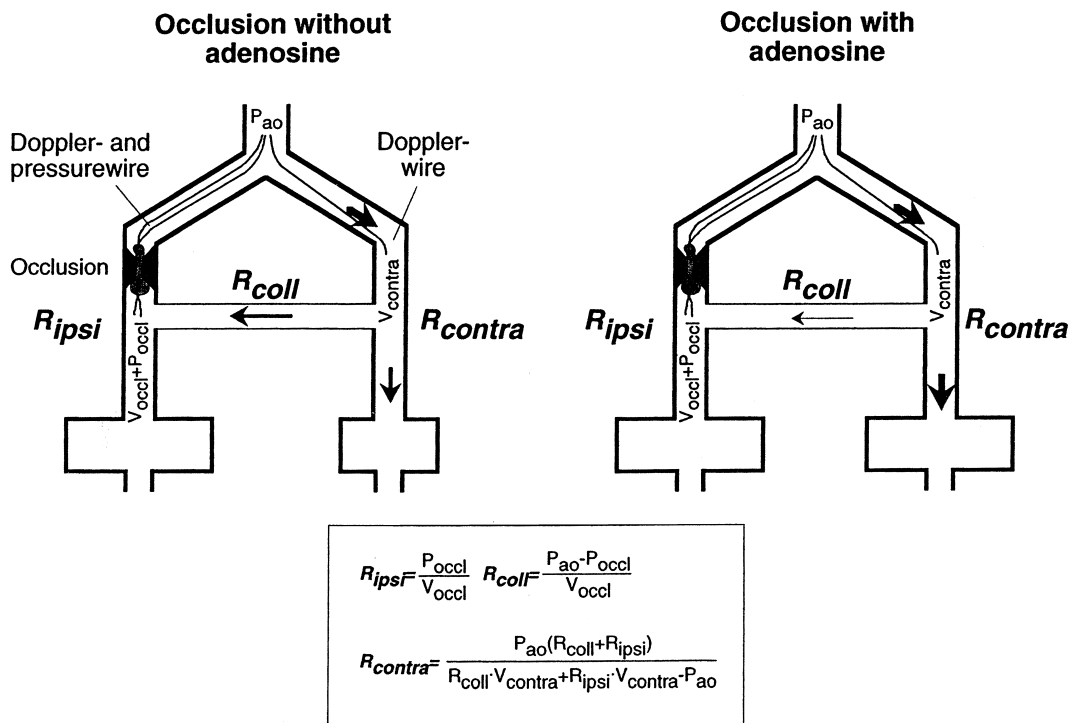

Fig. 1. Schematic of a coronary artery with intracoronary (i.c.) Doppler- and pressure wires located distal to the occluded, collateral-receiving (i.e. ipsilateral) and in the collateral-supplying (i.e. contralateral) coronary artery. Simultaneous i.c. blood flow velocity and pressure measurements (V_{occl}, P_{occl}, V_{contra}) as well as mean aortic pressure (P_{ao}) via the angioplasty guiding catheter provided the variables for the calculation of a pressure-derived collateral flow index, and of ipsilateral, collateral and contralateral vascular resistance indices (R_{ipsi}, R_{coll}, R_{contra}, equations shown within the frame) before (left hand side) and during (right hand side) intravenous adenosine infusion.

estimated quantitatively as percent diameter reduction. Angiographic collateral degrees (0–3) were determined before PTCA: 0=no contrast filling of the epicardial ipsilateral vessel via collaterals, 1=small side branches filled, 2=major side branches of the main epicardial vessel filled, 3=main epicardial vessel filled [12].

2.3. Coronary flow velocity reserve measurement

Coronary flow velocity reserve (CFVR) during vessel patency distal to the stenosis to be dilated and in the contralateral vessel was determined using a 0.014-inch Doppler guidewire (Flowire®, Endosonics, Mountain View, CA, USA). CFVR was calculated by dividing hyperemic peak flow velocity averaged over two cardiac cycles (APV, cm/s) by APV at rest. Hyperemia was induced using intracoronary (i.c.) adenosine, 18 μg for the left and 12 μg for the right coronary artery [13].

2.4. Coronary collateral assessment

Pressure-derived CFI: A 0.014-inch fiberoptic pressure wire (Pressureguide®, Radi Medical, Uppsala, Sweden) was used to determine i.c. pressure-derived CFI (CFI, no unit) by simultaneous measurement of mean aortic pressure (P_{ao}, mmHg, via the angioplasty guiding catheter) and the distal coronary artery perfusion pressure during balloon occlusion (P_{occl}, mmHg, Fig. 1). Central venous pressure (CVP) was estimated to be equal to 5 mmHg. CFI was calculated as (P_{occl}-CVP) divided by (P_{ao}-CVP) [14,15].

Doppler-derived CFI: The velocity-derived CFI is calculated as the ratio of flow velocity time integral distal to the occluded stenosis (Vi_{occl}, cm) divided by that obtained at identical location after PTCA (i.e. not occluded, $Vi_{ø-occl}$, cm): $Vi_{occl}/Vi_{ø-occl}$ (Fig. 1) [15].

2.5. Resistance indices calculations

The ipsilateral distal, collateral and contralateral distal vascular resistance indices (Fig. 1, R_{ipsi}, R_{coll}, and R_{contra}, mmHg/cm/s) were calculated using an electrical analogue to model the vascular network as depicted in Fig. 1 [9,16]. The necessary i.c. pressure and velocity parameters for the mentioned resistance calculations were obtained simultaneously.

2.6. Study protocol

Following diagnostic coronary angiography, an i.c. bolus of 0.2 mg of nitroglycerin was given in order to maintain epicardial coronary artery calibers constant. A Doppler guidewire was positioned distal to the stenosis undergoing PTCA, and CFVR was determined during vessel patency. The Doppler guidewire was later used to transport the PTCA balloon. An i.c. ECG obtained from the Doppler guidewire was recorded. Then, the ipsilateral

pressure guidewire was positioned distal to the stenosis to be dilated, and a second i.c. Doppler guidewire was placed into the distal part of the coronary artery supplying the collaterals to the ipsilateral vessel (i.e. the contralateral vessel; Fig. 1). CFVR was measured in the contralateral vessel ($CFVR_{contra}$). Following ipsilateral CFVR measurements during vessel patency, occlusive ipsilateral and contralateral (no occlusion), simultaneous measurements of V_{occl} and P_{occl} as well as mean aortic pressure via the angioplasty guiding catheter (P_{ao}) were performed without adenosine, and during hyperemia induced by intravenous adenosine (140 μg/kg/min) (Fig. 2). Velocity and pressure values obtained after 1 min of occlusion were used for the calculation of CFI and resistance indices. Blood pressure and heart rate were recorded continuously.

Following completion of PTCA and after cessation of reactive hyperemia, $Vi_{ø-occl}$ was measured distal to the dilated stenosis for the assessment of Doppler-derived CFI (CFI provided in Tables 1–4 and Figs. 1–4 are pressure-derived CFI unless otherwise indicated).

2.7. Statistical analysis

Between-group comparisons of continuous data were performed by an unpaired Student's t-test. A chi^2-test was used for comparison of categorical variables among the two study groups. A paired Student's t-test was employed to test intra-individual statistical significance of adenosine-induced CFI changes. Linear regression analysis was used for assessing the relation between CFVR and the stenosis severity of the lesion undergoing PTCA, and hyperemic vascular resistance changes. Mean values±standard deviation are given. Statistical significance was defined at a P value of <0.05.

3. Results

3.1. Patient characteristics and clinical data

Eleven patients were in the group with CFI<0.15 and nine patients in the group with CFI≥0.15. There were no statistically significant differences between the two study groups regarding age of the patients, gender, degree of angina pectoris, the frequency of cardiovascular risk factors, or the use of vasoactive and lipid-lowering substances (Table 1). All patients were in sinus rhythm.

3.2. Angiographic and coronary collateral data

The occurrence of a previous non-Q-wave myocardial infarction in non-PTCA territory, the frequency of previous PTCA, and LV ejection fraction were similar in the study groups (Table 2). The number of vessels affected by CAD, and the severity of the stenosis undergoing PTCA as well as that of the contralateral vessel did not differ
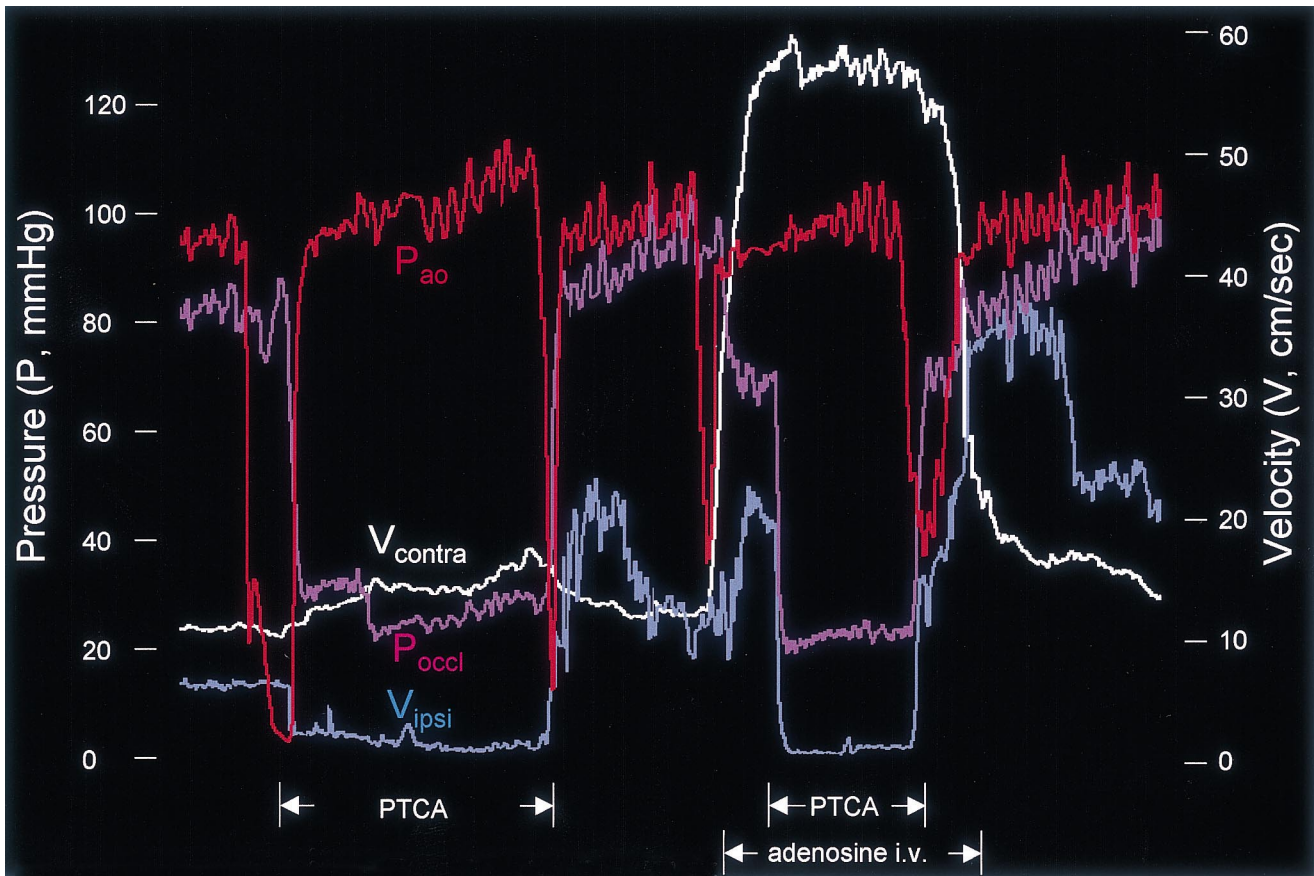
Fig. 2. Tracing of temporally recorded, simultaneous intracoronary (i.c.) pressure and velocity measurements in the ipsi- and contralateral coronary artery before and during (suffix 'occl') two stenosis occlusions. Pink line: i.c. distal ipsilateral pressure; red line: mean aortic pressure obtained via the guiding catheter (P_{ao}); blue line: i.c. distal ipsilateral blood flow velocity; white line: i.c. contralateral blood flow velocity. The two stenosis occlusions (PTCA) were performed without and with intravenous adenosine (140 μg/kg/min). The scale for pressure is depicted on the left hand side (vertical axis), the scale for velocity on the right hand side (vertical axis).

between the study groups (Table 2). There were no statistical differences in the frequency of the vessels treated by PTCA.

Table 1
Patient characteristics and clinical data[a]

	CFI<0.15	CFI≥0.15	P
n	11	9	
Age (years)	59±10	61±11	NS
Men (%)	10 (91)	9 (100)	NS
CCS class	1.5±1.2	1.9±1.1	NS
Smoking (%)	4 (36)	2 (22)	NS
Systemic hypertension (%)	5 (45)	5 (56)	NS
Hypercholesterolemia (%)	6 (55)	4 (44)	NS
Diabetes mellitus (%)	2 (18)	2 (22)	NS
Medication			
Calcium antagonist (%)	2 (18)	3 (33)	NS
ACE-Inhibitor (%)	7 (64)	3 (33)	NS
β-blocker (%)	5 (45)	4 (44)	NS
Nitrates (%)	2 (18)	1 (11)	NS
Lipid-lowering agents (%)	5 (45)	2 (22)	NS

[a] Abbreviations: CCS, Canadian Cardiovascular Society; NS, not significant.

Patients of the group CFI<0.15 more often had angina pectoris and ST-segment shift >1 mm on i.c. ECG during coronary occlusion when compared with the group CFI≥ 0.15 (Table 2). Angiographic collateral degree and pressure- as well as Doppler-derived CFI were lower in the group with CFI<0.15 than in that with CFI≥0.15.

3.3. Adenosine-induced hemodynamic changes in the ipsilateral, collateral, and contralateral vascular area

Pre-PTCA coronary flow velocities measured in the vessel undergoing PTCA showed an adenosine induced increase in the group with CFI<0.15 and no significant change in patients with CFI≥0.15 (Table 3). The respective values in the vessel supplying the collaterals revealed an increase in both groups by a factor of approximately three (CFVR of 3). Mean aortic pressure was not different between the groups, and it decreased under i.v. adenosine during vessel occlusion. Both ipsilateral occlusive pressure and velocity values were lower in the group with CFI< 0.15 versus ≥0.15, and they increased during i.v. adenosine, whereas they did not change in the group with

Table 2
Angiographic and coronary collateral data[a]

	CFI<0.15	CFI≥0.15	P
n	11	9	
Previous non-Q-wave infarction in non-PTCA territory (%)	3 (27)	1 (11)	NS
Previous PTCA (%)	1 (9)	1 (11)	NS
LV ejection fraction	63±10%	65±8%	NS
Number of coronary arteries involved	1.5±0.5	1.9±0.4	NS
Diameter stenosis before PTCA	78±10%	82±12%	NS
Diameter stenosis of the contralateral vessel	14±24%	24±37%	NS
Coronary artery undergoing PTCA			
LAD (%)	6 (55)	3(33)	NS
LCX (%)	3 (27)	4 (44)	NS
RCA (%)	2 (18)	2 (22)	NS
Angina pectoris during PTCA (%)	8 (73)	3 (33)	0.08
I.c. ECG ST-shift during PTCA (%)	11 (100)	4 (44)	0.004
Angiographic collateral degree (0–3)[b]	0.5±0.7	2.0±0.9	0.0005
Pressure-derived collateral flow index	0.10±0.04	0.26±0.13	0.001
Doppler-derived collateral flow index	0.14±0.08	0.27±0.13	0.01

[a] Abbreviations: i.c., intracoronary; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LV, left ventricular; NS, not significant; PTCA, percutaneus transluminal coronary angioplasty; RCA, right coronary artery;.

[b] Assessed before PTCA and before treatment with adenosine.

CFI≥0.15 (Table 3). Adenosine-induced contralateral flow velocity increased by a factor of about 2.5 during occlusion of the ipsilateral vessel.

Table 4 illustrates that the CFVR of the ipsilateral artery ($CFVR_{ipsi}$) was higher in the group with CFI<0.15 than in that with CFI≥0.15. $CFVR_{contra}$ was not different between the study groups. There was a trend towards lower $CFVR_{ipsi}$ with increasing stenosis severity of the lesion undergoing PTCA which was due to the group with CFI<0.15: $CFVR_{ipsi}=3.5-0.02\%$-stenosis, $r=-0.35$, $P=0.29$;

in CFI≥0.15: $P=0.91$. Fig. 2 provides an example of the behavior of simultaneously obtained i.c. pressure and velocity measurements in the ipsi- and contralateral coronary artery before and during two occlusions. Distal (P_{occl}) and aortic pressures (P_{ao}) during the two occlusions show that there is an increase in CFI in this particular case (i.e. reduced P_{ao} and constant P_{occl}). Fig. 3 provides individual data of CFI changes during i.v. adenosine, whereby there was an increase in the CFI<0.15-group and no statistical change in the CFI≥0.15-group. The lack of

Table 3
Effect of adenosine on velocity and pressure data[a]

	CFI<0.15		P	CFI≥0.15		P
	Baseline	Adenosine		Baseline	Adenosine	
Coronary flow velocity reserve obtained during vessels patency before PTCA		*Intracoronary*			*Intracoronary*	
Ipsilateral velocity (cm/s)	11.2±3.1	19.8±6.5[b]	0.02	12.4±7.1	16.0±10.2	NS
Contralateral velocity (cm/s)	14.1±4.2	37.3±5.5[b]	<0.0001	17.2±6.9	56.0±4.8	<0.0001
Mean aortic pressure, P_{ao}		*Intravenous*			*Intravenous*	
P_{ao} during ipsilateral occlusion (mmHg)	90.8±14.4	86.5±13.6	0.02	91.3±8.9	88.3±9.6	0.05
Ipsilateral occlusive pressure, P_{occl}						
P_{occl} (mmHg)	8.8±3.9[b]	11.5±5.8[b]	0.03	25.6±12.2	21.0±8.2	NS
Ipsilateral occlusive velocity, V_{occl}		*Intravenous*			*Intravenous*	
V_{occl} (cm/s)	2.6±1.5[b]	3.3±1.6	0.04	4.8±2.2	2.9±0.7	NS
Contralateral velocity, V_{occl}		*Intravenous*			*Intravenous*	
V_{occl} during ipsilateral occlusion (cm/s)	13.9±4.7	29.3±12.4	0.0001	18.6±7.5	44.9±8.0	0.0001

[a] N=number of patients; PTCA, percutaneous transluminal coronary angioplasty.

[b] $P<0.05$ versus the respective position in the group with CFI≥0.15. *Intracoronary* adenosine: 12 μg for the right, 18 μg for the left coronary artery; *intravenous* adenosine: 140 μg/kg body weight/minute.

Table 4
Adenosine induced hemodynamic changes of velocity and vascular resistance parameters[a]

	CFI<0.15	CFI≥0.15	P
n	11	9	
$CFVR_{ipsi}$	1.9±0.5	1.3±0.4	0.005
$CFVR_{contra\ pre\ PTCA}$	2.7±0.8	3.3±0.9	NS
$CFVR_{contra\ post\ PTCA}$	2.7±0.7	3.4±0.5	0.08
Collateral flow index without adenosine i.v.	0.10±0.04	0.26±0.13	0.001
Collateral flow index with adenosine i.v.	0.13±0.06	0.23±0.10	0.02
R_{ipsi}-change	0.9±0.2	1.3±0.4	0.04
R_{ipsi} without adenosine i.v. (mmHg/cm/s)	4.8±4.4	5.5±1.6	NS
R_{ipsi} with adenosine i.v. (mmHg/cm/s)	4.5±3.8	7.1±3.9	NS
P^{b}	NS	NS	
R_{coll}-change	0.7±0.2	1.7±0.9	0.002
R_{coll} without adenosine i.v. (mmHg/cm/s)	48.8±35.6	19.3±11.4	0.03
R_{coll} with adenosine i.v. (mmHg/cm/s)	32.8±24.1	24.7±6.7	NS
P^{b}	0.03	NS	
R_{contra}-change	0.4±0.1	0.3±0.2	0.05
R_{contra} without adenosine i.v. (mmHg/cm/s)	8.8±4.2	11±7.3	NS
R_{contra} with adenosine i.v. (mmHg/cm/s)	3.5±1.7	2.3±0.7	NS
P^{b}	0.0002	0.006	

[a] Abbreviations: $CFVR_{ipsi}$, ipsilateral coronary flow velocity reserve; $CFVR_{contra}$, contralateral coronary flow velocity reserve; i.v., intravenous; NS, not significant; PTCA, percutaneus transluminal coronary angioplasty; R_{coll}, collateral resistance index; R_{contra}, contralateral resistance index; R_{ipsi}, ipsilateral resistance index.
[b] Comparison between situation without and with adenosine.

an overall change in CFI≥0.15-group was related to the fact that four of its nine patients showed a marked CFI decrease whereas all the patients in the group with CFI<0.15 revealed an adenosine-induced increase in CFI. The $CFVR_{ipsi}$ values of those four patients in the group with CFI≥0.15 amounted to 0.7–1.4.

Relative and absolute ipsilateral, collateral and contralateral resistance changes during i.v. adenosine are shown in Table 4. There was a 10% decrease and a 30% increase in R_{ipsi} in the group with CFI<0.15 and with CFI≥0.15, respectively. The alterations in both groups were not

significant. The behavior of R_{coll} was similar as R_{ipsi} in the two groups: 30% decrease in the group with CFI<0.15 and 70% increase in that with CFI≥0.15, respectively. The decrease in R_{coll} among patients with CFI<0.15 was statistically significant. R_{contra} during ipsilateral stenosis occlusion was significantly reduced during adenosine i.v. in both groups, whereby the change was less pronounced in the group CFI<0.15 than in patients with CFI≥0.15.

There was no correlation between adenosine-induced alteration in occlusive R_{ipsi} and $CFVR_{ipsi}$ during vessel patency before PTCA (Fig. 4A). However, there was an
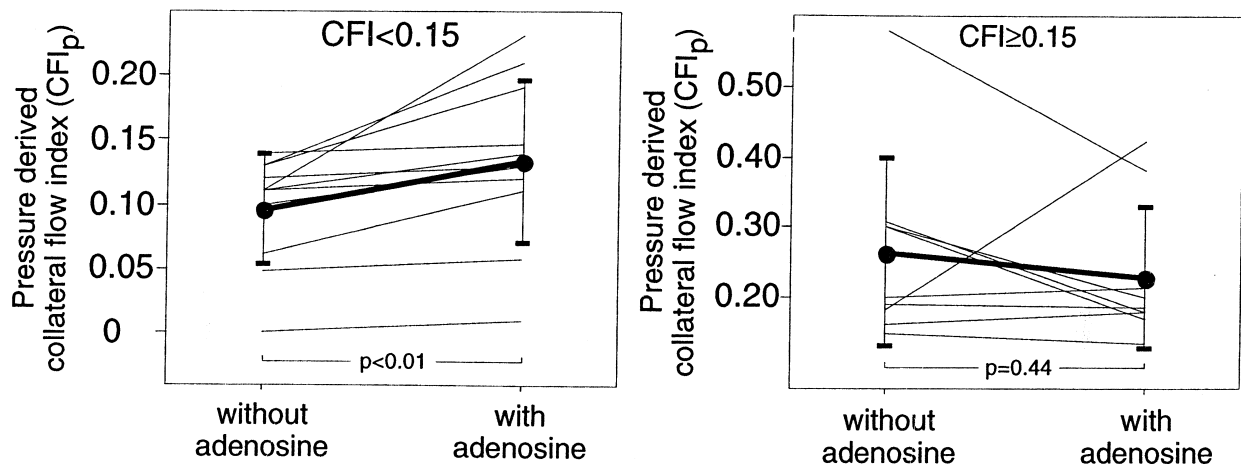

Fig. 3. Individual, collateral flow index values (CFI_p, vertical axis) at baseline and during adenosine infusion (horizontal axis) in the group with CFI<0.15 (left hand side panel) and in the group with CFI≥0.15 (right hand side panel). The closed circles indicate mean values (±standard deviation). While CFI_p increased on average among patients with CFI<0.15, it remained unchanged in the group with CFI≥0.15.
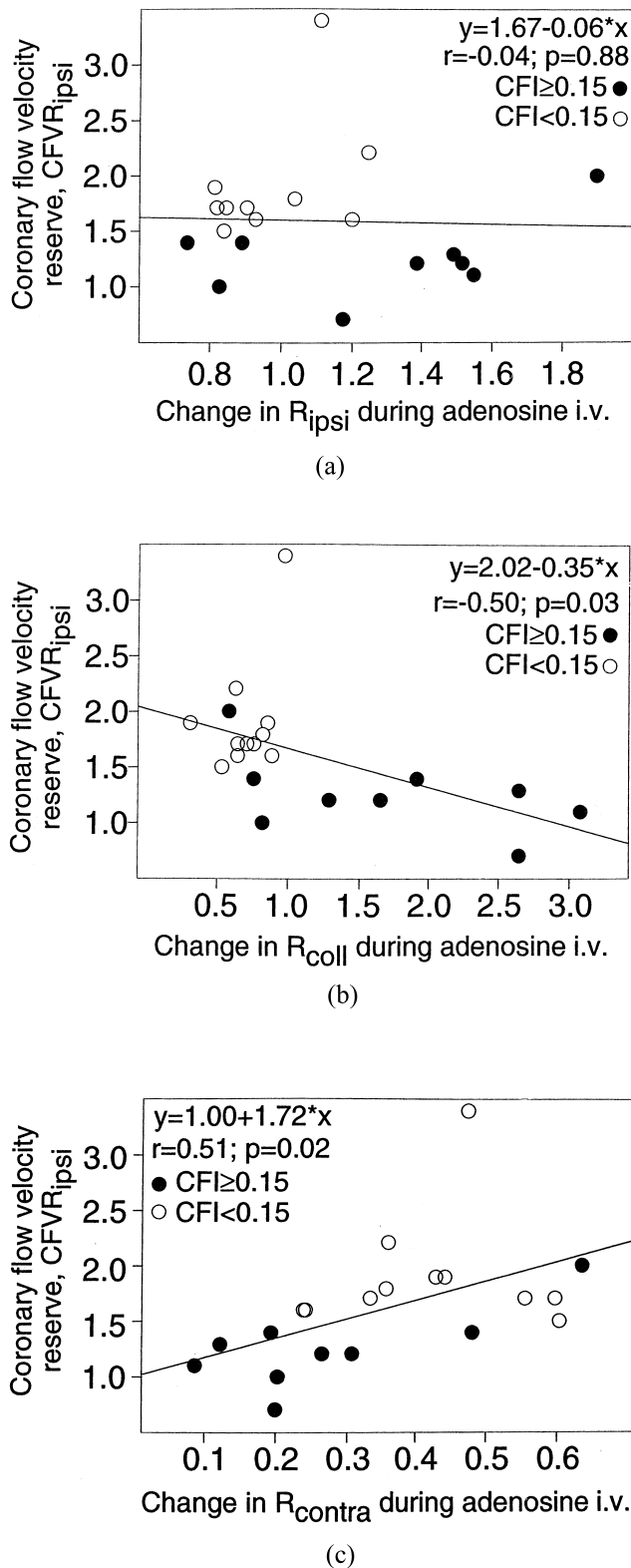
(a)

(b)

(c)

Fig. 4. Correlations between the occlusive adenosine-induced change in ipsilateral, collateral and contralateral vascular resistance indices (horizontal axes; R_{ipsi}: panel A, R_{coll}: panel B, R_{contra}: panel C), and the ipsilateral coronary flow velocity reserve (CFVR$_{ipsi}$, vertical axis) obtained during vessel patency using intracoronary adenosine. Open circled symbols: patients with CFI<0.15; closed circled symbols: patients with CFI≥0.15.

inverse relation between adenosine-induced change in R_{coll} and CFVR$_{ipsi}$ (Fig. 4B), and a direct association between adenosine-induced change in R_{contra} and CFVR$_{ipsi}$ (Fig. 4C). Focusing on the two study groups separately, these associations were present only in the group with CFI≥0.15 (Fig. 4B and C).

4. Discussion

This study in patients with CAD is the first to directly and comprehensively document that the coronary flow reserve of a collateral-receiving region may be more dependent on hyperemic vascular resistance changes of the collateral and collateral-supplying area than on the ipsilateral angiographic stenosis severity. However, such hemodynamic interactions between adjacent regions of the coronary circulation appear to require the presence of well developed collaterals. As a consequence of this interaction, coronary steal via collaterals can occur.

4.1. Occlusive collateral flow changes during hyperemia in humans

Whether coronary steal, a particular scenario of hyperemic flow redistribution, occurs via collaterals or via adjacent coronary branches can only be decided by measuring collateral flow alterations during hyperemia. Feldman et al. [17–19] have employed great cardiac vein flow measurements for the assessment of collateral flow changes to a balloon-occluded coronary artery in response to nitroglycerin, nicardipine and propranolol. Nitroglycerin and nicardipine diminished myocardial ischemia by increasing collateral flow [17,19], whereas propranolol caused a worsening of collateral supply [18]. Noninvasive studies using the model of naturally occurring occlusions in patients without myocardial infarctions have confirmed the beneficial action of nitroglycerin on collateral flow [20], and have revealed that dipyridamole enhanced collateral flow [21,22]. Piek and coworkers [9] as well as ourselves [10] have recently found that in patients with well developed collaterals the flow can be increased by adenosine, whereas it decreases in poorly grown collaterals. This seems to be in contradiction to the adenosine induced increase in collateral flow in the group with CFI<0.15, and no change in the group with CFI≥0.15. However, this apparent disparity is related to the large variability of collateral flow responses in the group with good collaterals, the extent of which is likely influenced by the presence of a contralateral in addition to the ipsilateral stenotic lesion. Accordingly in patients with >one vessel CAD and well developed collaterals, two of 11 individuals showed a flow decrease across the collaterals in a study by Vanoverschelde [22], 11 of 21 diminished flow in a recent

study of our laboratory [10], and four of nine revealed a reduced hyperemic collateral flow in this investigation (Fig. 3). Conversely, only two of 24 patients with one vessel CAD in the study by Piek et al. had a deteriorated collateral flow response as determined by Doppler flow wires [9].

Recently, it has been demonstrated in humans that an occlusive collateral flow increase during hyperemia is the result of a reduced collateral resistance [9,10], and possibly also a lowered peripheral vascular resistance of the collateral recipient artery [9]. Whether hyperemic collateral flow alterations measured during *occlusion* of a vascular area are clinically relevant may be questionable, particularly in the setting of the patent albeit stenosed coronary artery. A possible approach to this problem is to determine whether the hyperemic flow heterogeneity during vessel *patency* in the vascular territory investigated is associated with vascular resistance alterations in neighboring regions.

4.2. Coronary flow heterogeneity and adjacent vascular resistance alterations

A major difficulty in assessing how adjacent vascular hyperemic resistance changes contribute to the flow heterogeneity of a region is to separate the relevance of the neighboring vasculature from several other structural and hemodynamic variables influencing the coronary circulation. Two of those co-variables leading to a non-uniform regional flow distribution are the irregular structure of the coronary artery tree, and the possibility of flow redistribution between adjacent vascular areas at vessel bifurcations. Flow heterogeneity due to an irregular design of the coronary circulation is a feature inherent already in the normal situation [23]. In the situation of certain coronary stenoses combinations at a vascular bifurcation, it has been directly documented in dogs without collaterals that flow during hyperemia can be redistributed via adjacent branches [24]. The variability in the associations between occlusive collateral and contralateral vascular resistance changes and the ipsilateral CFVR (Figs. 4B and 4C) indicates that the co-factors just described must have played an important role.

The finding that a hemodynamic influence on the ipsilateral CFVR is exerted by the adjacent vascular resistances only in patients with well developed collaterals has been suggested before [9]. Additionally, the different behavior of the hyperemic response depending on the collaterals is also corroborated in our study by the fact that in the group with CFI<0.15 versus ≥0.15, CFVR$_{ipsi}$ was associated much closer to the severity of the stenosis to be dilated. The fact that in patients with few collaterals the contralateral CFVR did not improve after PTCA of the ipsilateral stenosis (Table 4) further indicates that there is no hemodynamic interaction among adjacent vascular areas in the absence of extensive collaterals.

4.3. Documentation of a mechanism causing coronary steal

One of the goals of this study was to test whether the hemodynamic changes during hyperemia were in accordance with the electric analogue model explaining the occurrence of coronary steal [8]. The specific situation of an ipsilateral coronary flow decrease during hyperemia occurred in two patients with well developed collaterals. Both of them revealed the two largest collateral flow drops during hyperemia (Fig. 3). This together with a simultaneous resistance decrease in the contralateral vessel to 20% of the baseline value indicates that steal took place via the collaterals and not via adjacent branches or vertically within the myocardium [6]. That both the ipsilateral and the collateral resistance increased and decreased, respectively during hyperemia in the two cases with steal suggests that the hyperemic resistance alteration of the collateral supplying vessel may be the major determinant in the occurrence of steal. This complies with experimental [7] as well as theoretical model studies [8]; the latter predict that a severely stenotic, collateral-receiving vascular region with exhausted microcirculatory vasodilator capacity undergoes a drainage of flow during hyperemia towards the still lowerable resistance of the collateral-supplying bed.

4.4. Study limitations

Aside from the limitations alluded to above there are confounders of the relation between CFVR$_{ipsi}$ and collateral/contralateral resistance changes such as technical limitations of obtaining satisfactory flow velocity signals. These problems have been described in detail elsewhere [15,25]. We tried to avoid them by careful patient selection (no patients with tortuous vessels or multiple stenoses in series) and by appropriate positioning of the Doppler guidewire away from regions of turbulent flow. Pressure guidewire measurements are more robust to positional influence than velocity measurements, and satisfactory tracings can be obtained almost always unless the wire is located too proximally in the vicinity of the stenosis.

The routes of adenosine administration (i.c. or i.v.) used in this study may theoretically induce different levels of hyperemia. This is unlikely, since Wilson et al. have shown that the dosages used in this investigation for i.c. and i.v. administration are equivalent [13]. Additionally, a comparison of CFVR induced by adenosine in 12 of our own patients provided a value of 2.4±0.9 for i.c. and a CFVR of 2.3±0.5 for i.v. administration. Statistically non-significant differences between the study groups regarding drug therapy (which was not stopped prior to the study) may have influenced the results of the investigation.

A potential pathophysiologic limitation concerning pressure measurements is related to the fact that large ischemic myocardial territories in patients with few collaterals may

lead to an overestimation of intracoronary pressures via increased LV filling pressures [16]. The latter were not determined in this study. Simultaneous measurements of pressure- and Doppler-derived collateral flow indices have, however, shown that both methods differ only moderately over a wide range of CFI by a standard error of estimate of 0.08 [15]. Increased LV filling pressures could also have influenced CFVR values [26], thus accounting for some of the variability in the above mentioned relation. With large guiding catheters (seven to eight French), the aortic pressure recordings may be influenced by the size of the coronary ostium (which may too small for the catheter). Six French guiding catheters were used throughout the entire study, and no damping of the pressure signals was observed.

The fact that occlusive ipsilateral flow velocity and pressure and contralateral flow velocity are terms used to calculate resistance indices leads to the situation of some inherent association among adenosine-induced collateral flow and resistance alterations. This relation would have an impact on the study results irrespective of the absence or presence of well developed collaterals. That a significant relation between vascular resistance changes and ipsilateral CFVR exists among patients with well but not poorly developed collaterals indicates that the mentioned 'calculative' association does not preclude the assessment of the pathophysiologic interaction between collateral-adjacent vascular areas.

References

[1] for the TIMI investigators, Habib GB, Heibig J, Forman SA et al. Influence of coronary collaterals on myocardial infarct size in humans: results of phase I Thrombolysis in Myocardial Infarction (TIMI) Trial. Circulation 1991;83:739–746.

[2] Hansen J. Coronary collateral circulation: clinical significance on survival in patients with coronary artery occlusion. Am Heart J 1989;117:290–295.

[3] Probst P, Baumgartner C, Gottsauner-Wolf M. The influence of the presence of collaterals on restenoses after PTCA. Clin Cardiol 1991;14:803–807.

[4] Wahl A, Billinger M, Fleisch M, Meier B, Seiler C. Quantitatively assessed coronary collateral circulation and restenosis following percutaneous revascularization. Eur Heart J 2000;22:in press.

[5] Seiler C, Fleisch M, Meier B. Direct intracoronary evidence of collateral steal in humans. Circulation 1997;96:4261–4267.

[6] Gould K. Coronary steal — is it clinically important? Chest 1989;96:227–229.

[7] Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation 1978;57:1103–1110.

[8] Demer LL, Gould KL, Goldstein RA, Kirkeeide RL. Noninvasive assessment of coronary collaterals in man by PET perfusion imaging. J Nucl Med 1990;31:259–270.

[9] Piek JJ, van Liebergen AM, Koch KT et al. Pharmacological modulation of the human collateral vascular resistance in acute and chronic coronary occlusion assessed by intracoronary blood flow velocity analysis in an angioplasty model. Circulation 1997;96:106–115.

[10] Seiler C, Fleisch M, Billinger M, Meier B. Simultaneous intracoronary velocity- and pressure-derived assessment of adenosine-induced collateral hemodynamics in patients with one- to two-vessel coronary artery disease. J Am Coll Cardiol 1999;34:1985–1994.

[11] Schaper W, Lewi P, Flameng W, Gijpen L. Myocardial steal produced by coronary vasodilation in chronic coronary artery occlusion. Basic Res Cardiol 1973;68:3–20.

[12] Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty in human subjects. J Am Coll Cardiol 1985;5:587–592.

[13] Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. Circulation 1990;82:1595–1606.

[14] Pijls NHJ, van Son JAM, Kirkeeide RL, de Bruyne BLGK. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous coronary angioplasty. Circulation 1993;86:1354–1367.

[15] Seiler C, Fleisch M, Garachemani AR, 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.

[16] Schaper W, Winkler B. Determinants of peripheral coronary pressure in coronary artery occlusion. In: Maseri A, editor, Primary and secondary angina pectoris, New York, San Francisco, London: Grune and Stratton, 1978, pp. 351–361.

[17] Feldman R, Joyal M, Conti R, Pepine C. Effect of nitroglycerin on coronary collateral flow and pressure during acute coronary occlusion. Am J Cardiol 1984;54:958–963.

[18] Feldman R, Macdonald R, Hill J et al. Effect of propranolol on myocardial ischemia occurring during acute coronary occlusion. Circulation 1986;73:727–733.

[19] Feldman R, Macdonald R, Hill J, Pepine C. Effect of nicardipine on determinants of myocardial ischemia occurring during acute coronary occlusion produced by percutaneous transluminal coronary angioplasty. Am J Cardiol 1987;60:267–270.

[20] Aoki M, Sakai K, Koyanagi S, Takeshita A, Nakamura M. Effect of nitroglycerin on coronary collateral function during exercise evaluated by quantitative analysis of thallium-201 single photon emission computed tomography. Am Heart J 1991;121:1361–1366.

[21] McFalls EO, Araujo LI, Lammertsma A et al. Vasodilator reserve in collateral-dependent myocardium as measured by positron emission tomography. Eur Heart J 1993;14:336–343.

[22] Vanoverschelde J, Wijns W, Depre C et al. Mechanisms of chronic regional postischemic dysfunction in humans: new insights from the study of noninfarcted collateral-dependent myocardium. Circulation 1993;87:1513–1523.

[23] VanBavel E, Spaan JAE. Branching patterns in the porcine coronary arterial tree: Estimation of flow heterogeneity. Circ Res 1992;71:1200–1212.

[24] Seiler C. Assessment of functional significance of the stenotic substrate by doppler flow measurements. In: Nienaber C, Sechtem U, editors, Imaging and intervention in cardiology, Dodrecht, The Netherlands: Kluwer, 1995, pp. 315–330.

[25] Segal J, Kern M, Scott N. Alterations of phasic coronary artery flow velocity in humans during percutaneous coronary angioplasty. J Am Coll Cardiol 1992;20:276–286.

[26] McGinn A, White C, Wilson R. Interstudy variability of coronary flow reserve. Influence of heart rate, arterial pressure, and ventricular preload. Circulation 1990;81:1319–1330.