CLINICAL RESEARCH
Pathophysiology

Instantaneous coronary collateral function during supine bicycle exercise

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Aims	The instantaneous response of the collateral circulation to isometric physical exercise in patients with non-occlusive coronary artery disease (CAD) is not known.
Methods and results	Thirty patients (age 59 ± 9 years) undergoing percutaneous coronary intervention because of stable CAD were included in the study. Collateral function was determined before and during the last minute of a 6 min protocol of supine bicycle exercise during radial artery access coronary angiography. Collateral flow index (CFI, no unit) was determined as the ratio of mean distal coronary occlusive to mean aortic pressure both subtracted by central venous pressure. To avoid confounding due to recruitment of coronary collaterals by repetitive balloon occlusions, patients were randomly assigned to a group 'rest first' with CFI measurement during rest followed by CFI during exercise, and to a group 'exercise first' with antecedent CFI measurement during exercise before CFI at rest. Simultaneously, coronary collateral conductance (occlusive myocardial blood flow per aorto-coronary pressure drop) was determined by myocardial contrast echocardiography in the last 10 consecutive patients. Overall, CFI increased from 0.168 ± 0.118 at rest to 0.262 ± 0.166 during exercise ($P = 0.0002$). The exercise-induced change in CFI did not differ statistically in the two study groups. Exercise-induced CFI reserve (CFI during exercise divided by CFI at rest) was 2.2 ± 1.8. Overall, rest to peak bicycle exercise change of coronary collateral conductance was from 0.010 ± 0.010 to 1.109 ± 0.139 mL/min/100 mmHg ($P < 0.0001$); the respective change was similar in both groups.
Conclusion	In patients with non-occlusive CAD, collateral flow instantaneously doubles during supine bicycle exercise as compared with the resting state. ClinicalTrials.gov Identifier: NCT00947050.
Keywords	Coronary circulation • Collateral circulation • Physical exercise • Bicycle exercise

Introduction

Well-developed coronary collaterals have been documented to be lifesaving in patients with chronic stable coronary artery disease (CAD).[1] The possibility of maintaining *resting* myocardial blood supply via collaterals has not been disputed recently, but their sustaining an *increased* cardiac workload has been generally disbelieved. This view appears to be prevalent despite the existence of numerous experimental studies indicating the coronary collaterals' capability to respond with vasomotion to neurologic, pharmacologic, and physiologic stimuli.[2] In humans, much less evidence exists indicating that collateral vasomotor tone depends on sympathetic stimuli such as cold pressor[3,4] or handgrip exercise,[5] and is responding to dipyridamole[6] or adenosine.[7] However, it is unknown so far, whether the most physiologic form of physical exercise, dynamic isometric exercise induces instantaneous coronary collateral function changes. The paucity of such an investigation in patients with chronic, non-occlusive CAD may relate to the fact that coronary collateral assessment requires a brief vascular occlusion, which has to occur during the last portion of an exercise test.

In this context, the present study tested the hypothesis that coronary collateral function instantaneously increases in response to supine bicycle exercise.

Methods

Patients

Thirty patients (age 59 ± 9 years, 28 men) with chronic stable, non-occlusive CAD eligible for percutaneous coronary intervention (PCI) of one stenotic lesion were included in the study. All underwent diagnostic coronary angiography because of symptoms related to CAD. Patients were prospectively selected on the basis of the following criteria: (i) no previous transmural infarction in the myocardial area assessed for coronary collateral function, (ii) normal left ventricular (LV) ejection fraction, (iii) no congestive heart failure, (iv) no baseline electrocardiogram (ECG) ST-segment abnormalities, (v) written informed consent to participate in the study prior to the start of the invasive procedure.

Patients underwent an intra-individual comparison of collateral function at rest and during supine bicycle exercise using radial artery access coronary angiography (Figure 1). In order to account for the possibility of collateral recruitment following the first coronary balloon occlusion,[8] patients were randomly assigned to a group 'rest first' in which the first collateral function measurement occurred at rest and the second during the last minute of the exercise test ($n = 15$; Figure 2), and vice versa to a group 'exercise first' ($n = 15$).

This investigation was approved by the Ethics Committee of the Kanton of Bern, Switzerland.

Cardiac catheterization and coronary angiography

Patients underwent left heart catheterization for diagnostic purposes from the right radial artery approach (Figure 1). This route was chosen in the context of the supine bicycle exercise protocol to prevent potentially harmful, leg-movement-induced pushing of the guiding catheter into the coronary ostium. Aortic pressure was measured using a 6F PCI guiding catheter. Central venous pressure (CVP) was obtained via the right femoral vein by a 5F pigtail catheter. Left ventricular end-diastolic pressure was determined before collateral function assessment. Monoplane left ventriculography was performed followed by monoplane coronary angiography. Coronary artery stenoses were determined quantitatively as percent diameter narrowing.

Invasive coronary collateral assessment

Primary study endpoint

Coronary collateral flow relative to normal antegrade flow through the non-occluded coronary artery (collateral flow index, CFI) was determined using coronary pressure measurements. A 0.014 inch pressure monitoring angioplasty guidewire (Pressure Wire®, Radi, Uppsala, Sweden) was set at zero, calibrated, advanced through the guiding catheter, and positioned in the distal part of the vessel of interest. Collateral flow index was determined by simultaneous measurement of mean aortic pressure (P_{ao}, mmHg), the distal mean coronary artery pressure during balloon occlusion (P_{occl}, mmHg), and the mean CVP (mmHg; Figure 3). Collateral flow index was calculated as ($P_{occl} -$ CVP) divided by ($P_{ao} -$ CVP).[9] The accuracy of pressure derived CFI measurements in comparison to ECG signs of myocardial ischaemia during occlusion and to absolute myocardial perfusion measurements has been documented previously.[9–11]

Secondary study endpoints

Myocardial ischaemia during the 1 min coronary occlusion was characterized by the presence or absence of angina pectoris. In the 10 last consecutive patients of the study, absolute myocardial blood flow (simultaneous to CFI) was assessed quantitatively using myocardial contrast echocardiography (MCE), whereby a previously described and validated algorithm was employed.[12] Briefly, for the calculation of absolute blood flow, the constituent factors relative myocardial blood volume rBV and its refill rate β following destruction of echo-contrast microbubbles were obtained during vessel occlusion. Myocardial blood flow is equal to the product of rBV and β divided by myocardial tissue density.[12] Coronary collateral conductance was calculated as the ratio of myocardial blood flow during coronary occlusion (mL/min/g) per mmHg of collateral driving pressure ($= P_{ao} - P_{occl}$).

Study protocol

At the start of the invasive procedure, all patients received 5000 units of heparin intravenously. No oral isosorbide dinitrate was given until after completion of the study protocol. Nitrates were withhold in
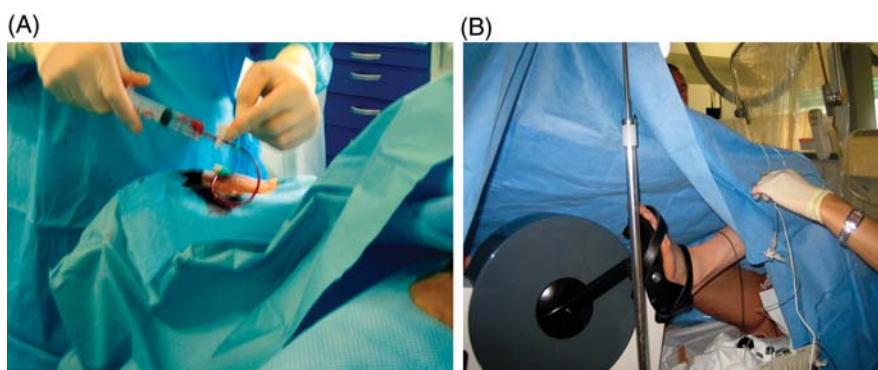

Figure 1 Invasive set-up for the implementation of the supine bicycle exercise stress protocol. (A) Right radial artery access coronary angiography via a 6F sheath. The patient's right groin is prepared in order to allow femoral vein access (central venous pressure measurement). (B) Image of the supine bicycle ergometer with the patient's feet attached to the pedals.
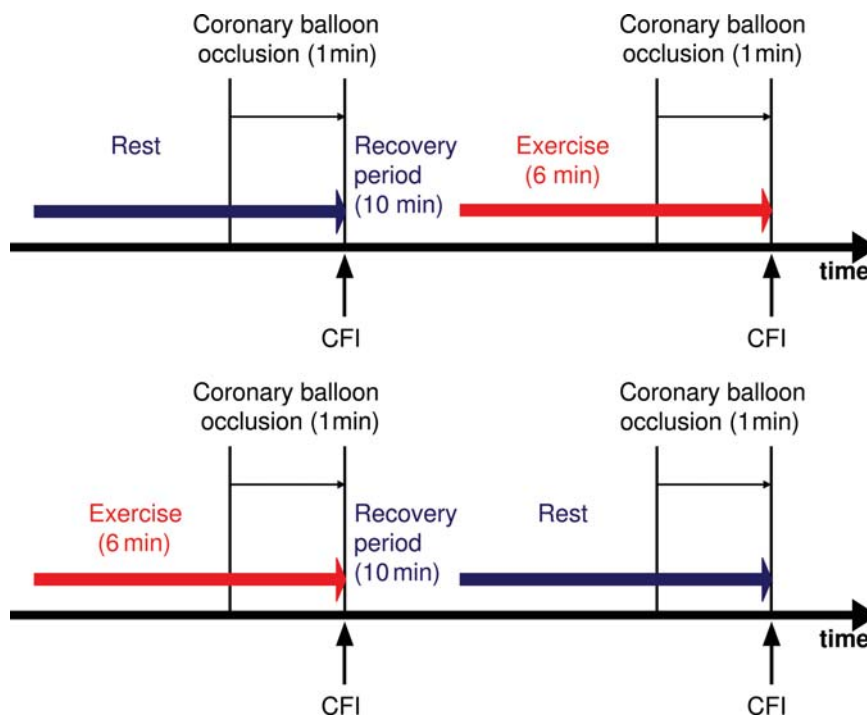
Figure 2 Chart of the study protocol. CFI, collateral flow index measurement (vertical arrows).
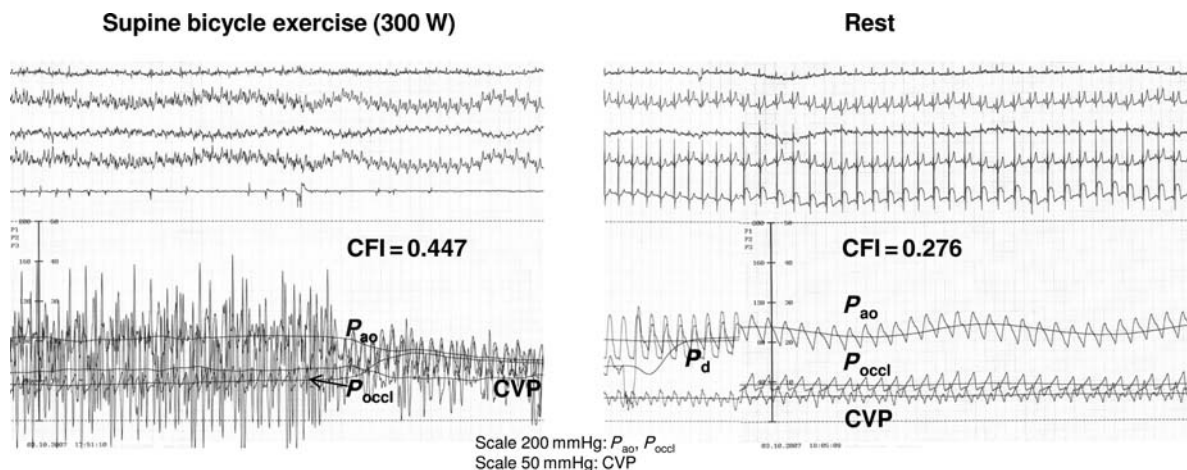

Figure 3 Simultaneous electrocardiogram/pressure tracings obtained in the proximal left anterior descending coronary artery during supine bicycle exercise (left side; patient of the 'exercise first' group) and at rest (right side). The lowest electrocardiogram lead is the intracoronary lead obtained via the pressure sensor guidewire (not attached during exercise due to motion artefacts). CVP, central venous pressure (scale 50 mmHg); P_{ao}, aortic pressure (scale 200 mmHg); P_d, distal coronary pressure (scale 200 mmHg); P_{occl}, distal coronary occlusive pressure (scale 200 mmHg; arrow in the left panel). Collateral flow index, CFI = $(P_{occl} - CVP)/(P_{ao} - CVP)$; all pressure values taken as mean values.

order to determine nitric oxide-mediated endothelium-dependent collateral vasomotor function as induced by exercise and to avoid influence of endothelium-independent vasomotion. Diagnostic coronary angiography was performed, and the culprit lesion responsible for the patient's symptoms was selected (online quantitative coronary angiography). Before starting the protocol, patients were randomly assigned to the group 'rest first' or to the group 'exercise first'. The randomization scheme was generated using the Web site Randomization.com (http://www.randomization.com) before study begin, whereby a closed envelope for each consecutive patient was prepared

containing the group assignment. In the 'rest first' group, a CFI measurement at rest in all patients with simultaneous MCE in the respective region of interest in the last 10 patients was performed during a 1 min coronary balloon occlusion at the site of the culprit lesion (low balloon inflation pressure). A 10 min recovery period followed this first collateral function assessment (*Figure 2*). Subsequently, the 6 min supine bicycle ergometry followed in three 2 min stages at low, intermediate, and high workload. Starting with the fourth minute of the exercise test, the angioplasty balloon was again positioned at the culprit lesion site, and the balloon was inflated shortly before the beginning of the sixth minute of the exercise test. CFI and—where applicable—MCE measurements were performed during 1 min until the end of the exercise test. In the 'exercise first' group, the protocol started with the described procedure during supine bicycle ergometry, followed by a 10 min recovery period, followed by the collateral function measurement at rest (*Figure 2*). The recordings during both rest and exercise measurements included P_{ao}, P_{occl}, CVP, 3 to 4 ECG leads (4 peripheral and 1 intracoronary lead via the guide wire), and—where applicable—MCE video clips. Owing to motion artefacts during maximum bicycle ergometry, the mean pressure curves necessary for CFI calculation (*Figure 3*), and the echo-video clips were the only recordings utilizable; i.e. ECG information on myocardial ischaemia in addition to CFI and MCE was analysable only at rest and, therefore, of no use for the specific study purpose. Following the study protocol, two puffs of isosorbide dinitrate was given and PCI was performed at the site of the culprit lesion.

Statistical analysis

The sample size of the study was estimated on the basis of previous clinical coronary arteriogenesis studies.[13,14] Sample size calculated prior to the study was based on the following assumptions regarding the CFI endpoint: ability to detect an increase of 50% during exercise as compared with the situation at rest (CFI mean value of 0.15) with a power of 80% (alpha error level of 5%); CFI standard deviation = 0.15. Accordingly, a total sample size of 28 patients with paired measurements was required. All continuous data are given as mean $\pm$ standard deviation. The distribution of the data for normality was tested by the Kolmogorov–Smirnov test. Baseline characteristics between the groups were analysed by Student's t-tests for continuous data and by χ^2/Fisher's exact tests for categorical data. Intra-individual comparison of CFI between the resting and maximum exercise condition was performed by a paired student's t-test. Linear regression analysis was used to assess an association between CFI and MCE-derived coronary collateral conductance at rest and during exercise. Differences were considered statistically significant at a two-sided P-value of <0.05. Statistical analysis was performed using StatView.

Results

Patient characteristics and clinical data at baseline

There were no statistically significant differences between the two groups regarding age of the patients, gender, duration of angina pectoris, history of myocardial infarction in a remote vascular area and body mass index. There were no statistical differences either in the frequency of cardiovascular risk factors, or the use of cardiovascular medication (*Table 1*).

Table 1 Patient characteristics and clinical data at baseline

Variable	Rest first (*n* = 15)	Exercise first (*n* = 15)
Age (years)	59 ± 7	59 ± 9
Male gender (%)	14 (93)	14 (93)
Duration of chest pain (months)	2.4 ± 2.2	5.8 ± 9.2
History of prior myocardial infarction (%)	8 (53)	6 (40)
Body mass index (kg/m^2)	27 ± 4	26 ± 4
Cardiovascular risk factors		
Dyslipidaemia (%)	13 (87)	10 (67)
Diabetes mellitus (%)	1 (7)	2 (13)
Systemic hypertension (%)	9 (60)	9 (60)
Smoking (%)	7 (47)	4 (27)
Obesity (%)	6 (40)	4 (27)
Family history for coronary artery disease (%)	7 (47)	2 (13)
Cardiovascular medication		
Beta-blockers (%)	12 (80)	8 (53)
Nitrates (%)	1 (7)	1 (7)
Acetylsalicylic acid (%)	14 (93)	13 (87)
Statin (%)	13 (87)	10 (67)
ACE-inhibitor (%)	5 (33)	4 (27)
Diuretics (%)	2 (13)	4 (27)

Invasive and haemodynamic data at baseline

Invasively obtained haemodynamic parameters at baseline such as heart rate, blood pressure, LV end-diastolic pressure, and LV ejection fraction did not differ between the groups (*Table 2*). The vessel undergoing CFI measurement at rest and during exercise and the severity of CAD as well as the severity of the stenosis being treated by PCI were similar between the groups (right-dominance in all patients). Percent diameter stenosis of the vessels not treated by PCI was 25 ± 15 (no difference between the groups). Collateral function data obtained at rest were not statistically different between the 'rest first' and the 'exercise first' group (*Table 2*).

Invasive data during supine bicycle exercise

The maximum workload achieved was not different between the study groups (*Table 3*; range from 60 to 300 W). There was no correlation between the maximum workload achieved and the change in CFI during exercise. Heart rate and systolic blood pressure increased significantly within both groups during exercise, and they did not differ between the groups at maximum exercise (*Table 3*).

Primary study endpoint

Exercise-induced increase in CFI was significant in both groups (*Table 3* and *Figure 4*), and the respective CFI reserve (=CFI during maximum exercise divided by CFI at rest) was not different

Table 2 Invasive data at baseline

Variable	Rest first (*n* = 15)	Exercise first (*n* = 15)	*P*
Heart rate at rest (beats per minute)	73 ± 16	71 ± 10	0.69
Systolic blood pressure at rest (mmHg)	125 ± 25	129 ± 28	0.71
Diastolic blood pressure at rest (mmHg)	81 ± 16	80 ± 19	0.78
Left ventricular end-diastolic pressure (mmHg)	11 ± 5	14 ± 5	0.14
Left ventricular ejection fraction (%)	59 ± 7	58 ± 6	0.67
Vessel undergoing CFI measurement (LAD/LCX/RCA)	8/3/4	9/3/3	0.90
Number of vessels diseased	1.9 ± 0.7	1.8 ± 0.9	0.83
Number of stenoses	1.9 ± 1.5	2.4 ± 2.0	0.47
Percent diameter stenosis of vessel treated by PCI	78 ± 24	76 ± 32	0.82
Collateral function data at rest			
Site of CFI measurement (proximal/mid/distal)	8/6/1	8/6/1	1.0
Angina pectoris during coronary occlusion (%)	10 (67)	11 (73)	0.69
ECG ST-segment elevation during coronary occlusion (%)	10 (67)	10 (67)	1.0
Collateral flow index, CFI (no unit)	0.137 ± 0.117	0.200 ± 0.114	0.15

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Table 3 Invasive data during supine bicycle exercise

Variable	Rest first (*n* = 15)	Exercise first (*n* = 15)	*P*
Maximum workload (watt)	114 ± 14	119 ± 53	0.71
Heart rate at rest (beats per minute)	73 ± 16	71 ± 10	0.69
Heart rate at peak exercise (beats per minute)	116 ± 15*	118 ± 21*	0.80
Systolic blood pressure at rest (mmHg)	125 ± 25	129 ± 28	0.71
Systolic blood pressure at peak exercise (mmHg)	149 ± 37*	153 ± 30*	0.72
Diastolic blood pressure at rest (mmHg)	81 ± 16	80 ± 19	0.78
Diastolic blood pressure at peak exercise (mmHg)	88 ± 16	82 ± 23	0.38
Collateral function data			
Angina pectoris during coronary occlusion at rest (%)	10 (67)	11 (73)	0.69
Angina pectoris during coronary occlusion at peak exercise (%)	10 (67)	10 (67)	1.0
Collateral flow index at rest, CFI (no unit)	0.137 ± 0.117	0.200 ± 0.114	0.15
Collateral flow index at peak exercise, CFI (no unit)	0.239 ± 0.140**	0.284 ± 0.190**	0.47
CFI reserve (CFI during exercise/CFI at rest)	2.25 ± 1.24	2.04 ± 2.26	0.76

*$P < 0.001$ vs. rest; **$P < 0.01$ vs. rest.

between the study groups (*Table 3*). In 24 patients, CFI increased during exercise, whereas it decreased in six patients. Rate–pressure product (systolic pressure) at rest and during maximum exercise correlated significantly with CFI (CFI = −0.02 + 0.00002 rate–pressure product; $r^2 = 0.25$, $P = 0.002$).

Secondary study endpoints

The occurrence of angina pectoris during coronary occlusion did not change during exercise vs. resting conditions (*Table 3*). Collateral flow index and MCE-derived coronary collateral conductance correlated directly at rest and during exercise, and they both increased equivalently during exercise in 7 of 10 patients undergoing simultaneous CFI and MCE measurements, whereas in 3 of 10 patients, CFI decreased during exercise, whereas collateral conductance increased (*Figure 5*).

Discussion

This first clinical study on coronary collateral behaviour during isometric physical exercise documents a two-fold increase in CFI compared with resting conditions. In a minority of every fifth patient, however, collateral function instantaneously decreases during exercise.

Instantaneous coronary collateral function changes: non-exercise stimuli

Exercise-induced CFI increase in our entire study population was from 0.168 to 0.262 ($P = 0.0002$). The question evolving in this context is whether such a response is solely due to supine bicycle exercise or whether it can be attributed to variables
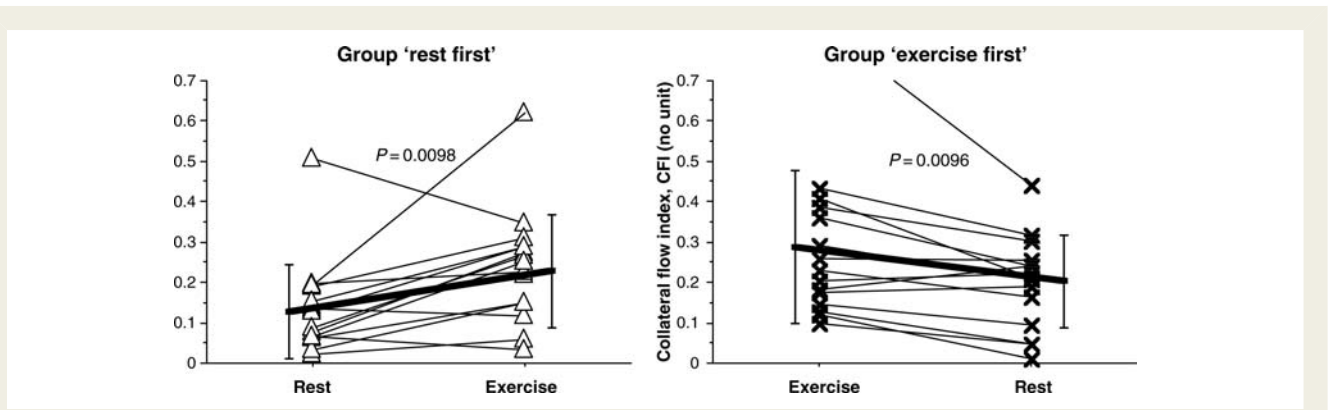
Figure 4 Individual changes (thin lines) of collateral flow index (collateral flow index; vertical axes) from the resting condition to the peak supine bicycle exercise condition in the group 'rest first' (left panel; triangular symbols) and vice versa in the group 'exercise first' (right panel; cross symbols). The thick lines indicate the mean change between the resting and exercise condition. Error bars: standard deviation.
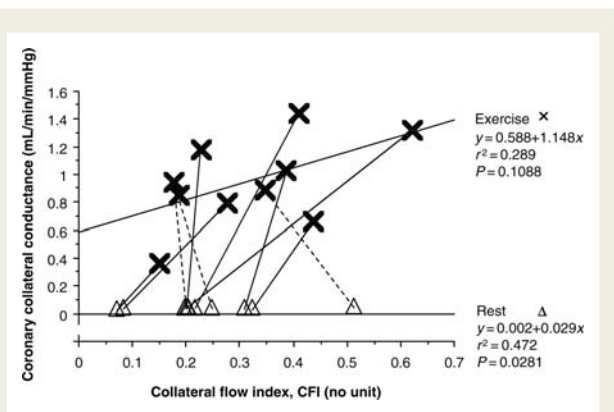

Figure 5 Correlation between collateral flow index (collateral flow index; horizontal axis) and simultaneously obtained coronary collateral conductance (vertical axis) at rest (open triangles) and during peak supine bicycle exercise (cross symbols). Connecting lines between the triangles and crosses indicate intra-individual changes between the resting and exercise condition. A minority of 3 of 10 patients showed an opposite change of CFI as compared with contrast echo-derived collateral conductance (dashed connecting lines).

other than exercise present in the study. The key co-candidate for instantaneous collateral function enhancement is preceding ischaemia. Collateral recruitment in response to ischaemia is caused via intrinsic myocardial adenosine excretion. The design of our study accounted for this mechanism by randomly allocating half the patients to a protocol with the resting condition as the initial measurement, and the other half with the exercise condition as the first collateral assessment. In the former group without ischaemic event immediately preceding the resting condition, CFI was lower than in the presence of an earlier occlusion ('exercise first' group); this difference was not statistically significant, which could be due to the low power of the study. Thus, the influence on the study results of ischaemia-induced collateral recruitment aside from the bicycle test cannot be entirely excluded.

Instantaneous coronary collateral function changes: exercise as stimulus

Earlier clinical studies on the acute effect of exercise on collateral function have employed thallium-201 perfusion imaging in patients with entirely collateralized, viable myocardial regions providing a qualitative, dichotomous measure of absent or present perfusion defects.[15–17] Rigo et al. concluded from their study that 'coronary collateral vessels may help maintain relative myocardial perfusion during exercise'.[15] Eng et al. studied collateral function by analysis of exercise thallium-201 myocardial perfusion images from 31 patients who had at least one non-infarcted, entirely collateralized myocardial region. Twenty-two of 41 of the collateralized regions manifested exercise-induced perfusion defects and 19 were normally perfused, whereby the latter 19 consisted of 13 with defects in other myocardial regions supplied by diseased vessels and were considered negative relative to other jeopardized regions.[17] Thus only in about one-seventh of all collateralized regions ($n = 6$), perfusion was adequate during maximal exercise, and in about half exercise-induced coronary steal occurred. More recent clinical work using the model of entirely collateralized anterior wall myocardium as assessed by technetium-99m perfusion imaging has documented exercise-induced perfusion defects in all of the 20 patients studied, whereby 30% of them had fixed defects (necrosis).[18] The study by Aboul-Enein et al.[19] included 56 patients with single-vessel chronic total occlusion and viable myocardium who underwent rest-exercise myocardial perfusion imaging and coronary angiography within 6 months. The authors concluded that well-developed angiographic collaterals could prevent resting regional wall motion abnormalities but not stress-induced perfusion defects. In comparison to these qualitative data, the present study obtained quantitative, continuous data to a temporarily collateralized, viable myocardial region. A parameter remotely equivalent to the extent of myocardial ischaemia in the scintigraphic studies is the rather blunt variable of angina pectoris during coronary occlusion, which remained unchanged during exercise. The more sensitive parameter of ECG ST-segment changes during occlusion indicative of ischaemia was available only at rest due to motion artefacts during exercise;

10 of 30 patients fulfilled the ECG criteria of sufficient collaterals at rest (data not shown), and seven of them showed an increase in CFI during exercise. In 17 of 30 patients, CFI rose under exercise to a value known to represent collateral flow sufficient to prevent signs of ischaemia during a 1 min occlusion ($\geq$0.215).[20]

Instantaneous coronary collateral function changes: steal; potential influence of left ventricular filling pressure

Exercise-induced collateral steal, i.e. a fall in CFI during exercise, occurred in 6 of 30 patients. Collateral steal in a study protocol such as the present one may be clinically irrelevant, but serves as quality control of collateral function measurements in two ways. First, its prevalence (20%) should be in the range of that reported in the literature (10% in non-occlusive CAD[21]), the fact of which heightens the plausibility of the data obtained. In addition, determinants of steal reported in the literature such as well-developed collaterals should correspond to those found in the present study to indicate reliability of the measurement result: patients with steal as compared with those with exercise-induced collateral flow increase had a CFI at rest of 0.227 ± 0.150 and 0.154 ± 0.107 ($P = 0.07$), respectively, and a collateral conductance of 0.016 ± 0.017 and 0.006 ± 0.005 ($P = 0.13$), respectively. Accordingly, the prevalence of collateral steal amounts to almost half in patients with chronic coronary occlusion.[22] Second, the occurrence of steal as obtained from *pressure*-derived CFI serves as indicator against the hypothesis that coronary pressure measurements during exercise reflect an elevated LV filling pressure rather than collateral perfusion pressure. In principle, it is imaginable that the elevated myocardial oxygen consumption during exercise causes more tissue ischaemia, translating into more dysfunctional, thinner myocardium with higher LV filling pressure as compared with the resting state. Considering the existence of a waterfall phenomenon in the coronary circulation operative at LV filling pressures beyond 27 mmHg,[23] the just mentioned hypothesis is plausible. It can be directly falsified in the six cases with steal, since in all of them collateral perfusion pressure fell during exercise. In order to account differently for this potential problem, MCE-derived collateral conductance was measured simultaneously with CFI in 10 patients. The two parameters correlated with each other at rest and during exercise, and more importantly, all conductance values increased during exercise.

Study limitations

Study limitations not alluded to above are the absence of contrast myocardial perfusion data in part of the patients, and the fact that no LV pressure or pulmonary capillary wedge pressure was obtained during the exercise protocol in order to account for the potential problem discussed in the above paragraph. Both limitations are primarily due to the complexity of the supine bicycle protocol with radial artery access to allow a safe 1 min coronary balloon occlusion during peak exercise. It was only after the 20th patient included in the study that the operators felt secure enough to add another measurement technique simultaneous to the invasive collateral assessment. The insertion of a pigtail catheter into the LV via a femoral artery access would have been a simple procedure, but the risk of causing ventricular arrhythmias during exercise would have been high, thus heightening the risk of ventricular fibrillation and lowering the chance of obtaining a representative LV filling pressure. Measurement of pulmonary capillary wedge pressure via femoral-vein-access right heart catheter was not performed, because the pressure signal during peak exercise was not predicted stable enough due to the leg movements.

The principle explanation for the incomplete agreement between CFI and collateral conductance is mainly related to the difficult examination conditions for transthoracic echocardiography during exercise with the patient lying on his back on the cath lab table. In comparison to the usual left lateral supine position, respiratory artefacts impair the ultrasound image quality much more in the supine back position.

As further potential limitations, the continuing medication with vasoactive drugs until the day of the study protocol and the variable exercise levels achieved have to be mentioned.

Conclusion

In patients with non-occlusive CAD, collateral flow instantaneously doubles during supine bicycle exercise as compared with the resting state.

Conflict of interest: none declared.

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