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Exercise-Induced Human Coronary Collateral Function: Quantitative Assessment during Acute Coronary Occlusions

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Key Words
Coronary circulation · Collateral circulation · Exercise · Coronary artery disease · Pathophysiology

Abstract
In 50 patients undergoing percutaneous transluminal coronary angioplasty because of chronic angina pectoris, a collateral flow index (CFI) was determined at the start and the end of two 1-min coronary occlusions, randomly accompanied by a resting state or a 3-min dynamic handgrip exercise (DHE). CFI expressing collateral flow relative to normal antegrade flow was determined by simultaneous coronary occlusive pressure, mean aortic pressure and central venous pressure measurements. When comparing CFI without and with DHE at the start as well as at the end of balloon occlusions, a significant increase was observed with DHE (overall $p < 0.0001$); start: 0.18 ± 0.12 vs. 0.22 ± 0.13, respectively ($p = 0.01$); end of occlusion: 0.21 ± 0.14 vs. 0.25 ± 0.14, respectively ($p = 0.007$).

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Introduction

The existence of human coronary collateral vessels [1] and their benefit against cardiac events has been recognized for many years [2], but their functional capacity in response to physical exercise has remained elusive. It had been investigated but by crude estimates of collateral flow in a highly selected population of patients with chronic total coronary artery occlusions without myocardial infarction [3–6].

In up to 50% of patients with chronic total coronary artery occlusions, there may be no infarcted myocardium within the vascular territory supplied by the blocked vessel [7]. It is unknown how many such patients remain completely asymptomatic, and therefore consult no physician, and are thus not referred for studies. However, some of the patients with chronic total occlusions without myocardial infarction suffer from chest pain on exertion, and they have been suggested to be a subset of patients with coronary artery disease (CAD) in which to study human coronary collaterals during exercise [8]. Such inference from clinical data on the existence of coronary collateral function has been verified histologically by demonstrating well-developed collaterals with a muscular media capable of vasomotor activity [9]. Experimental studies have illustrated collateral functional capacity by showing that physical exercise induces a more than two- to threefold perfusion increase in collateral-dependent

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myocardium via β-adrenergic and nitric oxide mechanisms [10–13].

The purpose of this study using the acute coronary occlusion model in patients with stable CAD was to directly measure the effect of physical exercise (i.e. dynamic handgrip exercise [14]) on recruitable collateral flow.

Methods

Patients

Fifty patients (age 64 ± 11 years, 32 men, 18 women) with one- to three-vessel CAD were included in the study. All patients underwent routine percutaneous transluminal coronary angioplasty (PTCA) of one stenotic lesion. Patients were included if the following criteria were fulfilled: absence of unstable angina pectoris, absence of acute or previous Q-wave myocardial infarction, absence of chronic total coronary occlusion. The study individuals were randomly assigned to dynamic handgrip exercise (DHE) or to remain at rest before and during the first of at least two 1-min coronary balloon occlusions. Before and during the second occlusion, all individuals crossed over. This study design was chosen in order to distinguish between collateral flow alterations due to the repetitive coronary occlusions itself [15] and due to dynamic exercise. Twenty-five patients were on β-blockers and 25 patients were not.

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

Coronary Angioplasty and Assessment of Hemodynamic Parameters

Diagnostic coronary angiography was performed from the right femoral approach using 5-Fr Judkins catheters for both the left and right coronary artery. For PTCA, 6-Fr guiding catheters were used. Coronary occlusive (i.e. wedge) pressure measurements (P_{occl}, mm Hg) were performed using guidewires equipped with a pressure sensor at the tip of the wire (WaveWire®, Jomed, Beringen, Switzerland). Mean aortic pressure (P_{ao}, mm Hg) was measured via the guiding catheter. Central venous pressure (CVP, mm Hg) was assessed using a 5-Fr pigtail catheter inserted from the right femoral vein. An intracoronary ECG obtained from the guidewire was recorded in addition to the standard limb leads. Heart rate (HR, beats/min) was assessed from the ECG and the rate pressure product ($RPP = P_{ao} \times HR$) was calculated. All parameters were monitored and printed continuously at a paper speed of 25–50 mm/s. Measurements were performed at the start and end, i.e., after 1 min of each occlusion.

Coronary Collateral Assessment

Coronary pressure-derived collateral flow index (CFI) was determined according to the following formula, using simultaneously obtained mean coronary perfusion pressure during vessel occlusion (P_{occl}), mean aortic perfusion pressure (P_{ao}) and central venous pressure (CVP): $CFI = (P_{occl} - CVP)/(P_{ao} - CVP)$.

This method has recently been validated against intracoronary ECG signs of myocardial ischemia during coronary balloon occlusion, and against Doppler flow velocity measurements for the assessment of collateral flow [16].

Study Protocol

Left heart catheterization, including biplane left ventricular angiography and coronary angiography for diagnostic purposes, was performed. Coronary artery stenoses were assessed quantitatively as percent diameter reduction using the guiding catheter for calibration. Following diagnostic examinations, an intracoronary bolus of 0.2 mg of nitroglycerin was given in order to maintain epicardial coronary artery calibers constant. All patients underwent two balloon occlusions of 1-min duration during which simultaneous coronary, aortic and CVP measurements were performed to assess CFI. Before the balloon occlusions, testing of supine maximal voluntary contraction force (32 ± 7 kg) using a hydraulic hand dynamometer (BASELINE®, Fabrication Enterprises Inc., New York, N.Y., USA) was carried out. In order to account for collateral recruitment occurring between subsequent coronary occlusions, patients were randomly assigned to perform DHE during the first or during the second occlusion. DHE (at approximately 60% of maximum contraction force and at a frequency of about 60 contractions/min) was started 2 min before and continued during the coronary occlusion. Patients were instructed to avoid a Valsalva maneuver to maintain stable filling pressures. An interval of 5 min was allowed before the second occlusion. Individuals allocated to DHE during the first occlusion changed to no DHE during the second, and vice versa. Data were analyzed at the start and at the end of each of the two balloon occlusions in order to account for collateral recruitment during each of the occlusions. Coronary occlusions were carried out at the site of the stenosis as part of the planned PTCA.

Statistical Analysis

For intraindividual comparisons of hemodynamic data without and with DHE, analysis of variance for repeated measures was used. In case of a significant p value, the Wilcoxon signed rank test was performed to determine the relevance of differences between various measurement points. To assess a correlation between continuous variables, linear regression analysis was performed. Paired Student's t-tests were used for assessing intraindividual differences between values of coronary collateral flow reserve without (i.e. CFI at the end of first or second occlusion without DHE divided by CFI at the start of the respective occlusion) and with DHE (i.e. CFI at the start of first or second occlusion with DHE divided by CFI at the start of occlusions without DHE). Coronary collateral flow reserve without DHE is a measure for collateral recruitment during a single as opposed to during subsequent occlusions [15]. For comparisons of continuous variables between groups on or off β-blocker, unpaired Student's t-tests were performed. Mean values ± SD are given. Statistical significance was defined at $p < 0.05$.

Results

Patient Characteristics and Clinical Data

Patient characteristics are summarized in table 1. Baseline characteristics in patients without and with β-blocker treatment did not differ significantly, except for the stenosis severity of the lesion undergoing PTCA, which was higher in patients without than with β-blocker therapy (78 ± 14% vs. 68 ± 14%, p = 0.02).

Table 1. Patient characteristics and clinical data

Number of patients	50
Male gender	32
Age, years	64 ± 11
Body mass index, kg/m^2	27 ± 4
Systolic aortic pressure, mm Hg	136 ± 23
Diastolic aortic pressure, mm Hg	72 ± 12
Heart rate, beats/min	71 ± 12
LV ejection fraction, %	60 ± 10
LVEDP, mm Hg	10 ± 7
One-, two-, three-vessel CAD	24/16/8
Stenosis undergoing PTCA (LAD/LCX/RCA)	23/7/19
Localization of stenosis (proximal/mid/distal)	17/24/6
Percent diameter stenosis	73 ± 14
Previous myocardial infarction in another myocardial region	11 (22%)
Dynamic handgrip exercise (DHE)	
Maximum voluntary contraction force (kg)	32 ± 7
Contraction force during DHE (kg)	25 ± 7
Cardiovascular risk factors	
Systemic arterial hypertension	31 (63%)
Hypercholesterolemia	28 (57%)
Smoking	26 (53%)
Diabetes mellitus	12 (25%)
Family history of CAD	15 (31%)
Obesity	11 (23%)
Cardiovascular medication	
Acetylsalicylic acid	35 (71%)
Nitrates	25 (51%)
β-Blockers	25 (50%)
Cholesterol-lowering drugs	24 (49%)
Calcium antagonists	11 (22%)
ACE inhibitors	7 (14%)
Diuretics	7 (14%)

ACE = Angiotensin-converting enzyme, CAD = coronary artery disease, LVEDP = left ventricular end-diastolic pressure, LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, RCA = right coronary artery.

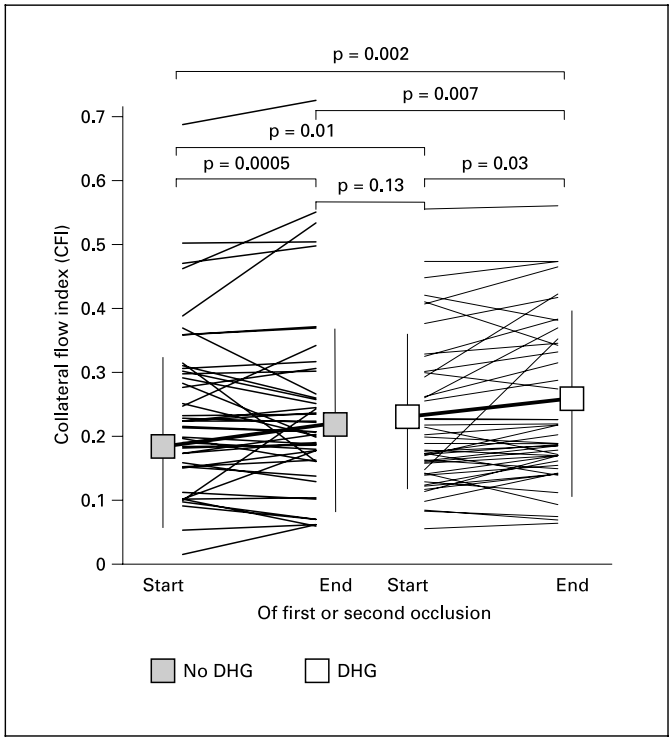


Fig. 1. Individual values of collateral flow index (CFI, vertical axis) depicted for all patients (n = 50) at the start and end of coronary artery balloon occlusions randomly selected to be the first or second, respectively, without and with dynamic handgrip exercise (DHE, horizontal axis).

Collateral Flow at Baseline

CFI at the start of coronary occlusions without DHE was not associated with the above-mentioned difference in stenosis severity among patients without and with β-blocker therapy: 0.15 ± 0.11 in individuals without and 0.22 ± 0.16 in those with β-blockers (p = NS). Irrespective of β-blocker treatment and at the start of CFI measurements without DHE, it was 0.18 ± 0.13 in the 25 patients with DHE during the first occlusion and 0.19 ± 0.15 among the 25 patients undergoing DHE during the second occlusion (p = NS). Without DHE, 14 patients (28%) had CFI ≥ 0.25 (fig. 1). In 11 patients (22%), no angina pectoris appeared during vessel occlusion, and in 12 patients (24%) no ECG signs of ischemia (i.e. sufficient coronary collaterals) were detected during vessel occlusion without DHE.

Effects of Dynamic Handgrip Exercise

During occlusions with DHE, 16 patients (32%) had CFI ≥ 0.25 (fig. 1). In 14 patients (28%), no angina pectoris appeared during vessel occlusion, and in 16 patients (32%), there were sufficient collaterals. Average data of CFI, P_{occl}, P_{ao}, CVP, HR and RPP are given for the entire study group in table 2. Mean coronary occlusive and aortic pressure were lower during occlusions without than with DHE. A similar pattern was observed in the case of HR and RPP during occlusions without and with DHE. There was a significant increase of CFI during occlusions without and with DHE, reflecting collateral recruitment during ischemia (table 2, fig. 1). When comparing CFI without and with DHE in all patients at the start as well as at the end of occlusions, a significant increase was ob-

Table 2. Hemodynamic parameters at start and end of first or second coronary artery occlusion in all patients

	Occlusions without dynamic handgrip exercise (n = 50)		Occlusions with dynamic handgrip exercise (n = 50)		p overall
	start	end	start	end	
Collateral flow index (CFI, no unit)	0.18 ± 0.12	0.21 ± 0.14*	0.22 ± 0.13	0.25 ± 0.14	<0.0001
P_{occl}, mm Hg	28 ± 14**	28 ± 15	35 ± 16**	33 ± 16	<0.0001
P_{ao}, mm Hg	96 ± 13**	97 ± 13	116 ± 17	109 ± 18	<0.0001
Central venous pressure, mm Hg	12 ± 6	9 ± 6	12 ± 8	8 ± 4	NS
Heart rate, beats/min	69 ± 13	71 ± 14	78 ± 12**	79 ± 14	<0.0001
Rate pressure product, mm Hg × beats/min	6,685 ± 1,609**	7,001 ± 1,608	9,116 ± 2,091**	8,667 ± 2,391	<0.0001

P_{ao} = Mean aortic pressure; P_{occl} = mean coronary artery occlusive pressure.
p 'overall' by analysis of variance for repeated measures.
* Not significant vs. occlusion at start with handgrip (other differences significant at $p < 0.03$).
** Not significant vs. situation at end of occlusion (other differences significant at $p < 0.02$).

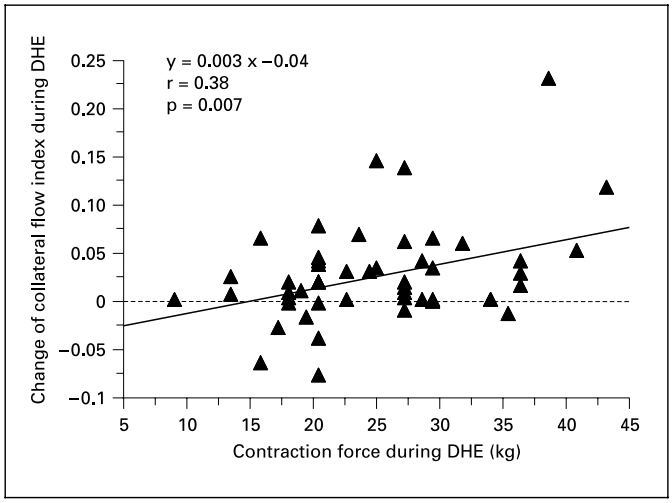
Table 3. Hemodynamic parameters at start and end of first or second coronary artery occlusion in patients without and with β-blockers

	Occlusions without dynamic handgrip exercise		Occlusions with dynamic handgrip exercise		p overall
	start	end	start	end	
Patients without β-blockers (n = 25)					
Collateral flow index (CFI, no unit)	0.15 ± 0.11	0.18 ± 0.11	0.22 ± 0.11	0.26 ± 0.14	<0.0001
P_{occl}, mm Hg	24 ± 11*	24 ± 12	32 ± 10*	30 ± 10	0.002
P_{ao}, mm Hg	91 ± 14	93 ± 18	108 ± 23	101 ± 23	NS
Central venous pressure, mm Hg	12 ± 7	9 ± 6	10 ± 5	6 ± 5	NS
Heart rate, beats/min	72 ± 11**	73 ± 13**	79 ± 11	79 ± 12	0.04
Rate pressure product, mm Hg × beats/min	6,753 ± 1,409*	6,957 ± 1,504	9,471 ± 2,489*	8,846 ± 2,525	<0.0001
Patients with β-blockers (n = 25)					
Collateral flow index (CFI, no unit)	0.22 ± 0.16	0.24 ± 0.17	0.22 ± 0.14	0.24 ± 0.14	NS
P_{occl}, mm Hg	33 ± 22*	33 ± 22	40 ± 22*	37 ± 23	0.01
P_{ao}, mm Hg	101 ± 15*	103 ± 12	121 ± 12*	117 ± 13	<0.0001
Central venous pressure, mm Hg	13 ± 8	10 ± 5	15 ± 8	10 ± 6	NS
Heart rate, beats/min	65 ± 10	69 ± 12	77 ± 10*	79 ± 14	<0.0001
Rate pressure product, mm Hg × beats/min	6,656 ± 1,877*	6,979 ± 1,811	8,793 ± 1,714*	8,584 ± 2,128	<0.0001

P_{ao} = Mean aortic pressure; P_{occl} = mean coronary artery occlusive pressure.
p 'overall' by analysis of variance for repeated measures.
* Not significant vs. situation at end of occlusion (other differences significant at $p < 0.02$).
** $p < 0.05$ vs. occlusions with handgrip.

served with DHE (table 2, fig. 1). In the entire study group, no differences in CFI were found between the end of occlusions without DHE and the start of occlusions with DHE. Overall, there was a direct association between the force exerted during DHE and the absolute change of CFI during the 1-min coronary occlusions (fig. 2).

Average data of CFI, P_{occl}, P_{ao}, CVP, HR, and RPP for the subgroups of patients without and with β-blockers are given in table 3. In patients without β-blocker treatment, the effect of DHE on CFI was more pronounced when compared with the entire study group (fig. 3). In the subgroup with β-blockers, CFI did not change significantly



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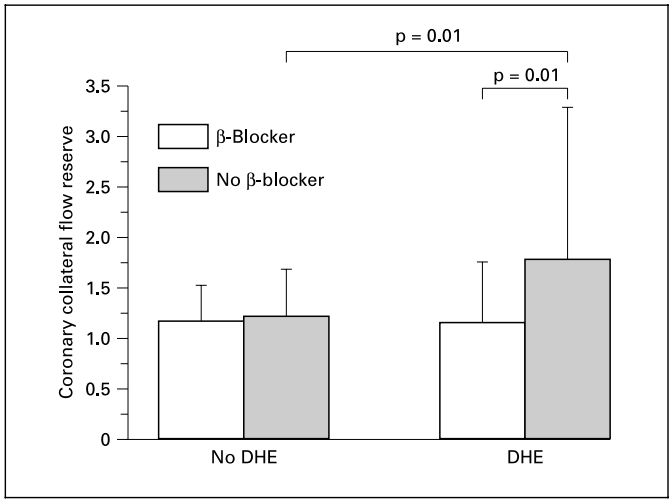

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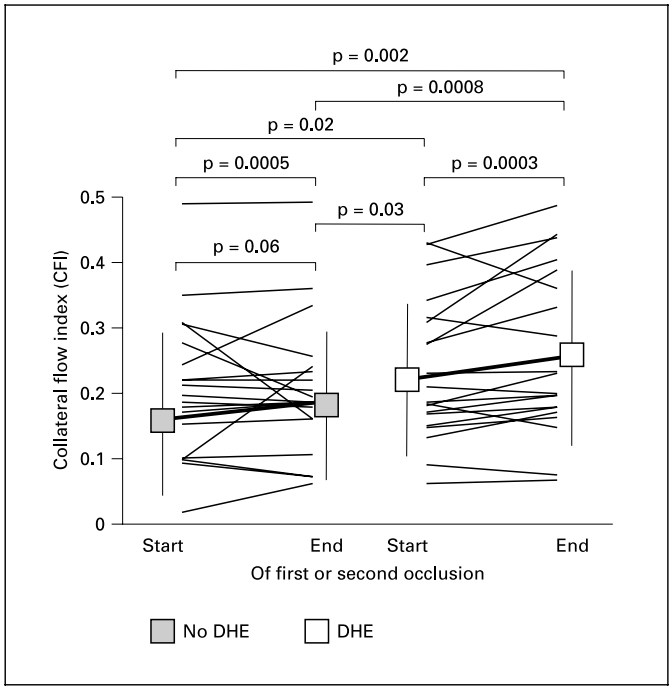

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Fig. 2. Association between voluntary contraction force exerted during 3 min of dynamic handgrip exercise at a frequency of 60/min (DHE, horizontal axis), and the exercise-induced change of collateral flow index (CFI) (CFI at the end minus CFI at the start of occlusions with handgrip, horizontal axis).

Fig. 3. Individual values of collateral flow index (CFI, vertical axis) depicted for patients receiving no β-blocker treatment (n = 25) at the start and end of coronary artery balloon occlusions randomly selected to be the first or second, respectively, without and with dynamic handgrip exercise (DHE, horizontal axis).

Fig. 4. Coronary collateral flow reserve values (vertical axis) obtained during vessel occlusions without and with dynamic handgrip exercise (DHE) in patients with and without β-blocker treatment (horizontal axis). Coronary collateral flow reserve without DHE was calculated as collateral flow index (CFI) at the end of first or second occlusions without DHE divided by CFI at the start of the respective occlusions; coronary collateral flow reserve with DHE was computed as CFI at the start of first or second occlusions with DHE divided by CFI at the start of occlusions without DHE.

between the different stages of occlusions without and with DHE (table 3). However, HR and RPP showed similar patterns of increase with DHE irrespective of β-blocker treatment (table 3). Figure 4 shows average values of balloon occlusion-induced and DHE-induced coronary collateral flow reserve in patients with and without β-blockers. In 13/50 patients (24%), coronary collateral flow reserve during DHE was <1 (7/50 in the absence of DHE, $p < 0.05$). Compared with the effect of the 1-min occlusion itself, coronary collateral flow reserve did not change in response to DHE among patients with β-blockers, whereas it increased to 1.8 ± 1.5 at the start of occlusions with DHE and without β-blockers ($p = 0.01$; fig. 4).

Discussion

The reaction of the collateral circulation to dynamic exercise in humans has been investigated only indirectly. This study using direct and quantitative assessment of

coronary collateral flow, overall, revealed an almost twofold increase in response to exercise in acutely occluded vessels of patients with chronic CAD. This effect was more pronounced than collateral flow recruitment due to the vessel occlusion(s) itself, and it was absent in individuals under β-blocker treatment.

Measurement of Collateral Function in Chronic and Acute Coronary Occlusion Models

The continuing debate on the functional capacity of coronary collateral vessels is reflected by contradicting results found in older [4, 17] and even experimental investigations [10, 18], as well as more recent clinical studies [19, 20]. This may be related to methodological/technical factors or actual biological variables influencing collateral vascular function differently. Early clinical investigations of collateral function have used exercise electrocardiography in patients with chronic total coronary occlusions [3]. The inability of exercise ECG to localize the coronary lesion causing ischemia renders this test unsuitable for studying coronary collaterals. The relatively high regional specificity of noninvasive myocardial perfusion imaging using radioactive isotopes permits a better correlation of angiographically determined pathoanatomy with regions of perfusion, although their misinterpretation may still be a source of error [19], when compared to the placement of an intravascular pressure sensor directly within the artificially occluded region of interest. Conversely, modern isotope techniques using positron emission tomography measure actual perfusion (in milliliters per gram per minute) instead of the CFI obtained in this study which expresses collateral flow as a fraction of normal antegrade flow. However, the only available studies investigating collateral function in response to exercise have employed thallium-201 perfusion imaging providing a dichotomous, purely qualitative measure of absent or present perfusion defects [4–6].

Inherent to all noninvasive techniques for estimating collateral flow is the requirement of a chronic total occlusion preferably in the absence of myocardial infarction since the latter would render any results on collateral function difficult to interpret. The chronic total occlusion model introduces a substantial selection bias in the clinical investigation of collaterals since only very well-developed collaterals are considered, a situation which is not representative for chronic stable CAD as a whole, whereby two thirds of the patients have collateral flow values less than 25% of normal antegrade flow [21]. That the chronic total occlusion model may produce contradicting results with respect to collateral function has been illustrated even in the experimental setting. Whereas Schaper et al. [18] documented a reduced hyperemia-induced myocardial perfusion (i.e. steal) in the collateral-dependent vascular area among dogs 3–6 weeks after ameroid-based coronary occlusion, Lambert et al. [10] using the same model after 6 months of occlusion demonstrated a threefold exercise-induced increase in the collateralized region. It has been suggested that different developmental stages of collateral vessels between the two studies were related to the respective outcomes [4], a hypothesis which has not been verified by more recent work [22]. The selection of the acute coronary occlusion model for assessing collaterals in our study has, however, not prevented the coexistence of contradicting results with regard to collateral function, because the occurrence of both hyperemia-induced collateral flow enhancement as well as decrease are biological realities and not methodological artifacts [23, 24]. In our study, exercise-induced flow reduction took place in almost one fourth of the patients, whereas a 1-min occlusion without exercise was accompanied by collateral flow decrease about half as many times. Although our clinical investigation illustrates that exercise may induce both flow improvement and decline in a collateral-dependent myocardial area, the term *steal* cannot be used in the present context as it was in the description by Schaper et al. [18], because our study is limited by the lack of simultaneous flow measurements in the collateral providing and receiving area.

Collateral Response to Exercise

However, considering the variable responses to exercise in collateral-dependent myocardium just described, Blumgart's [1] initial postulate that collateral vessels are able to maintain the resting requirement of the heart, but not the demands of an increased workload, becomes more comprehensible. The classification into present or absent exercise-induced thallium-210 perfusion defects used in the mentioned clinical studies has led to less affirmative conclusions that 'coronary collateral vessels may help maintain relative myocardial perfusion during exercise' [4]. Eng et al. [6] observed that approximately half of the collateralized, viable myocardial regions revealed exercise-induced perfusion similar to that in the adjacent, normal area, whereas the other half showed defects. A more recent clinical study using also the chronic total occlusion model, but dipyridamole as hyperemic stimulus, has found more precisely by ^{13}N ammonia positron emission tomography that about 30% (i.e. 3/10) of the above-mentioned defects of collateralized versus remote regions are due to a collateral flow reserve <1 [25]. In the acute coro-

nary occlusion model during PTCA, pharmacological responsiveness in a higher powered study has been demonstrated to be similarly variable, with adenosine- and nitroglycerin-induced increase in collateral flow in the presence of spontaneously visible collaterals during angiography, and without flow alterations in patients with angiographically invisible, i.e. recruitable collaterals [26].

As in our study, all antianginal medication was continued until cardiac catheterization in the investigation by Piek et al. [26], the influence of which may have been a factor contributing to the variable study results. In any event, this can be extrapolated from our results revealing an overall exercise-induced collateral flow increase only in the absence of β-blocker treatment. It has to be emphasized, however, that our patients were not assigned to β-blocker treatment in a controlled fashion. Thus, variable degrees of β-blockade may have been present, which is also suggested by the fact that HR at the start of balloon occlusions without exercise was not much lower in patients on than in those off β-blocker therapy (table 3). Consequently, it is a rather conservative estimate on the basis of our study that β-blockade tends to reduce effects of exercise on collateral function. This is in agreement with previous observations made in clinical [20, 27] but also in numerous experimental studies according to which exercise and other forms of stress are mediated as hyperemic stimulus by β-adrenergic receptor activation with vasodilatation of coronary collateral vessels [12, 28]. As an additional mechanism contributing to exercise-induced collateral vasomotion, flow-mediated, nitric oxide-dependent dilatation has been shown to play a role [13, 29]. Because at the onset of our study protocol, intracoronary nitroglycerin was given, nitric oxide-dependent collateral vasodilatation during exercise was probably not part of the mechanism by which it effected collateral function. Coronary collateral vasoconstriction has been recently documented to be the result of platelet activation via the production of serotonin and thromboxane A_2 [30, 31]. Statistically, the 15 patients in our study not on acetylsalicylic acid at the time of the protocol did not reveal exercise-induced collateral flow decrease more often than the patients on this drug.

Study Limitations

The level of precision of pressure-derived CFI measurement is not absolute but has a standard error of estimate of 0.08 when compared with Doppler-derived CFI measurement [16]. In comparison, the average change of CFI in the present study is rather small. However, it is the almost uniformly occurring increase of CFI in response to dynamic handgrip among patients without β-blockers (fig. 3) which translates into a statistically highly relevant alteration.

In conclusion, dynamic exercise among patients with CAD induces an overall increase in coronary collateral flow during acute vessel occlusion, the effect of which is statistically more relevant than that of collateral flow enhancement due to the occlusion itself. In about one fourth of these patients, exercise is associated with reduced collateral flow to the ischemic region. β-Blocker treatment appears to abolish the mentioned effects of dynamic exercise.

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