Direct Quantitative Assessment of the Peripheral Artery Collateral Circulation in Patients Undergoing Angiography

Running title: Traupe et al.; Assessment of peripheral collaterals

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Abstract:

**Background**—Despite the fact that numerous studies pursued the strategy of improving collateral function in patients with peripheral artery disease (PAD), there is currently no method available to quantify collateral arterial function of the lower limb.

**Methods and Results**—Pressure-derived collateral flow index [CFIp=(Poccl-CVP)/(Pao-CVP); pressure values in mmHg)] of the left superficial femoral artery (SFA) was obtained in patients undergoing elective coronary angiography using a combined pressure/Doppler wire (n=30). Distal occlusive pressure (Poccl) and toe oxygen saturation (SaO2) were measured for 5 minutes (min) under resting conditions, followed by an exercise protocol (repetitive plantar-flexion movements in supine position, n=28). In all patients, balloon occlusion of the SFA over 5 min was painless under resting conditions. CFIp increased during the first 3 min from 0.451±0.168 to 0.551±0.172 (P=0.0003), while SaO2 decreased from 98±2% to 93±7% (P=0.004). Maximal changes of SaO2 were inversely related to maximal CFIp (r²=0.33, P=0.003). During exercise, CFIp dropped within 1 min from 0.560±0.178 to 0.393±0.168 (P<0.0001) and reached its minimum after 2 min of exercise (0.347±0.176) while SaO2 declined to a minimum of 86±6% (P=0.002). Twenty-five patients (89%) experienced pain or cramps/tired muscles, while 3 (11%) remained symptom-free for an occlusion time of 10 min. CFIp values were positively related to the pain-free time span (r²=0.50, P=0.002).

**Conclusions**  Quantitatively assessed collateral arterial function at rest determined in the non-stenotic SFA is sufficient to prevent ischemic symptoms during a total occlusion of 5 minutes. During exercise, there is a decline in CFIp indicating a supply-demand mismatch via collaterals or –alternatively–a steal phenomenon.

**Clinical Trial Registration Information**—clinicaltrials.gov. Identifier: NCT01742455.

**Key words:** angiogenesis, balloon, collateral circulation, peripheral vasculature, peripheral artery disease, arteriogenesis, assessment, balloon occlusion, exercise physiology
Introduction

Peripheral artery disease (PAD) of the lower extremities is due to arterial obstruction leading to reduced arterial flow during exercise and/or at rest. The disease is present in approximately 4 percent of persons older than 40 years, but in 15-20 percent of those older than 65 years.1, 2 

Revascularization therapies are indicated in patients with disabling claudication persisting despite exercise training and pharmacotherapy or in patients with critical limb ischemia. However, in about 1/4 of these patients endovascular or surgical therapy fails or is not applicable, making alternative approaches necessary.3, 4 Thus, promotion of arteriogenesis, which refers to positive remodeling of preformed collateral arterioles, i.e., collateral growth should be induced in these patients.4-6 Despite the fact that numerous studies pursued the important therapeutic strategy of improving collateral function in patients with PAD, there is no method available to quantify collateral arterial function of the lower limb and, thus, to determine therapeutic effects.3, 7, 8

In contrast to peripheral arteries, collaterals of the heart can be assessed quantitatively by coronary flow velocity or pressure measurements, which have become the gold standard.9-11 The theoretical basis of this method relates to the fact that perfusion pressure (minus the central venous "back" pressure) or flow velocity signals obtained distal to an occluded stenosis originate from collaterals (during a brief coronary balloon occlusion or in case of a chronic total occlusion).9 The measurement of aortic and coronary pressure or flow velocity provides the basis for the calculation of a pressure- or velocity-derived collateral flow index (CFI_p or CVI_v), both of which express the amount of flow via collaterals to the vascular region of interest as a fraction of the flow via the normally patent vessel. CFI measurements have been documented to be very accurate with regard to ECG derived dichotomous collateral assessment, with regard to each
other, but also to quantitative myocardial perfusion imaging by contrast echocardiography during balloon occlusion.\textsuperscript{10,12} Pressure- and velocity-derived coronary collateral measurements are accepted as the reference method for quantitative clinical assessment of coronary collateral flow.\textsuperscript{11}

Concerning the promotion of peripheral collateral growth, clinical studies investigating new therapeutic strategies have determined rather “weak” endpoints obtained during vessel patency such as ankle-brachial index or 6-minute walking distance. In contrast to the coronary circulation, there is currently no reference method available to document successful promotion of collateral growth in patients suffering from PAD.\textsuperscript{3,7,8} Therefore, the purpose of this study was to evaluate a new invasive method to quantify arterial collateral function in the lower extremity in patients undergoing elective coronary angiography.

Methods

Patients and study design

Thirty patients electively referred for a diagnostic coronary angiography were included in the study. Criteria for study exclusion were as follows: 1) rest pain, ulceration or gangrene due to PAD (Rutherford 4-6), 2) known significant stenoses (>50\%) or occlusion of superficial femoral, profunda femoral, or aortoiliac arteries, 3) known aneurysm of abdominal aorta or iliac arteries, 4) acute coronary syndrome, 5) congestive heart failure NYHA III-IV, 6) severe pulmonary hypertension, 7) severe hepatic or renal failure.

This was a prospective exploratory study. As the primary study endpoint, pressure-derived collateral flow index (CFIp) of the temporarily occluded left superficial femoral artery during rest and a subsequent exercise protocol was determined (\textbf{figure 1}). The main secondary
endpoints were oxygen saturation (SaO2) of the left toe and velocity-derived collateral flow index (CFIv, see below) as obtained simultaneously with CFIp. This investigation was approved by the ethics committee of the Kanton of Bern, Switzerland and all patients gave written informed consent to participate in the study.

**Cardiac catheterization and coronary angiography**

Left heart catheterization including coronary angiography for diagnostic purposes using the right femoral artery approach was conducted in every patient. Biplane left ventriculography was performed followed by coronary angiography. Aortic pressure (Pao) was obtained using a 6 French coronary artery guiding catheter.

**Peripheral collateral function measurements**

A 0.014 inch pressure and Doppler sensor-tipped angioplasty guidewire (Volcano, Rancho Cordova, CA, USA) was placed in the proximal third of the contra-lateral, left superficial femoral artery (SFA) distally from the profunda femoral artery take-off, using a crossover sheath from the right SFA. Subsequently, the wire was set at zero, advanced through the guiding catheter, calibrated, and positioned distal to the SFA angioplasty balloon occlusion (figure 1). Central venous pressure (CVP) was assessed via the right femoral vein using a 5 French pigtail catheter. During SFA occlusion, simultaneous femoral occlusive pressure (Pocci), aortic pressure (Pao), central venous pressure (CVP) and flow velocity (Vocci; figure 2) were obtained for the calculation of pressure-derived collateral flow index [CFIp = (Pocci-CVP) / (Pao-CVP); pressure values in mmHg)].10, 12 CFIp has been documented to reflect collateral relative to normal antegrade flow as quantified by contrast echocardiography very closely and precisely.12 For the calculation of velocity-derived collateral flow index, CFIv, the non-occlusive baseline flow velocity (Vnon-occi) was obtained at the identical location, but before angioplasty balloon occlusion.
occlusion of the SFA (figure 2; $\text{CFI}_v = V_{\text{occl}} / V_{\text{non-occl}}$, velocity in cm/s). Velocities were determined as average peak flow velocity (APV) as obtained over 3 cardiac cycles. In the coronary arterial circulation, $\text{CFI}_v$ has been documented to be closely related to $\text{CFI}_p$. In the setting described, the SFA was the collateral-receiving (ipsilateral) and the profunda femoral artery the collateral-supplying (contralateral) artery (figure 1).

**Study protocol**

Following diagnostic coronary angiography (and percutaneous coronary intervention if indicated), lower extremity angiography was performed using retrograde femoral access. At the start of the protocol, 5’000 units of heparin were given intravenously. The angioplasty pressure/Doppler sensor guide wire was positioned distal to the site of the imminent balloon occlusion. During the entire protocol, peripheral oxygen saturation (SaO₂) was monitored by pulse-oximetry of the ipsi-lateral, left toe. Simultaneous recording of $P_{ao}$, distal P (becoming $P_{\text{occl}}$), CVP, $V$ and SaO₂ was started before and continued throughout the balloon occlusion for a maximum of 10 minutes. An adequately sized angioplasty balloon was selected (Fox plus 7.0 - 9.0x20 mm; Avion plus 7.0x20 mm) and balloon inflation at low inflation pressure was performed (1 – 6 atmospheres). Complete occlusion of the vessel was confirmed by contrast injection. After the first 5 minutes of distal occlusive pressure and velocity measurement under resting conditions, patients performed repetitive plantar-flexion movements in supine position for another 5 minutes or until pain occurred (exercise protocol was performed in n=28 patients). Subsequently, the angioplasty catheter and pressure/Doppler guidewire were removed and a final angiography was performed to ensure unaltered vascular anatomy.

**Statistical analysis**

Data are given as mean ± standard deviation unless stated otherwise. Categorical data are given
as number (percent). ANOVA for repeated measures followed by Bonferroni-Dunn post hoc test was used for analyses when appropriate. Linear regression analysis was performed between CFI_p as the independent variable and SaO_2-changes or pain-free time span, respectively, as the dependent variable. P-values <0.05 were considered as statistically significant.

Results

Patient characteristics and clinical data

Characteristics and clinical data of study patients are presented in table 1. Study patients were predominantly men and 57% of them suffered from angina pectoris. Systemic arterial hypertension and dyslipidemia were the cardiovascular risk factors present in most patients, which were usually treated with acetylsalicylic acid, statins, and inhibitors of the renin-angiotensin system.

Angiographic, hemodynamic, and collateral circulation data

Angiographic and hemodynamic data taken before the start of the study protocol are given in table 2. Coronary artery disease was observed by coronary angiography in 90% of study patients. In 12 patients (40%), angiography of the left lower limb revealed wall irregularities or non-significant stenoses of the SFA, respectively, and in one patient a non-significant stenosis of the left iliac artery. Initially, one patient was excluded from the study because of an occluded left popliteal artery (59-year old male patient without coronary artery disease).

Under resting conditions, balloon occlusion of the SFA over 5 minutes (min) was painless in all patients. Consistently, angiography demonstrated 1 to 4 sites of collateral inflow during balloon occlusion (figure 2). CFI_p increased during the first 3 min of occlusion under resting conditions from 0.451±0.168 to 0.551±0.172 (P=0.0003; figure 3), while SaO_2 decreased...
from 98±2% to 93±7% (P=0.004). In the patient excluded from the analysis due to popliteal artery occlusion, CFI_p was 0.563 after 1 minute, and therefore higher than in the absence of significant stenoses (i.e. 0.451±0.168 after 1 minute).

During exercise, CFI_p dropped within 1 min (i.e. after 6 min of the study protocol) from 0.560±0.178 to 0.393±0.168 (P<0.0001; figure 3) and reached its minimum after 2 min of exercise (0.347±0.176), while SaO2 further declined to a minimum of 86±6% (P=0.002). This consistent CFI_p course during rest and exercise is also illustrated by an individual recording shown in figure 4. Both, Pao2 and CVP remained stable during resting conditions and increased with exercise (P<0.0001 and P=0.007, respectively; p values for overall trends over time; table 2).

There was a direct correlation between CFI_p and CFI_v both at rest and during exercise (1st minute and 6th minute; figure 5). During vessel occlusion, Doppler flow velocity spectra were often difficult to obtain in analyzable quality for technical reasons, and thus, could be used for CFI_v calculation in only 16 of 30 patients. The main reason for poor Doppler flow velocity signals was wall motion artifacts in the context of relatively low flow velocities resulting in low signal-to-noise ratio.

There was a direct relation between the minimal and maximal CFI_p values under exercise versus those under resting conditions (r²=0.652, P<0.0001 and r²=0.527, P<0.0001, respectively; data not shown).

Regarding symptoms during the exercise protocol, 16 patients (57%) experienced pain after a mean occlusion time of 473±74 seconds (sec) and 12 (43%) suffered from cramps or tired muscles after 491±71 sec (3 patients suffered from both pain and cramps/tired muscles). Of all patients, 3 (11%) remained symptom-free for an occlusion time of 10 min. The small group of
patients without symptoms until the end of SFA occlusion of 10 min showed a significantly higher maximal CFI (0.642±0.157) than the group with symptoms (0.437±0.210; p=0.0048, unpaired t test for subgroup analysis). The mean total occlusion time was 534±82 sec. CFI\textsubscript{p} values were directly related to the pain-free time span during exercise (e.g. for minimal CFI under exercise: r\textsuperscript{2}=0.50, P=0.002; figure 6A), but not with other symptoms (cramps/tired muscles, data not shown). Maximal changes of \textit{SaO} sub{2} (i.e., maximal \textit{SaO} sub{2} – minimal \textit{SaO} sub{2}) at rest were inversely associated with the maximal CFI\textsubscript{p} values (r\textsuperscript{2}=0.33, P=0.003; figure 6B).

**Discussion**

The present study demonstrates for the first time a quantitatively assessed functional and clinically relevant collateral circulation in the lower limb. Using direct invasive pressure measurements in humans, we show that collateral function as determined by CFI\textsubscript{p} of the superficial femoral artery (SFA) amounts to more than half the mean aortic perfusion pressure at rest. Importantly, this pre-existent collateral blood supply in the absence of significant stenoses is sufficient to prevent symptoms during five minutes of acute ischemia at rest. Measurements of CFI\textsubscript{p} as taken in the present study can be performed in every stenotic artery, which is suitable for percutaneous recanalization using a guide wire. Pressure measurements can be performed simultaneously with therapeutic dilatation and/or stenting of a stenosis or immediately thereafter during a second “diagnostic” balloon occlusion. Therefore, CFI\textsubscript{p} measurements are even feasible in chronic occlusions. Importantly, this method has been successfully used in stenotic and chronically occluded coronary arteries for many years.\textsuperscript{9}

In order to increase collateral blood vessel development, capillary number, and blood flow, many clinical studies have used the administration of growth factors (mostly bFGF or...
VEGF, either as protein or gene therapy) or stem and progenitor cells.\textsuperscript{3, 4, 8, 13, 14} In addition, supervised exercise rehabilitation programs have been shown to improve symptoms of claudication and meta-analyses have found an increase of the average distance walked to the onset of claudication.\textsuperscript{15, 16} Usual, yet imprecise measures of therapeutic effects in clinical studies are absolute walking distance, ulcer healing/decrease of ulcer size or amputation rates, rest pain and various questionnaires assessing walking impairment and/or quality of life.\textsuperscript{3} Moreover, clinical studies have investigated various endpoints such as changes in ankle-brachial index (ABI), digital subtraction angiography (DSA), flow reserve, endothelial function, or transcutaneous oxygen pressure.\textsuperscript{3}

In contrast to the numerous investigations in the field, current diagnostic methods for the assessment of PAD are limited due to their inability to directly and quantitatively measure collateral function. Only in experimental animal angiography studies, but not in their clinical counterparts, an angiographic classification for assessing peripheral collaterals is currently used (0 = no filling of collaterals, 1 = filling of collaterals only, 2 = partial filling of distal femoral artery, 3 = complete filling of distal femoral artery).\textsuperscript{17} Alternatively, a transverse line marking the inferior border of the obliteration can be drawn and all vessels crossing the line at the inferior border are counted as collaterals.\textsuperscript{7} Although this method has been successfully used in a clinical study identifying risk factors for poor collateral development in PAD,\textsuperscript{7} its use may lead to a rather arbitrary classification of collaterals. Importantly, digital angiography is limited by a low resolution (>0.2 mm),\textsuperscript{9, 18} and therefore, lacks the precision and reproducibility to study small collaterals.\textsuperscript{3} Moreover, functional assessment is not feasible at all when using angiography alone for follow-up; therefore, the actual relevance of newly developed collaterals may be entirely missed.
CT angiography (CTA) holds the advantage that - due to the intravenous injection of contrast - collaterals are filled and also arteries distal to the occlusion are opacified that otherwise may be occult to angiography.\textsuperscript{19, 20} Alternatively, duplex ultrasound\textsuperscript{21} or pulse volume recording (PVR)\textsuperscript{22} may be used to assess both primary and collateral flow. However, with the use of (follow-up) angiography, CTA, duplex ultrasound and/or semi-quantitative PVR miss not only functional aspects of collaterals, but also the role of the microcirculation for peripheral collateral blood flow and muscle perfusion. In this context, laser Doppler flowmetry can be used to assess the local microcirculation,\textsuperscript{8} and contrast-enhanced ultrasound (CEU) has been recently introduced for the determination of tissue perfusion in patients with PAD.\textsuperscript{23, 24} Moreover, functional assessment using MRI has been described in single individuals but not yet evaluated in a clinical trial.\textsuperscript{8, 25}

Apart from the invasive measurement of antegrade flow velocity in a single patient back in the early days of angiogenesis research (certainly without balloon occlusion),\textsuperscript{26} to date no attempts have been made to directly quantify the collateral circulation of the lower limb. In the present study, not only pressure but also simultaneous flow velocity measurements were used for the first time to directly quantify collateral function; additionally, angiographic evidence of consistent collateral inflow to the SFA was provided (see \textbf{figure 2}). Angiographies performed during SFA occlusion demonstrated rapid inflow of contrast distal to the balloon, originating from the circumflex femoral arteries and the perforating arteries, including the fourth perforating artery whose potential clinical relevance has been proposed earlier.\textsuperscript{27} Our results show that these arteries form pre-existent collaterals that provide more than half the antegrade flow within 3 minutes of a sudden artificial SFA occlusion. Since actual collateral flow was not obtained in this study, the question may be raised whether its primary endpoint, CFI\textsubscript{p}, does really reflect
collateral to normal antegrade flow. The fact that simultaneously obtained, flow velocity-derived CFIv was directly related to CFIp both at rest and during exercise strongly supports the concept of CFIp being a direct measure of collateral flow.

Coronary collateral flow is mainly determined by the stenosis severity of the collateral receiving artery,28 which is obviously also true for the setting used in the present study, since collateral flow significantly decreases after removal of a femoral artery stenosis.21 Regarding the absence of any pre-existent significant femoral artery stenosis, the amount of instantaneous collateral function observed in our study was remarkably high (CFIp of 45±17% after one minute and 56±18% after five minutes of occlusion), especially in comparison to what has been previously described for normal (18±8%)29 and stenotic coronary arteries (22±15%).28 In this context, it is reasonable to speculate that CFIp would be even higher in the presence of a significant SFA stenosis. It is important to note that collateral function was sufficient enough in all patients to completely prevent ischemia-related symptoms at rest, which is not the case for the coronary collateral circulation since only 25% of patients with normal coronary arteries have no symptoms during a one-minute balloon occlusion.29

With foot exercise, pressure-derived collateral function decreased significantly. It is obvious from the original recording shown in figure 4, that this effect was due to a drop of the distal occlusive pressure and not a relevant change of central venous and/or aortic pressure. Collateral supply to the ischemic region may have –only insufficiently- increased in response to the exercise-induced demand, and the occlusive pressure drop during exercise reflects heightened viscous energy loss across inadequately dilated collaterals. Alternatively, an exercise-induced steal phenomenon via well developed collaterals may be responsible for this observation, due to peripheral hyperemia with a more pronounced decrease in microvascular resistance in the
collateral-supplying than the collateral-receiving region, thus leading to a relative flow diversion away from the occluded vascular territory.\textsuperscript{30} Considering pure foot dorsi plantar movement, such a mechanism of steal would seem unlikely, because of the inactive thigh musculature. However, a combined knee and foot movement could be observed in practically all patients despite they had been instructed otherwise. To test this hypothesis, simultaneous flow measurements in the thigh and calf supply region would have been needed, which were not performed in our study. The decrease of collateral function was clinically relevant, since the majority of patients (89\%) suffered from ischemia-related symptoms during exercise, and there was a positive correlation between CFI\textsubscript{p} and the time until the onset of pain.

**Limitations of the study**

In the above context of potential mechanisms of the observed exercise-induced drop in CFI\textsubscript{p}, it is obvious that actual flow measurements would have provided an answer on whether a supply-demand mismatch or collateral steal is responsible. Thus, the lack of direct tissue perfusion data can be regarded as the major study limitation. Ultimately, contrast-enhanced ultrasound should have been performed simultaneously and optimally in different supply regions during balloon occlusion. However, it would be technically not feasible to obtain these additional measurements while the patient is in supine position during angiography and especially while performing leg movements.

In addition to CFI measurements, other markers of collateral function that are easier to obtain should be evaluated with regard to CFI\textsubscript{p} as a potential reference method. Although the time until the onset of pain and the drop of SaO\textsubscript{2} during occlusion correlated well with the amount of collateral function, other possible methods could have been tested during this study such as toe pressure, ankle-brachial index, or washout angiography.\textsuperscript{31} However, it would have
been too demanding to perform several different measurements during the same study protocol.

In conclusion, the present study did not only assess collateral function of the lower limb using pressure measurements during SFA occlusion, but did also demonstrate the feasibility and short-term safety of this method. Since only indirect and weak endpoints have been used in past studies to evaluate collateral growth, we propose that our method may possibly be used as a reference method in future clinical studies. CFI_p determined in the SFA after a five minute occlusion under resting conditions could serve as a reliable and reproducible endpoint, and its use should not be withheld despite higher equipment costs or possible concerns regarding the long-term safety of diagnostic balloon occlusions.32

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Conflict of Interest Disclosures: None.

References:


Table 1. Patient characteristics and clinical data

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<th>Variable</th>
<th>(n=30)</th>
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<tr>
<td>Age (years)</td>
<td>63 ± 10</td>
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<tr>
<td>Male gender</td>
<td>25 (83%)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>26 ± 3</td>
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<td>Duration of angina (months; median and interquartile range)</td>
<td>2.0 (6.7)</td>
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<tr>
<td>History of prior myocardial infarction</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Prior coronary artery bypass grafting</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>History of prior peripheral artery intervention</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

**Cardiovascular risk factors**
- Arterial hypertension | 20 (67%)
- Current smoker | 8 (27%)
- Dyslipidemia | 22 (73%)
- Family history for coronary artery disease | 14 (47%)
- Obesity (BMI ≥30 kg/m²) | 2 (7%)
- Diabetes mellitus | 8 (27%)

**Medication**
- Acetylsalicylic acid | 26 (87%)
- Clopidogrel | 12 (40%)
- Betablockers | 17 (57%)
- Calcium channel blockers | 4 (13%)
- Nitrates | 3 (10%)
- Statins | 25 (83%)
- ACE inhibitors / Angiotensin receptor blockers | 20 (67%)
- Diuretics | 9 (30%)

**Blood values**
- Hemoglobin (g/l) | 137 ± 15
- Leucocytes (10⁹/l) | 7.21 ± 2.19
- Potassium (mmol/l) | 4.08 ± 0.20
- Creatinine kinase (U/l) | 106 ± 53
- Creatinine (mmol/l) | 76 ± 17
- Total cholesterol (mmol/l) | 4.47 ± 1.07
- Low density lipoprotein cholesterol (mmol/l) | 2.45 ± 1.01
- High density lipoprotein cholesterol (mmol/l) | 1.36 ± 0.43
- Triglycerides (mmol/l) | 1.56 ± 1.20
- Fasting glucose (mmol/l; median and interquartile range) | 5.88 (1.5)
Table 2. Angiographic and hemodynamic data

<table>
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<tr>
<td>Coronary artery disease</td>
<td>27 (90%)</td>
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<tr>
<td>Number of coronary vessels diseased: 1, 2, 3</td>
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</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69 ± 10</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129 ± 25</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74 ± 14</td>
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<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>56 ± 10</td>
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<tr>
<td>Left ventricular end-diastolic pressure (mmHg)</td>
<td>14 ± 8</td>
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<td>Mean aortic pressure (mmHg) - before occlusion</td>
<td>91 ± 17</td>
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<tr>
<td>- at rest</td>
<td>94 ± 17</td>
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<tr>
<td>- during exercise</td>
<td>108 ± 19</td>
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<tr>
<td>Central venous pressure (mmHg) - before occlusion</td>
<td>6 ± 3</td>
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<tr>
<td>- at rest</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>- during exercise</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Ankle-brachial index, left leg</td>
<td>1.12 ± 0.19</td>
</tr>
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Figure Legends:

Figure 1. Peripheral collateral flow measurement during balloon occlusion at low angioplasty balloon inflation pressure using a 0.014 inch pressure/Doppler sensor-tipped angioplasty guide wire (left panel). Right panel: Schematic diagram of a two-branch peripheral circulation with a stenotic, balloon-occluded vessel (left) and a non-stenotic vessel (right), both connected via a collateral vessel. The microcirculation is indicated by two rectangles. The red arrows show the direction and give an estimate of the amount of flow.

Figure 2. Determination of the peripheral pressure-derived collateral flow index (CFI_p) in a 66-year old man without peripheral artery disease. Upper left panel: Collateral inflow (see arrow) during balloon occlusion of the left superficial femoral artery (SFA; balloon size: 8.0x20mm, 4 bar). Lower left panel: Original simultaneous recording of mean and phasic aortic pressure (P_{ao},
scale: 120mmHg), distal femoral artery occlusive pressure ($P_{occl}$, scale: 120mmHg) and central venous pressure (CVP scale: 30mmHg) during balloon occlusion resulting in a CFI$_p$ of 0.418.

Right panels: Doppler-derived SFA flow velocity spectra (right vertical scale, cm/s) of the same patient as obtained during vessel occlusion ($V_{occl}$; simultaneous to CFI$_p$; upper panel) and before occlusion at baseline ($V_{non-occl}$; lower panel). CFI$_v$ amounted to 0.551.

**Figure 3.** Pressure-derived collateral flow index (CFI$_p$) of the left superficial femoral artery (panel A) and left toe oxygen saturation (panel B) under both resting conditions and during exercise (indicated by arrows). Data are given as mean±SEM. *P<0.01 vs. 5 min, †P<0.001 vs. 1 min, ‡P<0.01 vs. 0 min

**Figure 4.** Representative example showing the time course during balloon occlusion of the left superficial femoral artery in a 49-year old male patient without peripheral or coronary artery disease. Upper panel: Mean aortic pressure ($P_{aortal}$, red), distal occlusive pressure ($P_{occl}$, black) and central venous pressure (CVP, blue) during rest and exercise (as indicated by arrow). Lower panel: Calculated instantaneous pressure-derived collateral flow index (CFI$_p$).

**Figure 5.** Correlation between pressure- and flow velocity-derived collateral flow index (CFI$_p$, horizontal axis; CFI$_v$, vertical axis) at rest (left panel) and during exercise (right panel).

**Figure 6.** Upper panel: Positive correlation for minimal pressure-derived collateral flow index (CFI$_p$) vs. time duration patients remained pain free during the exercise protocol. Lower panel: Inverse correlation for maximal CFI$_p$ vs. maximal changes of SaO$_2$ (i.e., maximal SaO$_2$ – minimal SaO$_2$) during resting conditions.
Figure 1
Figure 2

\[ CF_{\text{p}} = \frac{(37-7.5)}{(78-7.5)} = 0.418 \]

- \( P_{\text{portal}} = 78 \text{ mmHg} \)
- \( P_{\text{occl}} = 37 \text{ mmHg} \)
- \( CVP = 7.5 \text{ mmHg} \)
Figure 3
Collateral flow index at rest (1st minute)  

\[ y = 0.019 + 0.66x \]

\[ r^2 = 0.27 \]

\[ p = 0.0376 \]

Collateral flow index during exercise (6th minute)  

\[ y = 0.012 + 1.14x \]

\[ r^2 = 0.47 \]

\[ p = 0.0094 \]
Figure 6

- Equation 1: $y = 366 + 355x$
  - $r^2 = 0.50$
  - $p = 0.002$

- Equation 2: $y = 18 + 19x$
  - $r^2 = 0.33$
  - $p = 0.003$
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