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

Tobias Traupe, MD; Jana Ortmann, MD; Michael Stoller, MD; Iris Baumgartner, MD; Stefano F. de Marchi, MD; Christian Seiler, MD

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

Methods and Results—Pressure-derived collateral flow index (CFIp, calculated as (occlusive pressure−central venous pressure)/(aortic pressure−central venous pressure); pressure values in mm Hg) of the left superficial femoral artery was obtained in patients undergoing elective coronary angiography using a combined pressure/Doppler wire (n=30). Distal occlusive pressure and toe oxygen saturation (Sao₂) were measured for 5 minutes under resting conditions, followed by an exercise protocol (repetitive plantar-flexion movements in supine position; n=28). In all patients, balloon occlusion of the superficial femoral artery over 5 minutes was painless under resting conditions. CFIp increased during the first 3 minutes from 0.451±0.168 to 0.551±0.172 (P=0.0003), whereas 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 declined within 1 minute from 0.560±0.178 to 0.393±0.168 (P=0.0001) and reached its minimum after 2 minutes of exercise (0.347±0.176), whereas Sao₂ declined to a minimum of 86±6% (P=0.002). Twenty-five patients (89%) experienced pain or cramps/tired muscles, whereas 3 (11%) remained symptom-free for an occlusion time of 10 minutes. CFIp values were negatively related to the pain-free time span (r²=0.50, P=0.002).

Conclusions—Quantitatively assessed collateral arterial function at rest determined in the nonstenotic superficial femoral artery is sufficient to prevent ischemic symptoms during a total occlusion of 5 minutes. During exercise, there is a decline in CFIp that indicates a supply-demand mismatch via collaterals or, alternatively, a steal phenomenon.


Key Words: angiogenesis • balloon occlusion • collateral circulation • peripheral artery disease

Peripheral artery disease (PAD) of the lower extremities is caused by arterial obstruction that leads to reduced arterial flow during exercise or at rest. The disease is present in approximately 4% of persons older than 40 years but in 15% to 20% of those >65 years of age.¹,² Revascularization therapies are indicated in patients with disabling claudication that persists despite exercise training and pharmacotherapy or in patients with critical limb ischemia. However, in approximately one fourth of these patients, endovascular or surgical therapy fails or is not applicable, which makes alternative approaches necessary.³,⁴ Thus, promotion of arteriogenesis, which refers to positive remodeling of preformed collateral arterioles, that is, collateral growth, should be induced in these patients.³,⁴,⁶

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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).² 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, or CFL), 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.10,12 Pressure- and velocity-derived coronary collateral measurements are accepted as the reference method for quantitative clinical assessment of coronary collateral flow.11 Concerning the promotion of peripheral collateral growth, clinical studies investigating new therapeutic strategies have determined rather weak end points obtained during vessel patency, such as ankle-brachial index or walking distance. In contrast to the coronary circulation, there is currently no reference method available to document successful promotion of collateral growth in patients with PAD.3,7,8 Therefore, the purpose of the present 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 caused by PAD (Rutherford categories 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 (New York Heart Association functional class III–IV); (6) severe pulmonary hypertension; and (7) severe hepatic or renal failure. This was a prospective exploratory study. As the primary study end point, pressure-derived collateral flow index (CFI) of the temporarily occluded left superficial femoral artery during rest and a subsequent exercise protocol was determined (Figure 1). The main secondary end points were oxygen saturation (SaO) of the left toe and velocity-derived collateral flow index (CFI; see below) as obtained simultaneously with CFI. 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-sided heart catheterization including coronary angiography for diagnostic purposes by the right femoral artery approach was conducted in every patient. Biplane left ventriculography was performed, followed by coronary angiography. Aortic pressure (PAO) was obtained with a 6F coronary artery guiding catheter.

Peripheral Collateral Function Measurements

A 0.014-inch pressure and Doppler sensor–tipped angioplasty guidewire (Volcano, Rancho Cordova, CA) was placed in the proximal third of the contralateral left superficial femoral artery (SFA) distal from the profunda femoral artery takeoff 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 with a 5F pigtail catheter. During SFA occlusion, simultaneous femoral occlusive pressure (PAO, CVP, and flow velocity (VOC) were included in the study. Criteria for study exclusion were as follows: (1) Rest pain, ulceration, or gangrene caused by PAD (Rutherford categories 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 (New York Heart Association functional class III–IV); (6) severe pulmonary hypertension; and (7) severe hepatic or renal failure. This was a prospective exploratory study. As the primary study end point, pressure-derived collateral flow index (CFI) of the temporarily occluded left superficial femoral artery during rest and a subsequent exercise protocol was determined (Figure 1). The main secondary end points were oxygen saturation (SaO) of the left toe and velocity-derived collateral flow index (CFI; see below) as obtained simultaneously with CFI. 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.

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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 had 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 nonsignificant stenoses of the SFA, respectively, and in 1 patient, a nonsignificant stenosis of the left iliac artery. Initially, 1 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 was painless in all patients. Consistently, angiography demonstrated 1 to 4 sites of collateral inflow during balloon occlusion (Figure 2). CFIp increased during the first 3 minutes of occlusion under resting conditions, from 0.451±0.168 to 0.551±0.172 (P=0.0003; Figure 3), whereas \( \text{Sa}_2 \) decreased from 98±2% to 93±7% (P=0.004). In the patient excluded from the analysis because of popliteal artery occlusion, CFIp was 0.563 after 1 minute and therefore higher than in the absence of significant stenoses (ie, 0.451±0.168 after 1 minute).

During exercise, CFIp decreased within 1 minute (ie, after 6 minutes 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 minutes of exercise (0.347±0.176), whereas \( \text{Sa}_2 \) further declined to a minimum of 86±6% (P=0.002). This consistent CFIp course during rest and exercise is also illustrated by an individual recording shown in Figure 4. Both Pao and CVP remained stable during resting conditions and increased with exercise (P<0.0001 and P=0.007, respectively; probability values are for overall trends over time; Table 2).
There was a direct correlation between CFIp and CFIv both at rest and during exercise (first minute and sixth 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 CFIv 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 that resulted in a low signal-to-noise ratio. There was a direct relation between the minimal and maximal CFIp values under exercise versus those under resting conditions ($r^2=0.652$, $P<0.0001$ and $r^2=0.527$, $P<0.0001$, respectively; data not shown).

Regarding symptoms during the exercise protocol, 16 patients (57%) experienced pain after a mean occlusion time of 473±74 seconds, and 12 (43%) experienced cramps or tired muscles after 491±71 seconds (3 patients had both pain and cramps/tired muscles). Among all patients, 3 (11%) remained symptom-free for an occlusion time of 10 minutes. The small group of patients without symptoms until the end of SFA occlusion of 10 minutes 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 seconds. CFIp values were directly related to the pain-free time span during exercise (eg, for minimal CFI under exercise: $r^2=0.50$, $P=0.002$; Figure 6A) but not to other symptoms (cramps/tired muscles; data not shown). Maximal changes of $\text{Sa}_2$ (ie, maximal $\text{Sa}_2$−minimal $\text{Sa}_2$) were significantly lower in patients with symptoms than in patients without symptoms ($P=0.0048$, unpaired $t$ test for subgroup analysis).
Sao2) at rest were inversely associated with the maximal CFIp values (r²=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 CFIp of the SFA amounts to more than half the mean aortic perfusion pressure at rest. Importantly, this pre-existing collateral blood supply in the absence of significant stenoses is sufficient to prevent symptoms during 5 minutes of acute ischemia at rest. Measurements of CFIp as taken in the present study can be performed in every stenotic artery that is suitable for percutaneous recanalization with a guidewire. Pressure measurements can be performed simultaneously with therapeutic dilation or stenting of a stenosis or immediately thereafter during a second diagnostic balloon occlusion. Therefore, CFIp measurements are even feasible in chronic occlusions. Importantly, this method has been used successfully in stenotic and chronically occluded coronary arteries for many years.9,11

To increase collateral blood vessel development, capillary number, and blood flow, many clinical studies have used the administration of growth factors (mostly basic fibroblast growth factor or vascular endothelial growth factor, either as protein or gene therapy) or stem and progenitor cells.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 in the average distance walked to the onset of claudication.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 that assess walking impairment or quality of life.3 Moreover, clinical studies have investigated various end points such as changes in ankle-brachial index, digital subtraction angiography, flow reserve, endothelial function, or transcutaneous oxygen pressure.3

In contrast to the numerous investigations in the field, current diagnostic methods for the assessment of PAD are limited because of their inability to directly and quantitatively measure collateral function. Only in experimental animal angiography studies, but not in their clinical counterparts, is an angiographic classification for assessing peripheral collaterals currently used (0=no filling of collaterals, 1=filling of collaterals only, 2=partial filling of distal femoral artery, and 3=complete filling of distal femoral artery).17 Alternatively, a transverse line marking the inferior border of the obliteration can be drawn, and all vessels that cross the line at the inferior border can be counted as collaterals.7 Although this method has been used successfully in a clinical study identifying risk factors for poor collateral development in PAD,7 its use may lead to a rather arbitrary classification of collaterals. Importantly, digital angiography is limited by a low resolution (>0.2 mm),9,18 and therefore, it lacks the precision and reproducibility needed to study small collaterals.3 Moreover, functional assessment is...
microcirculation, and contrast-enhanced ultrasound has been introduced recently for the determination of tissue perfusion. Additionally, angiographic evidence of consistent collateral inflow to the SFA was provided (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, the potential clinical relevance of which has been proposed previously. The results of the present study show that these arteries form preexistent collaterals that provide more than half the antegrade flow within 3 minutes of a sudden artificial SFA occlusion. Because actual collateral flow was not obtained in the present study, the question may be raised whether its primary end point, CFIp, truly reflects 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, which is obviously also true for the setting used in the present study, because collateral flow significantly decreases after removal of a femoral artery stenosis. Regarding the absence of any preexistent significant femoral artery stenosis, the amount of instantaneous collateral function observed in the present study was remarkably high (CFIp of 45±17% after 1 minute and 56±18% after 5 minutes of occlusion), especially compared with what has been described previously for normal (18±8%) and stenotic (22±15%) coronary arteries. In this context, it is reasonable to speculate that CFIv would be even higher in the presence of a significant SFA stenosis. Collateral function was sufficient in all patients to completely prevent ischemia-related symptoms at rest, which is not the case for the coronary collateral circulation, because only 25% of patients with normal coronary arteries have no symptoms during a 1-minute balloon occlusion.

With foot exercise, pressure-derived collateral function decreased significantly. It is obvious from the original recording shown in Figure 4 that this effect was caused by a drop in the distal occlusive pressure and not a relevant change in CVP or Pao. 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, because of 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. Considering pure foot dorsifluctant 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 the fact that 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 the present study. The decrease in collateral function was clinically relevant, because the majority of patients (89%) had ischemia-related symptoms during exercise, and there was a positive correlation between CFIp and time until the onset of pain.
Study Limitations

In the above context of potential mechanisms of the observed exercise-induced drop in CFIp, 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 not be technically feasible to obtain these additional measurements while the patient is in the 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 CFIp as a potential reference method. Although the time until the onset of pain and the drop in Sao2 during occlusion correlated well with the amount of collateral function, other possible methods could have been tested during the present study, such as toe pressure, ankle-brachial index, or washout angiography. However, it would have been too demanding to perform several different measurements during the same study protocol.

In conclusion, the present study not only assessed collateral function of the lower limb using pressure measurements during SFA occlusion but also demonstrated the feasibility and short-term safety of this method. Because only indirect and weak end points 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. CFIp determined in the SFA after a 5-minute occlusion under resting conditions could serve as a reliable and reproducible end point, and its use should not be withheld despite higher equipment costs or possible concerns regarding the long-term safety of diagnostic balloon occlusions.

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Disclosures

None.

References


Peripheral artery disease of the lower extremities is a common disease and present in 15% to 20% of persons older than 65 years. Endovascular or surgical therapy fails or is not applicable in approximately one fourth of patients who would need revascularization therapies, which makes alternative approaches such as arteriogenesis (the positive remodeling of preformed collateral arterioles) necessary. Despite the fact that numerous studies have pursued the important therapeutic strategy of improving collateral function, there is no method available to quantify collateral arterial function of the lower limb and thus to determine therapeutic effects. 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 flow index of the superficial femoral artery in the absence of any significant stenosis amounts to more than half the normal antegrade flow at rest (45±17% after 1 minute, 55±17% after 3 minutes). The amount of collateral flow observed in the present study is remarkably high, especially compared with what has been described previously for normal (18±8%) and stenotic (22±15%) coronary arteries. Importantly, this preexistent collateral blood supply in the absence of significant stenoses is sufficient to completely prevent symptoms during 5 minutes of acute ischemia at rest. Because only indirect and weak end points have been used in past studies to evaluate collateral growth, we propose that the method described in the present study may possibly be used as a gold standard in future clinical studies.

CLINICAL PERSPECTIVE

Peripheral artery disease of the lower extremities is a common disease and present in 15% to 20% of persons older than 65 years. Endovascular or surgical therapy fails or is not applicable in approximately one fourth of patients who would need revascularization therapies, which makes alternative approaches such as arteriogenesis (the positive remodeling of preformed collateral arterioles) necessary. Despite the fact that numerous studies have pursued the important therapeutic strategy of improving collateral function, there is no method available to quantify collateral arterial function of the lower limb and thus to determine therapeutic effects. 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 flow index of the superficial femoral artery in the absence of any significant stenosis amounts to more than half the normal antegrade flow at rest (45±17% after 1 minute, 55±17% after 3 minutes). The amount of collateral flow observed in the present study is remarkably high, especially compared with what has been described previously for normal (18±8%) and stenotic (22±15%) coronary arteries. Importantly, this preexistent collateral blood supply in the absence of significant stenoses is sufficient to completely prevent symptoms during 5 minutes of acute ischemia at rest. Because only indirect and weak end points have been used in past studies to evaluate collateral growth, we propose that the method described in the present study may possibly be used as a gold standard in future clinical studies.
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