Peripheral Flow Response to Transient Arterial Forearm Occlusion Does Not Reflect Myocardial Perfusion Reserve

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Background—Ultrasonographic evaluation of systemic arterial function is widely available, and a close relation of endothelial function in the coronary and brachial arteries has been documented. It is unknown, however, whether a similar correlation exists for their 2 microcirculatory territories and thus whether assessment of the systemic microcirculation can be used similarly as a surrogate marker of myocardial perfusion.

Methods and Results—Twenty-three patients with documented coronary artery disease (CAD; 66±9 years old, 18 men), 16 patients with syndrome X (SX; 56±5 years old, 13 women), and 45 healthy control subjects (C; 34±9 years old, 22 men) were studied. Myocardial perfusion was measured at rest and after dipyridamole (0.56 mg · kg⁻¹ · min⁻¹ over 4 minutes) by PET, and brachial artery blood flow was measured at rest and after transient forearm ischemia by standard Doppler ultrasound techniques. Dipyridamole increased myocardial perfusion in all groups (mL · g⁻¹ · min⁻¹: CAD, 0.89±0.27 versus 1.62±0.67, P<0.001; SX, 0.82±0.16 versus 1.67±0.49, P<0.001; and C, 0.82±0.15 versus 2.32±0.64, P<0.001). Postocclusion forearm flow increased similarly in all groups (CAD, 52±18 versus 174±77 mL/min, P<0.001; SX, 49±29 versus 202±82 mL/min, P<0.001; and C, 61±34 versus 229±108 mL/min, P<0.001). No significant correlations were found between peripheral and myocardial microcirculatory beds for either resting flow, hyperemic flow, or flow reserve in any of the groups (r²<0.1, P=NS).

Conclusions—The peripheral perfusion responses to transient forearm ischemia do not correlate with dipyridamole-induced myocardial hyperemia. The lack of correlation indicates different mechanisms of microvascular activation or regulation and confirms that extrapolations between findings in the 2 vascular beds are not suitable. (Circulation. 2001; 103:1109-1114.)

Key Words: ultrasonics microcirculation perfusion vasodilation blood flow

Ultrasonographic evaluation of systemic arterial dilatory function is widely available and has been proposed as a possible means to detect early signs of atherosclerosis. The technique is based on the assessment of endothelium-dependent and -independent vasomotor responses and has confirmed the association between vascular risk factors and endothelial dysfunction in large systemic conduit arteries such as the brachial artery. The use of this technique has gained further momentum, having now confirmed the close concordance in vascular reactivity in systemic and coronary arteries, and brachial artery responses as surrogate markers for the coronary artery involvement are now being used to assess the potential benefit of various therapeutic interventions.

Patients with coronary artery disease (CAD) risk factors such as hypercholesterolemia and diabetes mellitus exhibit not only large-vessel dysfunction but also microvascular dysfunction, eg, reduced responses to such vasoactive substances as adenosine and dipyridamole. Whether a functional correlation similar to that observed for endothelial function in the brachial and the coronary arteries also exists for the forearm and myocardial microvasculature is unknown.

The aim of this study, therefore, was to investigate whether a correlation exists between the peripheral perfusion reserve and the myocardial perfusion reserve. For this purpose, patients with documented CAD, patients with microvascular disease (syndrome X, SX), and young healthy control subjects were studied.

Methods

Study Population

The study population comprised 84 subjects. Group 1 included 23 patients (66±9 years old, 18 men) with either angiographically documented CAD or prior myocardial infarction with a left ventricular ejection fraction ≤40%. Current medications were continued in this group, and short-acting nitroglycerin was allowed up to 6 hours before both studies. Clinical characteristics are listed in Table 1. Group 2 included 16 patients with SX (56±5 years old, 3 men), ie, patients with typical exertional chest pain, positive exercise ECG...
Measurement of Myocardial Perfusion

Intravenous $^{13}$N-ammonia was used as flow tracer for dynamic PET. Twelve-lead ECG was monitored throughout each study. Heart rate (HR) were used for calculating the rate-pressure product (RPP=SBP×HR).

The dynamic imaging sequences were obtained with a positron emission tomograph (model EXACT HR 961, Siemens/CTI) with a 15-cm field of view that acquires 47 transaxial planes (plane separation 3.125 mm). The quantification of myocardial perfusion has been described previously.9 In brief, $^{13}$N-ammonia (740 MBq [20 mCi] diluted in 20 mL saline) was injected intravenously over 30 seconds while acquisition of a dynamic sequence of images (12 frames of 10 seconds) to obtain time-activity curves from the blood pool and from the myocardial tissue was started. In 3 midventricular planes of the static images, 3 regions of interest were placed within the left ventricular myocardium in the 3 territories of the major coronary arteries. These regions of interest were subsequently copied to the dynamic image sequence. In this way, myocardial tissue time-activity curves for $^{13}$N-ammonia were obtained.9 The arterial input function was obtained from a small region of interest in the left ventricular blood pool. The effect of partial volume was correction for by assuming a uniform left ventricular wall thickness of 1 cm.10 Reproducibility has been assessed previously.11 Myocardial perfusion was calculated by fitting the corrected tissue and blood pool time-activity curves to a validated 2-compartment model for $^{13}$N-ammonia.12 In the CAD patients, myocardial perfusion was measured in a myocardial region showing normal resting perfusion and no stress-induced hypoperfusion (reversibility) during dipyridamole testing. In the patients who had undergone angiography, it was checked that the supplying vessel did not show a significant stenosis (<30% luminal stenosis).

**Measurement of Brachial Artery Blood Flow**

Brachial artery flow was measured ultrasonographically at baseline and after postocclusion hyperemia. A detailed description of the method and its reproducibility has been published.1,13 The artery was scanned longitudinally 2 to 15 cm above the elbow with a 7-MHz transducer (Acuson 128 XP-10). Doppler measurements were obtained with the pulsed Doppler sample volume placed in the center of the vessel, adjusted for optimal flow-velocity tracings. After a baseline scan, a pneumatic tourniquet placed around the forearm was inflated to 250 mm Hg. After 270 seconds, the cuff was deflated while scanning was continued for another 30 seconds. Because flow tracings and 2D images could not be displayed simultaneously, flow velocities were recorded immediately before switching to image...
mode. For the postocclusion scan, flows were recorded for the first 15 seconds before switching to diameter recordings.

All scans were recorded on super-VHS tapes. Arterial diameters and flow-velocity integrals were measured from the tapes by 2 observers blinded to the scan sequence and the identity of the subject. Internal vessel diameters were measured from the anterior to the posterior interface (average of 4 measurements) between the media and the adventitia. Blood flow was calculated by multiplying the angle-corrected Doppler flow-velocity integral (mean of 4 measurements) by $\pi$ and the square of the radius of the artery.

### Study Protocol
All participants underwent 2 studies on 2 separate days in random order. On day 1, baseline myocardial perfusion was measured after $\geq$30 minutes rest and subsequently after dipyridamole infusion (0.56 mg · kg body weight$^{-1}$ · min$^{-1}$ over 4 minutes), with image acquisition starting 4 minutes after the dipyridamole infusion was discontinued.

On day 2, the brachial artery flow was measured at rest (baseline) and after reactive hyperemia.

### Statistical Analysis
Values are mean±SD. Paired $t$ test or the nonparametric Wilcoxon signed rank test was used to compare individual values (eg, rest versus dipyridamole flows or rest versus reactive hyperemia flows). Selection of parametric versus nonparametric methods was based on a normality test. Correlations were sought by standard linear regression (least squares). Differences were considered statistically significant at the 5% level.

### Results

#### Hemodynamic Values
Table 2 summarizes the hemodynamic measurements at baseline (PET and ultrasound) and during dipyridamole stimulation. Reliable blood pressure recordings could not be obtained during the immediate cuff deflation phase.

During dipyridamole infusion, a significant increase in heart rate, systolic blood pressure, and accordingly rate-pressure product was observed in all groups. In the control group, the baseline systolic blood pressure and rate-pressure product were higher at the PET study than at the ultrasound study.

#### Myocardial Perfusion and Brachial Artery Flow
Dipyridamole increased myocardial perfusion significantly in all 3 groups (mL · g$^{-1}$ · min$^{-1}$): CAD, 0.89±0.27 to 1.62±0.67; SX, 0.82±0.16 to 1.67±0.49; and Control, 0.82±0.15 to 2.32±0.64 ($P<0.001$ in all groups) (Figure 1). Postocclusion brachial artery flow also increased in all 3 groups (mL/min): CAD, 52±18 to 174±77; SX, 49±29 to 202±82; and Control, 61±34 to 229±108 ($P<0.001$ in all groups). The diameter of the vessels increased during reactive hyperemia in all 3 groups (mm): CAD, 3.90±0.73 to 3.99±0.71, $P<0.05$; SX, 3.78±0.76 to 3.90±0.74, $P<0.05$; and Control, 3.86±0.61 to 3.99±0.63, $P<0.05$. A correlation between the rate-pressure product and resting myocardial perfusion was found in all groups (CAD, $r^2=0.61$, $P<0.001$; SX, $r^2=0.25$, $P<0.01$; and Control, $r^2=0.28$, $P<0.0001$).

#### Correlation Between Stimulated Myocardial Perfusion and Brachial Artery Flow
The correlation between the maximal myocardial perfusion (mL · g$^{-1}$ · min$^{-1}$) and the maximal reactive brachial artery hyperemia (mL/min) is shown in Figure 2. No correlations were found in any of the 3 groups. Correlations were also sought between the myocardial perfusion reserve and the brachial artery flow reserve (Figure 3), but no significant correlations were found in any of the 3 groups.

#### Discussion
Recent years have seen an increasing interest in noninvasive assessment of vascular function. Ultrasound-based assessment of endothelial function in the brachial artery has gained particularly widespread acceptance, and endothelial dysfunction has been confirmed in subjects with atherosclerotic risk
factors. Although the brachial artery may not be considered an appropriate site for the total atherogenic burden, this artery is prone to develop significant atherosclerotic lesions that correlate with the extent of coronary arterial lesions. Similarly, endothelial dysfunction measured as reduced flow-mediated dilation in the brachial artery has been shown to correlate with endothelial dysfunction in the large coronary arteries as assessed by the response to vasoactive substances, such as acetylcholine. These findings suggest that peripheral surrogate markers for large coronary arterial function can be identified. In the myocardium, noninvasive evaluation of the coronary microcirculation can be performed with PET. A possible association between the vascular responses in 2 distinct vascular beds would be of importance, although neither would be sites for obstructive atherosclerosis per se. No studies, however, have compared microvascular responses in the coronary and peripheral circulation.

Venous occlusive plethysmography is the favored technique for assessment of peripheral microvascular function, but it is invasive. Studies have, however, confirmed a close relation between the vasodilator responses to vasoactive substances as assessed by venous occlusion plethysmography and flow changes occurring after transient cuff occlusion of the forearm as measured with Doppler technique. The present study in patients with microvascular or macrovascular disease and in normal control subjects, however, suggests that the correlation between vascular responses in the peripheral and coronary circulation seen for large vessels with 2 different stimuli does not extend to the microcirculation. Although similar directional changes were observed in the coronary circulation in response to dipyridamole and in the forearm circulation in response to transient flow occlusion, no significant association was seen for either the absolute flow or the flow reserve.

Resting myocardial perfusion depends on the coronary perfusion pressure. This has been demonstrated in several studies by a close correlation between the rate-pressure...
product and the myocardial perfusion and was confirmed in this study.9,16,17

A slight difference in the rate-pressure product was observed between the PET and ultrasound baseline studies in the control group. This finding may be explained by difference in time intervals allowed for rest before the scans or by variations in the blood pressure recordings. This difference would be expected to affect only the absolute myocardial and peripheral flow values but not any possible correlation between the 2 vascular beds.

Myocardial Perfusion and Brachial Artery Flows

A resting myocardial perfusion of 0.89 mL · g\(^{-1}\) · min\(^{-1}\) in the CAD patients is similar to previously reported values.9 Because myocardial segments supplied by a stenotic artery were excluded and scintigrams were checked to ensure that resting perfusion was normal and that dipyridamole did not induce relative hypoperfusion, these perfusion values were not affected by coronary stenosis. Raising myocardial perfusion is known to be affected by antianginal medications, particularly \(\beta\)-blockade,18 and this may have influenced perfusion values. As expected, hyperemic flow was also lower in the CAD patients than in the control subjects.19 In the SX patients, the resting flow was 0.82±0.16 mL · g\(^{-1}\) · min\(^{-1}\), as previously observed.20 With regard to the hyperemic flow, a significantly lower value was observed in the SX patients than in control subjects. The literature is not consistent on this.16,20–22 Because our groups were not matched for such factors as sex and age, results should be interpreted cautiously. It was not our aim to compare SX patients with control subjects, because this has been reported.16 In control subjects, the baseline and dipyridamole perfusion values were similar to previously reported values.8,18,23

The resting brachial artery flow and the 2- to 3-fold higher reactive hyperemic flow are normal responses.1,3,24 As was seen in the myocardium, SX patients showed a reduced hyperemic response compared with control subjects. In the CAD patients, the response to reactive hyperemia was also reduced compared with the control group. This finding has also been demonstrated in several studies and may be due to such factors as age, atherosclerosis, dyslipidemia, and possibly, medications.14,25

Several explanations might account for the lack of correlation between the 2 vascular beds. The number and properties of the microvessels in the 2 vascular beds are most likely different. For example, shunt vessels occur in the hand but are not seen in the myocardium.26 If forearm flow increase depends on recruitment of shunt vessels, the microcirculatory reactivity would be overestimated. Receptor occurrence and density may also differ between the 2 microcirculations, and the systems that are activated to induce hyperemia are likely to be different. In the myocardium, the hyperemic response is mediated via accumulation of adenosine and stimulation of adenosine A\(_2\) receptors.17,27 In contrast, ischemia-induced accumulation of vasodilating metabolites, such as CO\(_2\), is thought to be responsible for the increased flow after occlusion of the brachial artery. This assumption is based on studies showing that the addition of handgrip exercise to cuff occlusion increases the postocclusion vasodilatation, indicating that the degree of ischemia is of importance.28

To compare flow reserves in the 2 vascular beds, maximal vasorelaxation must be achieved in both. Leeson et al.29 examined the brachial flow response to increasing occlusion time intervals and found the hyperemic response to be maximal at 4.5 minutes of occlusion, as used in this study. For the myocardium, numerous attempts have been made to further increase the response to dipyridamole, but a double dose,17 addition of exercise30 and hand grip,17 or the use of direct adenosine receptor stimulation,27 have all failed.

Study Limitations

The 2 methods used to measure hyperemic responses have limitations. In the PET measurements, the myocardial wall thickness was assumed to be 1 cm. In the event of hypertrophy or infarction, this may introduce errors. SX and CAD patients, however, underwent detailed echocardiography to rule out abnormal wall thickness in the selected segments. In control subjects, the relatively young age, the inclusion criteria used, a normal blood pressure, and a normal scintigraphy yield a probability of hypertrophy or CAD of <5%. Measurement of absolute brachial artery flow with Doppler techniques have several inherent limitations, but relative flow changes are likely to be assessed accurately. The fact that measurements of peripheral and coronary perfusion were not performed simultaneously is a potential source of inaccuracy.
It could be seen as a limitation that 2 different stimuli were used to induce hyperemia. However, the aim of the study was to compare the 2 established methods rather than comparing regional responses to occlusive hyperemia and dipyridamole. Global occlusive ischemia is not an option in the heart, and the use of dipyridamole to induce forearm hyperemia could be influenced by the generalized effects on the heart and the peripheral vascular system, eg, increase in heart rate and sympathetic activation.

In the CAD group, patients were kept on their usual medication. We cannot rule out that medication selectively affected the dilatory reserve in the heart or the forearm. Because most of the patients had severe CAD and depressed LV function and received several different drugs, we chose to continue usual medication to maintain stable conditions during the studies.

Conclusions
Brachial artery perfusion reserve expressed as hyperemic flow after reactive hyperemia does not correlate with the dipyridamole-induced myocardial hyperemia. The lack of correlation between the 2 vascular beds indicates different mechanisms controlling peripheral and myocardial microcirculation during these 2 different stimulations. Direct extrapolation between the 2 vascular beds by the 2 techniques is therefore not suitable.

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References
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