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Relationship between Peipheral and Coronary Function Using Laser Doppler Imaging and Transthoracic Echocardiography

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Abstract

Vascular dysfunction in the coronary and peripheral circulations is an early prognostic marker of future cardiovascular events. Measurements of coronary and peripheral vascular function in resistance vessels can be made but rely on invasive procedures, which make them unsuitable for routine application. Aa assessment of the direct correlation between vascular responses in skin and coronary vessels has not been made previously. In 27 normal, healthy subjects (18 to 55 years old), we examined the relationship between peripheral and coronary vascular function. Cutaneous perfusion was measured using the non-invasive technique of laser Doppler imaging during iontophoresis of acetylcholine and sodium nitroprusside, and cutaneous vascular conductance was calculated (laser Doppler perfusion/mean arterial pressure). Coronary flow reserve was measured using transthoracic echocardiography during intravenous adenosine infusion. Mean diastolic velocities were measured at baseline and at peak hyperaemic conditions from the Doppler signal recordings. Coronary velocity reserve (CVR) was defined as the ratio of hyperaemic to basal mean diastolic velocities. There were significant positive correlations between coronary velocity reserve and cutaneous vascular conductance for acetylcholine (r=0.399, P=0.039) and for sodium nitroprusside (r=0.446, P=0.020). These results support the idea that peripheral measurements of skin blood flow are representative of generalised microvascular function including that of the coronary circulation in normal healthy subjects.

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Introduction

There is compelling evidence for the association between vascular dysfunction in the coronary or peripheral circulation and both atherosclerotic risk and future cardiovascular (CV) events [1,2], such as death, myocardial infarction, ischaemic stroke and the need for revascularisation procedures [3,4]. The ability to detect changes in areas away from the coronary and cerebral circulation, where the events actually occur, highlights the systemic nature of vascular dysfunction.

Several methods are available for assessing vascular function, such as ultrasound of the brachial artery and pulse wave analysis, but these provide a measure of large vessel function. Assessment of microvascular function is required since it plays an important role in many conditions, such as end-stage renal disease, diabetes and connective tissue diseases. Laser Doppler studies of the cutaneous circulation have provided valuable information regarding mechanisms of microvascular dysfunction [5,6]. As with any assessment of the peripheral vasculature, the question arises whether such measurements correlate with those in the coronary circulation. Sax et al., using plethysmograpghic assessments of the forearm, showed that peripheral vascular responses correlated with those in the coronary circulation in patients with microvascular angina [7]. Increased coronary heart disease score is associated with impaired skin microvascular responses, both endothelium-dependent and endothelium-independent [8], and patients with coronary vessel disease have been found to exhibit abnormalities of the cutaneous microcirculation [9,10]. While associations have been shown between coronary artery disease and skin microvascular function, a direct correlation between vascular responses in the coronary and skin circulation has not been studied in normal healthy subjects.

Recently, there has been increasing interest in the non-invasive assessment of coronary flow reserve using transthoracic Doppler echocardiography (TTDE) [11-13]. This technique has been used to measure coronary velocity reserve in stenosed

and normal epicardial coronary arteries [14-17]. Studies show that the epicardial coronary response to adenosine may be a surrogate marker of coronary resistance vessel dysfunction [18].

The combination of laser Doppler flowmetry and TTDE provides an ideal opportunity to non-invasively examine the direct relationship between peripheral and coronary resistance vessel function in normal healthy subjects. Our hypothesis was that coronary velocity reserve measured using TTDE in subjects with normal epicardial coronary arteries would be related to peripheral microvascular function, measured using laser Doppler imaging.

Methods

Subjects

Twenty-eight healthy, non-smoking, subjects (18 to 55 years old) were recruited from the student and staff population of the hospital. Subjects initially attended for a screening visit to determine their suitability to take part in the study. Written, informed consent was obtained at this visit. The study conformed to the standards set by the Declaration of Helsinki. Ethical approval for the study was obtained from the local ethics committee. On the day of study, subjects arrived having refrained from food and drink for at least 3 hours and avoided caffeine containing beverages for at least 12 hours.

Assessment of coronary function

Measurements of coronary flow velocity were carried out by an experienced echocardiographer who was blinded to the information on peripheral microvascular function. We have significant experience with this technique [11,14,18]. Imaging of the left anterior descending (LAD) artery and perforating branches and measurement of coronary blood flow was carried out at rest and after intravenous adenosine. We used a 7.0 MHz transducer (Acuson Sequoia 512, Siemens Medical Solutions, Berkshire, UK). In colour Doppler flow mapping, velocity range was set in the range of ±12 cm/s. The colour gain was adjusted to provide optimal images. The ultrasound beam was transmitted towards the heart to visualize coronary blood flow in the LAD coronary artery by colour Doppler echocardiography. First, the left ventricle was imaged in the long-axis cross section, and the ultrasound beam was inclined laterally. Next, coronary blood flow in the distal portion of the LAD coronary artery was searched for under the guidance of colour Doppler flow mapping. With a sample volume (2.5 or 3.0 mm wide) positioned on the colour signal in the LAD coronary artery, Doppler spectral tracings of flow velocity in the LAD artery was recorded by fast Fourier transformation analysis. Although we try to align the ultrasound beam direction to distal LAD coronary artery flow as parallel

as possible, angle correction is generally needed in each examination because of incident Doppler angle (mean angle 42°, range 31° to 58°). We first recorded baseline spectral Doppler signals in the distal portion of the LAD coronary artery over five cardiac cycles at end-expiration. Intravenous adenosine was then administered ($140\mu g/kg^{-1}/min^{-1}$) for 2 minutes to record spectral Doppler signals during hyperaemic conditions. Mean diastolic velocities were measured at baseline and at peak hyperaemic conditions from the Doppler signal recordings. Measurements were then averaged over three cardiac cycles. Coronary velocity reserve (CVR) was defined as the ratio of hyperaemic to basal mean diastolic velocities. The inter-observer and intra-observer variability for measurement of coronary Doppler velocity recordings in our laboratory are 4.9% and 4.0%, respectively determined from measurements made in 6 subjects on 2 separate occasions.

Assessment of peripheral vascular function

Measurements were conducted in a laboratory set at 22 ± 1 °C. Participants were seated comfortably with their arms supported at heart level. Microvascular function was assessed non-invasively in the forearm skin as described by us previously [19]. We measured skin blood flow responses to iontophoresis of acetylcholine (ACh; Sigma-Aldrich Co. Ltd, Poole, UK) and sodium nitroprusside (SNP; David Bull Laboratories, Warwick, UK), which are endothelium-dependent and endothelium-independent vasodilators, respectively. ACh and SNP were made up as 1% solutions in deionised, sterile water and iontophoresed using anodal and cathodal currents, respectively. ACh and SNP were delivered using consecutive increases in current; 10, 15, 20, 50 and 100 μAmps, with each current being applied for 4 minutes. Using large electrodes (internal diameter = 20mm), this sequence of delivery currents, in our experience, does not cause any non-specific electrical effects. The resulting change in microvascular skin blood flow, termed laser Doppler flux and measured in perfusion units (PU), was assessed using laser Doppler imaging (moorLDI; Moor Instruments Ltd, Axminster, UK). A measure of the overall microvascular response

was determined for the total drug delivery period by calculating the area under the perfusion x time curve (AUC) over baseline. Cutaneous vascular conductance was calculated as AUC divided by mean arterial pressure. The reproducibility of this technique in our hands, determined from repeat measurements on 2 separate occasions at least 1 day apart in 8 subjects, is 11%.

Statistical analysis

Values are expressed as means ± 1SD, unless stated otherwise. All data were normally distributed. The univariate association between CVR and peripheral microvascular function was tested using Pearson's correlations. A P value of < 0.05 was considered significant. All analyses were performed using SPSS statistical package (version 13).

Results

Satisfactory measurements were obtained in 27 subjects for CVR, and in all 28 subjects for iontophoresis and laser Doppler imaging. Table 1 summarises the measurements for CVR, laser Doppler imaging and haemodynamic parameters in the 27 subjects that completed both parts of the study. Figure 1 shows a spectral Doppler tracing of the LAD coronary artery flow at baseline and during adenosine-induced hyperaemia. Heart rate increased significantly during adenosine infusion (62.7 ± 8.9 to 76.2 ± 14.7 beats/min, P<0.001), although there was no association between this change and microvascular responses to ACh (P=0.212) or SNP P=0.649). There was no significant change in systolic and diastolic blood pressure during adenosine infusion (Table 1).

There were significant positive correlations between CVR and ACh AUC (r=0.434, P=0.024) and SNP AUC (r=0.362, P=0.042). Additionally, CVR was positively correlated with both ACh cutaneous vascular conductance (r=0.399, P=0.039) (Figure 2) and SNP cutaneous vascular conductance (r=0.446, P=0.020) (Figure 3). After adjusting for gender, age and BMI, there was a reduced, but still significant, association between CVR and ACh AUC (r=0.312, P=0.047) and SNP AUC (r=0.402, P=0.042.

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Discussion

Previous reports have shown an association between the peripheral and coronary circulations, but this correlation has been largely confined to studies that have used invasive procedures [7]. Although, laser Doppler imaging can be used non-invasively to assess peripheral microvascular function [19], and provide a good measure of generalised microvascular function [5,6], a direct comparison with coronary resistance vessels function has not been made. Very few studies have tested the direct association between resistance vessels in the peripheral and coronary circulations of normal healthy subjects, mainly because it has not been possible to measure coronary function in subjects in whom coronary angiography is not indicated.

Our findings that vascular responses in the forearm skin microvessels correlate with coronary velocity reserve support the idea that the function of peripheral and coronary resistance vessels is indeed related, and that assessment of peripheral vascular function using laser Doppler imaging can provide an indication of coronary vascular function, at least in healthy subjects. Further studies are needed to determine whether this relationship holds for subjects with established microvascular disease. Our findings in normal subjects contrast with those of Bøttcher and colleagues [20] who found no association, perhaps because the techniques for assessing the peripheral resistance vessels were different in the 2 studies. Additionally, differences in the size of vessels studied by Bøttcher and colleagues (coronary resistance vessels verses brachial artery function) may have accounted for this discrepancy [20].

We used TTDE to measure coronary flow reserve, which has shown to accurately reflect similar measurements obtained using invasive Doppler guide-wire [12]. Without estimation of the coronary artery diameter, the technique only allows measurement of coronary flow velocity, but not changes in coronary flow. However,

it has been shown that coronary flow reserve measured using both parameters is closely related [11]. In the absence of obstructive coronary artery disease, coronary velocity reserve in response to adenosine infusion provides a measure of the function of coronary resistance vessels. A reduced coronary flow reserve has been reported in women with chest pain [21], in young female patients with systemic lupus erythematosus [18], and in patients with systemic sclerosis [22], all in the absence of obstructive coronary artery disease. Coronary flow reserve may be abnormal when the resistance vessels are compromised by left ventricular hypertrophy, coronary endothelial dysfunction or other diseased rheological conditions.

Although studies using laser Doppler flowmetry do not conform to a single standardised protocol, making between study comparisons complex, it is nevertheless a relatively simple technique to use, which suffers less from user dependency, and is technically less challenging than other methods, such as assessment of brachial artery reactivity [23]. The combination of laser Doppler flowmetry and iontophoresis has been used successfully by us and other researchers to demonstrate microvascular dysfunction in several conditions [19,24-26], and the good reproducibility of the technique has been confirmed [24,27]. Importantly, changes in skin microvascular function are detectable in children with risk factors for cardiovascular disease, well before clinical presentation of symptoms [19,28], thus making laser Doppler flowmetry a useful potential tool for early detection of cardiovascular risk. Additionally, subtle changes in skin microcirculation can be detected following therapeutic intervention [29].

Data from other studies also demonstrate that peripheral assessments of skin microvascular function do relate to coronary vascular function and to coronary heart disease risk. Jadhav et al. found that skin microvascular responses were markedly impaired in cardiac syndrome X patients who have angiographically normal

coronary arteries, and also demonstrated the predictive value of the technique by showing an odds ratio for cardiac syndrome X of 7.38 [25]. Skin microvascular responses are decreased in patients with angiographically demonstrated coronary artery disease [10] and with higher cardiovascular risk scores in healthy individuals [30].

A limitation of the study is the relatively small sample size and a stronger association might have been achieved with a larger sample size. Based on our correlation, approximately 16-20% of the change on one variable could be explained or accounted for by a change in the other variable. While we accounted for confounders, such as age, gender and BMI, other confounding cardiovascular risk factors were not accounted for and the lack of these might explain the relative weakness of the association.

We also did not obtain a measure of resistance vessel structure such as minimal vascular resistance, which can be determined by measuring the blood flow response to maximal reactive hyperaemia. We did not measure this in the current study because the laser Doppler imager does not have the required speed to accurately measure this response. Furthermore, the main purpose of this study was to assess the association of coronary function with that of a commonly used method for assessing the skin microvascular response, and one that shows good reproducibility using the imager system. Using a single point laser Doppler flowmeter which continuously measures skin blood flow, but from a relatively very small sample area compared with the imager, we have shown in our pilot studies in 20 normal subjects, that the skin maximal hyperaemic response is highly correlated with laser Doppler imager measurements of skin vascular responses to ACh ($r=0.84$, $P<0.0001$) and SNP ($r=0.77$, $P<0.0001$). Thus, we believe it is likely that the maximal skin hyperaemic response would also correlate with CVR.

Our association between peripheral skin and coronary vascular function only applies to healthy subjects and we cannot extrapolate these findings to patient populations. In normal healthy subjects it is assumed that changes in flow velocity reflect coronary microvascular function and are not related to epicardial disease, which of course might not be the case in an older population with risk factors for coronary artery disease. Nevertheless, establishing this direct association between skin and coronary vasomotor function in normal subjects is important because it lends support to the use of the skin as useful vascular bed to study normal physiological control mechanisms, which are required in order to understand the how the microcirculation because altered in disease states.

Invasive techniques have been proven to be sensitive and specific for assessment of CV risk, but have limited practical value for routine use. Laser Doppler imaging has the advantage of being relatively easy to use with less operator dependency than other techniques, and is less expensive. Additionally, its completely non-invasive nature makes it well suited for studies in all age groups including young children and infants.

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Table 1. Subject characteristics, haemodynamic variables and values for measurements of peripheral microvascular function using laser Doppler imaging, and coronary flow using transthoracic echocardiography.

Characteristic	Mean ± SD
Age (years)	26.3 ± 10.5
Male/female	17/10
Height (cm)	165.2 ± 7.9
Weight (kg)	68.1 ± 12.7
Baseline heart rate (beats/min)	62.7 ± 8.9
Baseline systolic blood pressure (mmHg)	124.5 ± 8.8
Baseline diastolic blood pressure (mmHg)	71.8 ± 8.7
Baseline mean arterial pressure (mmHg)	85.1 ± 14.7
Peak heart rate during adenosine (beats/min)	76.2 ± 14.7
Systolic blood pressure after adenosine (mmHg)	122.7 ± 11.1
Diastolic blood pressure after adenosine (mmHg)	72.2 ± 8.1
Baseline diastolic velocity (m/s)	0.22 ± 0.06
Peak diastolic velocity during adenosine (m/s)	0.85 ± 0.27
Coronary flow velocity reserve	3.73 ± 0.72
ACh AUC	1796 ± 169
SNP AUC	1190 ± 121
ACh cutaneous vascular conductance ($mmHg^{-1}$)	21.4 ± 2.1
SNP cutaneous vascular conductance ($mmHg^{-1}$)	13.8 ± 1.3

PU arbitrary perfusion units, ACh acetylcholine,
SNP sodium nitroprusside, AUC area under curve over baseline

Figure 1. Spectral Doppler tracing of the LAD coronary artery flow at baseline (left) and during adenosine-induced hyperaemia (right).

Figure 2. Correlation between coronary flow velocity reserve during adenosine infusion and the cutaneous vascular response to acetylcholine in 27 subjects (r=0.399, P=0.039).

Figure 3. Correlation between coronary flow velocity reserve and the cutaneous vascular response to sodium nitroprusside in 27 subjects (r=0.446, P=0.020).

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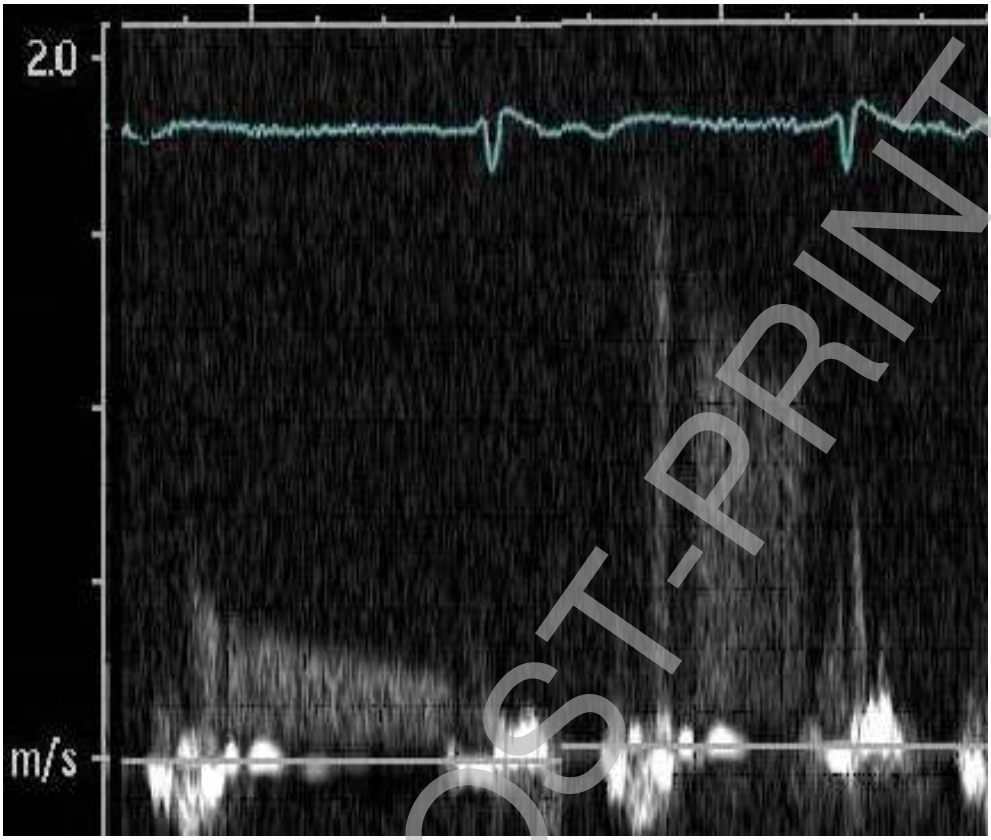

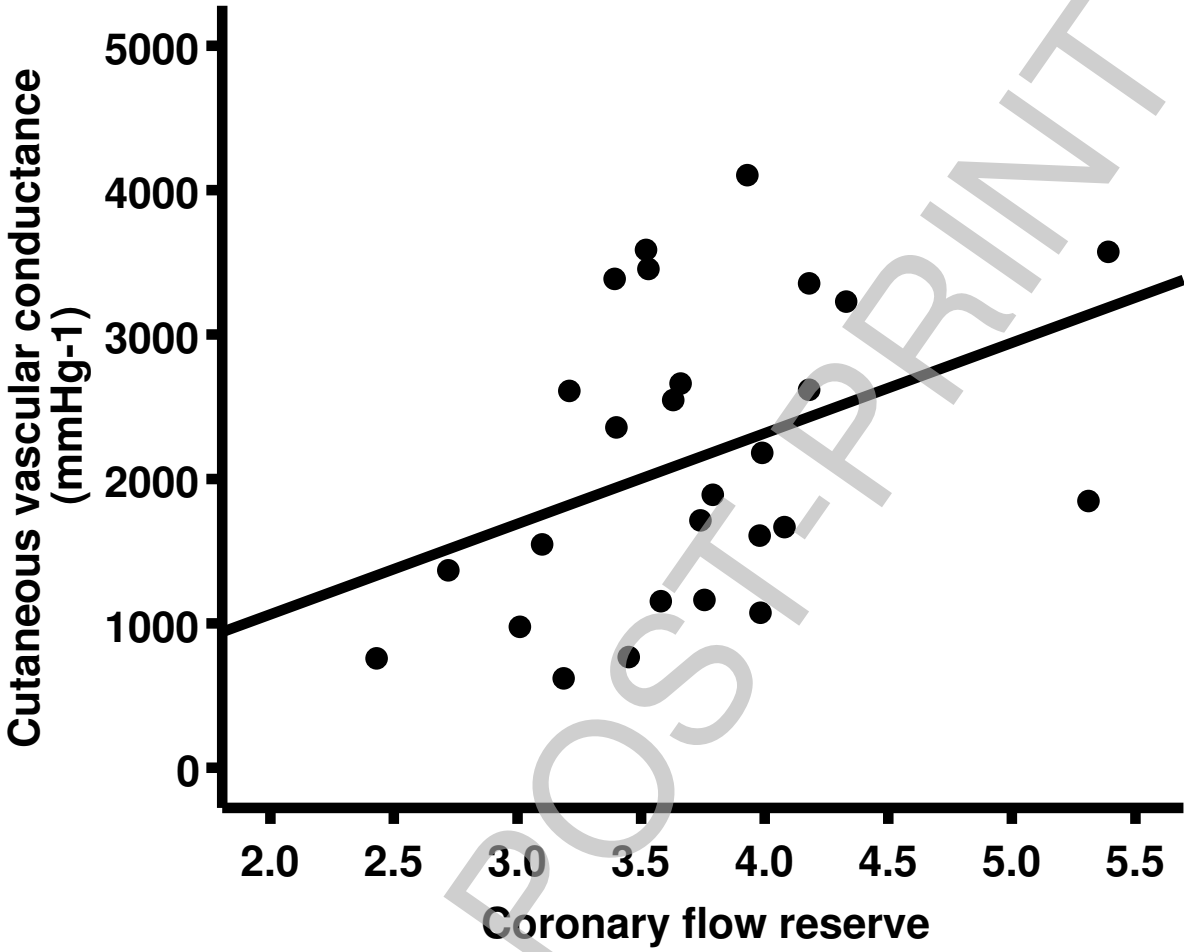

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