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Cardiac Imaging

Quantitative Hyperemic Reactivity in Opposed Limbs During Myocardial Perfusion Imaging

A New Marker of Coronary Artery Disease

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OBJECTIVES We sought to evaluate the feasibility and validity of a new method to quantify the hyperemic response of the forearms that can be incorporated into a rest myocardial perfusion protocol.

BACKGROUND Evaluation of the hyperemic response could provide useful clinical information in the detection and risk stratification of atherosclerotic vascular disease.

METHODS Patients with proven coronary artery disease (CAD) (n = 46) were compared with low-risk subjects without such evidence (n = 47). A regular dose of Myoview was injected after 5 min of right arm ischemia. Three dimensionless parametric ratios (right/left) were derived from the analysis of activity-time curves of the hyperemic right forearm and that of the contralateral left forearm.

RESULTS The maximal ingress upslope ratio was 40% lower in the CAD group (3.0 ± 0.2 vs. 4.2 ± 0.3, $p < 0.0005$), and the integral to peak ratio was also lower (23 ± 4 vs. 52 ± 11, $p < 0.01$), whereas the peak activity ratio was nonsignificantly lower (3.0 ± 0.3 vs. 3.8 ± 0.3, $p = 0.07$). Using a value of 3.55 for the maximal upslope ratio, this approach could predict the presence of CAD with a sensitivity of 0.70 and a specificity of 0.60.

CONCLUSIONS This simple and noninvasive method is feasible and can discriminate between patients with known CAD and those at low risk of atherosclerosis. Refinements of this approach and its inclusion in larger clinical trials are needed to determine whether it could provide additional value to myocardial scintigraphic imaging. (J Am Coll Cardiol 2004;44:1473–7) © 2004 by the American College of Cardiology Foundation

The reactive hyperemic response corresponds to an increase in blood flow after the relief of a period of ischemia. Various clinical approaches have been used in an effort to quantify this response and its physiologic determinants in the upper or lower limbs (1–3), the skin (4), the finger tips, and the nailbeds (5). A method that is rapidly gaining in popularity is the ultrasound measurement of flow-mediated dilation (FMD) of the brachial artery during reactive hyperemia (6). A reduced percent increase in brachial artery diameter, which is modulated by the integrity of the vascular endothelium, relates to risk factors for coronary artery disease (CAD), as well as to the presence of CAD itself, and is predictive of future cardiovascular events (6).

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These methods of evaluation of the hyperemic response, however, require specialized equipment and/or technical skills not currently readily available in most centers. We have developed a novel noninvasive method to evaluate the reactive hyperemic response that can be performed during the same session of a rest myocardial perfusion study. The approach is based on the intravenous injection of the myocardial perfusion agent Myoview and the simultaneous noninvasive external detection of the tracer ingress and transit into both forearms: the one submitted to reactive hyperemia and the contralateral non-hyperemic one. This noninvasive method would allow for repeated measurements, minimize human intervention, and provide numerical data allowing precise quantification, and, most importantly, it has the potential of easy incorporation into any center with nuclear medicine facilities.

The present study was therefore designed to validate the feasibility and explore the potential clinical utility of the determination of the scintigraphic hyperemic reactivity (SHR) by comparing a group of patients with known CAD to a low-risk group with no known CAD.

METHODS

The study protocol had been approved by the Research and Ethics Committee of the Montreal Heart Institute, and all subjects gave informed consent. Subjects were included if they were adults over 40 years old. Postmenopausal women not on hormonal replacement therapy could be included.

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Abbreviations and Acronyms

CAD = coronary artery disease
FMD = flow-mediated dilation
HDL = high-density lipoprotein
ROC = receiver operating characteristics
SHR = scintigraphic hyperemic reactivity
SPECT = single-photon emission computed tomographic

Subjects were excluded if they had known heart failure with an ejection fraction <40%, signs of peripheral artery disease in the upper limbs as evidenced by a >20 mm Hg blood pressure difference between arms, and a recent (<10 days) acute coronary syndrome. Premenopausal women were also excluded.

The CAD group (n = 46) was recruited among patients referred for myocardial scintigraphy at the Montreal Heart Institute. They all had previous evidence of CAD, as demonstrated by at least one of the following: revascularization procedure by surgery or angioplasty, acute coronary syndrome, and/or documented significant CAD by angiography or myocardial scintigraphy. The control group (n = 47) was recruited from health-conscious members of a health fitness facility affiliated with the Montreal Heart Institute. These subjects all had a negative symptom-limited exercise stress test. With the possible exception of older age, they were not included if they had more than one other known traditional risk factor for CAD. In this group, only a rest myocardial study was performed.

The SHR study was thus performed before the rest myocardial imaging study, taking advantage of the same injection of the myocardial perfusion agent technetium-99m–tetrofosmin (Myoview). A standard single-photon emission computed tomographic (SPECT) myocardial perfusion imaging at rest was carried out about 45 min later in all cases.

Scintigraphic forearm blood flow measurement procedures. The procedure used to determine SHR has been granted protection by the U.S. patent office (patent no. US-6445945). In a sitting position, both arms are extended over the top of a large field-of-view gamma camera facing upward, hands prone. The right upper arm was instrumented with a blood pressure cuff, and occlusion of arterial flow was achieved by rapidly inflating the cuff to 50 mm Hg higher than the systolic pressure for 5 min. After sudden release, a 30-s lag period was observed before injecting Myoview (0.42 mCi/kg) in a small catheter positioned in the bend of the left arm. Allowing for an estimated 30 s of circulation time delay, the timing was targeted to reach the detector at the moment corresponding to the maximum FMD detected using ultrasound probes (60 s). Dynamic images acquisitions were realized using 128 × 128 matrices at a sampling rate one frame per second for 10 min.

Archiving and data parameters analysis. Regions of interest over the two forearms, limited by the bend of the arm and excluding the wrist, were determined. The dynamic studies, together with the activity-time curves generated, were transferred to a standard personal computer environment. The raw activity-time curves were filtered, displayed, and analyzed using a proprietary software. Parameters indicative of the SHR were computed as the ratio of the hyperemic right arm over the control left arm (see Results section). The variability of this method was determined in 15 subjects on two consecutive days. The values for the ratio of maximal upslope were 5.3 ± 0.8 on day 1 and 4.9 ± 0.5 on day 2 (mean ± SEM), with an absolute difference of 1.33 ± 0.21 and a correlation coefficient of 0.89.

Statistical analysis. Comparisons of parameters between the CAD and control groups were evaluated by the two-tailed *t* test for continuous variables and the chi-square test for non-continuous variables. All data are presented as the mean value ± SEM. All analyses, including receiver operating characteristics (ROC) curves, were performed with the NCSS statistical package.

RESULTS

Demographic, physiologic, and biochemical parameters are shown in Table 1. Patients in the CAD group were about six years older. Systolic blood pressure in both arms was higher in the CAD group. Ejection fraction and other left ventricular parameters derived from myocardial SPECT imaging were similar in both groups. High-density lipoprotein (HDL) cholesterol was lower in the CAD group, whereas triglycerides were higher. The ratio of total/HDL cholesterol and levels of blood glucose and creatinine were all higher in the CAD subjects. Patients in the control group did not take any cardiovascular medications.

Typical examples of Myoview activity-time curves and scintigraphic imaging during SHR in the hyperemic right arm and non-hyperemic left arm of a control subject are shown in Figure 1A. Tracer activity in the hyperemic right arm appears first, displays a steeper slope, and reaches a higher peak than that in the non-hyperemic left arm. By comparison, an example taken from a patient with CAD (Fig. 1B) displays a less pronounced difference in the slopes of both arms, as well as peak tracer activity attained.

Based on the appearance of these curves and in order to quantify the hyperemic response of the right arm as compared with the control left arm, three dimensionless parametric ratios were derived: the ratios of the peak activities, of the maximal rate of rise of activities (upslope), and of the integral of the activity-time curves up to the peak activity of the hyperemic right arm. Consequently, these ratios should depart from unity in relation to the importance of the hyperemic response. In the particular example of a control subject (Fig. 1A), the parametric ratios were 6.0 for the peak activity, 7.7 for maximal slopes, and 344 for the integral, as compared with 1.3, 1.5, and 11 for the same parametric ratios in the CAD subject (Fig. 1B).

The mean ratio of peak activities (Fig. 2B) was lower in

Table 1. Sociodemographics and Clinical Description of Sample

	CAD Group	Control Group	p Value
Sociodemographics			
Age (yrs)	63.7 ± 1.5	56.5 ± 1.5	<0.001
Gender (M/F)	43/3	41/6	>0.3
Physiologic			
Blood pressure (mm Hg)			
Systolic			
Right	134 ± 3.6	121 ± 2.0	<0.001
Left	137 ± 3.7	122 ± 1.9	<0.0007
Diastolic			
Right	70 ± 1.6	71 ± 1.5	>0.5
Left	71 ± 1.6	70 ± 1.7	>0.8
End-diastolic volume (ml)	124.6 ± 5.7	113.3 ± 3.9	>0.1
End-systolic volume (ml)	60.0 ± 4.7	51.0 ± 2.5	>0.09
Stroke volume (ml)	64.4 ± 2.1	62.3 ± 1.7	>0.4
Ejection fraction (%)	54.2 ± 1.8	56.1 ± 1.0	>0.5
Weight (kg)	82.2 ± 2.1	79.6 ± 1.8	>0.4
Height (cm)	168 ± 1	167 ± 1	>0.7
Body mass index (kg/m^2)	28.8 ± 0.7	28.3 ± 0.5	>0.6
Biochemical			
Cholesterol total (mmol/l)	4.67 ± 0.16	5.00 ± 0.14	>0.1
HDL (mmol/l)	1.08 ± 0.03	1.43 ± 0.06	<0.000001
LDL (mmol/l)	2.70 ± 0.16	3.05 ± 0.12	>0.08
Triglycerides (mmol/l)	1.89 ± 0.16	1.28 ± 0.09	<0.002
Cholesterol/HDL	4.36 ± 0.16	3.76 ± 0.18	<0.01
Glucose (mmol/l)	6.62 ± 0.39	5.23 ± 0.08	<0.0005
Creatinine (mmol/l)	99.5 ± 3.2	91.4 ± 1.7	<0.03
C-reactive protein (mg/dl)	2.6 ± 0.6	3.0 ± 0.6	>0.5
Pharmacologic			
Beta-blockers	25 (61%)	NA	
Calcium blockers	14 (34%)	NA	
ACE inhibitors	17 (41%)	NA	
ASA	35 (85%)	NA	
Nitrates	9 (22%)	NA	
Lipid-lowering drugs	30 (73%)	NA	
ARB	4 (10%)	NA	
Coumadin	5 (12%)	NA	
Clopidogrel	2 (5%)	NA	

ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid; ARB = angiotensin receptor blocker; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable.

CAD patients (3.0 ± 0.3) compared with controls (3.8 ± 0.3), although this did not reach statistical significance ($p = 0.07$). The ratio of maximal upslopes (Fig. 2A) was 40% lower in the CAD patients (3.0 ± 0.2) compared with controls (4.2 ± 0.3, $p < 0.0005$). The ratio of the integrals up to the peak activity of the right arm (Fig. 2C) was about 50% lower in the CAD group (23 ± 4) compared with controls (52 ± 11, $p < 0.01$). Using a threshold value of 3.55, the ratio of the maximal slopes alone predicted the presence of known CAD with a sensitivity of 0.70 and a specificity of 0.60, with an area under the ROC curve of 0.70 (Fig. 3).

DISCUSSION

We evaluated the feasibility and potential clinical utility of testing the integrity of vascular reactivity using a novel noninvasive approach based on the reactive hyperemic response. The primary objective was to test the hypothesis that this new method that we called SHR would result in lower responses in a population with known CAD at high risk of cardiovascular events, as compared with a low-risk population without known CAD. Quantitative analysis revealed that the ratio of the maximal upslope between the hyperemic and the control arm best predicted whether subjects belonged to the CAD group ($p < 0.0005$). The increase in forearm blood flow during reactive hyperemia is a complex response modulated by several mechanisms, including the release of endothelium-derived vasoactive factors and adenosine (3,7–10), the activation of mechanical factors and neurogenic reflexes (11), and the modification of smooth muscle ion channels (1,12).

Different methods have been used and are being developed to noninvasively evaluate reactive hyperemia and its determinants in man. These include plethysmography, laser Doppler flowmetry, near infrared spectrometry, and transcutaneous oximetry. Other approaches include videophoto-

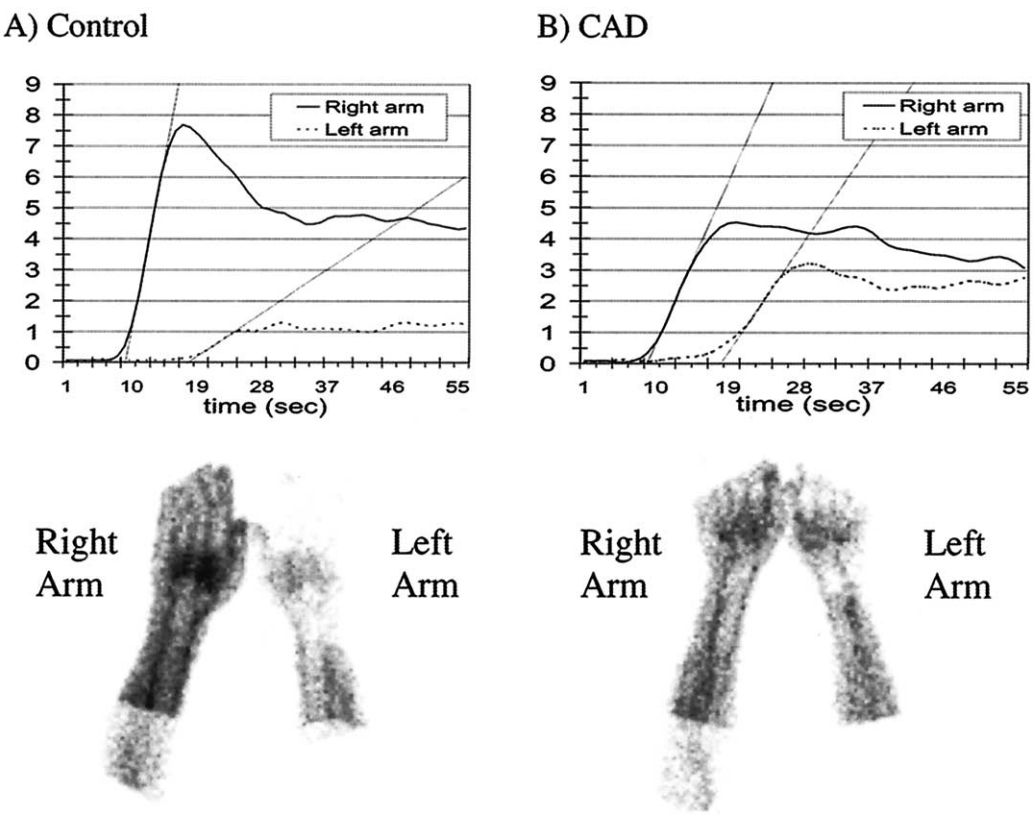

Figure 1. Typical example of scintigraphic hyperemic reactivity experiments from a control subject **(A)** and a patient with coronary artery disease (CAD) **(B)**. In the control subject, there is more intense tracer activity in the hyperemic right arm. The parametric ratios derived from the activity-time curves are higher in the control subject with a ratio of maximal upslopes between the hyperemic right arm over the control left arm of 7.7, a ratio of the peak activities of 6.0, and a ratio of integrals between t_0 and t_{max} of 344. The same values in the CAD patient were lower at 1.3, 1.4, and 11, respectively.

metric capillaroscopy of the nailbed and measurement of pulsatile variations in finger tip volume (5).

A method that is most rapidly gaining in popularity is the high-resolution ultrasound measurement of FMD of the brachial artery during the reactive hyperemic response (6). The maximal increase in the brachial artery diameter after the release of 5 min of forearm ischemia occurs after a mean of 1 min. Some recent trials have reported the potential value of the determination of FMD by brachial ultrasound as a predictor of future cardiovascular events. Brachial ultrasound, however, suffers from technical and interpretative limitations, which have thus far limited its use to research (6).

In the present experiments, in light of the potentially important clinical/practical value of an abnormal hyperemic response to predict future cardiovascular events, we explored another different approach to the evaluation of reactive hyperemia by taking advantage of the customary injection of Myoview for the resting phase of scintigraphic myocardial perfusion studies. We evaluated the SHR in the right hyperemic arm and used the non-hyperemic left arm as a control. We found marked significant differences of the order of 40% to 50% in the ratio of maximal upslopes and of

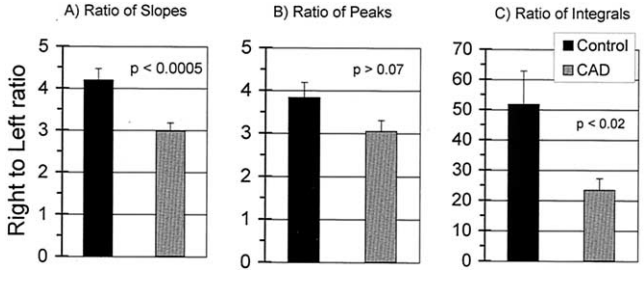

Figure 2. Mean values for the parametric ratios derived from the analysis of the activity-time curves of the hyperemic right arm divided by that of the contralateral left arm. CAD = coronary artery disease.

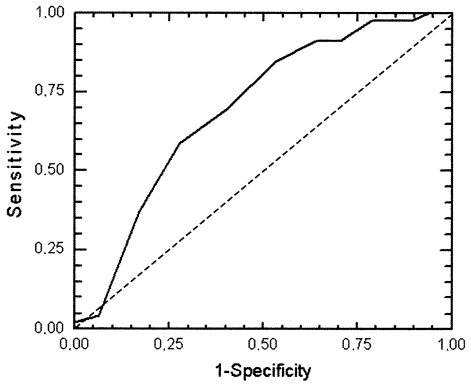

Figure 3. The receiver-operating characteristic curve of the predictive value the ratio of maximal upslopes during scintigraphic hyperemic reactivity for the detection of patients with proven coronary artery disease. Using a threshold value of 3.55, this parameter has a sensitivity of 0.70 and a specificity of 0.60 for the prediction of coronary artery disease.

the integrals of the time-activity curves during SHR. The ratio of the maximal upslopes between the arms was the most predictive of the presence of known CAD. Although the higher systolic blood pressure in the CAD group, with possibly higher systemic vascular resistance, may have affected our findings, the very small difference in blood pressure and the lack of correlation with the ratio of maximal upslopes ($r = -0.02$) suggest that this would be minimal, however.

The hyperemic response is determined by increased flow through modification of both small resistance vessels and larger conductance vessels. We measured the response at a time when maximal dilation of conductance vessels is known to occur, but after a peak increase in flow, which occurs immediately after cuff release. Although more studies are needed to understand the determinants of SHR, the respective role of conductance versus resistance vessels, and the optimal timing and analytical approach to the generated data, our results suggest a potential clinical utility of this method, which could be readily incorporated into any nuclear medicine department.

In order to perform the determination of SHR, we used the myocardial perfusion agent technetium-99m–tetrofosmin (Myoview). Use of a myocardial perfusion agent also confers potential advantages to SHR determination, as the test can be performed during the same session as the myocardial resting images, using the same injection. Whether additional diagnostic and prognostic information could be gained by simultaneous investigation of myocardial perfusion and endothelial function remains to be determined, but could easily be tested with this approach.

Conclusions. The SHR of the forearm can be evaluated at the same time as resting myocardial perfusion scintigraphy. This simple and noninvasive method can discriminate between patients with known CAD and those at low risk of atherosclerosis. Refinements of this approach and its inclusion in larger clinical trials are needed to determine whether SHR could provide additional value to myocardial scintigraphic imaging.

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