Simultaneous Noninvasive Assessment of Systemic and Coronary Endothelial Function

Micaela Iantorno, MD*; Allison G. Hays, MD*; Michael Schär, PhD; Rupa Krishnaswamy, MD; Sahar Soleimanifard, PhD; Angela Steinberg, RN, MS; Matthias Stuber, PhD; Gary Gerstenblith, MD; Robert G. Weiss, MD

Background—Normal endothelial function is a measure of vascular health and dysfunction is a predictor of coronary events. Nitric oxide-mediated coronary artery endothelial function, as assessed by vasomotor reactivity during isometric handgrip exercise (IHE), was recently quantified noninvasively with magnetic resonance imaging (MRI). Because the internal mammary artery (IMA) is often visualized during coronary MRI, we propose the strategy of simultaneously assessing systemic and coronary endothelial function noninvasively by MRI during IHE.

Methods and Results—Changes in cross-sectional area and blood flow in the right coronary artery and the IMA in 25 patients with coronary artery disease and 26 healthy subjects during IHE were assessed using 3T MRI. In 8 healthy subjects, a nitric oxide synthase inhibitor was infused to evaluate the role of nitric oxide in the IMA-IHE response. Interobserver IMA-IHE reproducibility was good for cross-sectional area ($R=0.91$) and blood flow ($R=0.91$). In healthy subjects, cross-sectional area and blood flow of the IMA increased during IHE, and these responses were significantly attenuated by monomethyl-L-arginine ($P<0.01$ versus placebo). In patients with coronary artery disease, the right coronary artery did not dilate with IHE, and dilation of the IMA was less than that of the healthy subjects ($P<0.01$). The blood flow responses of both the right coronary artery and IMA to IHE were also significantly reduced in patients with coronary artery disease.

Conclusions—MRI-detected IMA responses to IHE primarily reflect nitric oxide-dependent endothelial function and are reproducible and reduced in patients with coronary artery disease. Endothelial function in both coronary and systemic (IMA) arteries can now be measured noninvasively with the same imaging technique and promises novel insights into systemic and local factors affecting vascular health. (Circ Cardiovasc Imaging. 2016;9:e003954. DOI: 10.1161/CIRCIMAGING.115.003954.)

Key Words: atherosclerosis ■ coronary artery disease ■ endothelium ■ magnetic resonance imaging ■ vasodilation

In response to certain stresses, the healthy endothelium releases nitric oxide (NO), which induces local vascular smooth muscle dilation, inhibits platelet aggregation, attenuates inflammation, and decreases cellular proliferation.1 Endothelial dysfunction is characterized by decreased NO bioavailability, occurs early in the development of atherosclerosis, predicts adverse cardiovascular events,2 and is a potential target for medical interventions.2-7 Peripheral arteries are more accessible to study than the coronary arteries, but there is only a modest correlation between coronary and peripheral endothelial function measures,8,9 and the coronary vascular bed differs significantly from the systemic vasculature.9,10 Patients with coronary artery disease (CAD), in fact, manifest a paradoxical coronary artery vasoconstrictor response to endothelial-dependent stressors that normally cause vasodilation,11 whereas the brachial arteries of patients with CAD vasodilate less in response to endothelial dependent stressors than do those of healthy individuals.8,12 A recent meta-analysis identified a variable association between cardiovascular events and endothelial dysfunction, depending on whether a central or peripheral vascular bed was studied.13 Moreover, studies that compared vasoreactivity of the brachial and the coronary vascular beds were performed using different imaging modalities at different times.8 The measurement of endothelial function in systemic arteries that do not develop atherosclerosis, like the brachial artery, provides information about systemic vascular health, whereas coronary artery endothelial function (CEF) measures offer insights into the contributions of systemic and local coronary factors including the presence of coronary atherosclerosis. Ideally, endothelial function would be assessed in systemic and coronary arteries at the same time using the same endothelial-dependent stressor and imaging technology.13

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From the Division of Cardiology, Department of Medicine (M.I., A.G.H., R.K., A.S., G.G., R.G.W.), Division of Magnetic Resonance Research, Department of Radiology (M.S., S.S., M.S., R.G.W.), Department of Electrical and Computer Engineering (S.S.), Johns Hopkins University, Baltimore, MD; Critical Care Medicine Department, National Institutes of Health, Bethesda, MD (M.I.); and Department of Radiology, Centre Hospitalier Universitaires Vaudois, Center for Biomedical Imaging (CIBM), University of Lausanne, Lausanne, Switzerland (M.S.).

*Dr Iantorno and Hays contributed equally to this work.


Correspondence to Robert G. Weiss, MD, Division of Cardiology, Department of Medicine, The Johns Hopkins Hospital, Blalock 544, 600N. Wolfe St, Baltimore, MD 21287. E-mail rweiss@jhmi.edu

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Recently, the combination of new noninvasive 3T coronary magnetic resonance imaging (MRI) methods and isometric handgrip exercise (IHE), an endothelial-dependent stressor, has been reported as a means to noninvasively and reproducibly quantify CEF. Furthermore, we recently demonstrated in vivo that the coronary artery response to IHE is reproducible and primarily NO-mediated because it is blocked by the NO synthase inhibitor monomethyl-L-arginine (L-NMMA) in healthy subjects.

The internal mammary artery (IMA) is a systemic vessel that rarely develops atherosclerosis, is often used as a coronary artery graft, and has been used to study systemic endothelial function. Because the right and left IMA are visible in many coronary MRI, especially in axial planes, which also intersect the right coronary artery (RCA), we posited that measurements of the vasodilator and blood flow (BF) responses of the IMA could be obtained at the time of CEF measures and serve as an index of systemic endothelial function. We tested the hypotheses that 1) the IMA vasoreactive response to IHE is NO dependent, ie, the response can be blocked by L-NMMA, a NO synthase inhibitor and thus reflects NO-mediated endothelial function, 2) the IMA-IHE response is reproducible, 3) IMA endothelial function is reduced in patients with CAD compared with that of healthy subjects, and 4) among patients with CAD, the endothelial-dependent IMA vasoreactive response to IHE differs from the coronary response.

Methods

Participants

The protocol was approved by the Institutional Review Board of Johns Hopkins Medicine and complies with the Declaration of Helsinki. An Investigational New Drug Application was obtained from the Food and Drug Administration (#119574) for the administration of L-NMMA. All participants provided written informed consent. All subjects were outpatients with no known contraindications to MRI. Healthy subjects were those without history of CAD and for those >50 years of age, without repositioning, each subject then received an intravenous infusion of the NO synthase inhibitor, L-NMMA, at a dose of 0.3 mg/kg per minute, as previously described. A new set of baseline IMA images was obtained 5 to 10 minutes after initiation of the L-NMMA infusion. Each subject then performed a second IHE while intravenous saline (placebo) was infused. After 10 minutes of post-IHE recovery, without repositioning, each subject then received an intravenous infusion of the NO synthase inhibitor, L-NMMA, at a dose of 0.3 mg/kg per minute, as previously described. The entire L-NMMA infusion lasted 15 to 22 minutes, and the entire MRI-CEF-L-NMMA protocol lasted ≈60 minutes.

Magnetic Resonance Imaging

A commercial human 3.0 Tesla whole-body magnetic resonance scanner (Achieva, Philips, Best, NL) with a 32-element cardiac coil for signal reception was used. Cross-sectional anatomic and FV encoded spiral MRI were obtained using single breath-hold cine sequences. MRI parameters for anatomic imaging were repetition time, 18 ms; echo time, 2.1 ms; radio frequency excitation angle, 20°; acquisition window, 13 ms; to 21 spiral interleaves/cine frame; spatial resolution, 0.89×0.89×8.0 mm; and breath-hold duration, ≈14–24 s. MRI parameters for the velocity measurements were repetition time, 40 ms; echo time, 3.5 ms; radio frequency excitation angle, 20°; acquisition window, 33 ms; to 11 spiral interleaves/cine frame; spatial resolution, 0.8×0.8×8.0 mm3; velocity encoding, 35 to 75 cm/s; and breath-hold duration, 14 to 24 s.

Image Analysis

Baseline and IHE stress images were analyzed for RCA and IMA CSA using semiautomated software (Cine version 3.15.17, General Electric, Milwaukee, WI). A circular region-of-interest around the RCA and the IMA was traced during a period of least coronary motion over 3 sequential images. The 3 values (measured in mm2) were then averaged. The computer algorithm used an automated full width half maximum algorithm for CSA measurements. For flow measurements, velocity measurements of the same baseline and IHE stress at 30% of maximum grip strength. IHE was performed using an MRI-compatible handgrip dynamometer (Stoelting, Wood Dale, IL) under direct observation and coaching by a research nurse. Heart rate and blood pressure were measured throughout during the study using a noninvasive and MRI-compatible ECG and blood pressure monitor (In vivo; Precess, Orlando, FL). The rate pressure product (RPP) was obtained as previously described. The MRI end points were CSA, FV, and BF measures as described above.

To test the study hypotheses, we conducted 2 protocols outlined here:

1. Role of NO in the IMA vasomotor response to IHE: the L-NMMA protocol:

   To assess whether the IHE-induced vasoreactive changes of the IMA are NO-mediated and hence endothelial dependent, 8 healthy individuals underwent IMA imaging before and during IHE while intravenous saline (placebo) was infused. After 10 minutes of post-IHE recovery, without repositioning, each subject then received an intravenous infusion of the NO synthase inhibitor, L-NMMA, at a dose of 0.3 mg/kg per minute, as previously described. The entire L-NMMA infusion lasted 15 to 22 minutes, and the entire MRI-CEF-L-NMMA protocol lasted ≈60 minutes.

2. IMA and RCA MRI vasomotor responses to IHE in healthy volunteers and patients with CAD:

   Healthy subjects (n=26) and patients with CAD (n=25) were consecutively enrolled, and both the RCA and an IMA were imaged in cross-section for CSA and FV at rest, followed by repeat imaging during IHE. Interobserver reproducibility analysis of IMA measurements (CSA, FV, and BF) was performed in a randomly selected subset of both healthy volunteers (N=6) and patients with CAD (n=5), and none from the subset were excluded from analysis.
RCA and IMA images were made using commercially available software (QFLOW Version 3.0, Medis, The Netherlands). A region of interest was traced using semiautomated software around a cross-sectional RCA to obtain peak diastolic coronary FV and of the IMA for peak systolic FV (mean velocity of lumen pixels at peak flow), both referred to as FV hereafter. Velocity was measured in centimeters per second and coronary and IMA BF (in mL/min) were calculated and converted to units of milliliter per minute using the adapted equation: CSA×peak FV×0.3. Segments with poor image quality (blurring because of artifact/patient motion) on either baseline or stress exams were excluded from analysis.

Statistics
The data were tested for normality using the Shapiro–Wilk test. Parametric (Student’s t test) and nonparametric testing (Wilcoxon signed-rank test for paired data and Wilcoxon rank-sum test for non paired data) were used when appropriate for normally distributed and not normally distributed data, respectively, to compare the response to IHE from baseline measurements in the RCA and IMA of healthy subjects and patients with CAD for area, velocity, and flow measurements. A paired t test was used to compare IHE-induced IMA changes during placebo to those during l-NMMA infusion. For comparisons among 4 groups, 1-way ANOVA and Kruskal–Wallis were used for parametric and nonparametric comparisons, respectively, with Bonferroni adjustment used for pair-wise comparisons. Linear regression analysis was performed to assess inter-reader reproducibility, and the mean differences were displayed with Bland–Altman regression analysis was performed to assess inter-reader reproducibility. Linear regression analysis was performed to assess inter-reader reproducibility, and the mean differences were displayed with Bland–Altman analysis (Figure 1). The data were tested for normality using the Shapiro–Wilk test. Parametric (Student’s t test) and nonparametric testing (Wilcoxon signed-rank test for paired data and Wilcoxon rank-sum test for non paired data) were used when appropriate for normally distributed and not normally distributed data, respectively, to compare the response to IHE from baseline measurements in the RCA and IMA of healthy subjects and patients with CAD for area, velocity, and flow measurements. A paired t test was used to compare IHE-induced IMA changes during placebo to those during l-NMMA infusion. For comparisons among 4 groups, 1-way ANOVA and Kruskal–Wallis were used for parametric and nonparametric comparisons, respectively, with Bonferroni adjustment used for pair-wise comparisons. Linear regression analysis was performed to assess inter-reader reproducibility, and the mean differences were displayed with Bland–Altman analysis (Figure 1).

Results
All subjects completed the study. An example of typical changes seen in area and velocity with IHE in a healthy volunteer is shown for the IMA and RCA in Figure 1. Modest increases in CSA and larger increases in blood flow (shown by darker pixels in the velocity encoded phase contrast images indicating increased velocity in the caudal direction) occur during IHE in healthy subjects.

Role of NO in Mediating the IMA Response to IHE

Subject Characteristics and Hemodynamic Effects of l-NMMA

Eight healthy subjects underwent IMA imaging with the l-NMMA protocol (age: 30±4 years). The baseline RPP increased significantly with IHE (P<0.0001) and returned to baseline during the recovery period (P=0.8). During l-NMMA infusion, mean RPP was not different from that before l-NMMA. The increase in RPP during IHE was similar in the absence and presence of l-NMMA.

l-NMMA Infusion Blocks the Vasodilatory Response of the IMA to IHE

The IMA responses to IHE in 8 healthy subjects during placebo and l-NMMA infusion are presented in Figure 2B. There is an ≈15% increase in CSA, 30% increase in coronary FV, and ≈50% increase in coronary BF during placebo infusion (Figure 2B). IMA CSA increased from a baseline of 8.5±0.6 mm2 to 9.8±0.7 mm2 (P<0.001) during IHE. However, there was no significant increase in IMA CSA when IHE was repeated during l-NMMA infusion (second baseline: 9.0±0.8 mm2 versus l-NMMA-IHE: 9.2±0.8 mm2; P=0.2). In relative terms, %CSA change with IHE was 15.4±2.2% with placebo versus 2.3±1.3% with l-NMMA (P<0.001).

l-NMMA Infusion Blocks the IMA Increase in Blood Velocity and Flow With IHE

Peak systolic velocity and BF in the IMA significantly increased with IHE during placebo infusion. Velocity increased from a baseline of 21.4±3.3 to 27.4±4.2 cm/s (P<0.01) with IHE, whereas BF increased from a baseline of 50.2±3.1 to 74.1±4.7 mL/min (P<0.0001) with IHE during placebo. l-NMMA infusion did not change baseline IMA flow but completely blocked the IHE-induced increases in velocity and flow (Figure 2). This suggests that the normal vasoreactive IMA response to IHE is predominantly NO mediated.

Reproducibility of IMA Measurement

Changes of the IMA CSA, FV, and BF during IHE were analyzed by 2 observers (M.I. and A.H.). The results strongly correlated for the %CSA, %FV, and %BF changes with IHE (Figure 3A through 3C). The Bland–Altman analysis (Figure 3D and 3F) and intraclass correlation coefficients for %CSA, %FV, and %BF change with stress in the IMA (intraclass correlation coefficient=0.89, 0.97, and 0.93, respectively) indicated excellent confidence of agreement and little variability between the 2 measures.
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Subject Characteristics
We compared the responses of 26 consecutive healthy subjects (age: 45±3.5 years) and 25 patients with CAD (61±1.5 years). The study subject characteristics are summarized in the Table. To age-match healthy subjects with patients with CAD, the results from an older subset of the original healthy individuals (n=12; 61±3 years) were also compared with those from the patients with CAD (61±1.5 years; \( P \approx \text{NS} \)), and those data appear in the Data Supplement section.

Hemodynamic Effects of IHE in Healthy Volunteers and Patients With CAD
IHE induced significant and similar hemodynamic changes in healthy subjects and patients with CAD. In the healthy group, we observed a mean 35.4±4.6% increase in RPP, which was not different than the mean 28.7±3.9% RPP change with IHE in patients with CAD (\( P \approx 0.3 \) versus healthy subjects).

Coronary and IMA Area Changes
Both the RCA and IMA in healthy subjects dilated significantly in response to IHE (\( P \approx 0.001 \) and \( P \approx 0.0001 \) from baseline, respectively; Figure 4). In contrast, the RCA in patients with CAD showed no significant change (\( P = \text{NS} \)).

Figure 2. Intravenous infusion of monomethyl-l-arginine, a nitric oxide synthase inhibitor, blocks isometric handgrip exercise-induced vasodilation, and the increase in blood flow in the internal mammary artery of healthy volunteers. A, Diagram illustrating MRI l-NMMA study. B, Vasoreactive changes during IHE for placebo (blue striped) and l-NMMA (yellow) infusions showing that l-NMMA blocks IMA vasodilation and increase in velocity and blood flow with IHE. Comparisons of placebo- and l-NMMA responses were performed with a paired \( t \) test. IMA indicates internal mammary artery; IHE, isometric handgrip exercise; l-NMMA, monomethyl-l-arginine; and MRI, magnetic resonance imaging.

Figure 3. Interobserver reproducibility of noninvasive MRI measures of the IMA. Linear regression showing strong correlation between % area change with IHE between observer 1 and observer 2 (A), % velocity (B), and % flow change (C) between first and second observer. D–F, Bland–Altman plots indicate good confidence of agreement and little variability between the 2 measures. Lines represent 95% confidence of agreement. IMA indicates internal mammary artery; IHE, isometric handgrip exercise; and MRI, magnetic resonance imaging.
Dyslipidemia (%) 2 (7) 2 (17) 24 (96)
Male sex (%) 8 (31) 5 (42) 21 (84)
ACE-inhibitor (%) 1 (4) 1 (8) 15 (60)
Diabetes mellitus (%) 0 0 3 (12)
ACE indicates angiotensin-converting enzyme; ASA, aspirin; CABG, coronary artery bypass graft; CAD, coronary artery disease; HTN, hypertension; MI, myocardial infarction; and PCI, percutaneous intervention.

Table. Demographics

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Figure 4. Peripheral and coronary endothelial function in healthy volunteers and patients with CAD-CSA change. A, Protocol diagram illustrating MRI study. B, Summary results for mean CSA changes in the IMA (striped bars) and RCA (solid bars) during IHE for healthy volunteers (blue) and patients with CAD (red). Analysis performed with Kruskal–Wallis testing with Bonferroni adjustment for pair-wise comparisons. CAD, coronary artery disease; CSA, cross-sectional area; IMA, internal mammary artery; IHE, isometric handgrip exercise; MRI, magnetic resonance imaging; and RCA, right coronary artery.

Coronary and IMA Velocity and BF Measures

For the IMA, both FV and BF increased significantly with IHE in healthy individuals (P<0.001). In contrast, in patients with CAD, we observed an attenuated but significant increase in IMA BF with IHE from baseline (P<0.001). The IMA changes in patients with CAD were less than those of healthy individuals (P<0.001 CAD IMA versus healthy IMA; Figure 5B). Consistent with prior reports, the RCA vasoreactive responses were characterized by a significant increase in FV and BF in healthy subjects but not in CAD patients with IHE (Figure 5B and 5C). When comparing the 2 vascular beds, the coronary BF response was less than the IMA response in patients with CAD but did not reach statistical significance (P=0.07; Figure 5B). When the results on healthy subjects and patients with CAD were combined into a single group, there was a statistically significant relationship between IMA and RCA IHE responses (Figure 6). However, the correlations were not generally significant when the groups were considered separately, suggesting that the IMA–RCA correlation is highly influenced by group differences between healthy subjects and patients with CAD rather than by a close fundamental relationship between IMA and RCA responses.

Discussion

Abnormal vasomotor responses of systemic and coronary arteries to endothelial-dependent stressors predict subsequent cardiovascular events but the direction, magnitude, and prognostic value of the responses often differ between systemic and coronary arteries.5,9,23,26 Because systemic and coronary endothelial function measures are typically obtained at different times, with different endothelial-dependent stressors, and assessed with different techniques,8,14 it is difficult to know whether different responses between systemic and coronary arteries represent true disparities in local vascular biology or are simply because of differences in the stimulus, means of detection, and/or conditions at the time of study. In this article, we describe the first noninvasive means to simultaneously assess endothelial function in systemic and coronary circulations. The measures of systemic (IMA) and coronary (RCA) endothelial function are obtained at the same time, in response to the same stimulus, and detected with the same imaging technology. We demonstrate that the IMA response to IHE is indeed predominantly NO-mediated, reproducible between observers, differs between healthy subjects and those with CAD, and differs from the response of the coronary arteries in patients with CAD.

Role of NO in Mediating the IMA Response to IHE

We recently reported that the coronary response to IHE is measurable with MRI11,15,16 and mediated by NO in healthy individuals.17 Because it was not previously known whether the IMA response to IHE is NO-mediated,27 we report here that the NO synthase inhibitor L-NMMA abolishes the normal
IMA vasodilatory and BF IHE responses in healthy subjects (Figure 2). Our results are consistent with prior studies indicating that l-NMMA blocks ≈70% of the brachial artery macrovascular vasodilatory response in healthy subjects.\textsuperscript{28,29} Likewise, the microvascular peripheral response during IHE is also blocked by l-NMMA infusion.\textsuperscript{28} Together these findings in healthy subjects demonstrate that IHE is a predominately NO-mediated endothelial dependent stressor for both the coronary and systemic circulations. Our assumption that NO also acts in the CAD population is reasonable although not directly demonstrated. We did not administer l-NMMA to patients with CAD because l-NMMA reduces NO synthesis and one would expect minimal or no vascular effect in an already severely NO-deficient state like CAD, especially when monitoring the coronary vasoactive dilatory or flow effects of IHE that are already absent in patients with CAD. In addition, l-NMMA may pose risk in patients with CAD. Thus, continuous IHE as described here can be used with MRI or potentially other noninvasive imaging modalities to simultaneously probe coronary and systemic NO-mediated endothelial function.

**IHE-Induced Vasoreactivity of the IMA Is Reduced in Patients with CAD Compared With Healthy Subjects**

We observe a significant reduction of IHE-induced vasoreactivity of the IMA in patients with CAD compared with that of healthy subjects (Figures 4 and 5). These observations are in line with prior in vitro studies\textsuperscript{10,30} as well as in vivo studies showing an impaired IMA vasodilatory response to acetylcholine infusion in patients with CAD when compared with...
controls. Berkenboom et al showed that selective infusion of the IMA with L-arginine, a NO precursor, reversed the impaired IMA response to acetylcholine in patients with CAD, suggesting that decreased NO plays a critical role in the pathogenesis of the diminished IMA response in those patients. The IMA vasoreactive response generally resembles the brachial response in direction and magnitude in diseased states.

Systemic Versus Coronary Endothelial Function: Differences in Vascular Properties

Among patients with CAD, we observe that coronary arteries fail to dilate and sometimes vasoconstrict in response to IHE, whereas the IMA responds with reduced vasodilation, similar to the attenuated brachial response during forearm cuff occlusion. One obvious difference between the coronary and IMA vascular beds is that the latter does not develop atherosclerosis while the coronary arteries do. Furthermore, the vasoreactive responses of coronary and systemic vessels were previously compared, albeit at different time points and imaging modalities, and the correlation between systemic and coronary endothelial function was not strong. When the endothelial responses of the IMA and RCA were compared for individual subjects (Figure 6), the correlation was not significant for healthy subjects or for patients with CAD although significant when combined. One prior study showed that intra-arterial infusion of L-arginine did not affect acetylcholine-induced vasodilation in the coronaries of healthy individuals and patients with CAD, whereas it augmented the acetylcholine-induced increase in forearm BF in the 2 groups. Thus, the response to acetylcholine infusion differed between coronary and systemic arteries suggesting that mechanisms for vasodilation may vary between the vascular beds. Differences in vascular properties between coronary and systemic vessels may be because of a variable amount of NO production and/or bioavailability. Finally, although atherosclerosis is often regarded as a systemic process, the often-disparate vasoreactive responses of coronary and systemic arteries suggest differences in local milieu. Prior observations that coronary arteries display a heterogeneous coronary endothelial response depending on the degree of atherosclerotic disease suggest that local factors may contribute to local atherosclerotic plaque formation despite the exposure of all coronary segments to identical systemic factors. Therefore, the study of these 2 vascular territories may shed important insights into their relationship and how external and local factors may influence them in different ways. Because endothelial function is often considered a barometer of vascular health and responds rapidly to protective strategies, we postulate that this MRI technique could be used in the future to guide therapy (eg, lowering low-density lipoprotein not to an low-density lipoprotein number but until endothelial function improves), predict future events in at risk populations, and, importantly, to rapidly test the ability of new strategies to improve systemic and coronary vascular health.

Limitations

Sample size is relatively modest in the L-NMMA study but yet large enough to show highly statistically significant responses. Although the RCA was the only coronary artery studied here with the IMA, it is possible to acquire coronary endothelial function measures of the left coronary artery system during the same IHE session. Although phasic BF changes during the cardiac cycle may differ between RCA and left anterior descending coronary artery (LAD), the latter does not lie orthogonal to the axial plane like the IMA and RCA, and thus, the LAD would require an additional breath-hold acquisition. Local coronary factors likely play a major role in influencing macrovascular regional CEF, but we cannot exclude the possibility, based on the current data alone, that differences in distal NO production in the microvasculature could affect shear stress and thereby proximal coronary artery changes to IHE. Regardless, this new approach offers a reproducible measure of NO-mediated endothelial function in coronary and systemic vascular territories concurrently with the same stressor, under the same conditions and detected with the same imaging technology. In future studies, it would be useful to compare these measures of systemic endothelial function derived from IMA to those of other, more commonly studied arteries (ie, brachial and femoral) and to determine the extent to which these measures are associated with future cardiovascular events.

Conclusions

In summary, we report here the first noninvasive approach for concurrently measuring systemic and coronary vascular endothelial function. The IMA-IHE response is predominantly NO dependent, can be measured noninvasively with MRI simultaneously with CEF measures, and is reproducible both in healthy volunteers and patients with CAD. Importantly, the IMA-IHE response in patients with CAD differs significantly from that in healthy subjects. This noninvasive approach promises a more complete assessment of vascular health than measures of endothelial function in a single vascular territory and will enable the systematic study of interventions designed to improve endothelial function over time.

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Disclosures

None.

References

Endothelial dysfunction is characterized by decreased nitric oxide bioavailability, occurs early in the development of atherosclerosis, predicts adverse cardiovascular events, and is a potential target for medical interventions. Thus, endothelial function is considered a barometer of vascular health. Coronary artery and peripheral artery endothelial function are often, however, impaired in patients with coronary artery disease. Thus, endothelial dysfunction does not support its routine clinical use.


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Supplemental Material

IMA and RCA MRI vasomotor responses to IHE in CAD patients and age-matched healthy subjects

Subject Characteristics

In order to age-match healthy subjects with CAD patients, an older subset of the original healthy individuals (n=12: age-matched healthy subjects 61±3 years (range 50-83 years)) was compared to the CAD patients (n=25: 61±2 years, (range 52-76) p=NS).

Coronary and IMA area changes measures

Both coronary arteries and IMA in healthy subjects dilated significantly in response to IHE (p<0.001 and p=0.0001 vs baseline, respectively). The RCA area did not significantly change in response to IHE (p=0.4 vs baseline; Suppl Fig1) in CAD patients. In contrast, the IMA vasodilates with IHE in CAD patients (p<0.0001 vs baseline) although less as compared to that observed in healthy volunteers (% IMA change from baseline 15.9±2.9% in healthy vs 9.1±1.6% in CAD patients; p=NS; Suppl Fig 1).

Coronary and IMA velocity and blood flow measures

For the IMA, both FV and BF increased significantly with stress in healthy individuals (p=0.04; and p<0.01; vs baseline). In contrast, in CAD patients, although there was a mild increase in FV and a significant increase in BF with IHE in the IMA (p<0.0001 vs. baseline for both), the degree of change was significantly less than that seen in healthy individuals. In CAD patients, the IHE-induced change in flow was higher for the IMA compared to the RCA (%;p=0.04) (Suppl Fig1).

Suppl Fig.1. Peripheral and Coronary Endothelial Function in Age-Matched Healthy Volunteers and Patients with CAD.

A) Summary results for mean area changes in the Internal Mammary Artery (IMA) and Right Coronary artery (RCA) during Isometric Handgrip Exercise (IHE) (as % of baseline values) for age matched healthy volunteers and patients with CAD. Error bars indicate standard error of the
mean. B) Summary results for mean peak systolic velocity changes in the IMA and peak diastolic velocity changes in the RCA during IHE (as % of baseline values) for healthy volunteers and patients with CAD. Error bars indicate standard error of the mean. C) Summary results for mean blood flow changes in the IMA and the RCA during IHE (as % of baseline values) for healthy volunteers and patients with CAD. Error bars indicate standard error of the mean. Analysis performed with Kruskal-Wallis testing with Bonferroni adjustment for pair-wise comparisons.
Suppl Fig. 1

A) Area

B) Velocity

C) Flow

Legend:
- IMA- Healthy Volunteers N=12
- IMA - CAD Patients N= 25
- RCA- Healthy Volunteers N=12
- RCA - CAD Patients N=25

Significance levels:
- P<0.001
- P=0.04
- P=0.01
- P=0.04