Coronary vasomotor responses to isometric handgrip exercise are primarily mediated by nitric oxide: a noninvasive MRI test of coronary endothelial function

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1Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland; 2Critical Care Medicine Department, National Institutes of Health, Bethesda, Maryland; 3Division of Magnetic Resonance Research, Department of Radiology, Johns Hopkins University, Baltimore, Maryland; 4Department of Electrical and Computer Engineering, Johns Hopkins University, Baltimore, Maryland; and 5Department of Radiology, Centre Hospitalier Universitaire Vaudois, Center for Biomedical Imaging and University of Lausanne, Lausanne, Switzerland

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Hays AG, Iantorno M, Soleimanifard S, Steinberg A, Schär M, Gerstenblith G, Stuber M, Weiss RG. Coronary vasomotor responses to isometric handgrip exercise are primarily mediated by nitric oxide: a noninvasive MRI test of coronary endothelial function. Am J Physiol Heart Circ Physiol 308: H1343–H1350, 2015. First published March 27, 2015; doi:10.1152/ajpheart.00023.2015.—Endothelial cell release of nitric oxide (NO) is a defining characteristic of nondiseased arteries, and abnormal endothelial NO release is both a marker of early atherosclerosis and a predictor of its progression and future events. Healthy coronary respond to endothelial-dependent stressors with vasodilatation and increased coronary blood flow (CBF), but those with endothelial dysfunction respond with paradoxical vasoconstriction and reduced CBF. Recently, coronary MRI and isotonic handgrip exercise (IHE) were reported to noninvasively quantify coronary endothelial function (CEF). However, it is not known whether the coronary response to IHE is actually mediated by NO and/or whether it is reproducible over weeks. To determine the contribution of NO, we studied the coronary response to IHE before and during infusion of N\textsuperscript{\text{\textgreek{m}}}monomethyl-l-arginine (l-NMMA, 0.3 mg·kg\textsuperscript{-1}·min\textsuperscript{-1}), a NO-synthase inhibitor, in healthy volunteers. For reproducibility, we performed two MRI-IHE studies ~8 wk apart in healthy subjects and patients with coronary artery disease (CAD). Changes from rest to IHE in coronary cross-sectional area (%CSA) and diastolic CBF (%CBF) were quantified. l-NMMA completely blocked normal coronary vasodilation during IHE [%CSA, 12.9 ± 2.5 (mean ± SE, placebo) vs. −0.3 ± 1.6% (t-NMMA); P < 0.001] and significantly blunted the increase in flow [%CBF, 47.7 ± 6.4 (placebo) vs. 10.6 ± 4.6% (t-NMMA); P < 0.001]. MRI-IHE measures obtained weeks apart strongly correlated for CSA (P < 0.0001) and CBF (P < 0.01). In conclusion, the normal human coronary vasomotor response to IHE is primarily mediated by NO. This noninvasive, reproducible MRI-IHE exam of NO-mediated CEF promises to be useful for studying CAD pathogenesis in low-risk populations and for evaluating translational strategies designed to alter CAD in patients.

endothelial function; coronary artery disease; magnetic resonance imaging

ENDOTHELIAL CELL RELEASE of nitric oxide (NO) is a defining characteristic of nondiseased vascular tissue; it inhibits platelet aggregation, attenuates inflammation, decreases cellular proliferation, and induces local vascular smooth muscle vasodilation (4). Most classic and novel cardiovascular risk factors converge to impair endothelial function, including dyslipidemia, insulin resistance, inflammation, tobacco abuse, and oxidative stress, as well as hemodynamic and genetic factors (4, 33). Critically, endothelial dysfunction is a marker for subclinical disease, an independent predictor of adverse cardiovascular events, and a potential target for medical interventions (21, 24, 28).

Traditionally, coronary endothelial function (CEF) is assessed by the direction and magnitude of changes in coronary arterial area and flow in response to endothelial-dependent vasomotor interventions (15). From the seminal description of paradoxical coronary vasoconstriction in response to a vasorelaxant substance in patients with coronary artery disease (CAD) (15), the assessment of endothelial-dependent coronary vasoreactivity during cardiac catheterization has been widely studied to characterize endothelial function. However, the invasive nature of coronary angiography with Doppler-flow measures used in the traditional assessment of CEF has limited clinical and research investigations, particularly those benefiting from repeated studies and/or studies in clinically stable or healthy subjects. Recently, the combination of new noninvasive 3.0-tesla (T) coronary MRI methods and isometric handgrip exercise (IHE), a purported endothelial-dependent stressor, has been reported as a means to noninvasively quantify CEF. In healthy subjects without CAD risk factors, IHE induced significant coronary dilatation and increased flow measured by increases in MRI-detected coronary cross-sectional area (CSA), peak diastolic coronary flow velocity (CFV), and diastolic coronary blood flow (CBF) (8, 9). In contrast, patients with CAD exhibited paradoxical vasoconstriction with reductions in CSA, CFV, and CBF (8). The noninvasive 3.0-T MRI-IHE approach detected coronary changes consistent with endothelial functional responses anticipated in healthy subjects and patients with CAD (8), but because IHE can in theory stimulate sympathetic, neural, and neurohumoral responses, the extent to which the MRI-detected coronary responses to IHE primarily reflect NO-mediated endothelial function was questioned (13). Although nuclear/positron emission tomography and MRI perfusion techniques can measure downstream myocardial perfusion in response to endothelial-independent and endothelial-dependent stressors (25, 34), if these MRI-IHE coronary responses are shown to be primarily NO mediated,
they would be uniquely valuable for probing the local factors that might affect the pathophysiology of local plaque progression and rupture, since this approach quantifies local coronary segment vasodilatation. In addition, although MRI measures of CEF are unchanged during repeated IHE tests on the same day (10), it is not known whether the MRI-IHE test of CEF is reproducible over several days or weeks, as might be studied in an intervention trial. Such reproducibility of CEF measures over time is important because endothelial function is affected by a variety of external stimuli (36).

We therefore studied the normal coronary vascular response to IHE detected by MRI before and during the infusion of the endothelial NO synthase (eNOS) inhibitor (22) N\textsuperscript{G}-monomethyl-L-arginine (L-NMMA) to test the hypothesis that the coronary response to IHE is largely mediated by NO and thus primarily reflects CEF. In addition, we assessed the reproducibility of noninvasive MRI measures of coronary endothelial vasoreactivity in both patients with CAD and healthy adults over a mean 8-wk period, an interval useful in planning future intervention trials.

METHODS

Patients

Subjects were outpatients with no contraindications to MRI. The Institutional Review Board at The Johns Hopkins School of Medicine approved the protocol. An Investigational New Drug application was approved by the Food and Drug Administration (No. 119574) for the administration of L-NMMA, and all participants provided written informed consent. Healthy subjects were those under the age of 50 yr without a history of CAD and traditional CAD risk factors and for those over age 50 with an Agatston coronary artery calcium score (1) of <10 by computed tomography. CAD subjects were outpatients with stable CAD (luminal stenosis of 30 to 70%) on coronary X-ray angiography or computed tomography angiography with no active angina or evidence of ischemia on their most recent stress imaging studies. The subjects were consecutively recruited de novo and were not reported in prior published studies.

Study Protocol

MRI was performed in the morning in the fasting state (>8 h) before administration of any prescribed vasoactive medications. Images were taken perpendicular to a proximal, well-visualized straight (~20 mm) segment of a native coronary artery, as determined by double-oblique scout scanning (27), that had not undergone prior intervention or had a significant stenosis by invasive angiography. For the patients with CAD, the segment of the coronary artery selected for MRI measures of CSA, CFV, and CBF had no more than a 30% luminal stenosis.

For the L-NMMA study, each healthy volunteer (n = 10) underwent a first IHE period during which intravenous saline (placebo) was infused (Fig. 1). After postexercise recovery, each subject then received an intravenous infusion of L-NMMA at a dose of 0.3 mg·kg\textsuperscript{-1}·min\textsuperscript{-1}, as previously described (30). A new set of baseline coronary images was obtained after 5 min of L-NMMA infusion. A second IHE period was then initiated while L-NMMA infusion continued and coronary imaging was repeated at the same locations (Fig. 1). The entire L-NMMA infusion typically lasted 15–22 min. Heart rate and blood pressure were measured throughout using a noninvasive and MRI-compatible ECG and calf blood pressure monitor (Invivo, Orlando, FL). The rate pressure product (RPP) was calculated as systolic blood pressure × heart rate.

For the reproducibility study, 10 healthy subjects and 8 patients with CAD underwent two MRI-IHE exams at least 4 wk apart. There were no changes in clinical status or cardiovascular symptoms in patients with CAD between the two MRI exams. Both MRI-IHE exams were performed under similar fasting and experimental conditions. Special attention was given to repeat the study in the same coronary locations as in the first study, based on anatomic landmarks such as distance from coronary and branch vessel ostia.

MRI Acquisition Details

A commercial 3.0-T whole body MR scanner (Philips Healthcare, Best, The Netherlands) equipped with a 32-channel cardiac coil and multitransmit system was used. The imaging protocol and parameters have been detailed elsewhere (8). In each subject, a proximal or midsegment of a major coronary artery was selected for cross-sectional, anatomical (17), and flow velocity-encoded MRI (12), which were obtained using single breath-hold spiral cine sequences (31). Cine coronary imaging was performed at rest and repeated at the same location during IHE, performed using an MRI-compatible dynamometer (Stoelting, Wood Dale, IL) at 30% of maximum grip strength (32). In most cases, two coronary arteries per participant and/or different segments of the same vessel were imaged, and the results for each were quantified and reported. The total duration of MRI exams were ~60 and 40 min for the L-NMMA and reproducibility protocols, respectively.

Image Analysis

Images were analyzed for stress-induced CSA changes with semiautomated software (Cine, General Electric, Milwaukee, WI) using the full-width, half-maximum algorithm, and contours were made around each vessel during a quiescent period in diastole. For flow measurements, velocity-encoded images were analyzed using commercially available software (QFLOW, Medis, The Netherlands). Peak diastolic CFV (mean velocity of coronary artery lumen pixels at peak diastolic flow) was used for the velocity measurements, and coronary artery peak diastolic blood flow (CBF) was calculated as coronary artery CSA × coronary artery peak diastolic velocity × 0.5 (5) and converted to milliliters per minute. Coronary segments with poor image quality (blurring due to artifact/patient motion) on either the baseline or follow-up exams were excluded. Data analysis for the L-NMMA study was performed by two independent investigators (A. G. Hays and M. Iantorno) blinded (and MRIs deidentified) to study group (placebo vs. L-NMMA) and stage of the protocol (rest vs. stress).
Statistical Analysis

Data are expressed as means ± SE unless otherwise specified. The χ²-test for normality was performed, and each data set was found to be normally distributed. Parametric testing (paired Student’s t-test) was used to compare stress coronary artery CSA, CFV, and CBF measurements during IHE to the initial baseline measurements both with and without L-NMMA. The data from individual segments were treated as independent observations given the nature of the study (per segment analysis). Because L-NMMA results from different segments in the same individual may be correlated, in a separate analysis the results from different segments in a given individual were averaged and the data from each subject were treated as independent observa-

Table 1. Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CAD Reproducibility Study (n = 8)</th>
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<tr>
<td>Age, yr (mean ± SD)</td>
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</tr>
<tr>
<td>Male sex, %</td>
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<tr>
<td>Previous myocardial infarction</td>
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<tr>
<td>Percutaneous intervention/stents</td>
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<td>Coronary artery bypass graft surgery</td>
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<td>Angiotensin-converting enzyme inhibitor</td>
<td>3 (37)</td>
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<tr>
<td>Statin</td>
<td>8 (100)</td>
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<tr>
<td>β-Blocker</td>
<td>3 (37)</td>
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<td>6</td>
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<tr>
<td>Left anterior-descending coronary artery</td>
<td>6</td>
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<tr>
<td>Total vessels studied</td>
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</tbody>
</table>

CAD, coronary artery disease.

RESULTS

Subject Characteristics

All 10 healthy subjects (mean age ± SD, 31 ± 9 yr; 5 women) completed the L-NMMA study. For the reproducibility study, the mean age for the healthy subjects was 37 ± 10 yr (4 women). Baseline characteristics of the CAD subjects in the reproducibility study are presented in Table 1. Of the 18 subjects enrolled in the reproducibility study, one healthy subject could not complete the second scan because of claustrophobia. For the L-NMMA study, 25 coronary segments [13 in the right coronary artery (RCA) and 12 in the left anterior-descending coronary artery (LAD)] were analyzed for CSA, CFV, and CBF in 10 subjects. For the reproducibility study, 17 participants completed both visits (7.7 ± 1.2 wk apart, mean ± SE; range, 4–23 wk). In these subjects a total of 29 segments were suitable for CSA analysis and 26 segments were of good quality for CFV and CBF analysis (3 segments were excluded because of artifacts or blurred borders in the flow scans). Of the segments analyzed for CSA in the 9 healthy individuals, 10 were in the RCA and 7 in the LAD whereas in the 8 patients with CAD, 6 were in the RCA and 6 in the LAD. An example of typical changes seen in CSA and CFV with IHE are shown in a healthy subject (Fig. 2). The CSA, CFV, and CBF responses to IHE were significantly attenuated in these patients.
with CAD compared with the responses in healthy subjects (Fig. 3), consistent with prior reports in other patients with CAD and healthy subjects (8, 9).

Role of NO in Mediating the Coronary Response to IHE: the L-NMMA Study

Hemodynamic results. Hemodynamic changes during each stage of the L-NMMA protocol (Fig. 1) are presented in Fig. 4. The baseline RPP increased with IHE and returned to baseline during the recovery period (Fig. 4). L-NMMA infusion increased mean arterial pressure (baseline, 80 ± 3 vs. L-NMMA, 96 ± 4 mmHg; P = 0.002) and decreased heart rate (baseline, 66 ± 3 vs. L-NMMA, 57 ± 3 beats/min; P = 0.002); however, mean RPP during L-NMMA infusion was not different from that before L-NMMA. The increase in RPP during IHE was similar in the absence and presence of L-NMMA (Fig. 4).

L-NMMA infusion blocks the normal coronary vasodilatory response to IHE. Coronary arteries in healthy subjects significantly dilated in response to IHE (CSA baseline 1: 11.2 ± 0.6 vs. stress 1, 12.6 ± 0.7 mm²; P < 0.0001, Fig. 5), consistent with prior reports (8–10). Resting CSAs before the first IHE episode (during placebo infusion) and before the second IHE episode (during L-NMMA infusion) did not differ (CSA baseline 1, 11.2 ± 0.6 vs. baseline 2 with L-NMMA, 11.3 ± 0.7 mm²; P = 0.7). However, in contrast to the vasodilatory CSA response to IHE during placebo, there was no significant increase in CSA when IHE was repeated during L-NMMA infusion (baseline 2, 11.3 ± 0.7 vs. stress 2, 11.3 ± 0.7 mm²; P = 0.6). When comparing the IHE response between placebo and L-NMMA conditions, the CSA increase with IHE (as %baseline) was completely blocked by L-NMMA infusion (12.9 ± 2.5 vs. −0.3 ± 1.6%, placebo vs. L-NMMA; P < 0.0001, Fig. 5).

L-NMMA infusion blocks the normal increase in CFV and CBF with IHE. Peak diastolic CFV significantly increased in response to IHE during placebo infusion, also consistent with prior reports (8–10), and was attenuated by L-NMMA as shown in Fig. 5. Likewise, peak diastolic CBF increased in response to IHE during placebo in healthy subjects (CBF, 39.2 ± 3.8 vs. 56.9 ± 5.1 ml/min; P < 0.0001), consistent with prior reports (8, 9). L-NMMA infusion did not change baseline CBF (39.2 ± 3.8 vs. 39.8 ± 3.7 ml/min; P = 0.6). Although CBF increased by ~50% with IHE during placebo, L-NMMA infusion attenuated but did not completely block the CBF increase with IHE (47.7 ± 6.4 vs. 10.6 ± 4.6%, placebo vs. L-NMMA; P < 0.0001, Fig. 5). The findings that L-NMMA attenuated the normal IHE-induced increases in CFA, CFV, and CBF were consistently observed regardless of whether the data were analyzed on a per segment or per subject basis (data not shown).

Reproducibility over Weeks of the Coronary Response to IHE Detected by MRI

As expected, IHE induced significant hemodynamic changes in both healthy subjects (n = 9) and those with CAD (n = 8), and the change in RPP with stress was not significantly different between the first and second visits (11,805 ± 423 vs. 11,075 ± 496 mmHg·beats·min⁻¹; P = 0.09). Among subjects...
(n = 17) that underwent repeat MRI after a mean ~8-wk period, we observed no significant differences in IHE-induced changes in CSA, CFV, and CBF between the two studies (see Bland-Altman plots in Fig. 6). Importantly, there was a strong correlation between the %CSA change with IHE during the first and second visits weeks apart (R = 0.9; P < 0.0001) (Fig. 6). Similarly, there was a significant correlation between the %CFV and %CBF change at the first visit versus the second visit (R = 0.75; P < 0.01 and R = 0.8, P < 0.001, respectively; Fig. 6). The Bland-Altman analysis (Fig. 6) and intraclass correlation coefficients for %CSA, %CFV, and %CBF change with stress (intraclass correlation coefficients = 0.90, 0.75, and 0.80, respectively) indicated good confidence of agreement and little variability between the two measures.

DISCUSSION

Role of NO in the Coronary Vasomotor Response to IHE

We previously reported a novel approach to noninvasively quantify CEF that uses high-field (3.0-T) MRI combined with IHE and which detected increases in coronary CSA and peak diastolic CBF in healthy subjects but paradoxical vasoconstriction and decreases in blood flow in patients with CAD during IHE (8–10). These responses to IHE are consistent with classic coronary vasomotor responses to endothelial-dependent stressors; however, the extent to which the IHE response is in fact mediated by NO was not tested. Because the role of NO in the IHE response was not known and questioned (13), we administered L-NMMA, a direct eNOS inhibitor, and observed that it abolishes the normal coronary vasodilatory response and CBF increase that occurs with IHE, demonstrating that IHE is a predominately endothelial-dependent coronary stressor that can be used with MRI or potentially other noninvasive imaging modalities to probe NO-mediated CEF.

Our observation that the coronary vasoreactive response to IHE is NO mediated supports earlier vasomotor flow studies of the role of NO in the peripheral circulation. Sanders et al. (23) reported that atropine but not β-blockers blocked the forearm vascular resistance change in healthy volunteers during IHE, demonstrating a role for acetylcholine-mediated activation in handgrip exercise-mediated vasodilation. L-NMMA specifically inhibits the synthesis of NO in a concentration- and stereo-specific manner (22). Prior studies showed that L-NMMA blocks ~70% of the brachial artery macrovascular vasodilatory response in healthy subjects, indicating that IHE results in endothelial-dependent, NO-dependent vasodilation in peripheral arteries (35). Furthermore, the microvascular peripheral response is also blocked by L-NMMA infusion during IHE (29). Thus prior studies suggest that the peripheral vascular responses to IHE are mediated, at least in part, by NO and reflect endothelial function.

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**Fig. 6.** Coronary artery vasoreactivity and blood flow response to IHE over a period of weeks both in healthy volunteers and patients with CAD. A: linear regression showing strong correlation between %CSA change during the first visit compared with second visit (A) and %peak diastolic CBF change between first and second visit (C). B and D: Bland-Altman plots comparing %CSA change and %CBF change between the 2 separate visits (n = 29) and indicate good confidence of agreement and little variability between the 2 measures. Lines represent 95% confidence of agreement. White circles/diamonds represent healthy volunteers, and black circles/diamonds represent patients with CAD.

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Despite studies suggesting a predominant role of NO mediating IHE-induced changes in peripheral vasoreactivity (23), there is a paucity of data regarding coronary vasoreactivity. The coronary arteries respond differently than do peripheral arteries to endothelial stressors (2, 3) and, in contrast to brachial arteries, are prone to atherosclerosis and plaque rupture. IHE has been used since the 1960s as a tool to study the cardiovascular response to stress, and the effects of IHE on the coronary vasculature were thought to be mediated by sympathetic vasoconstriction and vagal withdrawal (20). Brown et al. (2) using coronary angiography showed that significant vasoconstriction occurs during IHE in patients with CAD. However, when IHE was repeated after intracoronary nitroglycerin administration, vasodilation occurred, suggesting that decreased NO bioavailability contributes to an abnormal IHE response. In contrast to prior studies indicating an important role of NO in mediating the vascular response to IHE in brachial and coronary arteries, one study did not observe an effect of L-NMMA during IHE (19). That study differs from the current one in that handgrip exercise was greater (80 vs. 30% of maximal effort in the current study), and the additional stress may have triggered sympathetic and neurohumoral pathways not blocked by L-NMMA. Importantly, our population of healthy, young individuals without cardiovascular risk factors significantly differs from that in the prior study conducted in middle-aged patients with angina but whose cardiac angiograms did not demonstrate critical stenoses. Such patients often exhibit impaired NO production and endothelial dysfunction (28), and therefore, a NO synthase inhibitor is expected to have less of an effect in them than it does in healthy subjects with normal, robust coronary NO release, as studied here.

The significant attenuation of the normal coronary vasmotor response to handgrip with L-NMMA that we observed cannot be explained by changes in hemodynamics caused by L-NMMA itself or by a potential “memory effect” of the endothelium. We recently reported that two sequential IHE episodes (~10 min apart) in the absence of L-NMMA elicit similar changes in CSA and CBF in healthy subjects [Fig. 7, reproduced from Hays et al. (10)], indicating that the attenuation of the vascular response during IHE by L-NMMA infusion during the second IHE (Fig. 5) is due to L-NMMA and not to a nonspecific “memory” effect of repeated IHE intervals. The significant attenuation of the normal increase in CSA and CBF in response to IHE by L-NMMA is in contrast to the modest attenuation of the increase in CBF by L-NMMA to low-dose adenosine but no attenuation with high-dose adenosine previously reported (30), suggesting that unlike adenosine, the predominant impact of IHE on coronary vasoreactivity is NO mediated. These findings have significant implications for CEF testing using IHE, which is not limited to only MRI, and may pertain to alternate imaging modalities, including positron emission tomography and computed tomography.

Reproducibility of MRI Measures of CEF

We previously reported that MRI measures of CEF are unchanged during repeated IHE tests on the same day (10). However, the reproducibility over a longer time period was not previously investigated. We report here for the first time a reproducible response of CSA and CBF changes to IHE on different days and in this case over a mean 8-wk period. Endothelial function can change over the course of days and several weeks in response to a variety of stimuli including diet, exercise training, and therapeutic interventions (21), reflecting changes in expression of eNOS and altered NO bioavailability (7). The finding that the coronary MRI-IHE vasmotor responses for both CSA and CBF are reproducible over several weeks indicates that this noninvasive approach is potentially valuable for short- to medium-term intervention studies that target coronary endothelial dysfunction. Moreover, the MRI-IHE approach used in these studies is tolerated by both healthy subjects and patients with CAD and can be carried out in a reasonable time period (<45 min), with minimal risk since there is no intravenous contrast administration or radiation. The observation that the macrovascular CSA changes in response to IHE appear to be more reproducible and less variable over time than CBF responses (Fig. 6) suggests that the CSA end point may allow intervention trials with smaller sample sizes or detection of smaller group differences than the CBF end point. Furthermore, this MRI-IHE approach may facilitate the translation from the bench to the bedside of novel agents (6, 14) that may be safely and noninvasively tested in humans.

Limitations

The sample size of these studies is relatively modest but nonetheless statistically large enough to test the proposed hypotheses. L-NMMA profoundly blocked the normal coronary vasmotor response in only 25 segments in 10 subjects such that it was difficult to justify additional studies, especially with L-NMMA, a nonapproved agent. MRI measures of coronary area (16) and CFV (11, 18) were validated in prior studies, and our results are comparable with those reported using invasive techniques (2, 15, 24). Although systemic L-NMMA infusion caused a slight decrease in heart rate and increase in mean arterial pressure possibly mediated by neurohumoral mechanisms (26), the changes in RPP with IHE stress were not different during the placebo and L-NMMA IHE stress sessions. This suggests that the predominant effect of systemic L-NMMA to prevent IHE-induced coronary endothelial dilatation was due...
to its well-documented ability to inhibit NO rather than a modest sympathetic response that cannot be excluded.

Conclusions

In summary, we report here that the IHE response of the coronary arteries measured noninvasively with MRI is predominantly attenuated by l-NMMA, indicating that the normal coronary artery response to IHE is primarily NO mediated. In addition, MRI measures of NO-mediated CEF remain stable over an ~8–wk period. This too is important for designing future studies designed to noninvasively assess the effects of therapeutic interventions on CEF.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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