JACC: CARDIOVASCULAR IMAGING VOL. 1, NO. 2, 2008

ISSN 1936-878X/08/$34.00
PUBLISHED BY ELSEVIER INC. DOI:10.1016/j.jcmg.2007.12.001

Impaired Coronary Vasodilation by Magnetic Resonance Angiography Is Associated With Advanced Coronary Artery Calcification

Masahiro Terashima, MD, PHD, FACC,* Patricia K. Nguyen, MD,* Geoffrey D. Rubin, MD,† Carlos Iribarren, MD, MPH, PHD,§ Brian K. Courtney, MD,* Alan S. Go, MD,§‖ Stephen P. Fortmann, MD,‡ Michael V. McConnell, MD, MSEE, FACC*

Stanford, Oakland, and San Francisco, California

OBJECTIVES This study evaluated the hypothesis that impaired nitroglycerin (NTG)-induced coronary vasodilation is associated with advanced coronary atherosclerosis in asymptomatic older patients.

BACKGROUND Atherosclerosis is associated with both structural and functional abnormalities of the vessel wall. Noninvasive functional measures of subclinical coronary atherosclerosis may help characterize high-risk subjects and guide preventive therapy.

METHODS A total of 236 older patients (age 60 to 72 years, 33% female) without a history of cardiovascular disease were studied. Nitroglycerin-induced coronary vasodilation was measured by magnetic resonance angiography (MRA). Cross-sectional images of the right coronary artery were acquired before and 5 min after 0.4-mg sublingual NTG using a gated, breath-held spiral coronary MRA sequence (0.7-mm resolution). Quantitative analysis of the increase in cross-sectional area was performed in the 90% of patients (n = 212) with adequate image quality. Quantitation of coronary artery calcification (CAC) was performed by multidetector computed tomography using the Agatston method.

RESULTS Forty patients (19%) had advanced CAC (≥400). Coronary vasodilation to NTG was significantly impaired (p = 0.02) in patients with advanced CAC (median [interquartile range] = 15.9% [4.2% to 28.0%] vs. 21.5% [9.6% to 36.6%] for CAC <400). Importantly, NTG-induced coronary vasodilation remained independently associated with advanced CAC after multivariate analysis incorporating risk factors (p = 0.02) and other potential confounders (p = 0.04). There was no significant difference in coronary vasodilation between men and women, but few women (n = 3) had advanced CAC.

CONCLUSIONS Impaired NTG-induced coronary vasodilation by MRA is associated with advanced coronary atherosclerosis in a community-based cohort of older asymptomatic subjects. Coronary MRA may provide a noninvasive functional assessment of subclinical coronary atherosclerosis. (J Am Coll Cardiol Img 2008;1:167–73) © 2008 by the American College of Cardiology Foundation

From the *Division of Cardiovascular Medicine, †Department of Radiology, and ‡Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, California; §Division of Research, Kaiser Permanente of Northern California, Oakland, California; and the ‖Departments of Epidemiology, Biostatistics, and Medicine, University of California, San Francisco, San Francisco, California. This study was supported by grants from the Donald W. Reynolds Foundation (Las Vegas, Nevada); National Heart, Lung, and Blood Institute (grant R01HL39297, Bethesda, Maryland); and General Electric Healthcare (Waukesha, Wisconsin). Dr. Rubin is a consultant/advisory board member for TeraRecon, Inc., and Siemens Medical Solutions. Dr. McConnell receives research support from GE Healthcare, is on a scientific advisory board for Kowa, Inc., and has been an advisor for Philips Medical Systems.

Manuscript received October 18, 2007; revised manuscript received December 5, 2007, accepted December 8, 2007.

JACC: CARDIOVASCULAR IMAGING, VOL. 1, NO. 2, 2008
MARCH 2008:167–73

Noninvasive measures of subclinical coronary atherosclerosis have the potential to help identify patients at increased risk for future coronary events and guide therapy that may reduce the risks of death and disability attributable to coronary artery disease. Atherosclerosis is associated with both structural and functional abnormalities of the vessel wall. For structural assessment, coronary artery calcium (CAC) by computed tomography (CT) has been the most widely studied direct noninvasive measure of coronary atherosclerosis. Coronary artery calcium is supported by histological studies, with the presence and extent of CAC correlated to the magnitude of coronary plaque burden (1).

See page 174

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium/calcification
CT = computed tomography
ECG = electrocardiography
HDL = high-density lipoprotein
MDCT = multidetector computed tomography
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
NTG = nitroglycerin
RCA = right coronary artery
RCAC = coronary artery calcification score for the right coronary artery
SNR = signal-to-noise ratio

For functional assessment, the standard has been the measurement of epicardial coronary artery vasodilation by invasive X-ray angiography using intra-arterial stimuli. The impairment of endothelium-*dependent* vasodilation is recognized as an early step in the development of atherosclerosis (2). Nitroglycerin (NTG) is an exogenous source of nitric oxide and causes endothelium-*independent,* smooth muscle cell–dependent vasodilation, which may also be affected by atherosclerotic changes in the vessel wall. Previous studies have demonstrated that impaired coronary vasodilation to NTG, as assessed by invasive X-ray angiography, is present in patients who have coronary artery disease and diabetes (3), and has been associated with an increased risk of future cardiac events (4,5).

We and others have developed a noninvasive method to measure NTG-induced coronary vasodilation with magnetic resonance angiography (MRA) (6,7). In this study, we hypothesized that coronary vasodilation by MRA may be impaired in older patients with advanced subclinical coronary atherosclerosis.

METHODS

Patient characteristics. Two hundred fifty-three patients (age 60 to 72 years, 34% women) without a history of cardiovascular disease, other major comorbidities (including prior systemic malignancy, dementia, cirrhosis, human immunodeficiency virus/acquired immunodeficiency syndrome, and organ transplantation), or contraindication to magnetic resonance imaging (MRI) were randomly selected from the membership of Kaiser Permanente of Northern California as a substudy of the ADVANCE (Atherosclerotic Disease, Vascular Function, and Genetic Epidemiology) study (8). The recruitment of these patients was performed by Kaiser Permanente of Northern California Division of Research, and all subjects underwent evaluation through the Stanford Prevention Research Center, including CT for CAC. Patients were evaluated without any alteration of their medical regimen per their health care provider, including continuation of vasoactive medications. Magnetic resonance imaging was not completed in 17 subjects due to claustrophobia, back pain, or technical problems, leaving an MRI cohort of 236 patients (mean age 66.0 ± 2.7 years, 33% women, and 37% non-Caucasian). Magnetic resonance imaging was performed within 1 week of CT in all subjects. Written informed consent was obtained from all participants. The study protocol was approved by the Institutional Review Boards at Stanford University and the Kaiser Foundation Research Institute.

NTG-induced coronary vasodilation with MRA. Nitroglycerin-induced coronary vasodilation by MRI was performed using methods described in more detail previously (7). A 1.5-T Signa MRI scanner (GE Healthcare, Waukesha, Wisconsin) equipped with high-performance gradients (40 mT/m, 150 mT/m/ms) was used. A commercial 4-channel cardiac phased-array surface coil provided signal reception (GE Healthcare). A real-time interactive MRI system (iDrive, GE Healthcare) was used for coronary localization. High-resolution coronary MRA was performed using a multislice spiral sequence, as previously reported (9), with cardiac gating, breath-holding, and acquisition during diastole (field of view = 22 cm, in-plane spatial resolution = 0.7 mm, slice thickness = 5 mm, 3 slices, repetition time = 1 heart beat, echo time = 2.5 ms, 18 interleaves, flip angle = 60°, acquisition window = 35 ms). A subject-specific trigger delay time during diastole was determined from reviewing a 4-chamber cardiac cine magnetic resonance acquisition (10).

After real-time interactive MRI was used to prescribe in-plane views of the right coronary artery (RCA), a cross-sectional view of a linear portion of the proximal- to mid-RCA was then prescribed. Cross-sectional high-resolution coronary MRA images were then acquired both before and 5 min after

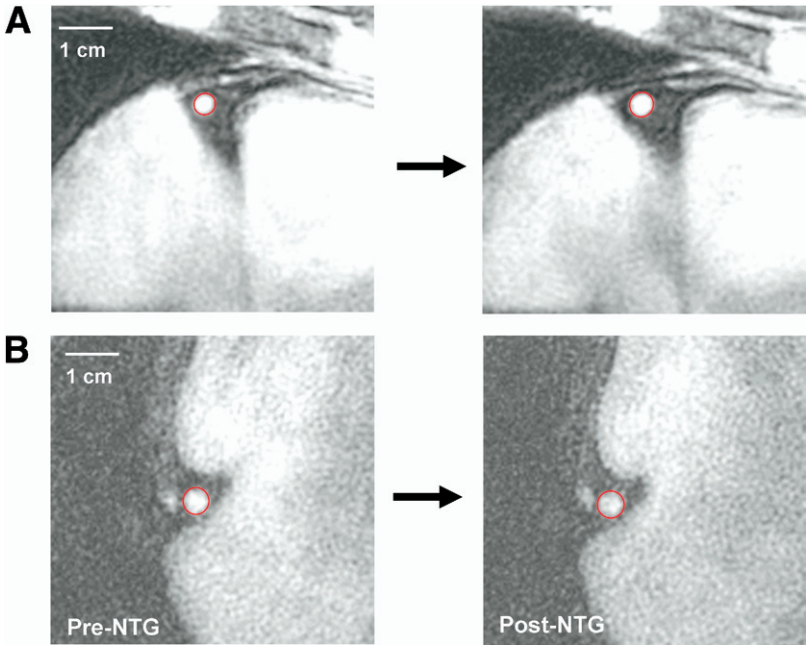

Figure 1. Coronary MRA of NTG-Induced Coronary Vasodilation

Coronary magnetic resonance angiography (MRA) images are shown demonstrating the analysis of nitroglycerin (NTG)-induced vasodilation. Coronary MRA of the right coronary artery (RCA) was performed pre- and post-NTG using a 0.7-mm gated, breath-held spiral MRA sequence. Cross-sectional area of the RCA was traced manually **(red circles)**. The MRA images **(A)** from the patient with a coronary artery calcium (CAC) score = 0 show a greater degree of NTG coronary vasodilation (28.6%) compared with MRA images **(B)** from the patient with a CAC score = 443 (coronary vasodilation = 17.0%).

0.4-mg sublingual NTG was administered to the subject while in the magnet (Fig. 1). The time point after NTG (5 min) was chosen based on our previous data (7) on the time course of NTG-induced coronary vasodilation, demonstrating the most consistent coronary vasodilation at 3 to 7 min after NTG. Matching pre- and post-NTG images were identified, as described previously (7), and then all images were pooled and randomized, with neither patient nor NTG information provided on the images. Prior to analysis, images were judged to be good, fair, or poor based on signal-to-noise ratio (SNR), vessel border sharpness, and artifacts. The cross-sectional area of the RCA was traced by a single investigator, with a similar low intraobserver variability as found previously (7) (mean difference in cross-sectional area, expressed as a percentage of the overall mean, was 6.3 ± 5.0% with correlation coefficient = 0.97).

CAC. The presence and severity of CAC was assessed by 4- or 16-row multidetector CT (MDCT) scanners (GE Healthcare and Siemens Medical Solutions, Erlangen, Germany, respectively) (8). After a scout image had been acquired, a prospective electrocardiography (ECG)-triggered breath-held CT scan through the heart was performed with either a 4 × 2.5-mm or a 16 × 1.25-mm nonhelical acquisition, gated to mid-diastole based upon a graphical prescription from the ECG tracing. Two identical scans were acquired. Contiguous 2.5-mm transverse sections were reconstructed using a half-scan reconstruction algorithm to give an effective temporal resolution of 200 to 250 ms per section. An experienced technologist analyzed the CT sections using an AccuImage coronary calcium scoring workstation (Merge/eFilm, South San Francisco, California) to determine the Agatston score (11), with the final score equal to the average of the 2 scans (providing both total CAC score and CAC score for the RCA). The total CAC was considered advanced if the score was ≥400, as indicated by previous reports (12,13).

Statistical analysis. Continuous variables are expressed as means with standard deviations or medians with interquartile ranges. The differences between CAC groups were compared using the unpaired *t* test if data were normally distributed; if otherwise distributed, the nonparametric Mann-Whitney *U* test was used. Differences among the 4 CAC groups, 0 ≤ CAC < 10, 10 ≤ CAC < 100,

Table 1. Characteristics of Study Patients Stratified by CAC Score

Characteristics	CAC <400 (n = 172)	CAC ≥400 (n = 40)	p Value
Age (yrs)	65.9 ± 2.7	66.4 ± 2.7	0.30
Gender (men/women)	106/66	37/3	**<0.001**
Body mass index (kg/m^2)	26.9 ± 4.1	27.9 ± 4.7	0.19
Diabetes mellitus (%)	15.7%	30%	**0.04**
Systolic blood pressure (mm Hg)	132 ± 18	135 ± 19	0.32
Total cholesterol/HDL cholesterol ratio	3.9 ± 1.1	3.9 ± 0.9	0.68
Current smoker (%)	8.1%	10%	0.70

Results are given as mean ± standard deviation or proportions. Values in **bold** indicate statistical significance.
CAC = coronary artery calcium; HDL = high-density lipoprotein.

100 ≤ CAC < 400, and CAC ≥ 400, were analyzed by the Kruskal-Wallis test. Differences in distribution of CAC scores <400 and ≥400 were assessed by the chi-square test. Regression analysis was performed comparing NTG-induced coronary vasodilation to $\log_{10}$ (CAC score + 1). Multivariable logistic regression analysis was performed to identify independent predictors of advanced CAC, incorporating conventional coronary risk factors, such as age, gender, body mass index, diabetes mellitus (history of treatment or fasting glucose ≥126 mg/dl), systolic blood pressure, total cholesterol/high-density lipoprotein (HDL) cholesterol ratio, and smoking into the model. For multivariate analysis, tertiles of the percentages of coronary vasodilation were also used. A 2-tailed p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics. Of the 236 patients, 10% were excluded prior to analysis because of poor image quality on either the pre- or post-NTG MRA, leaving 212 subjects for quantitative analysis. Median CAC was 37 (interquartile range 1 to 269). Forty patients (19%) had advanced CAC, defined as CAC ≥400. Clinical characteristics of the 2 groups are shown in Table 1. In subjects with CAC ≥400, there was a significantly higher proportion of men (p < 0.001) and of subjects with diabetes mellitus (p = 0.04).

NTG-induced coronary vasodilation and coronary artery calcium. Patients with CAC ≥400 had significantly impaired coronary vasodilation (median [interquartile range] = 15.9% [4.2% to 28.0%]) compared with patients with CAC <400 (21.5% [9.6% to 36.6%], p = 0.02) (Fig. 2). The results of multivariable logistic regression analysis are shown in Table 2. The degree of NTG-induced coronary vasodilation was independently and inversely associated with CAC ≥400 (p = 0.02) after adjustment for age, gender, body mass index, diabetes, systolic blood pressure, total cholesterol/HDL cholesterol ratio, and current cigarette smoking. The association of NTG-induced coronary vasodilation in patients with advanced CAC also remained significant (p = 0.04) in multivariable logistic regression analysis after vasoactive medication use was included as a potential confounder.

Further analysis of NTG coronary vasodilation in less advanced CAC did not reveal a "dose-response" relationship, as regression analysis of vasodilation versus $\log_{10}$ (CAC + 1) was not significant (p = 0.15), and the degree of vasodilation was relatively flat for CAC subgroups: 0 ≤ CAC < 10: 21.4% (10.7% to 36.2%); 10 ≤ CAC < 100: 25.1% (8.8 to 36.8%); and 100 ≤ CAC < 400: 21.4% (9.7% to 37.3%) (p = 0.16). High CAC did affect image quality (CAC ≥400: 68% fair, 32% good vs. CAC <400: 45% fair, 55% good, p = 0.01), but the percent vasodilation was similar for fair and good image quality (p = 0.87).

NTG-induced coronary vasodilation by gender. Overall there was not a significant difference in NTG-induced coronary vasodilation between men and women (men: 20.8% [8.0% to 36.3%] vs. women: 21.1% [6.9% to 34.0%], p = 0.9). In men only (n = 143), the impaired NTG-induced coronary vasodilation in patients with CAC ≥400 remained significant by both univariate (p = 0.02) and multivariate analysis (p = 0.01). The sample size for women (n = 3 for CAC ≥400) was too small for meaningful statistical evaluation.

NT-induced coronary vasodilation and RCA coronary artery calcium. As the MRI measurement was done on the RCA, we also compared the MRI vasodilation measures to the coronary artery calcification score for the right coronary artery (RCAC). Median RCAC was 0 (interquartile range 0 to 47). There was +RCAC (RCAC score >0) in 86 patients (41%, 71 male). Only 2 subjects with CAC ≥400 did not have +RCAC. The degree of NTG-induced coronary vasodilation was significantly impaired in patients with +RCAC compared to patients with −RCAC by univariate analysis (17.4% [5.0% to 33.7%] vs. 22.6% [11.4% to 36.5%], p = 0.049) and multivariate analysis (p = 0.03).

DISCUSSION

Coronary MRA was successfully applied to assess NTG vasodilation in a large cohort of asymptom-

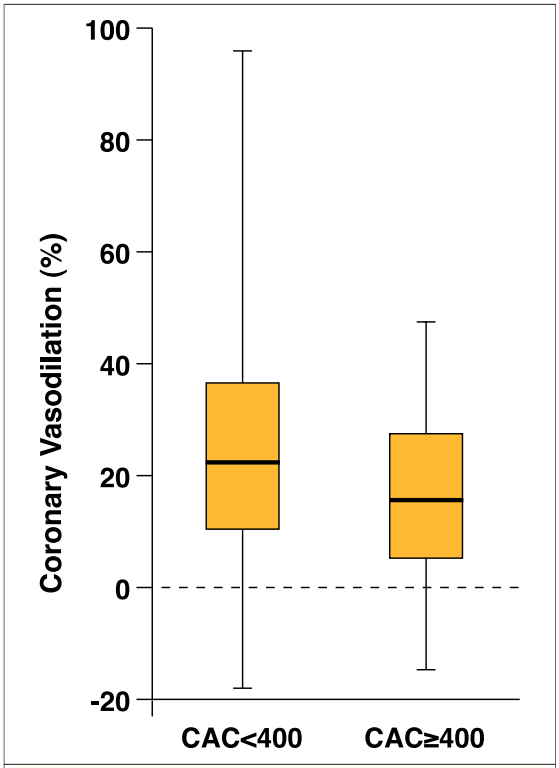

Figure 2. Comparison of NTG-Induced Coronary Vasodilation and CAC

The degree of coronary vasodilation is shown for patients with and without advanced CAC. Coronary MRA images were analyzed in 212 patients and coronary vasodilation to NTG was quantified. Coronary artery calcium scoring was performed by computed tomography. Box and whisker plots show the median, interquartile range, and full range of percent coronary vasodilation between groups with and without advanced CAC (≥400). Patients with CAC ≥400 had significantly impaired NTG-induced coronary vasodilation compared to patients with CAC <400 by univariate and multivariate analysis ($p = 0.02$). Abbreviations as in Figure 1.

atic, older community-based patients. We found that NTG coronary vasodilation was impaired in patients with advanced CAC, which were primarily men in this cohort. In addition, this association was independent of other major coronary risk factors, suggesting that NTG coronary vasodilation by MRA may be a functional measure of subclinical coronary atherosclerosis.

Coronary vasodilation and CAC. Coronary vasomotor function plays an important role in the onset and progression of coronary atherosclerosis. Endothelial dysfunction, as measured by the impairment of endothelium-*dependent* vasodilation, is considered to be an early marker of atherosclerosis, which can be found without overt angiographic or ultrasound evidence of coronary atherosclerosis (14,15). The assessment of epicardial coronary vasodilation is distinct from the assessment of coronary flow or perfusion reserve, which are primarily indicators of microvascular dysfunction or flow-limiting stenoses. Several studies have found a predictive value of endothelium-dependent epicardial coronary vasodilation in response to intracoronary infusion of acetylcholine in patients with mild coronary atherosclerosis or normal coronary angiograms by invasive coronary angiography (4,15,16). Although NTG-induced (endothelium-*independent*) vasodilation has typically been used as a "positive control" in these patients, impairment has been found (17). Schachinger et al. (4) investigated both endothelium-dependent and -independent coronary vasodilation in 147 patients with coronary artery disease and reported that NTG-induced coronary vasodilation was a significant predictor of prognosis. Similarly, von Mering et al. (5) studied 163 women with suspected myocardial ischemia and reported that women with a confirmed acute ischemic event had significantly impaired NTG-induced coronary vasodilation. These data suggest that atherosclerotic changes to the vessel wall can impair vasodilation beyond the effects on the endothelium, although the precise mechanisms underlying the impairment remain unclear. Our data suggest that there may be a threshold effect, with NTG vasodilation remaining intact until atherosclerosis is advanced.

Interestingly, smooth muscle cells are not only the primary mediators of NTG-induced vasodilation (18), but are also thought to be responsible for the formation of vascular calcification (19,20). Kullo et al. (21) recently reported that a decreased brachial artery vasodilator response to NTG, but not flow-mediated endothelium-dependent vasodilation, is associated with subclinical coronary atherosclerosis as measured by CAC in 441 asymptomatic patients. A recent study of subclinical atherosclerosis in 292 participants from

Table 2. Multivariate Analysis of NTG-Induced Coronary Vasodilation and Advanced CAC (≥400)

Variable	Adjusted Odds Ratio (95% Confidence Interval)	p Value
NTG coronary vasodilation (per SD increment)	0.60 (0.34–0.91)	**0.02**
Age (per yr)	1.08 (0.94–1.24)	0.28
Gender (men vs. women)	8.45 (2.37–30.09)	**0.001**
Body mass index (per kg/m^2)	1.03 (0.94–1.13)	0.54
Diabetes mellitus (yes/no)	1.66 (0.7–3.95)	0.25
Systolic blood pressure (per mm Hg)	1.01 (0.99–1.03)	0.54
Total cholesterol/HDL cholesterol ratio	0.87 (0.53–1.42)	0.57
Current smoker (yes/no)	1.25 (0.32–4.94)	0.75

Values in **bold** indicate statistical significance.
NTG = nitroglycerin; SD = standard deviation; other abbreviations as in Table 1.

the Framingham Heart Study included aortic MRI, coronary and thoracic aortic calcification by CT, and carotid intima-media thickness by ultrasound (22). The results indicated that a combination of imaging tests may be needed to fully identify higher-risk asymptomatic patients. Further studies of the prognostic significance of NTG-induced coronary vasodilation by coronary MRA and its value relative to CAC and other cardiovascular tests and risk factors are clearly needed.

Risk factors. According to previous reports, age and gender are strong risk factors for advanced burden of CAC (23–26). In our study, the age range of enrolled subjects was narrow (60 to 72 years), and therefore we did not observe a significant association between age and advanced CAC. However, male gender was a strong predictor of advanced CAC in our study, which is consistent with prior studies (26). In other studies of asymptomatic patients, many conventional coronary risk factors, such as obesity, hypertension, hypercholesterolemia, diabetes, and smoking, were strongly associated with CAC (23,27). Interestingly, in our study, only male gender and diabetes were significantly associated with CAC ≥400. Besides the sample size and the relatively advanced age range, this may have been attributed to, in part, the relatively low prevalence of the other coronary risk factors in our sample compared with samples from previous studies (Table 1) (23,28). For example, the mean total cholesterol/HDL cholesterol ratio and systolic blood pressure were 3.9 and 133 mm Hg in our study compared with 4.0 to 5.3 and 139 to 144 mm Hg in other studies (23,28), and current smokers were 8.5% compared with 15% to 19% (23,28).

Study limitations. The main limitation of the current study is that we assessed only endothelium-independent coronary vasodilation using NTG. Prior studies indicate that an endothelium-dependent method may detect abnormalities at an earlier stage of disease (2,29) and produce more divergent responses (vasoconstriction vs. vasodilation) to improve discrimination. Nonpharmacologic endothelium-dependent stimuli, such as the cold-pressor test and mental stress, are challenging in the MRI environment, and pharmacological agents, such as acetylcholine, cannot safely be given systemically. A preliminary MRI report using the cold-pressor test shows promise (30). The other main limitation is the interpatient variability of NTG vasodilation in this study. Although the RCA was used for higher SNR and spatial resolution, and has been shown previously to be very reproducible (7,31), further improvements (32,33) in SNR, resolution, and breath-hold reproducibility may improve image quality and reduce variability.

Multidetector CT angiography has emerged as a high-resolution noninvasive approach for coronary artery imaging. A recent study did look retrospectively at patients who had more than 1 coronary CT scan, where NTG was used in 1 and not in another, and did show significantly larger coronary diameter with NTG (34). However, the radiation and contrast involved make it suboptimal for repeat imaging to measure coronary vasodilation, particularly in asymptomatic subjects.

CONCLUSIONS

In an asymptomatic older community patient cohort, impaired NTG-induced coronary vasodilation by MRA was significantly and independently associated with advanced CAC. Noninvasive assessment of coronary vasodilation may provide an additional functional measure of subclinical coronary atherosclerosis.

Acknowledgments

The authors thank the staff of the Kaiser Permanente of Northern California Division of Research and the Stanford Prevention Research Center for their assistance in patient recruitment and evaluation.

Reprint requests and correspondence: Dr. Michael V. McConnell, Division of Cardiovascular Medicine, Stanford University School of Medicine, 300 Pasteur Drive, Room H-2157, Stanford, California 94305-5233. *E-mail: mcconnell@stanford.edu.*

REFERENCES

1. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995;92:2157–62.
2. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003;23:168–75.
3. Vavuranakis M, Stefanadis C, Triandaphyllidi E, Toutouzas K, Toutouzas P. Coronary artery distensibility in diabetic patients with simultaneous measurements of luminal area and intracoronary pressure: evidence of impaired reactivity to nitroglycerin. J Am Coll Cardiol 1999;34:1075–81.
4. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101:1899–906.

5. von Mering GO, Arant CB, Wessel TR, et al. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004;109:722–5.
6. Pepe A, Lombardi M, Takacs I, Positano V, Panzarella G, Picano E. Nitrate-induced coronary vasodilation by stress-magnetic resonance imaging: a novel noninvasive test of coronary vasomotion. J Magn Reson Imaging 2004;20:390–4.
7. Terashima M, Meyer CH, Keeffe BG, et al. Noninvasive assessment of coronary vasodilation using magnetic resonance angiography. J Am Coll Cardiol 2005;45:104–10.
8. Fair JM, Kiazand A, Varady A, et al. Ethnic differences in coronary artery calcium in a healthy cohort aged 60 to 69 years. Am J Cardiol 2007;100: 981–5.
9. Yang PC, Meyer CH, Terashima M, et al. Spiral magnetic resonance coronary angiography with rapid real-time localization. J Am Coll Cardiol 2003; 41:1134–41.
10. Kim WY, Stuber M, Kissinger KV, Andersen NT, Manning WJ, Botnar RM. Impact of bulk cardiac motion on right coronary MR angiography and vessel wall imaging. J Magn Reson Imaging 2001;14:383–90.
11. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
12. He ZX, Hedrick TD, Pratt CM, et al. Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. Circulation 2000;101:244–51.
13. Newman AB, Naydeck BL, Sutton-Tyrrell K, et al. Relationship between coronary artery calcification and other measures of subclinical cardiovascular disease in older adults. Arterioscler Thromb Vasc Biol 2002;22:1674–9.
14. Nishimura RA, Lerman A, Chesebro JH, et al. Epicardial vasomotor responses to acetylcholine are not predicted by coronary atherosclerosis as assessed by intracoronary ultrasound. J Am Coll Cardiol 1995;26:41–9.
15. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr., Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101:948–54.
16. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002;106:653–8.
17. Adams MR, Robinson J, McCredie R, et al. Smooth muscle dysfunction occurs independently of impaired endothelium-dependent dilation in adults at risk of atherosclerosis. J Am Coll Cardiol 1998;32:123–7.
18. Mehta JL. Endothelium, coronary vasodilation, and organic nitrates. Am Heart J 1995;129:382–91.
19. Iyemere VP, Proudfoot D, Weissberg PL, Shanahan CM. Vascular smooth muscle cell phenotypic plasticity and the regulation of vascular calcification. J Intern Med 2006;260:192–210.
20. Trion A, van der Laarse A. Vascular smooth muscle cells and calcification in atherosclerosis. Am Heart J 2004; 147:808–14.
21. Kullo IJ, Malik AR, Bielak LF, Sheedy PF 2nd, Turner ST, Peyser PA. Brachial artery diameter and vasodilator response to nitroglycerine, but not flow-mediated dilatation, are associated with the presence and quantity of coronary artery calcium in asymptomatic adults. Clin Sci (Lond) 2007;112:175–82.
22. Kathiresan S, Larson MG, Keyes MJ, et al. Assessment by cardiovascular magnetic resonance, electron beam computed tomography, and carotid ultrasonography of the distribution of subclinical atherosclerosis across Framingham risk strata. Am J Cardiol 2007;99:310–4.
23. Oei HH, Vliegenthart R, Hofman A, Oudkerk M, Witteman JC. Risk factors for coronary calcification in older subjects. The Rotterdam Coronary Calcification Study. Eur Heart J 2004; 25:48–55.
24. Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol 2001;87:1335–9.
25. Raggi P, Shaw LJ, Berman DS, Callister TQ. Gender-based differences in the prognostic value of coronary calcification. J Womens Health (Larchmt) 2004;13:273–83.
26. Janowitz WR, Agatston AS, Kaplan G, Viamonte M Jr. Differences in prevalence and extent of coronary artery calcium detected by ultrafast computed tomography in asymptomatic men and women. Am J Cardiol 1993;72:247–54.
27. Hoff JA, Daviglus ML, Chomka EV, Krainik AJ, Sevrukov A, Kondos GT. Conventional coronary artery disease risk factors and coronary artery calcium detected by electron beam tomography in 30,908 healthy individuals. Ann Epidemiol 2003; 13:163–9.
28. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210–5.
29. Ludmer PL, Selwyn AP, Shook TL, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315:1046–51.
30. Jain H, Borges A, Iwuchukwu C, et al. Noninvasive assessment of the relationship of coronary vasomotion to plaque burden (abstr). Circulation 2006;114 Suppl II:II541.
31. Keegan J, Horkaew P, Buchanan TJ, Smart TS, Yang GZ, Firmin DN. Intra- and interstudy reproducibility of coronary artery diameter measurements in magnetic resonance coronary angiography. J Magn Reson Imaging 2004;20:160–6.
32. Yang PC, Nguyen P, Shimakawa A, et al. Spiral magnetic resonance coronary angiography—direct comparison of 1.5 Tesla vs. 3 Tesla. J Cardiovasc Magn Reson 2004;6:877–84.
33. Santos JM, Cunningham CH, Lustig M, et al. Single breath-hold whole-heart MRA using variable-density spirals at 3T. Magn Reson Med 2006; 55:371–9.
34. Dewey M, Hoffmann H, Hamm B. Multislice CT coronary angiography: effect of sublingual nitroglycerine on the diameter of coronary arteries. Rofo 2006;178:600–4.