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Physical Activity in Older Subjects Is Associated With Increased Coronary Vasodilation

The ADVANCE Study

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OBJECTIVES We investigated the association between physical activity and coronary vasodilation to nitroglycerin (NTG) in the ADVANCE (Atherosclerotic Disease, Vascular Function, and Genetic Epidemiology) cohort of older healthy subjects.

BACKGROUND Physical activity may exert its beneficial effects by augmenting coronary responsiveness to nitric oxide. The relationship between physical activity and coronary vasodilatory response to NTG, an exogenous nitric oxide donor, has not been studied in a community-based population with typical activity levels.

METHODS In 212 older adults (ages 60 to 72 years) without cardiovascular disease, we measured the coronary vasodilatory response to NTG using magnetic resonance angiography and physical activity using the Stanford Seven-Day Physical Activity Recall Questionnaire. The primary predictor measure was total physical activity (kcal/kg/day). The primary outcome measure was coronary vasodilatory response (percent increase of cross-sectional area post-NTG).

RESULTS Coronary vasodilation was 27.6% in more active subjects (>35 kcal/kg/day, e.g., 1 h of walking per day) compared to 18.9% in less active subjects ($p = 0.03$). Regression analysis showed a significant positive correlation between coronary vasodilation and physical activity ($p = 0.003$), with a slope (beta) of 1.2% per kcal/kg/day. This finding remained significant after adjustment for cardiac risk factors, coronary calcium, the use of vasoactive or statin medications, and analysis of physical activity by quintiles ($p < 0.05$). Coronary vasodilation was also associated with physical activity intensity ($p = 0.03$).

CONCLUSIONS In an asymptomatic, community-based cohort of older adults, increased coronary vasodilatory response was independently associated with greater physical activity, supporting the benefits of exercise on the order of 1 h of walking per day. (J Am Coll Cardiol Img 2011;4:622–9) © 2011 by the American College of Cardiology Foundation

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It is well established that exercise reduces cardiovascular morbidity and mortality and helps prevent the development of coronary artery disease (CAD) (1–4). One possible mechanism for these beneficial effects is that physical activity favorably alters the function of the coronary vasculature. Nitric oxide (NO) is a key vasculoprotective substance, and increased responsiveness to NO may confer a cardiovascular benefit. Previous studies have demonstrated that athletes have greater coronary vasodilatory response to nitroglycerin (NTG), an NO donor, compared to physically inactive subjects (5–7). However, these studies involved invasive measures in small, select groups of men only. Thus, it is unknown if physical activity confers the same favorable coronary vasodilatory response in a broader population with more typical levels of exercise.

We and others have shown that the coronary vasodilatory response to NTG can be measured noninvasively by magnetic resonance angiography (MRA) (8–12). The ADVANCE (Atherosclerotic Disease, Vascular Function, and Genetic Epidemiology) study investigated clinical, imaging, and genetic abnormalities in an older community-based patient cohort without cardiovascular disease (13–15). Here, we report on the relationship of physical activity of this cohort to their coronary vasodilatory response to the NO donor NTG.

METHODS

Study design and population. This cross-sectional analysis was performed as part of the ADVANCE study, which investigated 1,023 healthy older adults without cardiovascular disease or other major comorbidities recruited from Kaiser Permanente of Northern California; details of this cohort have been published previously (14,15). At study baseline, all subjects underwent a comprehensive visit, including a health survey, lipid profile, blood pressure, anthropometric measurements, and coronary calcium scoring (15). A standardized and validated questionnaire, the Stanford Seven-Day Physical Activity Recall Questionnaire (PARQ) (16–19), was used to collect physical activity data. A subset of these healthy older adults (n = 212) underwent coronary MRA for assessment of NTG-induced coronary vasodilation (12). There were no significant differences in demographic or clinical parameters between the ADVANCE cohort and this subset (all $p > 0.2$). The study protocol was approved by the institutional review boards at Stanford University and the Kaiser Foundation Research Institute. Written informed consent was obtained from all participants.

The Stanford PARQ. The Stanford PARQ is an interviewer-administered questionnaire estimating energy expenditure in kilocalories per kilogram per day (kcal/kg/day), which has been used in epidemiological, clinical, and behavioral studies since the 1980s (16,20). It has been validated in prior studies with good test-retest reliability (17,18) and used in diverse populations up to 79 years of age (19,21,22). Briefly, the PARQ is designed to estimate the amount of time that a person engages in light, moderate, hard, and very hard intensity activities during the previous 7 days. Fourteen items are used to estimate energy expenditure. The subject is guided through the recall process by a trained interviewer to determine the duration and intensity of physical activities performed. Subjects are provided with examples of various activity levels (e.g., moderate = mopping, brisk walk; hard = construction work, doubles tennis; very hard = chopping wood, running) (16). The time engaged in light activity is calculated by subtracting the time spent sleeping and performing moderate, hard, and very hard intensity activities from the total 24 h/day (16). Energy expenditure is calculated by multiplying the hours sleeping and engaging in the different physical activity categories by the average metabolic equivalent value for each intensity category (sleep = 1 MET, light = 1.5 METs, moderate = 4 METs, hard = 6 METs, and very hard = 10 METs). A standard procedure was employed for the administration, certification of staff, and scoring of the PARQ. Additionally, all staff were recertified annually in the proper administration and scoring of the PARQ.

Coronary vasodilatory response to NTG. The coronary vasodilatory response to NTG was measured by MRA, as previously described (10–12). Briefly, a 1.5-T magnetic resonance imaging (MRI) scanner equipped with a 4-channel cardiac phased-array surface coil was used (GE Healthcare, Milwaukee, Wisconsin). Real-time interactive MRI was used to prescribe in-plane and then cross-sectional views of the right coronary artery (RCA). Specifically, an imaging plane perpendicular to the long axis of the RCA was prescribed to yield the cross-sectional view. High-resolution spiral coronary MRA of the RCA in cross-section was performed with electro-

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
NO = nitric oxide
NTG = nitroglycerin
PARQ = Physical Activity Recall Questionnaire
RCA = right coronary artery

cardiography cardiac gating, breath holding, and acquisition during diastole (field of view = 22 cm, in-plane spatial resolution = 0.7 mm, slice thickness = 5 mm, repetition time = 1 heart beat, echo time = 2.5 ms, 18 interleaves, flip angle = 60°) (23). This was repeated 5 min after administration of 0.4 mg sublingual NTG while the patient remained inside the magnet, based on our prior time-course data showing the peak reliable vasodilation at this time point (10). To ensure good spatial correspondence on pre-NTG and post-NTG images for accuracy of the measurements, structures adjacent to the RCA were matched (e.g., atrioventricular groove, right atrium, right ventricle, and chest wall). The pre-NTG and post-NTG cross-sectional RCA images were all pooled and then randomized, with neither patient nor NTG information provided on the images. A custom image analysis program was used to trace the RCA border and calculate cross-sectional area (10,12). This method has been shown to have low interobserver and intraobserver variability (10,12).

Statistical analysis. Continuous variables are expressed as means with standard deviations or as medians with interquartile ranges for variables with non-normal distributions. Differences in parameters for less versus more active subjects and men versus women were assessed by Student *t* test for continuous variables and Pearson chi-square test for categorical variables. For differences in vasodilation (which was not normally distributed), the Wilcoxon rank-sums test was performed. Subjects were considered less active if their daily energy expenditure was ≤35 kcal/kg/day based on the PARQ, which is equivalent to an energy expenditure of 2,450 kcal/day by a 70-kg person. This cutoff value was chosen because it was the mean activity level for our study population and has been used previously in a large multicenter trial comparing physically less versus more active older adults in stable health without serious chronic disease (24). Before versus after NTG coronary areas were used to calculate percent change from baseline: Δ = 100% (post-NTG area − pre-NTG area)/pre-NTG area. The percent coronary vasodilation was analyzed as a continuous variable and, as this variable was skewed, a square root transformation was also performed to normalize this variate in the regression models.

The primary independent (predictor) variable was physical activity (in kcal/kg/day) assessed by the PARQ. Multivariate stepwise linear regression analyses were performed to identify independent predictors of percent coronary vasodilation. The following variables, which are known risk factors for CAD, were entered into the initial multivariate regression model: energy expenditure, age, ethnicity, sex, diabetes mellitus, smoking status, body mass index, systolic and diastolic blood pressure, and total cholesterol/high-density lipoprotein ratio. In a second model, total coronary calcium score, statin usage, and vasoactive medication usage (calcium-channel blockers, beta-blockers, nitrates, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor blockers) were added. Physical activity was evaluated first as a continuous variable and, because it was skewed, also analyzed as a categorical variable by dividing into quintiles. The resulting 5 groups were used to assess the change in vasodilation by Jonckheere test for ordered alternatives and the quintiles score as an independent variable in regression analyses. Comparisons of NTG-induced coronary vasodilation to categorical variables (e.g., maximum intensity of reported physical activity) were evaluated using a Kruskal-Wallis 1-way analysis of variance. A 2-tailed p value <0.05 was considered statistically significant.

All statistical analyses were performed with StatView (version 5, SAS Institute, Cary, North Carolina) and SAS (version 9.1, SAS Institute).

Statement of responsibility. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Demographic and baseline clinical characteristics. Patient characteristics are shown stratified by sex in Table 1 and by physical activity in Table 2. For the 212 subjects (62.7% Caucasian, 9.4% African American, 9.0% Hispanic, 9.9% Asian, and 9.0% other), mean age was 66.0 ± 2.7 years, 32.1% were women, and 35.2% were on vasoactive medications. The only significant differences in clinical characteristics between men and women in this cohort were that fewer women had diabetes (p = 0.03), and total cholesterol/high-density lipoprotein cholesterol was higher in men (p = 0.001).

For physical activity, the mean energy expenditure was 35.0 ± 3.4 kcal/kg/day and was significantly higher in men than in women (35.5 ± 3.7 kcal/kg/day vs. 33.8 ± 2.2 kcal/kg/day, p < 0.001). Accordingly, there was a lower proportion of physically active (>35 kcal/kg/day) women than men

(16% vs. 47%, $p < 0.001$). The durations of engagement in different intensity activities by time of day and by sex are also provided (Online Table 1). There were no significant differences in ethnic distribution ($p = 0.92$) and use of vasoactive medications (37.7% vs. 31.0%, $p = 0.35$) between the less active and more active groups. The proportion of women with a history of taking hormone replacement therapy was not significantly different between the less active and more active groups (82.5% vs. 63.6%, $p = 0.16$).

Regarding the maximum intensity of physical activities, the majority of patients fell into the moderate (48.1%) or hard (31.1%) groups, with a minority in the light (8.5%) or very hard (12.3%) groups. For each maximum intensity group, the average duration of time engaged in the different intensity activities is shown in Table 3.

There were no significant differences in baseline coronary artery cross-sectional area between less and more active subjects: 20.2 mm^2 (interquartile range: 15.8 to 24.7 mm^2) for ≤35 kcal/kg/day versus 20.6 mm^2 (16.1 to 24.5 mm^2) for >35 kcal/kg/day ($p = 0.64$).

NTG-induced coronary vasodilation. The median coronary vasodilatory response to NTG was 20.9% (interquartile range: 7.8% to 36.2%). The degree of coronary vasodilation was significantly higher in the more active patient group: 27.6% (12.6% to 38.7%) for >35 kcal/kg/day versus 18.9% (5.7% to 33.4%) for ≤35 kcal/kg/day ($p = 0.03$).

Linear regression analysis of the relationship between coronary vasodilation and physical activity also showed a significant positive correlation (beta = 1.2; $p = 0.003$), treating physical activity as a continuous variable. Importantly, this relationship remained significant after normalizing the coronary vasodilation distribution (by square root transformation) and including CAD risk factors in a multivariate regression model ($p = 0.003$). After incorporating additional potential confounders into the model, including coronary artery calcium score and use of vasoactive and statin medications, the positive correlation between NTG-induced coronary vasodilation and physical activity remained significant ($p = 0.01$). The relationship between coronary vasodilation and physical activity was also positive and significant ($p = 0.01$) when physical activity was entered into the model by quintiles. Stratifying subjects by quintiles of physical activity (Table 4) showed an ~50% increase in coronary vasodilation for the highest physical activity quintile relative to the lowest quintile.

Table 1. Demographic and Cardiovascular Risk Factors by Sex

Characteristics	Men (n = 144) (67.9%)	Women (n = 68) (32.1%)	Total (n = 212)	p Value
Age, yrs	66.0 ± 2.6	66.0 ± 2.8	66.0 ± 2.7	0.91
Diabetes mellitus, %	22% (32/144)	9% (6/68)	18% (38/212)	0.03
Current smoker, %	8% (12/144)	12% (8/68)	9% (20/212)	0.59
Body mass index, kg/m^2	27.4 ± 3.9	26.5 ± 4.8	27.1 ± 4.2	0.13
Systolic blood pressure, mm Hg	132.9 ± 16.5	132.1 ± 20.6	132.9 ± 17.9	0.76
Total cholesterol/HDL ratio	4.03 ± 1.1	3.5 ± 1.05	3.87 ± 1.09	0.001
Energy expenditure, kcal/kg/day	35.5 ± 3.7	33.8 ± 2.2	35.0 ± 3.4	<0.001
Percent >35 kcal/kg/day	47% (67/144)	16% (11/68)	37% (78/212)	<0.001

Values are mean ± SD or % (n/N). The p values for continuity-corrected chi-square values are shown.
HDL = high-density lipoprotein.

Finally, we investigated the relationship between NTG-induced coronary vasodilation and the intensity of physical activity obtained from the PARQ (Fig. 1). Stratifying subjects by their maximum reported physical activity intensity (light, moderate, hard, and very hard) showed a significant positive relationship (Kruskal-Wallis, $p = 0.03$). Thus, subjects who only reported light activities had the lowest coronary vasodilation (16.3% [3.5% to 21.9%]). In contrast, subjects who reported very hard intensity activities had almost double the NTG-induced coronary vasodilation (30.5% [16.6% to 44.6%]).

Analyzing for interaction by sex showed no significant difference in the coronary vasodilatory response: women, 21.2% (7.5% to 34.1%); and men, 20.7% (8.2% to 36.3%). Women did have a smaller baseline coronary area, 19.4 mm^2 (15.7 to 22.2 mm^2) versus 21.3 mm^2 (15.9 to 26.6 mm^2; $p = 0.03$) for men, but had a similar increase in coronary vasodilation with activity: more active versus less active women, 28.6% (5.1% to 63.0%) versus 20.1% (8.0% to 33.4%); more active versus less active men, 27.4% (14.4% to 38.7%) versus 18.6% (3.5% to 31.0%).

Table 2. Demographic and Cardiovascular Risk Factors by Physical Activity

Characteristics	Inactive (≤35 kcal/kg/day) (n = 134)	Active (>35 kcal/kg/day) (n = 78)	p Value
Age, yrs	65.9 ± 2.7	66.1 ± 2.7	0.66
Percent men	42% (56/134)	85% (66/78)	0.001
Diabetes mellitus, %	16% (21/134)	22% (17/78)	1.0
Current smoker, %	11.2% (15/134)	6.4% (5/78)	1.0
Body mass index, kg/m^2	27.3 ± 4.3	26.7 ± 4.1	0.33
Systolic blood pressure, mm Hg	132.1 ± 17.6	133.5 ± 18.5	0.60
Total cholesterol/HDL ratio	2.5 ± 1.7	2.9 ± 3.2	0.35

Values are mean ± SD or % (n/N).
HDL = high-density lipoprotein.

Table 3. Time Subjects Engaged in Different Intensity Activities for the Previous 7 Days

Maximum Reported Intensity Level	Sleep	Light Activities	Moderate Activities	Hard Activities	Very Hard Activities
Light (8.5% of cohort)	55.8 (39.8–71.1)	112.2 (96.9–128.3)	0	0	0
Moderate (48.1%)	57.3 (28.0–81.2)	105.0 (74.9–128.3)	5.6 (0.3–36.5)	0	0
Hard (31.1%)	57.1(24.5–84.0)	101.9 (70.3–136.1)	5.2 (0.0–37.0)	3.6 (0.3–27.0)	0
Very hard (12.3%)	56.4 (47.0–72.0)	101.6 (78.0–118.0)	5.6 (0.0–18.0)	1.8 (0.0–10.5)	2.5 (0.5–8.0)

Data presented in hours, mean (range).

DISCUSSION

To our knowledge, this is the largest study to date evaluating the relationship between physical activity and coronary vasodilation. Our primary finding is that there is a positive, independent association between the coronary vasodilatory response to NTG, an exogenous NO donor, and physical activity in a large, community-based cohort of healthy older adults. Importantly, this relationship remained significant after adjustment for multiple potential confounders and risk factors, including coronary calcification and statin use, and did not differ by sex. Finally, the level of exercise intensity was also associated with an increased coronary vasodilatory response.

Exercise enhances coronary vasodilatory response. Exercise is the most powerful physiological stimulus for increased myocardial oxygen demand, which is primarily met by augmentation of coronary blood flow (25). While coronary vasodilation acutely with exercise is predominantly an endothelial-dependent phenomenon, previous animal and human studies show that exercise training enhances the capacity of epicardial arteries to dilate in response to endothelium-independent stimuli (5–7,26). In a porcine model (26), after 16 to 22 weeks of training, there was augmented vasodilator capacity in response to adenosine in large epicardial arteries even after removal of the endothelium. Among the few small human angiographic studies (5–7), we originally demonstrated a significantly greater vasodilator capacity of epicardial coronary arteries in response to NTG in 11 middle-aged ultradistance runners compared with 11 inactive men (5). Another study also found an increase in coronary artery vasodilation to dipyridamole in 16 male endurance athletes compared to 32 hypertensive or sedentary men (6). More recently, improved coronary vasodilation to NTG by angiography has been shown in 8 healthy men after undergoing 5 months of endurance training (7). Our current study is consistent with the prior studies showing that increased physical activity enhances the coronary vasodilatory response, but we cannot exclude that increased coronary vasodilation contributes to increased physical activity. Importantly, our data substantially expand the prior findings to a community cohort of both men and women engaged in usual physical activities. Moreover, the data indicate that greater epicardial coronary artery vasodilator capacity is present even with relatively modest amounts of physical activity, as >35 kcal/day can be achieved with approximately 1 h of walking per day.

Coronary vasodilation as a potential measure of vascular health. Greater vasodilatory response to the NO donor NTG in more active subjects likely results from functional adaptations within the coronary vasculature (27,28). It is known that exercise training affects the bioavailability of NO by increasing NO synthase (29,30) and superoxide dismutase (31), the latter limiting the inactivation of NO by reactive oxygen species (32). Exercise may also directly affect vascular smooth muscle cell respon-

Table 4. Coronary Vasodilation by Quintiles of Physical Activity

Quintile	Physical Activity kcal/kg/day, Mean (Range)	% Coronary Vasodilation		Increase in Coronary Vasodilation, Relative to Quintile 1	p Value vs. Quintile 1
		Unadjusted, Mean ± SD	Adjusted, Mean ± SD		
1	31.8 (30.4–32.4)	20.4 ± 21.0	18.3 ± 2.6	1.00	
2	32.9 (32.4–33.3)	17.5 ± 16.6	19.1 ± 2.8	1.04	0.8
3	34.0 (33.4–34.5)	24.6 ± 21.1	21.0 ± 3.0	1.15	<0.001
4	35.8 (34.6–37.3)	26.6 ± 22.1	22.3 ± 3.0	1.22	<0.001
5	40.4 (37.4–51.2)	29.1 ± 20.4	27.8 ± 5.2	1.52	<0.001

Adjustment variables were age, ethnicity, sex, diabetes, smoking status, body mass index, systolic and diastolic blood pressure, total cholesterol/high density lipoprotein ratio, coronary calcium score, statin usage, and vasoactive medication usage.

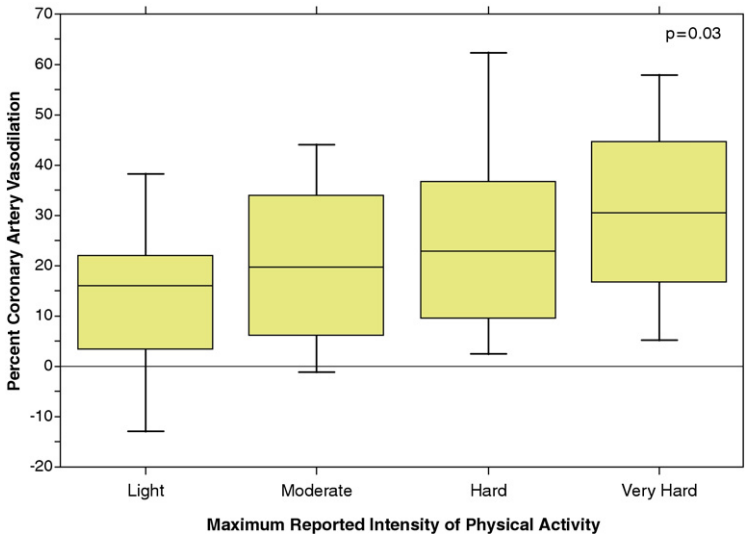

Figure 1. Coronary Vasodilation and Physical Activity Intensity

A box-and-whisker plot displays the degree of nitroglycerin-induced vasodilation according to categories of maximum reported intensity of physical activity. The degree of nitroglycerin-induced coronary vasodilation increases significantly with the maximum reported intensity of physical activity (Kruskal-Wallis, $p = 0.03$). The **box** represents the interquartile range, the **line** dividing the box is the median, and the **whiskers** extend to 1.5 × the interquartile range.

siveness to NO by altering ion channel activity and density (25,33). All of these adaptations in response to exercise may increase the vasodilatory effect of NTG as a direct NO donor. Assessing coronary vasodilatory response to NTG may, therefore, provide a measure of coronary health, as studies have shown endothelial-independent coronary vasodilation can affect prognosis (34,35).

Noninvasive assessment of coronary vasodilation. MRI has been shown to have sufficient resolution to detect coronary vasodilation to NTG in 4 prior studies of healthy subjects or patients (9–12), with low interobserver and intraobserver variability (10,12). As it is noninvasive and does not require ionizing radiation or contrast agents (8), MRI is ideal for serial assessment of asymptomatic subjects. Computed tomography can also provide high-resolution imaging of the coronary lumen (36) and vasodilation with NTG (37), but the radiation and iodinated contrast involved make it suboptimal for serial imaging of coronary vasomotor changes. The feasibility of transthoracic echocardiography for measuring epicardial coronary vasodilation has been shown in healthy men (32,38). An alternative approach is to assess coronary microvascular function by measuring coronary flow reserve in response to vasodilators. That can be performed by MRI (39–41), positron emission tomography (42), and transthoracic Doppler techniques (43,44), and has been shown to be impaired in patients with coronary risk factors (40). Comparing the significance of epicardial versus microvascular vasomotor function warrants future study.

Study limitations. A limitation of this study is that we did not also incorporate a measure of endothelial-dependent coronary vasodilation, an early marker of atherosclerosis, which has been shown in previous studies to be affected by physical activity (25,27,28,45). The measurement of endothelial-dependent vasodilation is challenging in the magnetic resonance environment but deserves further investigation. Reports using the cold pressor test or exercise show promise (41,46), including a recent study showing both impaired vasodilation and blunted flow response to hand-grip exercise in CAD patients (47).

Another potential limitation of the study is that a more objective measure of physical activity was not used. Although the PARQ has been validated in multiple previous studies, and is commonly used in large epidemiologic studies, it is an interviewer-administered questionnaire that is subject to recall bias (17–19,21,22,24). Also, the physical activity estimate is not altered on the basis of age or sex, and it assumes 1.5 METs for awake hours not spent in moderate or more vigorous activities, which may overestimate energy expenditure in very sedentary subjects. However, misclassification of activity level

would tend to bias the results toward the null. Future studies would be strengthened by incorporating objective measures of physical activity or cardiopulmonary fitness (17,19).

CONCLUSIONS

In an asymptomatic older patient population, higher physical activity, on the order of walking for an hour a day, is associated with greater coronary vasodilatory response to the NO donor NTG, independent of other major cardiovascular risk factors. This is a promising approach for the noninvasive assessment of coronary physiology and may contribute to population-based studies of preventative strategies. Finally, our findings are consistent with the known benefits of regular moderate exercise on cardiovascular health.

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Key Words: coronary arteries ■ magnetic resonance imaging ■ nitroglycerin ■ vasodilation.

▶APPENDIX

For a supplementary table, please see the online version of this article.