

High Prevalence of Myocardial Perfusion Abnormalities on Positron Emission Tomography in Asymptomatic Persons With a Parent or Sibling With Coronary Artery Disease

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Background—We hypothesized that asymptomatic persons with a parent or sibling with coronary artery disease (CAD) have myocardial perfusion defects on positron emission tomography (PET) as markers of early CAD.

Methods and Results—After medical and family histories were recorded, 90 subjects underwent rest-dipyridamole cardiac PET perfusion imaging, including 18 index cases (a subject with CAD documented by PET and arteriography), 32 asymptomatic adults without known CAD who had a parent or sibling with CAD among these index cases, 30 asymptomatic subjects with comparable coronary risk factors without CAD or a family history of CAD, and 10 volunteer control subjects with no risk factors and no family history. PET perfusion images were quantified with automated software for size of abnormalities as percent of the cardiac image outside 95% CIs of normal controls and for severity as the lowest quadrant average relative activity. Of asymptomatic subjects with a parent or sibling with CAD (first-degree relatives), 50% had dipyridamole-induced myocardial perfusion defects that involved $\geq 5\%$ of the cardiac image outside normal 95% CIs with or without other risk factors. The size of perfusion defects was larger in first-degree relatives than in control subjects ($11 \pm 13\%$ versus $1 \pm 1\%$, $P=0.02$) and larger than in asymptomatic subjects with comparable risk factors but no family history of CAD ($11 \pm 13\%$ versus $5 \pm 6\%$, $P=0.02$).

Conclusions—This study documents the presence of quantitative, statistically significant, dipyridamole-induced myocardial perfusion abnormalities on PET in 50% of asymptomatic persons with a parent or sibling with CAD, independent of other risk factors, indicating preclinical coronary atherosclerosis. (*Circulation*. 2001;103:496-501.)

Key Words: tomography ■ perfusion ■ genetics ■ risk factors ■ coronary disease

Family history of coronary artery disease (CAD) is an independent determinant of coronary risk.^{1,2} However, coronary arteriography is not justifiable on the basis of family history alone. Coronary arteriography also fails to identify diffuse atherosclerosis throughout the length of the epicardial coronary arteries³⁻⁷ that is commonly the substrate for plaque rupture and coronary events.⁸⁻¹¹ Cardiac PET has a diagnostic accuracy of $\approx 95\%$, even in asymptomatic subjects.^{5,12-17} In patients with abnormal coronary arteriograms, coronary flow reserve on PET is reduced in myocardial regions without arteriographic stenoses^{18,19} due to diffuse disease that is not apparent on the arteriogram,³⁻⁷ which, however, may cause perfusion abnormalities on dipyridamole PET.²⁰

Accordingly, we tested the hypothesis that significant myocardial perfusion defects on dipyridamole PET are common in asymptomatic persons with a parent or sibling with CAD either with or without other risk factors or lipid disorders.

Methods

Patient Selection

After informed consent, PET perfusion imaging was carried out at rest and after dipyridamole in 90 subjects, who included 18 index cases with CAD documented on arteriography and on PET, 32 asymptomatic subjects with a parent or sibling among these 18 index cases, 30 asymptomatic subjects with comparable other risk factors but without family history of vascular disease, and 10 normal control subjects with no risk factors and no family history of vascular disease, as established in the normal database before these clinical studies were undertaken.

Detailed medical and family histories were obtained from every subject, including control subjects, particularly for risk factors defined as age of >45 years in men and >55 years in women, current cigarette smoking, blood pressure of $>140/90$ mm Hg or on antihypertensive medication, diabetes mellitus, HDL cholesterol of <35 mg/dL, LDL cholesterol of >130 mg/dL, triglyceride level of >200 mg/dL, and obesity. All subjects were advised prospectively to undergo cardiac PET with family history and/or risk factors as the only reason. Asymptomatic and control subjects were not taking cardiovascular medications.

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ORIENTATION OF HEART AND CORONARY ARTERIES ON PET SCANS

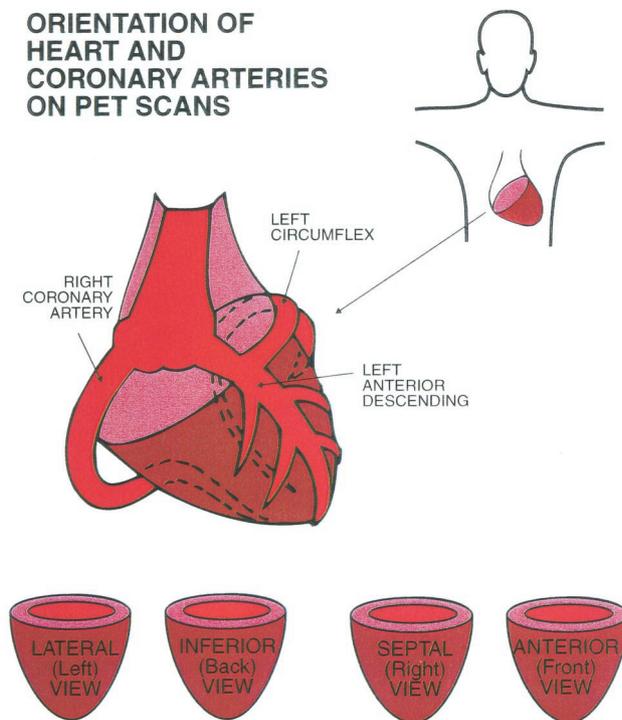


Figure 1. Four views of a 3D image of myocardial perfusion on PET (from left to right): left lateral, inferior, right or septal, and anterior or superior, each corresponding to distribution of coronary arteries.

PET Perfusion Imaging

PET imaging of myocardial perfusion was performed as previously described.^{5,21,22} Patients stopped smoking for 4 hours, fasted for 8 hours, and abstained from ingesting caffeine and theophylline for 24 hours before the PET study. PET was performed with the University of Texas–designed Posicam BGO multislice tomograph with a reconstructed resolution of 10-mm full width at half-maximum (FWHM). Transmission images were obtained to correct for photon attenuation. Emission images obtained after the intravenous injection of 18 mCi of cyclotron-produced [¹³N]ammonia contained 20 to 40 million counts.

At 40 minutes after administration of the first dose of ammonia to allow for decay of the first radionuclide dose, dipyridamole (0.142 mg·kg⁻¹·min⁻¹) was infused intravenously over 4 minutes. Four minutes after this infusion, a second dose of 18 mCi of [¹³N]ammonia was injected. Four minutes later, to allow blood pool clearing, PET imaging was repeated. Aminophylline (125 mg) was administered intravenously on a routine basis.

Automated Quantitative Analysis of PET

To obtain objective, quantitative measurements of PET perfusion defects without observer bias in interpretation or selection of regions of interest, a completely automated analysis of severity of PET abnormalities was carried out with the use of previously described software,^{5,21,22} which is briefly reviewed here. A 3-dimensional (3-D) restructuring algorithm generates true short- and long-axis views from PET transaxial cardiac images, perpendicular to and parallel to the long axis of the left ventricle. To avoid the visual spatial distortion inherent in polar displays, the circumferential profiles are used to reconstruct 3-D topographic views of the left ventricle that show relative regional activity distribution. The 3-D topographic views are divided into fixed sections that consist of a septal, an anterior, a lateral, and an inferior quadrant of the 3-D topographic display (Figure 1).

A mean algorithm determines, for each of the 3-D topographic views, the mean activity level in each of these 4 quadrants expressed

as relative activity normalized to the maximum 2% of pixels in the whole heart data set and scaled as 100% in control subjects and patients. Finally, an algorithm automatically identifies regions of each topographic quadrant with values that deviate outside 95% CIs of normal values on the basis of studies of 10 normal volunteers without risk factors or family history and computes the percentage of the cardiac image outside 95% CIs.

PET End Points

The end points that were measured automatically on PET images were size of the perfusion defects, quantified as the percent of the cardiac images outside 95% CIs of the normal control group, and severity, defined as the lowest quadrant average relative activity (ie, the average relative activity for the quadrant with the lowest average activity of the anterior, septal, lateral, and inferior quadrants for each subject). The quadrant with the lowest or minimum relative activity contains the perfusion defect or defects and quantifies the relative severity of segmental perfusion abnormalities at rest and after dipyridamole stress. For example, a value of 60% indicates that the mean relative activity for the quadrant with the lowest counts, and therefore containing the perfusion defect, is 60% of the normal maximum of 100%. In prior studies, automated quantification of size and severity has been most sensitive and reliable with the least statistical variability for distinguishing between groups of patients with PET perfusion imaging.^{5,21,22}

For determination of the proportion of subjects in each group as abnormal or normal in a binary classification, a conservative threshold of >5% of the perfusion images outside 95% CIs was used that had to be a contiguous circumscribed perfusion defect (not random pixels) on the basis of objective software determined criteria. The 5% threshold size is a defect that is visually obvious, that is not due to small variations in activity, and that is outside normal 95% CIs. However, all patient categorizations in this study were based on objective software criteria with no end points that used visual interpretation.

Statistical Analysis

Automated measures of differences in these end points between groups of patients were analyzed as continuous variables using ANOVA with the Bonferroni/Dunn post hoc correction in StatView (Abacus Concepts) software.^{23,24} Data are reported as mean ± 1 SD. For discrete variables such as number or percent of subjects showing changes outside 95% CIs, significance of differences between groups was determined by the χ^2 test (StatView).

Results

Fifty percent of 32 asymptomatic subjects (first-degree relatives) with a parent or sibling with documented CAD had perfusion defects on dipyridamole PET images that involved $\geq 5\%$ of the myocardium outside normal 95% CIs of (Figure 2) on the basis of objective criteria not dependent on visual interpretation. To examine the influence of family history of CAD separately from other risk factors, we separately analyzed a subset of 10 of these asymptomatic first-degree relatives with no other risk factors except family history; this subset also had a comparable prevalence (50%) of perfusion defects with $\geq 5\%$ of their cardiac image outside the normal 95% CIs (Figure 2).

To compare the relative influence of family history of CAD with the influence of other risk factors, we also compared the asymptomatic subjects with a family history of CAD with persons with no family history of CAD but with other comparable risk factors (30 patients). The prevalence of dipyridamole PET perfusion abnormalities in these 2 groups was not significantly different (50% versus 36%) (Figure 2). Therefore, a person with a parent or sibling with CAD but no

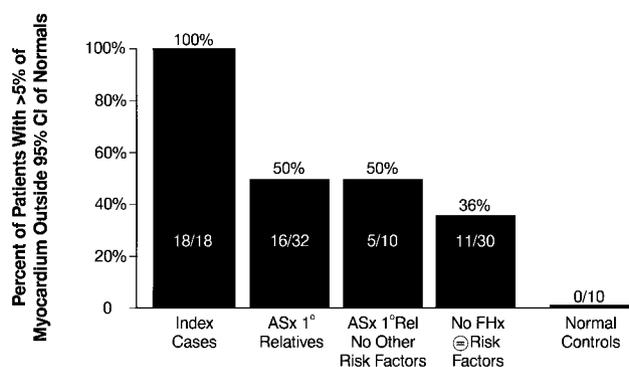


Figure 2. Prevalence of patients with $\geq 5\%$ of cardiac image outside normal 95% CIs on PET. ASx 1° indicates asymptomatic persons (first-degree relatives) with parent or sibling with documented CAD; Rel, relatives; No FHx, no family history of vascular disease; ⊕, comparable other risk factors.

other risk factors had a prevalence of abnormal dipyridamole PET images comparable to that of persons with other risk factors but no parent or sibling with CAD. The prevalence of dipyridamole-induced perfusion abnormalities among all groups compared with normal controls with no family history of vascular disease and no risk factors was significant ($P < 0.001$, χ^2).

Determination of prevalence through categorization of subjects as normal or abnormal in this analysis is not directly relatable on a clinical basis to an individual. For clinical purposes, we also analyzed average size and severity of perfusion abnormalities, so that the results for an individual could be compared with standard deviation limits of normal controls. The average size of perfusion defects in asymptomatic persons with a parent or sibling with CAD (first-degree relatives) was $11 \pm 13\%$ of the myocardial image, significantly larger than that of normal controls ($P = 0.02$) (Figure 3, top). The mean severity of perfusion defects, measured as the lowest quadrant average of relative activity, was $68 \pm 6\%$ in these first-degree relatives, significantly worse than the value of $76 \pm 6\%$ in normal controls ($P < 0.001$) (Figure 3, bottom), the normal range incorporating biological and imaging variability.

We also compared the average size and severity of perfusion defects in asymptomatic persons with and without family history but comparable other risk factors. In the asymptomatic group with a parent or sibling with CAD, the size of dipyridamole-induced perfusion defects was larger than in subjects with comparable risk factors but no family history of CAD (Figure 3, top). However, the severity of perfusion defects did not differ between the 2 groups (Figure 3, bottom). Therefore, a family history was associated with more extensive disease (larger defects) but not more severe disease (intensity of the perfusion defects) compared with subjects with comparable other risk factors but no family history of vascular disease. Although control subjects demonstrated perfusion heterogeneity (Figure 3), none had 5% of the cardiac image outside 2 SD limits of normal.

Finally, the size and severity of dipyridamole-induced perfusion defects in the subset of asymptomatic subjects with a parent or sibling with CAD but no other risk factors were

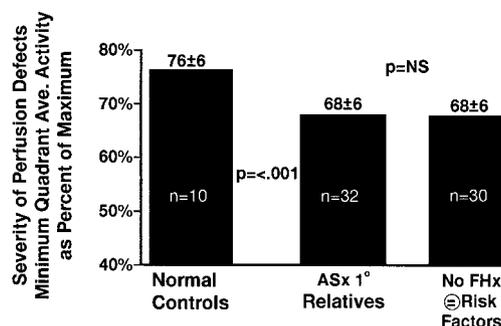
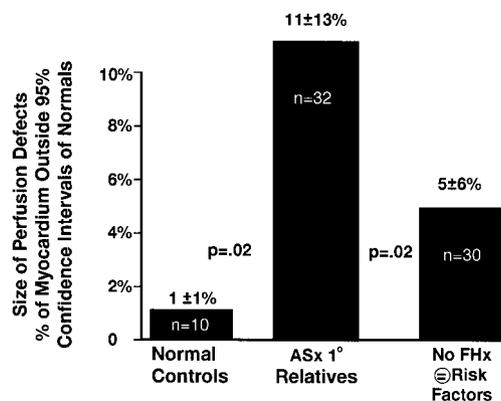


Figure 3. Size (top) and severity (bottom) of myocardial perfusion defects in asymptomatic persons with parent or sibling with CAD (ASx 1° relatives) compared with normal control subjects and with subjects with comparable risk factors but no family history of CAD (no FHx). Size of perfusion defects is quantified as percent of cardiac image outside normal 95% CIs. Severity of perfusion defects are measured as lowest quadrant average (Ave.) relative activity of 4 quadrants expressed as percent of maximum activity in image; ⊕, comparable other risk factors.

compared with control subjects with neither family history nor other risk factors. The size ($12 \pm 14\%$) (Figure 4, top) and severity ($67 \pm 6\%$) (Figure 4, bottom) of perfusion defects in this subset of the first-degree relatives with no other risk factors except family history were also significantly abnormal compared with those of normal controls ($P \leq 0.02$).

As evidence against selection bias, there were no significant differences in characteristics other than PET scans between asymptomatic persons with a parent or sibling with heart disease and asymptomatic persons with no family history of CAD in any relative, either a first-degree relative or a more distant relation (Table).

Within the asymptomatic group with a parent or sibling with CAD, the 13 subjects with LDL cholesterol concentrations of > 130 mg/dL had perfusion defects (as percent of the cardiac image outside 95% CIs; $11 \pm 2\%$) of a size that was not significantly different from the size in 11 patients with concentrations of < 130 mg/dL ($8 \pm 1\%$); both groups had HDL cholesterol above 35 mg/dL. Therefore, the influence of family history on the size and severity of dipyridamole-induced perfusion defects was independent of cholesterol levels.

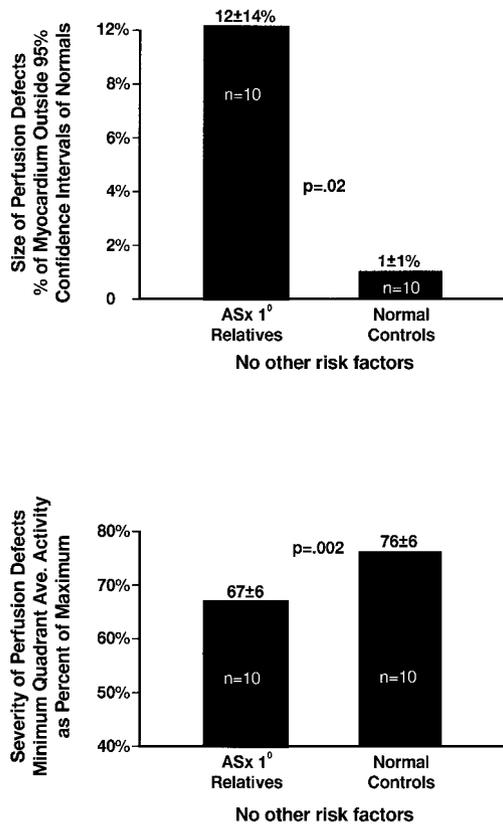


Figure 4. Size and severity of myocardial perfusion defects in asymptomatic persons with parent or sibling with CAD (ASx 1°) but no other risk factors compared with normal control subjects. Ave. indicates average.

Dipyridamole PET from 2 separate families illustrates visually the perfusion abnormalities that were quantified objectively for the study.

The myocardial perfusion images after dipyridamole PET from a 73-year-old woman with mild-to-moderate defects in 3-vessel distribution (Figure 5) indicate mild 3-vessel CAD confirmed on arteriography. Her 3 asymptomatic sons aged 43 to 55 years had moderate perfusion abnormalities outside the normal 95% CIs, indicating mild-to-moderate 3-vessel CAD.

The myocardial perfusion images after dipyridamole in a 68-year-old man showed severe CAD on PET confirmed

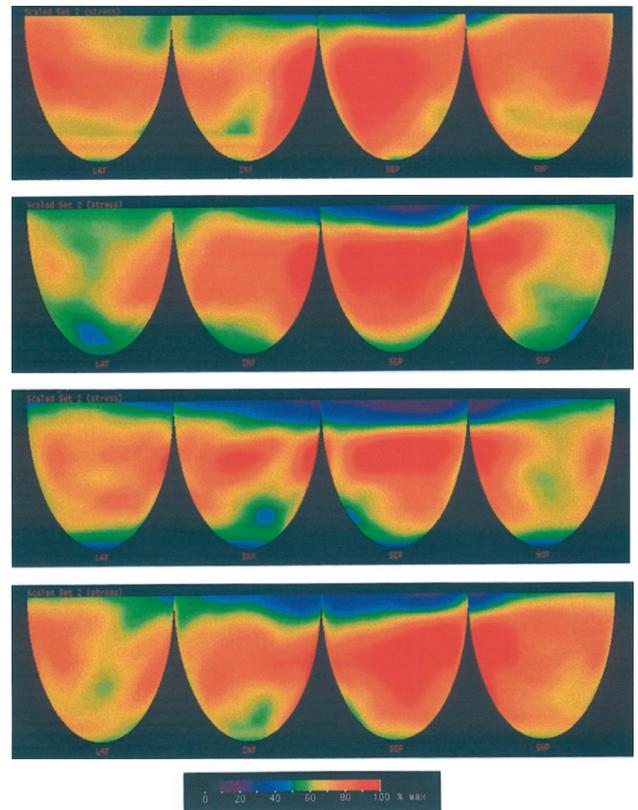


Figure 5. Myocardial PET perfusion images after dipyridamole of a woman (top row) and her 3 asymptomatic sons (second, third, and fourth rows). Red indicates highest flow; yellow, intermediate; and green and blue, progressively lower perfusion. A yellow-to-green transition corresponds to normal 95% CIs.

with arteriography (Figure 6). His youngest son, aged 37, has moderately severe perfusion abnormalities in the left circumflex and right coronary artery distributions with mild defects in the left anterior descending distribution, all outside normal 95% CIs. The other son, aged 42, has a borderline image with mild perfusion defects in the left circumflex and left anterior descending distribution with a mild longitudinal base-to-apex perfusion gradient typical of mild diffuse coronary atherosclerosis.²¹ The daughter's scan is normal.

Group Characteristics

Risk Factor	Control	Index Cases	ASx Relatives	ASx Relatives, No Other Risk Factors		P, Relatives vs No FHx
				No FHx	ASx Relatives	
No. of subjects	10	18	32	10 of 32	30	
Age, y	50 ± 22	66 ± 8	44 ± 11	39 ± 10	55 ± 8	NS
Total cholesterol, mg/dL	198 ± 27	213 ± 38	218 ± 28	190 ± 19	226 ± 52	NS
LDL cholesterol, mg/dL	126 ± 18	139 ± 38	140 ± 25	114 ± 9	148 ± 44	NS
HDL cholesterol, mg/dL	55 ± 12	39 ± 10	45 ± 16	48 ± 15	45 ± 17	NS
Triglycerides, mg/dL	122 ± 70	134 ± 70	186 ± 156	125 ± 78	176 ± 42	NS

ASx relatives indicates asymptomatic subjects with a parent or sibling who has documented CAD; index case, a parent or sibling with CAD documented by PET and arteriography; and FHx, family history.

n=90.

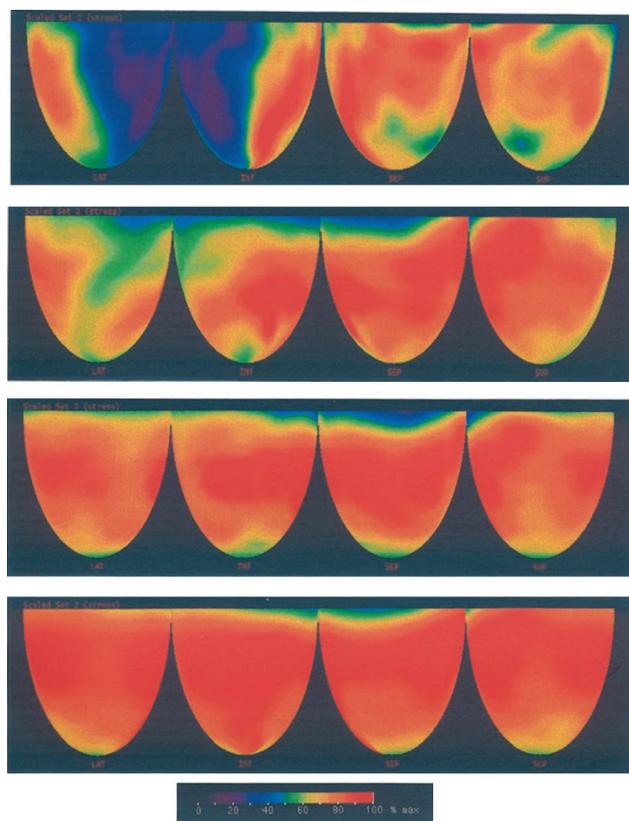


Figure 6. Myocardial PET perfusion images after dipyridamole stress of a man (top), his 2 asymptomatic sons (second and third rows), and his asymptomatic daughter (lowest row). Red indicates highest flow; yellow, intermediate; and green and blue, progressively lower perfusion. A yellow-to-green transition corresponds to normal 95% CIs.

Discussion

The extent of preclinical coronary atherosclerosis in asymptomatic persons with a parent or sibling with CAD has not been well described. Our study demonstrates that half of asymptomatic persons with a parent or sibling with CAD also have quantitative, statistically significant, abnormal myocardial perfusion defects on dipyridamole PET. The size and severity of these perfusion abnormalities are outside 95% CIs of normal controls, independent of other risk factors; these dipyridamole-induced perfusion abnormalities are larger, indicating more extensive disease, but not more severe, than in subjects with comparable risk factors but without family history of CAD.

There are 2 potential mechanisms that cause perfusion abnormalities after dipyridamole in asymptomatic persons with a parent or sibling with CAD. The first is reduced coronary flow reserve due to preclinical, mild, diffuse, and/or segmental coronary artery narrowing without ischemia.^{5,20} The second is endothelial dysfunction, preceding luminal narrowing and cardiac events.²⁵ Although a direct coronary arteriolar vasodilator, dipyridamole-induced increase in coronary flow may normally be augmented by shear-sensitive endothelium-mediated additional arteriolar dilation. Endothelial dysfunction due to preclinical atherosclerosis may therefore reduce flow reserve somewhat by reducing the shear-sensitive component of vasodilation and flow capacity.^{21,22}

Study Limitations

Any unrecognized diffuse CAD in the normal subjects with no risk factors or family history of CAD would tend to reduce the significance of differences between the patient groups and the normal control subjects, shown here as significant. The partial volume error in this study was addressed by comparing subjects with the normal 95% CIs of the normal volunteers, because the partial volume errors apply equally to all groups studied with the same PET scanner and software. Coronary arteriograms were not routinely obtained in asymptomatic persons with a parent or sibling with CAD for ethical and technical reasons. Although percent diameter stenosis on coronary arteriography is commonly used as the standard measure of severity of CAD, there are major problems⁵⁻⁷ with this end point.

Absolute myocardial perfusion in $\text{mL} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ was not determined in this study because the relative distribution of radionuclide uptake is the most conservative end point for identification of CAD. Flow-calculating models correct for the "roll off" or declining radionuclide extraction that occurs with higher myocardial perfusion rates. Therefore, the relative regional differences in radionuclide uptake are magnified into greater differences in absolute perfusion with any flow model depending on the perfusion level and the radionuclide. Quantification of absolute perfusion and coronary flow reserve would increase the number of subjects with perfusion abnormalities to more than 50% by identifying patients with diffusely reduced coronary flow reserve even in the absence of objectively quantified relative regional perfusion defects.¹⁸⁻²⁰ Therefore, as a conservative measure, we quantitatively analyzed only the relative myocardial uptake of radionuclide.

Conclusions

In the present study, asymptomatic persons with a parent or sibling with CAD have a 50% probability of having quantitatively statistically significant dipyridamole-induced myocardial perfusion abnormalities on PET as preclinical noninvasive, scintigraphic markers of CAD. These preclinical scintigraphic markers are independent of risk factor profile and are related to the history of CAD in immediate family members (ie, parents or siblings). In addition to this high prevalence of preclinical atherosclerosis, asymptomatic persons with a parent or sibling with CAD have more extensive but not more severe dipyridamole-induced perfusion abnormalities than do subjects with comparable other risk factors but without a family history of CAD. These observations suggest that the effects of vigorous risk factor modification and pharmacological lipid lowering on clinical outcome in asymptomatic adults with a parent or sibling with CAD should be evaluated.

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