Noninvasive Delineation of the Effects of Moderate Aging on Myocardial Perfusion

Martha J. Senneff, Edward M. Geltman, and Steven R. Bergmann, and Judy Hartman

Cardiovascular Division, Washington University School of Medicine, St. Louis, Missouri

Aging is accompanied by a decline in many aspects of cardiovascular function but little is known regarding its influence on myocardial perfusion. Eleven young adults (mean age 25 ± 4 (s.d.) yr) and 15 older adults (mean age 55 ± 9 yr) without history or symptoms of cardiovascular disease were studied using $H_2{}^{15}O$ and positron emission tomography under resting conditions and following administration of intravenous dipyridamole. Myocardial perfusion at rest was similar in the older and younger subjects, averaging 1.17 ± 0.35 and 1.16 ± 0.32 ml/g/min, respectively (p = ns). Following dipyridamole, peak myocardial perfusion was blunted in the older subjects, averaging 3.12 ± 1.09 ml/g/min compared with 4.25 ± 1.54 ml/g/min in the young adults (p = 0.044). Accordingly, present standards for normal perfusion responses to intravenous dipyridamole may require adjustment for age.

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Over the last 50 yr, life expectancy has increased dramatically due to advances in medical technology and improved habits regarding health and fitness. As older adults enjoy a more active lifestyle, a greater understanding of the effects of aging on the cardiovascular system is imperative to characterize normal physiology and to define changes in physiologic responses that may be inherent to an aging population.

It has been demonstrated previously that maximal cardiac performance diminishes with advancing age. Increased systolic blood pressure, mild cardiac hypertrophy, increased myocardial collagen deposition, prolonged ventricular contraction, slowed ventricular filling rate, increased vascular loading of the heart during exercise, and diminished maximal responsiveness to catecholamines have all been observed in older adults and suggested as potential causes of reduced function (*1*). However, little clinical information is available regarding the effects of aging on resting myocardial perfusion and perfusion reserve in the absence of atherosclerotic coronary artery disease. Clearly, altered perfusion, especially an inability to augment perfusion in response to myocardial demand, may have a major impact on cardiovascular performance.

Weisfeldt et al. (*2*) and Abu-Erreish et al. (*3*) demonstrated a modest decrement in maximal coronary flow in hearts of senescent rats at rest and under conditions of increased myocardial work. Previous work by Marcus et al. (*4*) suggested no significant age-related reduction in coronary flow velocity reserve assessed in patients undergoing cardiac surgery measured with an external coronary Doppler flow meter using a 20-sec occlusion as the hyperemic stimulus. More extensive study of coronary flow in humans has been limited by the inability of conventional approaches such as myocardial scintigraphy with thallium-201 to provide absolute (as opposed to relative) estimates of perfusion. Other approaches, such as intracoronary Doppler flow velocity techniques and coronary sinus thermodilution, are invasive and their use constrained by separate technical limitations. For instance, although the intracoronary Doppler flow velocity technique provides estimates of flow velocity, measurement of absolute flow requires independent measurement of vessel area.

An additional obstacle to the understanding of the effects of age on myocardial perfusion in healthy humans is the increased incidence of occult coronary artery disease in older adults. Ackerman et al. and White et al., in separate autopsy series, demonstrated significant coronary stenoses in 50% to 60% of patients between the ages of 50 and 70 yr (*5, 6*). Thus, knowledge of the coronary anatomy is desirable for selection of a study population free from significant atherosclerotic disease for a true understanding of the effects of aging on myocardial perfusion. Unfortunately, it is imprudent and impractical to subject healthy volunteers to cardiac catheterization for nondiagnostic purposes, and a normal coronary arteriogram does not eliminate the possibility of microvascular disease.

Positron emission tomography (PET) is an emerging technology which permits the noninvasive assessment of myocardial perfusion and metabolism in humans (*7*). Using ^{15}O-labeled water, we have demonstrated that myocardial perfusion can be measured accurately over a wide range of flow and metabolic conditions (*8–11*) and have demonstrated the utility of this technique for assessment of the physiologic impact of both epicardial stenoses and microvascular disease on nutritive myocardial perfusion

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For reprints contact: Martha J. Senneff, MD, Cardiovascular Division, Washington University School of Medicine, Box 8086, 660 S. Euclid Ave., St. Louis, MO 63110.

in patients (*11–15*). The purpose of the present study was to evaluate the effects of moderate aging on resting myocardial perfusion and the response of the vasculature to pharmacologic coronary vasodilation.

METHODS

Clinical Characteristics

Sixteen healthy, older adults (mean 55 ± 9 s.d. yr; range 44–71 yr) without history of cardiovascular or bronchospastic disease were recruited prospectively for this study through advertisements and results were compared with those obtained from 11 healthy young adults recruited from the medical center (mean 25 ± 4 yr; range 20 to 35 yr). Myocardial perfusion results from the young adults have been reported previously (*11,14*), however the algorithm employed for the analysis of regional perfusion has been modified since the previous reports (see below).

All study participants who underwent tomographic imaging were free from symptoms suggestive of cardiovascular disease (chest pain, dyspnea, palpitations, etc.), diabetes mellitus, uncontrolled hypertension, hypercholesterolemia, and electrocardiographic abnormalities. All subjects over the age of 40 yr had normal physical exams within 3 mo of evaluation and had normal exercise stress tests within 2 wk of study. Using these inclusion criteria, the likelihood of significant coronary heart disease in our study groups was less than 2% (*16*).

Subjects over the age of 40 yr underwent exercise stress testing using the standard Bruce protocol, and were subsequently studied tomographically if they were able to reach 100% of their maximum predicted heart rate or completed Stage 5 without symptomatic or electrocardiographic evidence of myocardial ischemia. One subject was excluded when she developed 3 mm of asymptomatic ST-segment depression in the anterior leads of the electrocardiograms during stress testing. Cardiac catheterization in this patient subsequently revealed a 100% proximal left anterior descending lesion with extensive collateralization. One of the older adults gave a history of 30 pack years of smoking and hypertension well-controlled with hydrochlorothiazide, and another had a history of elevated total cholesterol, now controlled with diet alone. The remaining subjects were without coronary risk factors and were not taking medications. All subjects described their daily physical activity as moderate, with several of the older adults involved in walking programs.

Positron Emission Tomography

Subjects refrained from caffeine and other methylxanthines as well as all medications for at least 24 hr prior to study. After informed written consent was obtained, participants were positioned in Super PET I, a whole-body time-of-flight positron emission tomograph that permits simultaneous list-mode acquisition of seven transaxial slices with a center-to-center slice separation of 1.5 cm and a slice thickness of 1.14 cm, with a reconstructed transaxial FWHM resolution of 13.5 mm in the high-resolution mode (*17*). An initial scan was performed using an external ring of germanium-68/gallium-68 to assure optimal positioning and to account for attenuation of emitted photons. Subjects then underwent imaging following bolus administration of 0.4 mCi/kg of ^{15}O-labeled water ($t_{\frac{1}{2}}$ = 2.1 min) intravenously. After radioactivity had returned to background levels, imaging was repeated after inhalation of 30-40 mCi of ^{15}O-labeled carbon monoxide to label the blood pool and to define anatomic landmarks. Following collection of baseline data, dipyridamole (Persantine; Boehringer-Ingleheim) 0.56 mg/kg, was administered intravenously over 4 min using a Harvard infusion pump. Following a 4- to 5-min interval after completion of the infusion in order to allow the peak flow response to develop, the scanning sequence was repeated after a second administration of tracers. Subjects underwent continuous monitoring of blood pressure, heart rate, and the electrocardiogram, and were monitored closely for symptomatic evidence of ischemia.

Analysis of Tomographic Data

Tomographic data were reconstructed to yield seven parallel transverse images of myocardium. Composite images obtained from data collected for 150 sec after administration of ^{15}O-labeled water were corrected for counts attributable to labeled water in the cardiac blood-pool as described previously (*8,12*). Regions of interest were placed interactively on the composite images, corresponding to the septum, anterior, lateral and posterior walls of the left ventricle. An average of eight regions were analyzed in each subject under each condition (range 4–15).

For calculation of myocardial perfusion in absolute terms, data were reformatted into a sequence of 19 consecutive 5-sec tomographic reconstructions starting with the arrival of label in the left atrial blood pool. Regional nutritive myocardial blood flow at rest and following dipyridamole was determined using a kinetic one-compartment model (*10,11*) and estimates from all regions were averaged to obtain a mean value of perfusion in each subject. The input function, necessary for quantitative determination of perfusion, was obtained from a region of interest placed in the left atrial blood pool with the aid of the C^{15}O reconstructions. Since estimates of flow are sensitive to temporal misregistration of the input function and tissue activity (*10*), the time delay between arrival of tracer in the left atrium and aorta was measured for each subject from analysis of the dynamic data and incorporated into the operational flow equation.

Statistical Analysis

All data are presented as mean ± one standard deviation. Paired or unpaired t-tests were used for analysis within and between groups. P values ≤ 0.05 were considered statistically significant.

RESULTS

Hemodynamics at Rest and in Response to Dipyridamole

Subjects in both study groups tolerated the dipyridamole infusion without difficulty, the only symptomatic response being a mild flushing sensation. No subject exhibited symptomatic or electrocardiographic evidence of myocardial ischemia.

Table 1 summarizes the hemodynamic and perfusion data. Following administration of dipyridamole, diastolic blood pressure declined in the young adults and was accompanied by an increase in heart rate and systolic blood pressure. The response was more variable in the older subjects. Diastolic blood pressure changed minimally and there was a more modest increase in heart rate, suggesting a diminished peripheral response to dipyridamole (Fig. 1).

TABLE 1
Individual Hemodynamic and Perfusion Data

			REST					DIPYRIDAMOLE					
	Age (yr)	Sex	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	MBF (ml/g/min)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	MBF (ml/g/min)	MPR
Young Adults													
P297	26	F	66	100	74	83	0.86	93	110	74	86	4.19	5.6
P299	23	M	43	110	80	90	1.43	77	130	60	83	4.00	3.5
P300	25	M	67	110	76	87	1.29	87	110	60	77	3.54	3.3
P404	20	M	72	114	78	90	1.26	102	124	64	84	4.27	3.4
P420	28	F	67	112	80	91	1.92	96	110	70	83	5.58	2.9
P422	26	M	73	134	76	95	0.90	75	142	68	93	1.26	1.6
P572	26	M	71	133	NA	NA	1.03	94	144	NA	NA	6.31	6.1
P575	23	F	82	112	NA	NA	0.97	111	111	NA	NA	5.94	6.0
P582	35	F	63	110	67	81	1.24	81	121	70	87	6.01	4.9
P583	21	M	65	110	NA	NA	0.98	80	100	NA	NA	2.31	1.6
P589	20	F	81	103	NA	NA	0.91	119	119	NA	NA	3.32	3.6
mean±s.d.			68±10	114±10	76±4	88±5	1.16±0.32	92±14	120±13	67±5	85±5	4.25±1.54	3.9±1.5
								$p < 0.001$		$p < 0.001$		$p < 0.001$	
Older Adults													
P625	46	M	46	107	63	78	0.72	62	110	62	78	2.44	3.4
P627	44	F	60	102	60	74	1.05	73	90	53	65	5.02	4.8
P633	50	F	62	107	75	86	1.33	68	106	65	79	1.58	1.2
P641	45	F	86	113	79	90	1.25	103	116	79	91	3.32	3.7
P643	55	F	73	128	77	94	1.27	82	128	81	97	3.49	2.1
P661	65	M	66	120	82	95	1.08	76	124	73	90	3.69	3.5
P664	45	M	66	123	85	98	0.88	87	133	81	98	3.56	4.6
P668	53	M	59	108	72	84	0.84	87	120	72	88	2.89	3.7
P693	53	M	86	137	100	112	1.08	102	137	96	110	3.30	3.1
P715	71	M	57	116	73	87	0.69	72	128	67	87	4.21	5.7
P729	52	M	82	120	82	95	2.14	100	131	94	106	4.75	2.5
P733	58	F	79	130	90	103	1.27	89	131	83	99	1.81	1.5
P734	61	M	54	118	68	85	1.38	60	110	70	83	1.15	0.8
P736	70	F	61	130	74	93	1.46	67	108	67	81	2.13	1.6
P737	61	M	57	114	74	87	1.11	75	115	80	92	3.47	3.1
mean±s.d.			66±12	118±10	77±10	91±9	1.17±0.35	80±14	119±12	75±11	90±11	3.12±1.09	3.0±1.4
								$p < 0.007$ *		*		$p < 0.001$ *	

bpm = beats/minute; HR = heart rate; DBP = diastolic blood pressure; MAP = mean arterial pressure; MBF = myocardial perfusion; MPR = myocardial perfusion reserve; NA = not available due to technical difficulties; SBP = systolic blood pressure; p values represent within group comparisons (relative to values obtained at rest) and * = $p < 0.05$ between groups.

Myocardial Perfusion

Qualitative and quantitative interpretation of tomographic images revealed no evidence of focal perfusion deficits in any subject. Regional homogeneity, assessed by the coefficient of variation of the flow response, was similar in the older and younger adults, averaging 0.36 and 0.37 respectively under conditions of rest, and 0.20 in both groups following the administration of dipyridamole. No significant differences in regional myocardial perfusion were seen within either group at rest or following dipyridamole (Fig. 2).

Myocardial perfusion at rest was similar in the two groups, averaging 1.17 ± 0.35 ml/g/min in the older adults and 1.16 ± 0.32 ml/g/min in the younger subjects (p = ns). Following administration of dipyridamole, however, peak perfusion was diminished in the older adults compared with that measured in the younger subjects, averaging 3.12 ± 1.09 ml/g/min and 4.25 ± 1.54 ml/g/min, respectively (p = 0.044) (Fig. 3).

Myocardial perfusion reserve, defined as average myocardial perfusion following dipyridamole administration divided by average myocardial perfusion at rest, was slightly decreased, averaging 3.0 ± 1.4 in the older adults compared with 3.9 ± 1.6 in the younger subjects (Fig. 4), but this difference was not statistically different due to the range of responses. Myocardial perfusion reserve in 2 of the 11 (18%) younger adults fell below 2.6 (the mean minus 1 s.d. of the control group), similar to the 10%–20% nonresponder rate in healthy adults that has been reported by others using dipyridamole (*18*). In contrast, 6 of 15 (40%) older adults were found to have depressed perfusion reserves. Analysis of myocardial perfusion results in this cohort by decade failed to reveal a statistically significant reduction in peak myocardial perfusion or perfusion reserve with age.

DISCUSSION

Quantitative measurement of myocardial perfusion with PET at rest and following pharmacologic vasodilation offers the potential for noninvasive screening of patients

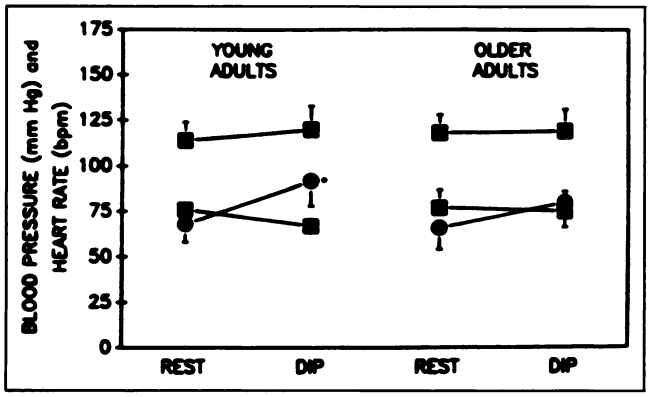

FIGURE 1. Hemodynamics at rest and following administration of dipyridamole (DIP). Filled circles indicate heart rate, filled squares indicate systolic and diastolic blood pressure. Although systemic hemodynamics at rest were not different between the two groups, the hemodynamic response to dipyridamole was blunted in the older adults. In this and all subsequent figures, values indicate mean ± 1 standard deviation. *reflects $p < 0.001$ compared with heart rate at rest.

at risk for coronary artery disease. This can be accomplished with ^{15}O-labeled water, as well as with extracted tracers such as ^{82}Rb or ^{13}N-ammonia if modeling is employed (*19–21*). We have demonstrated extensively in experimental studies that myocardial perfusion can be estimated over a wide range of flows using PET and ^{15}O-labeled water. Although less information is available for studies with ^{82}Rb or ^{13}N ammonia in intact experimental animals, recent studies using physiologically and mathematically appropriate kinetic models have suggested that similar results are attainable. Imperative in the use of PET in this capacity is an understanding of the physiologic changes associated with aging that can alter control of perfusion in both the coronary and peripheral circulations.

The results of this study suggest that although perfusion at rest is similar in older and younger adults, the response to the standard doses of dipyridamole is not. The older subjects in this cohort were at low risk for coronary artery disease based on history and excellent results in exercise stress testing, yet peak myocardial perfusion in response to pharmacologic vasodilation with dipyridamole was significantly blunted and occurred in the absence of focal deficits in regional perfusion.

In an effort to delineate the cause of the attenuated hyperemic response in older adults, we assessed peripheral hemodynamic responses to the vasodilator in both groups of subjects. Diastolic blood pressure fell promptly in the younger adults following administration of dipyridamole and was accompanied by increases in heart rate and systolic blood pressure. In contrast, diastolic blood pressure changed little in the older adults and the heart rate response was more blunted ($p=0.032$ and 0.004, respectively, compared with results for younger subjects). This suggests that the attenuated perfusion response to dipyridamole in the older subjects was secondary to a diminished responsiveness of the vasculature to the vasodilatory properties of the pharmacologic agent rather than a specific deficit in the capacity of the coronary microvasculature to dilate.

Despite the blunted peak perfusion response, the level of hyperemia induced by dipyridamole in the older adults exceeds that obtained through exercise stress testing. Holmberg et al. (*22*), using coronary sinus thermodilution methods, demonstrated a two-fold increase in coronary flow when normal subjects were exercised to a rate-pressure product of approximately two times baseline values. Others also using invasive techniques have reported a 2- to 3.5-fold increase in maximal perfusion with heavy exercise in healthy volunteers (*23–25*). Using PET and ^{13}N-ammonia, Krivokapich et al. (*26*) demonstrated a 2.2-fold increase in myocardial perfusion when healthy volunteers were exercised to rate-pressure products 2.7–2.8 times baseline values. Myocardial perfusion reserve in our older subjects averaged 3.0, while perfusion reserve in our younger subjects averaged 3.9. While the perfusion

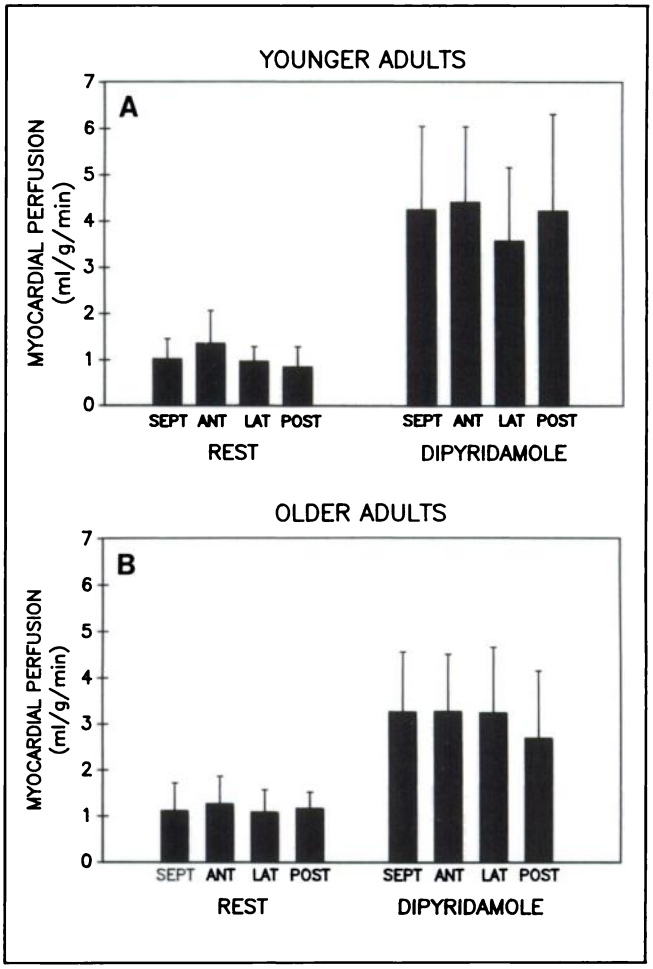

FIGURE 2. Regional myocardial perfusion was homogenous in young adults (A) and older adults (B) under baseline conditions and following administration of dipyridamole. SEPT = septal, ANT = anterior, LAT = lateral, and POST = posterior myocardial regions of interest.

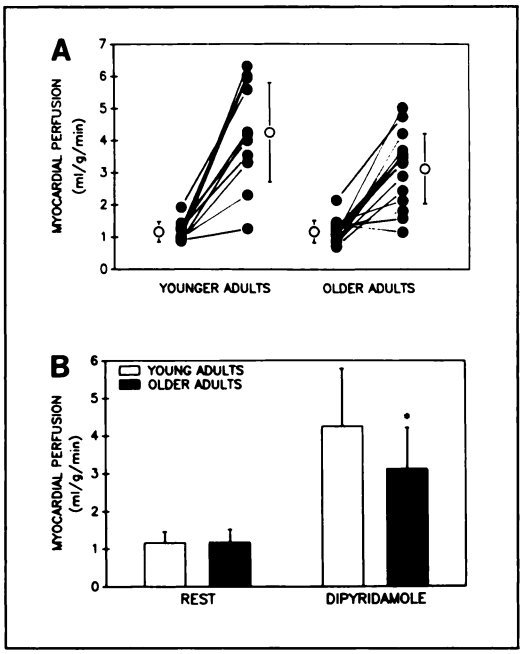

FIGURE 3. Myocardial perfusion at rest was similar but peak myocardial perfusion in response to dipyridamole was slightly blunted in the older adults. (A) perfusion results of individual subjects and (B) histogram of perfusion results by group. *p = 0.044 compared with peak myocardial perfusion in younger adults.

response to pharmacologic vasodilation is different than that achieved with physiologic exercise, pharmacologic vasodilation is useful in that it permits steady-state conditions difficult to attain with exercise, and is now widely-used in perfusion imaging (*27,28*).

Unfortunately, dipyridamole in standard doses does not provide maximal vasodilation in all subjects (*27–29*). Approximately 20% of our younger subjects demonstrated submaximal perfusion responses, a number similar to results of other investigations, while 40% of our older subjects demonstrated blunted responses. It is conceivable that the vasodilatory response to dipyridamole could be shifted with aging, and that age-related norms of perfusion responses will be required. Further studies with a higher dose of dipyridamole will be necessary to clarify this issue.

Technical Limitations

A potential limitation of this study is the absence of angiographic evaluation of the coronary vasculature. Although coronary artery disease may be occult in older asymptomatic subjects, arteriography was not performed in our volunteers as we felt it imprudent to perform invasive studies in healthy subjects for nondiagnostic purposes. Tomographic images and perfusion determinations, however, revealed no evidence of regional deficits in perfusion, making the presence of hemodynamically significant coronary stenoses unlikely (*9,12,13*). Additionally, as we have previously demonstrated (*14*), recruitment of subjects from the catheterization laboratory with normal

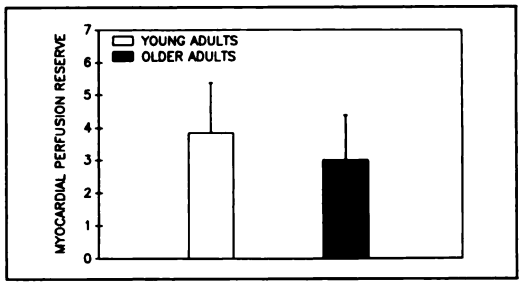

FIGURE 4. Myocardial perfusion reserve in older and younger adults. There was no significant difference in perfusion reserve between the two groups, although as a group, perfusion reserve tended to be lower in the older adults.

coronary angiograms does not exclude the presence of microvascular coronary disease. Although we cannot exclude microvascular disease as a potential cause of the blunted hyperemic response, none of the participants had experienced chest pain.

CONCLUSIONS

Perfusion imaging before and after pharmacologic vasodilation has proved a useful noninvasive means of screening for coronary artery disease, particularly in patients unable to perform treadmill or bicycle exercise. Quantitative measurement of perfusion with PET may provide better sensitivity and specificity than qualitative imaging techniques, but standard doses of dipyridamole may be inadequate in older adults. Further studies of the dose-response curves to intravenous dipyridamole will be necessary to determine whether age-related norms for perfusion response to the pharmacologic agent are necessary.

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