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Articles

Coronary Endothelial Dysfunction in Humans Is Associated With Myocardial Perfusion Defects

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▶ Abstract

Background Coronary endothelial dysfunction may occur in patients with minimally

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obstructive coronary artery disease and angina, and potentially may cause myocardial ischemia.

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Methods and Results Coronary endothelium-dependent vasodilation was examined in patients with angina and <50% coronary artery diameter (CAD) stenosis by selectively infusing acetylcholine (10^{-6} mol/L to 10^{-4} mol/L) into the left anterior descending coronary artery (LAD). Percent change in CAD ($\% \Delta$ CAD) was measured by quantitative coronary angiography, and percent change in coronary blood flow ($\% \Delta$ CBF) was calculated using intracoronary flow Doppler. Coronary endothelium-independent vasodilation was examined using intracoronary adenosine and nitroglycerin. ^{99m}Tc sestamibi was injected intravenously just prior to the infusion of the highest dose of acetylcholine. Patients were divided blindly into three groups: Perfusion defects in non-LAD territory (group 1, n=6), no perfusion defects (group 2, n=7), and perfusion defects in the LAD territory (group 3, n=7). All patients had intact endothelium-independent vasodilation. In group 1, perfusion defects outside the LAD territory reflected an increase in $\% \Delta$ CAD and $\% \Delta$ CBF by $24 \pm 5\%$ and $241 \pm 46\%$ in the LAD. In group 2, $\% \Delta$ CAD decreased by $26 \pm 5\%$, but $\% \Delta$ CBF increased by $54 \pm 17\%$. In group 3, perfusion defects were within the LAD territory, reflecting a decrease in $\% \Delta$ CAD and $\% \Delta$ CBF by $35 \pm 5\%$ and $51 \pm 14\%$, respectively.

Conclusions This study demonstrates that coronary endothelial dysfunction in humans may be temporally associated with myocardial perfusion defects and supports a role for the coronary epicardial and microcirculation endothelium in regulating myocardial perfusion. Myocardial ischemia may occur in humans with impaired endothelium-dependent coronary flow reserve of the coronary epicardial and microcirculation.

Key Words: coronary disease • angina • vasodilation • microcirculation • perfusion

► Introduction

The coronary endothelium regulates coronary vascular tone by releasing endothelium-dependent vasoconstricting and vasodilating factors.¹ Endothelium-derived relaxing factors, such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor are elaborated by the intact endothelium and mediate the increase in CBF in response to increased myocardial demand associated with physical and mental stress.²³⁴ This response is reproduced by the administration of acetylcholine,²³⁴ an endothelium-dependent vasodilator.⁵ Hence, the normal coronary vascular response to acetylcholine is an increase in CAD and CBF.⁵ Coronary endothelial dysfunction is characterized by an attenuated increase in CAD and CBF in response to acetylcholine.⁶⁷⁸⁹¹⁰¹¹¹² It is currently well-recognized that coronary endothelial dysfunction is detected in a proportion of patients with minimally obstructive coronary artery disease and angina.⁶⁸¹²¹³¹⁴¹⁵

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Myocardial ischemia may occur during coronary vasoconstriction associated with coronary endothelial dysfunction. Indeed, it has previously been shown that impaired endothelium-dependent coronary

vasodilation is associated with thallium scintigraphic defects suggestive of myocardial ischemia in response to exercise,² although a temporal relation between the two findings was not established. The current study was designed to examine the hypothesis that coronary endothelial dysfunction may be temporally associated with myocardial perfusion defects suggestive of myocardial ischemia, and that the abnormal myocardial perfusion is associated with impaired vasodilation of the coronary microcirculation. Toward this aim we prospectively evaluated myocardial perfusion using ^{99m}Tc-sestamibi SPECT imaging^{16 17} during intracoronary acetylcholine infusion in patients with chest pain, minimally obstructive coronary artery disease, and risk factors for coronary atherosclerosis.

► **Methods**

The following study protocol was approved by the Mayo Clinic Institutional Review Board. All patients gave written informed consent to participate in the study and were referred for coronary angiography due to recurrent chest pain.¹⁸ Exclusion criteria included $\geq 50\%$ diameter stenosis of any coronary artery, prior myocardial infarction,¹⁹ unstable angina pectoris,²⁰ uncontrolled hypertension, peripheral vascular disease, ejection fraction $< 55\%$, left ventricular hypertrophy, diabetes mellitus, and significant endocrine, hepatic, renal, or inflammatory disease. None of the patients had a left dominant system or a "wrap-around" LAD (ie, extending around the apex and subtending the inferior-posterior wall).

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Drug Infusion

Patients were brought to the cardiac catheterization laboratory in the fasting state after all cardiovascular medications had been discontinued for at least 48 hours. None of the patients were receiving lipid-lowering drugs, antioxidants, angiotensin converting enzyme inhibitors, or oral nitrates. The few patients with hypertension were treated either with calcium-channel blockers or β -adrenergic blockers, but these were stopped at least 48 hours prior to the study. Diagnostic coronary angiography was performed via the percutaneous femoral approach without prior administration of nitrates or calcium blockers. The coronary angiogram was reviewed prior to the infusion of drugs; severity of stenosis was assessed by online quantitative coronary angiography. Patients with significantly obstructive coronary artery disease ($\geq 50\%$ diameter stenosis of any coronary artery) were excluded from further studies.

The determination of endothelium-dependent and endothelium-independent flow reserve was performed as previously described.^{21 22} In all patients, acetylcholine was selectively infused into the LAD; other drugs were administered through the guiding catheter positioned in the ostium of the left main coronary artery. A Doppler guidewire (FloWire, Cardiometrics Incorporated) diameter of 0.014 in within a 2.2F coronary-infusion catheter (Ultrafuse, SciMed Life System) were advanced and positioned into the midportion of the LAD. The Doppler guidewire was then positioned 2 to 3 mm distal to the tip of the infusion catheter. Baseline APV as measured by Doppler echography was recorded. Intracoronary bolus injections of 24 to 36 μg adenosine (Fujisawa), an endothelium-independent vasodilator primarily of the microcirculation,²³ were administered into the guiding catheter, and the maximal APV was recorded. The endothelium-independent coronary flow reserve ratio was calculated by dividing the APV after adenosine injection by the baseline APV.²² To ensure that the increase in CBF did not merely reflect the forces of intracoronary bolus injection, coronary flow reserve in response to normal saline (3 to 4 mL)

was measured prior to adenosine injection.

After a 5-minute equilibration period, baseline APV was recorded, followed by coronary angiography using nonionic contrast medium (Omnipaque, Winthrop Laboratories). Acetylcholine (Iolab Pharmaceuticals) at concentrations of 10^{-6} , 10^{-5} , and 10^{-4} mol/L (to achieve estimated final blood concentrations in the coronary bed of 10^{-8} , 10^{-7} , and 10^{-6} mol/L) was infused for 3 minutes at each concentration. Doppler measurements and coronary angiography were obtained after each infusion. The infusion was terminated when the largest dose of acetylcholine (10^{-4} mol/L) was reached. Infusions were performed with a Harvard pump to maintain infusion rates at less than 1% of estimated CBF. Nitroglycerin (Abbott Laboratories) was then injected as an intracoronary bolus (200 μ g) through the guiding catheter to evaluate endothelium-independent coronary vasoactive response of vessels >200 μ m in diameter.²⁴ When the maximal effect of nitroglycerin was attained, measurements were obtained, and adenosine was injected again to determine the endothelium-independent coronary flow reserve ratio under conditions of epicardial vasodilation.

At each time interval, APV was recorded, followed by coronary angiography. The angles, skew rotation, and table height were kept constant during the procedure. In addition, the distances between the image intensifier and the x-ray tube to the patient were kept constant. CAD was measured by an independent investigator, unaware of other data (ie, Doppler flow and sestamibi perfusion data), using a computer-based image analysis system, as previously described.²⁵ The measurements were performed in the segment 5 mm distal to the tip of the Doppler wire. For each time interval, the diameter was measured in the same segment. CBF was calculated from the Doppler-derived time velocity integral and vessel diameter, as previously described²⁶:

$$CBF = \pi(APV/2)(CAD/2)^2$$

Following the intracoronary infusions, intravascular ultrasound of the LAD was performed with a Hewlett-Packard imaging system as described previously^{27, 28} to confirm the absence of significant obstructive coronary artery disease. Continuous images were recorded throughout the LAD on a 0.5-in videotape for off-line analysis. A special effort was made to keep the ultrasound catheter parallel to the long axis of the vessel lumen. Five to six segments of the LAD were identified in the videotape recording of the ultrasound images by the digital counter, and the exact position of the ultrasound catheter in relation to the artery was recorded on cinefilm at each position. The location of the catheter seen on the cinefilm of each segment was used to correlate the identified ultrasound image with the angiographic segment.

An off-line computer-interactive analysis system was used to digitize the intracoronary ultrasound video images onto a 256x256-bit matrix. Standard calibration markers directly from the ultrasound images were used for calibration of absolute measurements. This method and histopathological correlation have been validated for interpretation of intravascular ultrasound images.^{13, 29} All measurements were made in end diastole and measured at the media-adventitia interface. Measurements of CAD were averaged from two orthogonal planes. The segment was excluded if the two measurements of diameter differed by more than 20% to avoid measuring an ellipsoid image.³⁰ All measurements were made by an observer with no knowledge of the Doppler or angiographic findings.

Sestamibi Imaging

Imaged acquisition, processing, and interpretation have been reported in detail previously.[16](#) [17](#) [31](#) [32](#) In brief, all patients received an intravenous injection of 20 to 30 mCi of ^{99m}Tc sestamibi just prior to the infusion of the highest dose of acetylcholine. Tomographic imaging was performed within 2 hours. Images were acquired using a rotating gamma camera with an all-purpose collimator. Processing and reconstruction were performed using standard back-projection algorithms and a Ramp-Hanning filter. Circumferential count profiles were generated for five representative short-axis slices of the left ventricle extending from apex to base. The images were interpreted by an investigator (R.J.G.) blinded to the results of acetylcholine infusion. The patients were divided into three groups on the basis of results of sestamibi imaging: group 1, perfusion defect outside of the LAD distribution; group 2, no perfusion defect; group 3, perfusion defect within the LAD distribution. Since sestamibi SPECT imaging provides a measure of relative perfusion, the presence of a perfusion defect outside of the LAD distribution would be consistent with an increase in flow in the LAD. In contrast, a perfusion defect within the LAD distribution would be consistent with a decrease in flow in the artery.

Data Analysis

The maximal effect of acetylcholine infusion is expressed as percent change (mean \pm SEM) in CAD (% Δ CAD) and in CBF (% Δ CBF) relative to baseline. Differences between groups were analyzed using one-way ANOVA. Differences in baseline angiographic and clinical characteristics were analyzed using one-way ANOVA and the Fisher exact test. A value of $P < .05$ was accepted as significant.

► Results

The study population included 20 patients, 10 men and 10 women, ranging in age from 31 to 67 years. Of this group, 30% were smokers and 20% had hypertension. The mean plasma cholesterol level for the whole group was 204 \pm 15 mg/dL. There were no significant differences in baseline demographics and in risk factors for coronary artery disease between the three groups (Table 1 \square). The maximal percent area stenosis of the LAD was similar for all groups. There were no significant differences in calculated area stenosis as assessed by quantitative coronary angiography and intravascular ultrasound. All patients had mild coronary atherosclerosis as assessed by quantitative coronary angiography, with a similar distribution among the three major epicardial arteries for the three groups (Table 2 \square).

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View this table: **Table 1.** Demographic and Clinical Characteristics of the Study Groups

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View this table: **Table 2.** Mean Maximal Luminal Diameter Stenosis in the Three Major Epicardial Arteries

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Intracoronary injection of normal saline increased the APV insignificantly in all patients. The endothelium-independent coronary flow reserve, as assessed by intracoronary injection of adenosine, was similar in all groups (3.2 ± 0.5 , 2.9 ± 0.7 , and 3.0 ± 0.4 for groups 1 through 3, $P=NS$). Similar values were attained when adenosine was injected after nitroglycerin (3.4 ± 0.4 , 3.2 ± 0.8 , and 3.1 ± 0.5 for groups 1 through 3, respectively, $P=NS$).

There were significant differences, however, in the maximal response to acetylcholine between the three groups (Figure 1). The effects of acetylcholine on CAD and CBF at the three doses are presented in Table 3. In response to selective infusion of acetylcholine in the LAD, mean $\% \Delta CAD$ and $\% \Delta CBF$ of the LAD increased by as much as $25\pm 5\%$ and $241\pm 46\%$, respectively, in patients with filling defects in the non-LAD distribution (group 1). In patients without myocardial perfusion defects (group 2), $\% \Delta CAD$ in the LAD decreased by as much as $26\pm 5\%$, but $\% \Delta CBF$ increased by $54\pm 17\%$. In patients with perfusion defects in the LAD distribution (group 3), both $\% \Delta CAD$ and $\% \Delta CBF$ in the LAD decreased by $35\pm 5\%$ and $51\pm 14\%$, respectively. The $\% \Delta CAD$ in group 2 was significantly different from group 1 ($P<.05$) but similar to group 3 (Figure 1). In addition, the $\% \Delta CBF$ in group 2 was significantly different ($P<.05$) from groups 1 and 3 (Figure 1), as was the difference between groups 1 and 3.

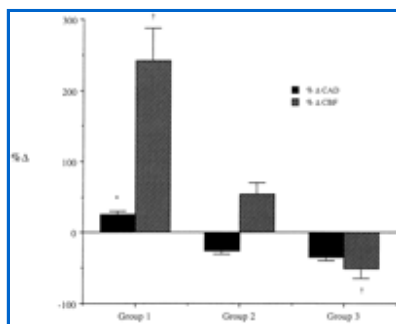


Figure 1. Maximal effect of acetylcholine infusion (10^{-4} mol/L) in the LAD expressed as mean percent change in CAD ($\% \Delta CAD$) and in CBF ($\% \Delta CBF$) relative to baseline. $*P<.05$ relative to $\% \Delta CAD$ for group 2; $\dagger P<.05$ relative to $\% \Delta CBF$ for group 2.

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View this table: **Table 3.** Dose Response to Acetylcholine

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There was no difference between the three groups in $\% \Delta CAD$ and $\% \Delta CBF$ in response to intracoronary nitroglycerin relative to baseline, indicating intact endothelium-independent coronary epicardial vasodilation.

To assess the incidence of perfusion defects during acetylcholine infusion among patients with coronary endothelial dysfunction, we used two criteria to define endothelial dysfunction. When defined as $\% \Delta CBF \leq 0$ in response to acetylcholine, 7 of 7 patients with endothelial dysfunction had perfusion defects in the LAD territory, as compared with 0 of 13 patients with $\% \Delta CBF > 0$. When defined as $\% \Delta CBF \leq 50$

in response to acetylcholine, 7 of 11 patients with endothelial dysfunction had perfusion defects in the LAD territory, compared with 0 of 9 patients with $\% \Delta \text{CBF} > 50$.

► Discussion

The current study demonstrates that coronary endothelial dysfunction in humans resulting in a decrease in CBF in the LAD (group 3) was associated with myocardial perfusion defects within the territory of the LAD by $^{99\text{m}}\text{Tc}$ -sestamibi SPECT imaging. Coronary endothelial dysfunction with a reduction in CAD but an attenuated increase in CBF (group 2) was not associated with myocardial perfusion defects by $^{99\text{m}}\text{Tc}$ -sestamibi SPECT imaging. Normal endothelial function, characterized by an increase in CAD in response to acetylcholine infusion with a large increase in CBF (group 1), was associated with a perfusion defect outside the territory of the LAD by $^{99\text{m}}\text{Tc}$ -sestamibi SPECT imaging, consistent with an increase in CBF in the LAD relative to other territories. These findings indicate that coronary vasoconstriction associated with endothelial dysfunction leading to a decrease in CBF may mediate myocardial perfusion defects suggestive of myocardial ischemia in humans.

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Gould et al³³ previously showed that risk factor modification in patients with coronary artery disease improved myocardial perfusion. The significant improvement in myocardial perfusion assessed by positron emission tomography was associated with only mild changes in coronary artery stenosis. The current study supports these findings, underscoring the importance of the coronary microcirculation endothelial function in the regulation of myocardial perfusion. Our data show that the changes in CAD in response to acetylcholine do not accurately reflect changes in CBF. Acetylcholine may cause coronary epicardial and microvessel vasoconstriction in states of endothelial dysfunction.^{6 7 8 9 10 11 12 13 14 15} However, despite the coronary epicardial vasoconstriction in response to acetylcholine in coronary endothelial dysfunction, CBF may be preserved or even increased.^{8 10 12 13 14 15}

In addition, although there is an interaction between endothelium-dependent and endothelium-independent mechanisms,³⁴ our results underscore the possible dissociation between the two pathways at both the epicardial and microcirculation levels. All patients had an intact response to adenosine and nitroglycerin, reflecting preserved endothelium-independent pathways, yet the response to acetylcholine was abnormal in patients with endothelial dysfunction (groups 2 and 3). The results in patients with endothelial dysfunction and myocardial perfusion defects (group 3) demonstrate that myocardial perfusion defects may occur in the absence of impaired endothelium-independent mechanisms.

Patients with coronary endothelial dysfunction may have symptomatic or silent episodes of myocardial ischemia. Yeung and colleagues³ previously reported that the response of diseased human coronary arteries to mental stress was a reduction in CAD and CBF. The degree of constriction during mental stress correlated with the response to the infusion of acetylcholine. Similarly, Zeiher and colleagues² showed that, in patients with minimally obstructive coronary artery disease and exercise-induced thallium perfusion defects, the rise in CBF in response to acetylcholine was blunted compared with patients with normal thallium imaging during exercise, underscoring the role of the endothelium in regulating the changes in CBF in response to increased myocardial demand. Moreover, impaired

coronary endothelial function has been suggested as a cause of acute myocardial infarction in patients with minimally obstructive disease.³⁵ These prior studies implicate impaired endothelial function as a possible cause of myocardial ischemia, although a causal relation between the response to acetylcholine infusion and myocardial ischemia was not established.

In a more recent report, transient perfusion defects were observed in a substantial proportion of patients with acetylcholine-induced coronary epicardial vasoconstriction injected with thallium during peak acetylcholine infusion.³⁶ The current study extends the findings of these prior studies, by demonstrating for the first time that acetylcholine-induced reductions in CBF may be temporally associated with regional myocardial perfusion defects suggestive of myocardial ischemia. Acetylcholine-induced reductions in CAD did not predict myocardial perfusion defects; epicardial CAD reduction occurred in a proportion of patients with endothelial dysfunction who had preserved CBF and no perfusion defects (group 2), indicating that the coronary resistance vessel vasodilation was effective in maintaining CBF in these patients.

Di Marco et al,⁸ using intracoronary Doppler for the measurement of CBF, previously reported that CBF in response to acetylcholine infusion was reduced in only 35% of patients with coronary artery disease. However, CAD was reduced at the maximal concentration of acetylcholine in all but 3 of the patients. The authors concluded that there is a dissociation between the impairments of endothelium-dependent vasodilation of conductance and resistance vessels. Our findings support such a phenomenon. In patients with normal endothelial function (group 1), CAD increased by 25%, yet CBF increased by 241%, indicating that coronary vasodilation occurred at both the epicardial and the microcirculation levels. In patients with endothelial dysfunction but no perfusion defects (group 2), CAD decreased by 26%, yet CBF increased by 54%. These patients had epicardial endothelial dysfunction but retained the coronary microcirculation endothelium-dependent vasodilator capability. It is possible that the vasodilator response of the coronary microcirculation in these patients was not completely intact, and that even in the face of a 26% reduction in CAD, a more pronounced rise in CBF would have been attained had the microcirculation fully dilated. Myocardial perfusion defects consistent with myocardial ischemia were evident when both CAD and CBF were reduced (group 3). In these patients, the reduction in CBF (51%) was comparable to the reduction in CAD (35%). In contrast to patients in group 2, in whom a similar decrease in CAD had occurred but CBF had increased, CBF in patients in group 3 decreased, indicating that the microcirculation did not dilate. Thus, groups 1 through 3 may reflect intact, partially impaired, and impaired endothelium-dependent coronary microcirculation vasodilation, respectively.

Prior studies have demonstrated that coronary microvascular endothelial dysfunction may contribute to the reduced vasodilator reserve in patients with minimally obstructive coronary artery disease. Quyyumi and coworkers¹⁵ demonstrated that patients with minimally obstructive coronary artery disease and depressed vasodilation in response to atrial pacing had reduced endothelium-dependent dilation with acetylcholine, presumably due to impaired coronary microcirculation vasodilation. Egashira and colleagues¹³ reported that the vasodilator response of the coronary microcirculation is blunted in patients with minimally obstructive coronary artery disease and angina. In this study, we have shown that myocardial perfusion defects may occur in patients whose coronary microcirculation endothelium-dependent reserve is altered.

In the present study we did not prove that the perfusion defects associated with a reduction in CBF resulted in myocardial ischemia. Moreover, we did not prove that these defects occur spontaneously or during physiological stress in patients with endothelial dysfunction, explaining their symptoms. Nevertheless, given that an impaired response to acetylcholine is associated with thallium scintigraphic defects suggestive of myocardial ischemia in response to exercise,² these findings lend credence to the hypothesis that coronary vasoconstriction may occur in patients with coronary endothelial dysfunction, resulting in impaired blood flow and myocardial ischemia. To further support this hypothesis, additional studies during physiological stress should be done. Even those studies may not be conclusive, since the presence of perfusion defects during physiological stress does not necessarily imply that the underlying mechanism is endothelial dysfunction.

Patients with minimally obstructive coronary artery disease and chest pain present a difficult diagnostic and therapeutic challenge.²² In our study, we demonstrate that coronary endothelial dysfunction may exist without myocardial perfusion defects, due to coronary microvessel dilation. Assuming that the endothelium-dependent response to acetylcholine reflects the response to stress,² the cause of symptoms in such patients is unclear, as CBF is not reduced. It is possible that nociceptive mediators are released during the coronary epicardial vasoconstriction. Indeed, endothelium-dependent vasodilators such as bradykinin are known to be cardiac algogenic substances.³⁷ In addition, nitric oxide attenuates the nociceptive effect of cholinergic stimulation.³⁸ Coronary endothelial dysfunction is characterized by reduced nitric oxide activity,¹ and hence these patients may have a lower pain threshold.

There are several limitations worth considering in interpreting our data. Our data were derived from a relatively small sample of highly selected patients referred to a tertiary-care center for the investigation of persistent chest pain. The proportion of patients with a decrease in CBF in response to acetylcholine may be different among patients being investigated for the cause of their chest pain in other settings. In addition, the blood flow velocities may be subject to some variability.

The treatment of coronary endothelial dysfunction is still investigational. Di Marco et al⁸ have suggested that different mechanisms underlie the endothelial dysfunction of conductance and resistance coronary vessels. Moreover, the vasoactive properties of epicardial and microcoronary vessels may be substantially different.³⁹ The results of the present study indicate that the severity of the clinical manifestations of coronary endothelial dysfunction may be determined by the degree of involvement of the coronary microcirculation. Hence, the treatment of coronary endothelial dysfunction should also target the coronary microcirculation.⁴⁰

► Selected Abbreviations and Acronyms

APV	= average peak velocity
CAD	= coronary artery diameter
CBF	= coronary blood flow
LAD	= left anterior descending coronary artery
SPECT	= single-photon emission computed tomography

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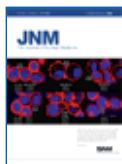
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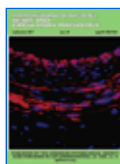
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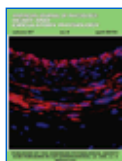
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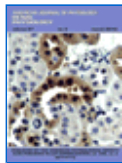
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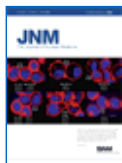
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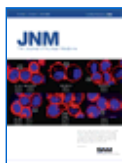
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