

EFFECTS OF CARDIAC SYMPATHETIC INNERVATION ON CORONARY BLOOD FLOW

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ABSTRACT

Background The role of cardiac sympathetic nerves in regulating coronary blood flow is controversial. We sought to determine the degree to which cardiac efferent sympathetic signals modulate coronary blood flow. The heterogeneous sympathetic reinnervation in transplanted hearts provides a model for studying the vasomotor responses to adrenergic stimulation in reinnervated and denervated coronary territories of the same heart.

Methods We studied 14 cardiac-transplant recipients who had normal coronary arteries and no evidence of rejection and 8 normal subjects. We used positron-emission tomography with [¹¹C]hydroxyephedrine, an analogue of norepinephrine, to delineate sympathetic innervation. Using [¹³N]ammonia, we measured myocardial blood flow at rest, during adenosine-induced hyperemia, and in response to sympathetic stimulation induced by cold pressor testing.

Results In the transplant recipients, the uptake of [¹¹C]hydroxyephedrine was greater in the territory served by the left anterior descending artery (mean \pm SE, 0.15 ± 0.01) than in those served by the right coronary artery (0.07 ± 0.01 , $P < 0.001$) or the circumflex artery (0.09 ± 0.01 , $P < 0.001$). The basal flow was similar in all three regions, as was the percent increase in flow during hyperemia. However, the increase in flow in response to cold pressor testing was higher in the territory of the left anterior descending artery (46 ± 10 percent) than in those of the right coronary artery (16 ± 5 percent, $P = 0.01$) or the circumflex artery (23 ± 6 percent, $P = 0.06$), although the changes in hemodynamics and levels of circulating catecholamines were similar. No such regional differences were observed in the normal subjects.

Conclusions Increases in coronary blood flow in response to sympathetic stimulation correlated with the regional norepinephrine content in the cardiac sympathetic-nerve terminals. These findings suggest that cardiac adrenergic signals play an important part in regulating myocardial blood flow. (N Engl J Med 1997;336:1208-15.)

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THE coronary microcirculation is a dynamic vascular bed that responds through changes in arteriolar resistance to metabolic tissue demands, changes in blood flow, and neurohormonal stimuli.¹⁻³ Adrenergic stimuli may modulate coronary vasomotor tone at rest or during common activities of daily life that activate the sympathetic

nervous system, such as exercise and mental stress. Increased sympathetic activity produces dilatation of coronary resistance vessels and thus increases myocardial blood flow.^{4,5} This vasodilator response appears to be modulated, at least in part, by endothelial function.⁵ However, it is not known whether the flow response to sympathetic activation depends on intact efferent function of the sympathetic fibers innervating the large and small coronary arteries or, alternatively, on the increase in circulating catecholamines that accompanies sympathetic activation.

The transplanted heart provides a unique model for studying adrenergic control of the coronary circulation. Cardiac transplantation results in total cardiac denervation due to the sectioning of the post-ganglionic neural axons that innervate the heart.⁶ Sympathetic reinnervation has been reported after cardiac transplantation,^{7,8} but it is only a regional process, favoring the territory of the left anterior descending coronary artery.^{8,9} Thus, it is possible to study the degree to which cardiac efferent sympathetic signals alter coronary vasomotion by comparing reinnervated and denervated territories in the same heart independently of changes in hemodynamic factors and circulating catecholamines that modulate coronary blood flow. These regions can be defined noninvasively with [¹¹C]hydroxyephedrine, an analogue of norepinephrine, and positron-emission tomographic (PET) imaging.⁸ Myocardial blood flow can also be quantified by PET with [¹³N]ammonia,¹⁰ a method that allows detailed study of adrenergic control of vascular resistance in the heart.

We sought to study the role of cardiac efferent sympathetic signals in regulating coronary blood flow. We used PET imaging to delineate cardiac sympathetic innervation and measure regional myocardial blood flow in the territories of reinnervated and denervated coronary arteries after cardiac transplantation. Myocardial blood flow was measured at rest, during maximal vasodilatation due to an infusion of adenosine, and in response to sympathetic-nerve stimulation by a cold pressor test. The blood-flow response in the territories of the reinnervated coronary arter-

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ies in transplant recipients was compared with that in denervated territories in the same patients.

METHODS

Study Population

We studied 14 patients a mean (\pm SE) interval of 7 ± 1 years (range, 5 to 10) after orthotopic heart transplantation. The patients were selected on the basis of angiographically normal coronary arteries on recent arteriography (performed within the preceding 10 ± 6 months) and the absence of acute rejection as determined by endomyocardial biopsy at the time of the study. The heart transplantations were performed to treat ischemic heart disease in five patients and to treat idiopathic cardiomyopathy in nine. There were 2 women and 12 men (age, 55 ± 9 years). All had normal left ventricular function as assessed by contrast left ventriculography and echocardiography.

Eight healthy volunteers (three men and five women; age, 28 ± 6 years) were studied who were matched for age to the transplanted hearts (age at the time of the study, 31 ± 10 years), and had a low likelihood of coronary artery disease on the basis of the absence of symptoms and risk factors, a normal resting electrocardiogram, and a normal maximal treadmill exercise test. This group was used to establish regional patterns of cardiac sympathetic innervation and to characterize the relations between regional sympathetic efferent signals and myocardial blood flow.

Study Design

The study design was approved by the Human Investigation Committee of Wayne State University, and all the study subjects gave written informed consent. Each subject made two visits to the hospital, during which cardiac sympathetic innervation and regional myocardial blood flow were assessed with a whole-body PET scanner (CTI EXACT HR, Siemens, Knoxville, Tenn.).

All the subjects refrained from drinking caffeine-containing beverages and taking theophylline-containing medications for 24 hours before the PET study. Calcium-channel blockers and beta-blockers were withheld for 24 hours before the study, and arterial vasodilators were withheld for 12 hours. None of the patients received medications known to interfere with catecholamine uptake in presynaptic nerve terminals. All the subjects were studied while fasting.

Assessment of Cardiac Sympathetic-Nerve Terminals

The presence and extent of catecholamine uptake in cardiac sympathetic-nerve terminals were evaluated with [^{11}C]hydroxyephedrine, an analogue of norepinephrine that has the same mechanisms of uptake and storage as the naturally occurring neurotransmitter.¹¹ A 15-minute transmission scan was acquired for the correction of photon attenuation by soft tissue. Beginning with the intravenous bolus administration of [^{11}C]hydroxyephedrine (0.286 mCi per kilogram of body weight), we acquired serial images for 40 minutes (six images for 30 seconds each, two for 60 seconds, two for 150 seconds, two for 300 seconds, and two for 600 seconds). Heart rate and blood pressure were monitored continuously throughout the study.

Assessment of Myocardial Blood Flow

Myocardial blood flow was measured at rest, during a standard intravenous infusion of adenosine (0.14 mg per kilogram per minute), and during cold pressor testing, with [^{13}N]ammonia used as a flow tracer. A 15-minute transmission scan was acquired for correction of photon attenuation. Beginning with the intravenous bolus administration of [^{13}N]ammonia (0.286 mCi per kilogram), images were acquired serially for 20 minutes (12 images for 10 seconds, 3 for 60 seconds, and 3 for 300 seconds). Thirty minutes later, intravenous adenosine was infused for four

minutes. Two minutes into the adenosine infusion, a second dose of [^{13}N]ammonia was injected and images were recorded in the same sequence. Thirty minutes later, a cold pressor test was performed by immersing the patient's hand and forearm in ice water for three minutes. Ninety seconds into the cold pressor test, a third dose of [^{13}N]ammonia was injected, and images were recorded in the same acquisition sequence. The patient's movement was minimized by fastening a Velcro strap across his or her chest. The heart rate, systemic blood pressure, and a 12-lead electrocardiogram were recorded at base line and every 60 seconds during and after the infusion of adenosine and the cold pressor test.

Analysis of Data

In each study, the 47 tomographic slices were reoriented into 12 short-axis slices extending from the apex to the base of the left ventricle. To quantify the regional myocardial storage of catecholamines, regions of interest in sectors encompassing the territories of the left anterior descending, circumflex, and right coronary arteries were automatically assigned to each of four midventricular short-axis slices of the [^{11}C]hydroxyephedrine images. An additional small circular region of interest was manually placed in the center of the left ventricular blood pool to quantify the arterial input. The regions of interest were then applied to the entire 40-minute sequence of [^{11}C]hydroxyephedrine images, and regional time-activity curves for myocardial tissue and the blood pool were obtained. In each coronary-artery territory, the fraction of [^{11}C]hydroxyephedrine that was retained was calculated by dividing the concentration in myocardial tissue by the integral of the concentration in arterial blood.

To quantify regional myocardial blood flow, the same regions of interest (the [^{11}C]hydroxyephedrine images) were automatically assigned to each of four midventricular short-axis slices of the [^{13}N]ammonia images, as described previously.¹² To ensure that the placement of these regions was identical, the same angle on the circumferential profile was used as the starting point for the sectors of interest on each of the four sets of images studied in each subject. An additional small circular region of interest was manually placed in the center of the left ventricular blood pool to quantify the arterial input. The regions of interest were then copied to the entire sequence of [^{13}N]ammonia images, and regional time-activity curves for myocardial tissue and the blood pool were obtained. In each vascular territory, a single time-activity curve was obtained by averaging the corresponding [^{13}N]ammonia data in adjacent ventricular planes. The curves were then fitted with the use of a previously validated kinetic model of the tracer.¹⁰ An index of coronary vascular resistance was calculated as the ratio between the mean aortic blood pressure and the myocardial blood flow. The coronary vasodilator reserve was defined as the ratio between the hyperemic and the basal myocardial blood flows.

Measurement of Circulating Catecholamines

Venous-blood samples for the measurement of circulating catecholamines were obtained from an indwelling venous catheter with the patient at rest (with the patient supine and with little stimulation) and during cold pressor testing. Plasma concentrations of norepinephrine, epinephrine, and dopamine (in picograms per milliliter) were measured by high-performance liquid chromatography.¹³

Statistical Analysis

Data are presented as means \pm SE. Differences between groups were assessed by paired or unpaired Student's t-tests, as appropriate. Differences between multiple groups were studied by a single-factor analysis of variance and by Tukey's test. P values of less than 0.05 were considered to indicate statistical significance. P values of less than 0.10 are also reported, because they were considered to indicate trends toward significance.

RESULTS

Regional Uptake and Storage of Catecholamines

In the transplant recipients, the myocardial uptake of [¹¹C]hydroxyephedrine was consistently lower in the territories of the right coronary artery (0.07 ± 0.01) and the circumflex artery (0.09 ± 0.01) than in that of the left anterior descending artery (0.15 ± 0.01 ; $P < 0.001$ for both comparisons) (Fig. 1). No such differences between regions were noted in the normal subjects.

Systemic Hemodynamics

The heart rate and the rate–pressure product increased with cold pressor testing and adenosine in both groups of subjects. Systolic and mean aortic blood pressure increased during the cold pressor test but remained unchanged during the infusion of adenosine (Table 1).

Circulating Catecholamines

Both the transplant recipients and the normal subjects had significant increases in plasma norepi-

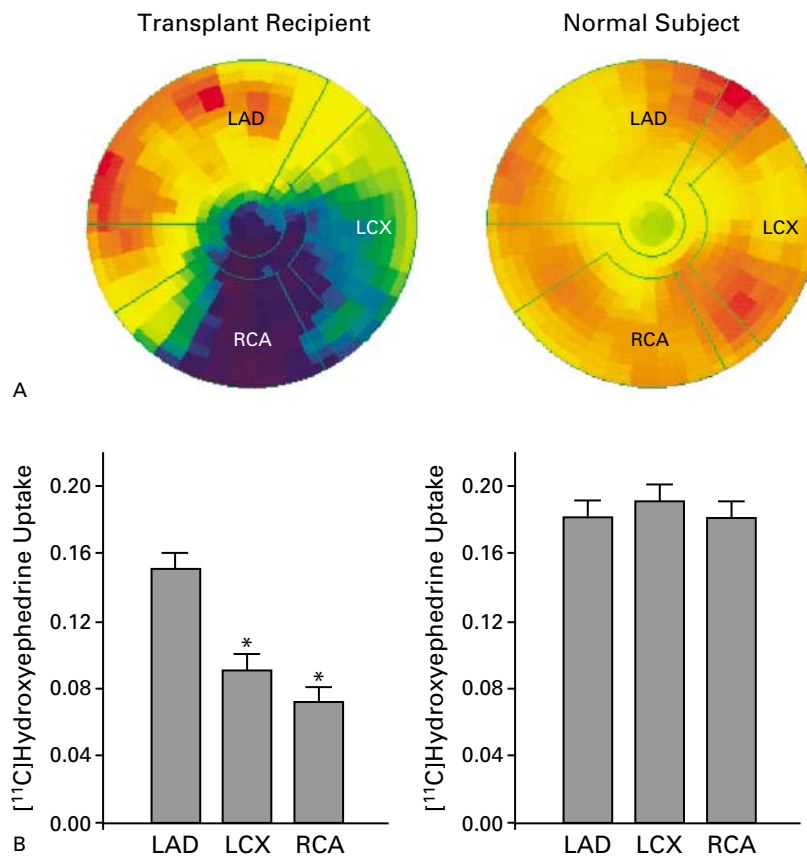


Figure 1. Uptake of [¹¹C]Hydroxyephedrine in Myocardium According to the Coronary Artery Serving the Region Studied. Panel A shows circumferential profiles of the activity of [¹¹C]hydroxyephedrine in a transplant recipient and a normal subject. In the coding of [¹¹C]hydroxyephedrine uptake, red indicates the highest uptake, yellow intermediate uptake, and green and blue the lowest uptake. In the polar maps shown, the left ventricular apex appears in the center and the base of the heart appears on the periphery; the anterior wall is at the top, the inferior wall at the bottom, the lateral wall at the right, and the interventricular septum at the left. The green lines demarcate the territories served by the coronary arteries: the left anterior descending artery (LAD), the circumflex artery (LCX), and the right coronary artery (RCA). The normal subject has homogeneous uptake of [¹¹C]hydroxyephedrine in all three territories. In contrast, the transplant recipient has nearly normal uptake in the territory served by the left anterior descending artery but severely reduced uptake in the territories served by the circumflex and the right coronary arteries. Panel B shows the mean (\pm SE) uptake of [¹¹C]hydroxyephedrine according to coronary-artery territory in the 14 transplant recipients and the 8 normal subjects. The asterisks indicate $P < 0.001$ for the comparison with the territory served by the left anterior descending artery. Uptake of [¹¹C]hydroxyephedrine was calculated by dividing the concentration in myocardial tissue by the integral of the concentration in arterial blood.

nephrine in response to the cold pressor test (Table 2). Epinephrine levels rose only slightly in the transplant recipients (Table 2).

Regional Myocardial Blood Flow and Coronary Vascular Resistance

Base-Line Measurements

The base-line blood flow in the transplant recipients was similar in all the coronary territories despite the differences in sympathetic reinnervation. The base-line flow was higher in the transplant recipients than in the normal subjects, reflecting the differences in cardiac work and oxygen demand as measured by the rate–pressure product (Table 3).

Blood-Flow Response to the Cold Pressor Test

During the cold pressor test, blood flow increased significantly in all coronary territories (Table 3). However, the magnitude of the increase in flow differed among regions: it was higher in the territory of the left anterior descending artery (46 ± 10 percent) than in the territories of the right coronary artery (16 ± 5 percent, $P=0.01$) and the circumflex artery (23 ± 6 percent, $P=0.06$) (Fig. 2), even though changes in levels of circulating catecholamines, the heart rate, and blood pressure produce global effects that should affect all the regions equally. The index of coronary vascular resistance decreased, although slightly, only in the territory of the left anterior descending artery. The magnitude of the increase in flow during cold pressor testing exactly mirrored the uptake of [^{11}C]hydroxyephedrine (Table 4). These differences were not observed in the normal subjects (Table 4).

Blood-Flow Response to Adenosine

During hyperemia, blood flow increased and coronary vascular resistance decreased to a similar degree in all the coronary-artery territories in both groups of patients. Although the peak myocardial blood flow was similar in the transplant recipients and the normal subjects, the estimates of coronary vasodilator reserve tended to be higher in the normal subjects because of a lower base-line flow (the denominator of the calculation of coronary flow reserve) (Table 3).

DISCUSSION

Coronary blood flow is regulated to a large extent by adrenergic mechanisms, through the direct activation of adrenergic receptors and indirectly by changes in metabolic autoregulation and endothelial function. However, the importance of cardiac efferent sympathetic signals, as compared with systemic adrenergic influences, in regulating myocardial perfusion remains controversial. Our findings provide evidence that the increase in coronary flow in re-

TABLE 1. SYSTEMIC HEMODYNAMICS IN THE 14 TRANSPLANT RECIPIENTS AND THE 8 NORMAL SUBJECTS.

HEMODYNAMIC MEASURE	AT BASE LINE	DURING COLD PRESSOR TEST	DURING ADENOSINE INFUSION
		mean \pm SE	
Transplant recipients			
Heart rate (beats/min)	77 \pm 1.8	86 \pm 2.5*	92 \pm 2.4*
Blood pressure (mm Hg)			
Systolic	141 \pm 3.4	183 \pm 4.7*	144 \pm 5.3
Mean aortic	103 \pm 2.0	128 \pm 2.5*	102 \pm 3.4
Rate–pressure product†	10.9 \pm 0.4	15.7 \pm 0.6*	13.3 \pm 0.7‡
Normal subjects			
Heart rate (beats/min)	70 \pm 3.9	81 \pm 7.3§	103 \pm 3.0*
Blood pressure (mm Hg)			
Systolic	118 \pm 4.6	136 \pm 5.4*	116 \pm 4.1
Mean aortic	85 \pm 2.8	101 \pm 3.6¶	81 \pm 3.1
Rate–pressure product†	8.3 \pm 0.6	10.9 \pm 1.1	11.9 \pm 0.5**

* $P < 0.001$ for the comparison with the corresponding hemodynamic measure at base line.

†The rate–pressure product was calculated by multiplying the heart rate by the systolic blood pressure by 0.001.

‡ $P = 0.001$ for the comparison with the corresponding value at base line.

§ $P = 0.04$ for the comparison with the corresponding value at base line.

¶ $P = 0.005$ for the comparison with the corresponding value at base line.

|| $P = 0.01$ for the comparison with the corresponding value at base line.

** $P = 0.003$ for the comparison with the corresponding value at base line.

TABLE 2. CIRCULATING CATECHOLAMINE LEVELS AT BASE LINE AND IN RESPONSE TO THE COLD PRESSOR TEST IN THE STUDY SUBJECTS.*

VARIABLE	BASE LINE	COLD PRESSOR TEST
	pg/ml	
Transplant recipients		
Norepinephrine	323 \pm 48	523 \pm 68†
Epinephrine	19 \pm 2	27 \pm 2‡
Dopamine	31 \pm 4	31 \pm 6
Normal subjects		
Norepinephrine	225 \pm 69	306 \pm 70†
Epinephrine	20 \pm 4	31 \pm 6
Dopamine	25 \pm 1	25 \pm 1

*Plus–minus values are means \pm SE.

† $P = 0.02$ for the comparison with the corresponding value at base line.

‡ $P = 0.001$ for the comparison with the corresponding value at base line.

TABLE 3. REGIONAL MYOCARDIAL BLOOD FLOW AND CORONARY VASCULAR RESISTANCE IN THE STUDY SUBJECTS.*

VARIABLE	TRANSPLANT RECIPIENTS			NORMAL SUBJECTS		
	LAD	LCX	RCA	LAD	LCX	RCA
	mean±SE					
Myocardial blood flow (ml/min/g of tissue)						
Base line	0.99±0.07	1.00±0.06	0.96±0.06	0.79±0.06	0.80±0.06	0.82±0.07
Cold pressor test	1.41±0.07†	1.21±0.07†	1.09±0.06‡	1.21±0.13†	1.19±0.15†	1.18±0.15†
Adenosine infusion	3.08±0.19†	2.98±0.21†	2.97±0.19†	2.94±0.12†	2.98±0.13†	2.94±0.17†
Coronary flow reserve	3.31±0.32	3.09±0.29	3.21±0.31	3.86±0.35	3.85±0.34	3.77±0.39
Coronary vascular resistance (mm Hg/ml/min/g of tissue)						
Base line	112±8.9	110±8.5	115±9.6	110±7.6	109±8.0	107±7.3
Cold pressor test	96±7.4	111±8.9	123±9.3§	90±7.4	93±9.5	92±9.1
Adenosine infusion	35±2.2	36±2.6	36±2.2	28±1.8	28±1.8	29±2.7

*LAD denotes the territory of the left anterior descending artery, LCX the territory of the circumflex artery, and RCA the territory of the right coronary artery.

†P<0.001 for the comparison with the corresponding value at base line.

‡P=0.006 for the comparison with the value for the territory of the left anterior descending artery, and P=0.002 for the comparison with the value at base line.

§P=0.07 for the comparison with the value for the territory of the left anterior descending artery.

sponse to sympathetic stimulation correlates with the magnitude of regional stores of norepinephrine in cardiac sympathetic-nerve terminals. In this study, blood flow increased by 46 percent in the territory of the left anterior descending artery (which had the highest uptake of [¹¹C]hydroxyephedrine) and by only 16 percent in the territory of the right coronary artery (which had the lowest uptake of [¹¹C]hydroxyephedrine) during the cold pressor test. This difference in flow was largely independent of changes in circulating levels of catecholamines and changes in hemodynamics (i.e., heart rate and blood pressure), since we compared reinnervated and denervated coronary territories in the same heart. These findings suggest that cardiac efferent adrenergic signals play an important part in modulating myocardial blood flow during activation of the sympathetic nervous system.

Exactly how the activation of cardiac sympathetic-nerve terminals may cause coronary vasodilatation cannot be determined from this study. Several potential mechanisms could explain our findings, however. It is possible that the increased density of sympathetic-nerve endings in reinnervated regions (i.e., the territory of the left anterior descending artery) caused relatively greater increases in regional contractility and oxygen demand after sympathetic activation, which in turn produced more metabolic vasodilatation. However, Zeiher et al.⁴ reported similar increases in blood flow in normal coronary arteries in response to the cold pressor test before and after an intracoronary β -adrenergic blockade with pro-

pranolol. This would suggest that changes in regional contractility (mediated by β_1 -adrenoceptors) may not be the determinant dilatory mechanism of resistance vessels during sympathetic stimulation.

Another possibility is that coronary vasodilatation in response to neurally released norepinephrine (a mixed β_1 - and α -adrenergic agonist) may result from the direct activation of β -adrenergic receptors on smooth muscle and endothelial cells in the vessel wall.^{3,14} The reported exacerbation of pain after propranolol therapy in patients with classic stable angina or vasospastic angina would support this hypothesis.^{15,16} However, the findings of Zeiher et al.⁴ showing that increases in blood flow in response to the cold pressor test are similar before and after treatment with intracoronary propranolol would argue against this mechanism. Finally, coronary vasodilatation may also result from the direct stimulation of α_2 -adrenergic receptors in intact endothelial cells and the release of nitric oxide,^{17,18} presumably through the activation of local kinin synthesis.¹⁸ Indeed, removing the vascular endothelium of isolated and intact canine arteries enhances the constrictor response to norepinephrine.^{19,20} In addition, patients with endothelial dysfunction have impaired microvascular dilatation in response to sympathetic stimulation.⁵ Furthermore, α -adrenergic vasoconstriction is potentiated by the inhibition of nitric oxide synthesis in coronary arteries in both dogs and humans.²¹

Another important finding in this study is that the basal flows in the transplant recipients were similar

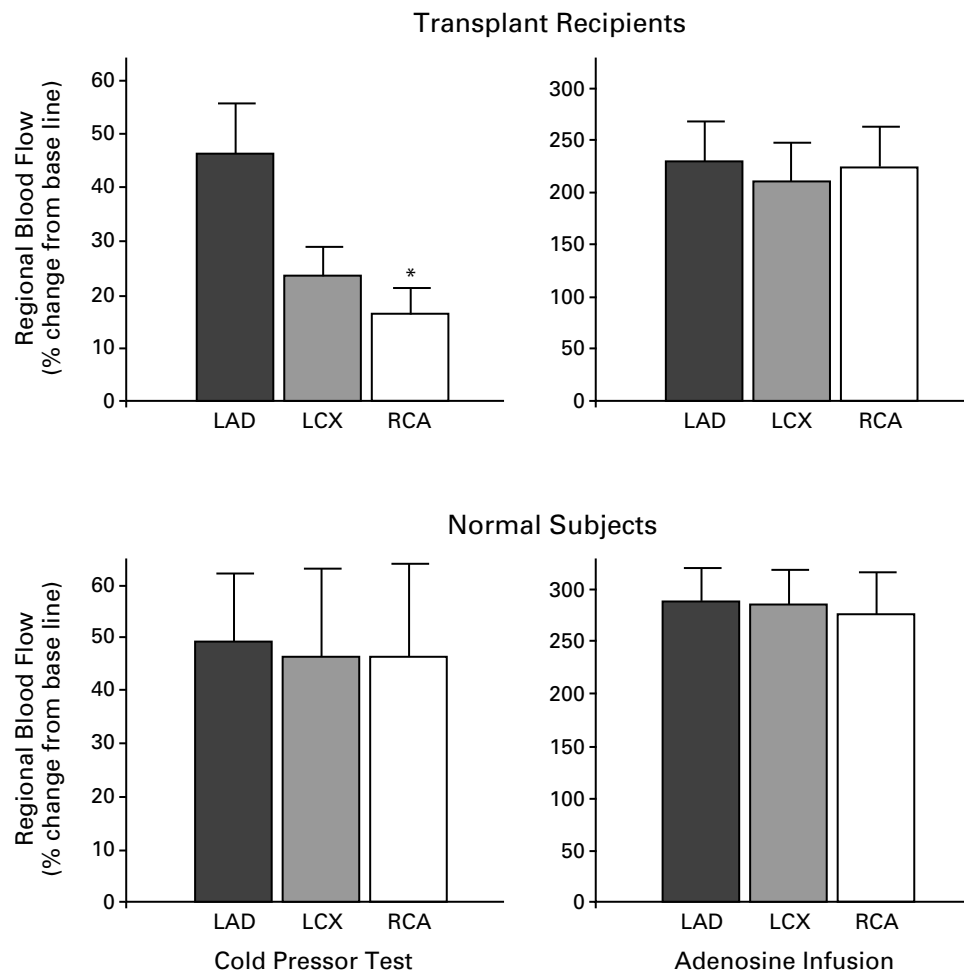


Figure 2. Changes in Regional Myocardial Blood Flow in Response to the Cold Pressor Test and the Infusion of Adenosine in the Transplant Recipients and the Normal Subjects.

LAD denotes the territory of the left anterior descending artery, LCX the territory of the circumflex artery, and RCA the territory of the right coronary artery. The asterisk indicates $P=0.01$ for the comparison with the territory served by the left anterior descending artery.

in all coronary territories despite the differences in sympathetic innervation, an observation that suggests that resting coronary flow is not substantially affected by either humoral or neural adrenergic influences. This finding is in agreement with the results of studies in animals²² and humans.²³ In addition, the maximal vasodilator response to adenosine was similar to that observed in the normal subjects and was not limited by regional differences in sympathetic innervation. This is consistent with the findings of Hodgson et al. demonstrating that coronary flow reserve, as assessed by the use of intracoronary papaverine, was similar in normally innervated and denervated transplant recipients and was unchanged after blockade with either α - or β -adrenergic receptors.²³

Data obtained by the noninvasive method of as-

sessing myocardial blood flow in vivo with PET imaging have been shown to be both accurate and reproducible.^{10,24} Evaluating the presence and severity of intimal disease was not part of our study design. Although it is possible that regional vasomotor dysfunction in territories with transplant-related vasculopathy that was not detected by coronary arteriography may have affected our results, such an effect is not very likely, because transplant-associated atherosclerosis is a diffuse rather than a regional process.²⁵ Furthermore, recent evidence shows that coronary vasomotor function may be preserved in long-term survivors of cardiac transplantation despite the presence of intimal disease.²⁶

Studies have shown the importance of endothelial function in modulating the coronary vasomotor response to increased sympathetic stimulation.⁵ We

TABLE 4. REGIONAL UPTAKE OF [¹¹C]HYDROXYEPHEDRINE IN THE STUDY SUBJECTS IN RELATION TO THE BLOOD-FLOW RESPONSE DURING COLD PRESSOR TESTING AND THE ADENOSINE INFUSION.*

VARIABLE	TRANSPLANT RECIPIENTS			NORMAL SUBJECTS		
	LAD	LCX	RCA	LAD	LCX	RCA
	mean ± SE					
Uptake of [¹¹ C]hydroxyephedrine	0.15±0.01	0.09±0.01†	0.07±0.01†	0.18±0.01	0.19±0.01	0.18±0.01
Blood-flow response (% change from base line)						
Cold pressor test	46±9.5	23±5.8‡	16±5.0§	49±13	46±17	46±18
Adenosine infusion	229±40	211±38	224±41	287±34	285±34	276±40

*LAD denotes the territory of the left anterior descending artery, LCX the territory of the circumflex artery, and RCA the territory of the right coronary artery.

†P<0.001 for the comparison with the value for the territory of the left anterior descending artery.

‡P=0.06 for the comparison with the value for the territory of the left anterior descending artery.

§P=0.01 for the comparison with the value for the territory of the left anterior descending artery.

have now demonstrated that the response of coronary blood flow to such stimulation is related to the norepinephrine content of cardiac sympathetic-nerve terminals and is largely independent of changes in hemodynamics and levels of circulating catecholamines. These findings suggest that signals from cardiac efferent sympathetic nerves play an important part in modulating the ability of the coronary vasculature to dilate and thus increase the flow of blood to the myocardium during periods of activation of the sympathetic nervous system, such as occurs during exercise, exposure to cold, and mental stress.

This novel mechanism of regulating myocardial perfusion may have several important implications. In patients with progressive transplant-associated atherosclerosis, an inadequate dilator response of resistance vessels distal to the stenosis could further limit the supply of blood to the myocardium and contribute to myocardial ischemia during periods of stress. Such vasomotor dysfunction could accentuate the alterations in myocardial perfusion caused by endothelial dysfunction²⁷ and contribute to the vascular complications of transplant-associated atherosclerosis.²⁸

Furthermore, studies of laboratory animals have shown that brief episodes of reversible ischemia can induce sustained abnormalities in the function of cardiac sympathetic nerves in reperfused myocardium.²⁹⁻³¹ Similar findings have also been reported in patients after myocardial infarction.^{32,33} These observations suggest that severe ischemia may cause regional "denervation" of ischemically injured but viable myocardium. This effect may be important in patients with unstable angina and myocardial infarction. Transient episodes of thrombotic vessel occlusion at the site of plaque rupture are frequent in unstable angina, and coronary occlusion is often intermittent

in myocardial infarction.^{34,35} In addition, the release of vasoactive substances by platelets and vasoconstriction due to endothelial dysfunction may contribute to reduced coronary flow.³⁶ These transient episodes of severe ischemia distal to the site of coronary thrombosis would lead to regional dysfunction of efferent sympathetic nerves, which in turn could reduce the dilator capacity of resistance vessels and influence the extent of myocardial damage. This abnormal vasomotor response may also be present in patients who have diabetic autonomic neuropathy that involves efferent sympathetic pathways. In such patients, impaired coronary vasodilation due to cardiac efferent adrenergic dysfunction may contribute to the pathogenesis of myocardial ischemia and possibly to left ventricular dysfunction.³⁷⁻³⁹

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REFERENCES

- Berne RM. Regulation of coronary blood flow. *Physiol Rev* 1964;44:1-29.
- Vanhoutte PM, ed. Vasodilatation: vascular smooth muscle, peptides, autonomic nerves, and endothelium. New York: Raven Press, 1988.
- Young MA, Knight DR, Vatner SF. Autonomic control of large coronary arteries and resistance vessels. *Prog Cardiovasc Dis* 1987;30:211-34.
- Zeiber AM, Drexler H, Wollschlaeger H, Saurbier B, Just H. Coronary vasomotion in response to sympathetic stimulation in humans: importance of the functional integrity of the endothelium. *J Am Coll Cardiol* 1989; 14:1181-90.
- Zeiber AM, Drexler H, Wollschlaeger H, Just H. Endothelial dysfunction of the coronary microvasculature is associated with coronary blood

- flow regulation in patients with early atherosclerosis. *Circulation* 1991;84:1984-92.
6. Norvell JE, Lower RR. Degeneration and regeneration of the nerves of the heart after transplantation. *Transplantation* 1973;15:337-44.
 7. Wilson RF, Christensen BV, Olivari MT, Simon A, White CW, Laxson DD. Evidence for structural sympathetic reinnervation after orthotopic cardiac transplantation in humans. *Circulation* 1991;83:1210-20.
 8. Schwaiger M, Hutchins GD, Kalff V, et al. Evidence for regional catecholamine uptake and storage sites in the transplanted human heart by positron emission tomography. *J Clin Invest* 1991;87:1681-90.
 9. Wilson RF, Laxson DD, Christensen BV, McGinn AL, Kubo SH. Regional differences in sympathetic reinnervation after human orthotopic cardiac transplantation. *Circulation* 1993;88:165-71.
 10. Muzik O, Beanlands RS, Hutchins GD, Mangner TJ, Nguyen N, Schwaiger M. Validation of nitrogen-13-ammonia tracer kinetic model for quantification of myocardial blood flow using PET. *J Nucl Med* 1993;34:83-91.
 11. Schwaiger M, Kalff V, Rosenspire K, et al. Noninvasive evaluation of sympathetic nervous system in human heart by positron emission tomography. *Circulation* 1990;82:457-64.
 12. Hutchins GD, Caraher JM, Raylman RR. A region of interest strategy for minimizing resolution distortions in quantitative myocardial PET studies. *J Nucl Med* 1992;33:1243-50.
 13. Goldstein DS, Feuerstein G, Izzo JL Jr, Kopin IJ, Keiser HR. Validity and reliability of liquid chromatography with electrochemical detection for measuring plasma levels of norepinephrine and epinephrine in man. *Life Sci* 1981;28:467-75.
 14. Graves J, Poston L. Beta-adrenoceptor agonist mediated relaxation of rat isolated resistance arteries: a role for the endothelium and nitric oxide. *Br J Pharmacol* 1993;108:631-7.
 15. Yasue H, Touyama M, Shimamoto M, Kato H, Tanaka S. Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. *Circulation* 1974;50:534-9.
 16. Yasue H, Omote S, Takizawa A, Nagao M, Miwa K, Tanaka S. Exertional angina pectoris caused by coronary artery spasm: effects of various drugs. *Am J Cardiol* 1979;43:647-52.
 17. Jones CJH, DeFily DV, Patterson JL, Chilian WM. Endothelium-dependent relaxation competes with α 1- and α 2-adrenergic constriction in the canine epicardial coronary microcirculation. *Circulation* 1993;87:1264-74.
 18. Kichuk MR, Seyedi N, Zhang X, et al. Regulation of nitric oxide production in human coronary microvessels and the contribution of local kinin formation. *Circulation* 1996;94:44-51.
 19. Cocks TM, Angus JA. Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin. *Nature* 1983;305:627-30.
 20. Young MA, Vatner SF. Enhanced adrenergic constriction of iliac artery with removal of endothelium in conscious dogs. *Am J Physiol* 1986;250:H892-H897.
 21. Berkenboom G, Unger P, Fang ZY, Fontaine J. Endothelium-derived relaxing factor and protection against contraction to norepinephrine in isolated canine and human coronary arteries. *J Cardiovasc Pharmacol* 1991;17:Suppl 3:S127-S132.
 22. Chilian WM, Boatwright RB, Shoji T, Griggs DM Jr. Evidence against significant resting sympathetic coronary vasoconstrictor tone in the conscious dog. *Circ Res* 1981;49:866-76.
 23. Hodgson JMB, Cohen MD, Szentpetery S, Thames MD. Effects of regional α - and β -blockade on resting and hyperemic coronary blood flow in conscious, unstressed humans. *Circulation* 1989;79:797-809.
 24. Sawada S, Muzik O, Beanlands R, Wolfe E, Hutchins G, Schwaiger M. Inter observer and inter study variability of myocardial blood flow and flow-reserve measurements with nitrogen 13 ammonia-labeled positron emission tomography. *J Nucl Cardiol* 1995;2:413-22.
 25. Ventura HO, Mehra MR, Smart FW, Stapleton DD. Cardiac allograft vasculopathy: current concepts. *Am Heart J* 1995;129:791-9.
 26. Anderson TJ, Meredith IT, Uehata A, et al. Functional significance of intimal thickening as detected by intravascular ultrasound early and late after cardiac transplantation. *Circulation* 1993;88:1093-100.
 27. Mügge A, Heublein B, Kuhn M, et al. Impaired coronary dilator responses to substance P and impaired flow-dependent dilator responses in heart transplant patients with graft vasculopathy. *J Am Coll Cardiol* 1993;21:163-70.
 28. Schoen FJ, Libby P. Cardiac transplantation graft arteriosclerosis. *Trends Cardiovasc Med* 1991;1:216-23.
 29. Inoue H, Zipes DP. Time course of denervation of efferent sympathetic and vagal nerves after occlusion of the coronary artery in the canine heart. *Circ Res* 1988;62:1111-20.
 30. Schwaiger M, Guibourg H, Rosenspire K, et al. Effect of regional myocardial ischemia on sympathetic nervous system as assessed by fluorine-18-metaraminol. *J Nucl Med* 1990;31:1352-7.
 31. Dae MW, Herre JM, O'Connell JW, Botvinick EH, Newman D, Munoz L. Scintigraphic assessment of sympathetic innervation after transmural versus nontransmural myocardial infarction. *J Am Coll Cardiol* 1991;17:1416-23.
 32. Stanton MS, Tuli MM, Radtke NL, et al. Regional sympathetic denervation after myocardial infarction in humans detected noninvasively using I-123-metaiodobenzylguanidine. *J Am Coll Cardiol* 1989;14:1519-26.
 33. Allman KC, Wieland DM, Muzik O, Degradó TR, Wolfe ER Jr, Schwaiger M. Carbon-11 hydroxyephedrine with positron emission tomography for serial assessment of cardiac adrenergic neuronal function after acute myocardial infarction in humans. *J Am Coll Cardiol* 1993;22:368-75.
 34. Fuster V, Badimon L, Cohen M, Ambrose JA, Badimon JJ, Chesebro J. Insights into the pathogenesis of acute ischemic syndromes. *Circulation* 1988;77:1213-20.
 35. Hackett D, Davies G, Chierchia S, Maseri A. Intermittent coronary occlusion in acute myocardial infarction: value of combined thrombolytic and vasodilator therapy. *N Engl J Med* 1987;317:1055-9.
 36. Bogaty P, Hackett D, Davies G, Maseri A. Vasoreactivity of the culprit lesion in unstable angina. *Circulation* 1994;90:5-11.
 37. Faerman I, Faccio E, Milei R, et al. Autonomic neuropathy and painless myocardial infarction in diabetic patients: histologic evidence of their relationship. *Diabetes* 1977;26:1147-58.
 38. Langer A, Freeman MR, Josse RG, Armstrong PW. Metaiodobenzylguanidine imaging in diabetes mellitus: assessment of cardiac sympathetic denervation and its relation to autonomic dysfunction and silent myocardial ischemia. *J Am Coll Cardiol* 1995;25:610-8.
 39. Kahn JK, Zola B, Juni JE, Vinik AI. Radionuclide assessment of left ventricular diastolic filling in diabetes mellitus with and without cardiac autonomic neuropathy. *J Am Coll Cardiol* 1986;7:1303-9.