

# Myocardial Beta-Adrenoceptor Density One Month After Acute Myocardial Infarction Predicts Left Ventricular Volumes at Six Months

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<b>OBJECTIVES</b>	To investigate whether myocardial beta-adrenoceptor (beta-AR) downregulation precedes and predicts left ventricular (LV) dilation after acute myocardial infarction (AMI), we measured beta-AR density within four weeks of AMI and correlated it with serial measurements of LV volumes.
<b>BACKGROUND</b>	Patients who develop heart failure following AMI have an increased sympathetic drive to the heart within the first four weeks after infarction.
<b>METHODS</b>	We prospectively studied 61 patients in whom AMI was the first presentation of coronary artery disease (CAD) and with no signs of heart failure. The LV volumes were measured one, three, and six months after AMI by echocardiography. Beta-AR density was measured using positron emission tomography with S-[ <sup>11</sup> C]CGP 12177. Seventeen matched healthy volunteers served as controls.
<b>RESULTS</b>	Whole heart beta-AR density was lower in patients than in controls ( $6.25 \pm 0.98$ pmol/g vs. $8.32 \pm 2.14$ pmol/g, $p < 0.0001$ ). In patients, beta-AR density was inversely correlated with end-systolic and end-diastolic volumes six months after AMI. Patients whose LV was dilated at six months had a lower beta-AR density in noninfarcted myocardium than patients without dilation ( $6.15$ pmol/g vs. $6.98$ pmol/g, $p = 0.008$ ). In addition, beta-AR density in noninfarcted myocardium was higher when the infarct-related artery was patent ( $6.87 \pm 1.14$ pmol/g vs. $5.76 \pm 0.86$ pmol/g occluded, $p < 0.01$ ).
<b>CONCLUSIONS</b>	Myocardial beta-AR density is reduced after AMI in the absence of heart failure, and the reduction predicts later LV dilation. These data are suggestive of an enhanced sympathetic drive to the heart, having an important etiologic role in LV remodeling after AMI. (J Am Coll Cardiol 2002;40:1216–24) © 2002 by the American College of Cardiology Foundation

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Congestive heart failure (CHF) is common and, as an absolute cause of death, mortality is increasing (1). In about 70% of cases, it is secondary to coronary artery disease (CAD) (2). In most of these patients there is evidence of a previous acute myocardial infarction (AMI), especially when the latter is extensive, transmural, and involves the anterior wall of the left ventricle (LV) (3). Development of overt CHF after AMI is often slow and is preceded by an asymptomatic phase in which changes in the shape, size, and properties of the LV occur (remodeling) (4).

A number of mechanisms contribute to LV remodeling (5), among which enhanced activation of the sympathetic nervous system (SNS) plays a major role. Myocardial beta-adrenoceptors (beta-AR), measured from endomyocardial biopsies, are downregulated in patients with overt CHF and the degree of receptor downregulation is related to the severity of CHF (6). Furthermore, these patients have higher levels of circulating catecholamines, which are inversely related to prognosis (7).

Positron emission tomography (PET) with the nonselective

beta-AR antagonist S-[<sup>11</sup>C]CGP 12177 (CGP) allows the noninvasive measurement of regional myocardial beta-AR density ( $B_{max}$ ) in humans in vivo. Merlet et al. (8) demonstrated downregulation of beta-AR in patients with CHF due to idiopathic dilated cardiomyopathy. Using the same technique, we demonstrated progressive beta-AR downregulation in those patients with hypertrophic cardiomyopathy (HCM) who proceed to LV dilation and CHF (9).

We hypothesized that the degree of myocardial beta-AR downregulation measured in the subacute phase after AMI might be predictive of subsequent LV remodeling. Therefore, we set up a prospective study of patients with AMI as their first presentation of CAD. Serial measurements of LV volumes were carried out up to six months after infarction, and beta-AR density and plasma catecholamines were measured within four weeks of AMI.

## METHODS

**Study population.** Sixty-one patients (age  $52 \pm 11$  years, 9 women) were recruited from St. Mary's, Hammersmith, Ealing, and Charing Cross Hospitals in London. Acute myocardial infarction was diagnosed on the basis of history, electrocardiogram, and cardiac enzyme rise (creatinine kinase greater than twice the upper limit of normal). Exclusion

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#### Abbreviations and Acronyms

AMI	= acute myocardial infarction
beta-AR	= beta-adrenoceptor
B <sub>max</sub>	= myocardial beta-adrenoceptor density
CAD	= coronary artery disease
CGP	= S-[ <sup>11</sup> C]CGP 12177
CHF	= congestive heart failure
EDV	= end-diastolic volume
ESV	= end-systolic volume
HCM	= hypertrophic cardiomyopathy
LV	= left ventricle/ventricular
MBF	= myocardial blood flow
PET	= positron emission tomography
ROI	= region of interest
SNS	= sympathetic nervous system
TIMI	= Thrombolysis In Myocardial Infarction

criteria were previous angina, hypertension, diabetes, renal failure, and significant CAD in arteries other than the infarct-related artery. Thus, if a noninfarct-related artery had a stenosis >50% in two orthogonal projections, or 75% in a single projection, the patient was excluded. Part of the study protocol was that patients would undergo diagnostic coronary angiography within 10 days of their AMI, with percutaneous coronary intervention to the relevant lesion as appropriate.

Treatment for AMI was left completely to the admitting physician and could include *acute* (i.e., intravenous) beta-blockade, but patients who required long-term beta-blockade were excluded (Table 1). (Because, during the period of recruitment [1995 to 1998], it was not routine practice in our institutions to use chronic beta-blockade for post-myocardial infarction patients, whether in heart failure or not, we do not believe that our protocol selectively excluded a subset of patients who would have required chronic beta-blockade.)

Seventeen healthy volunteers (9 men, age  $53 \pm 12$  years,  $p = \text{NS}$  vs. patients) were studied as controls for the measurement of myocardial beta-AR. They had no history of CAD and had normal resting and negative exercise electrocardiogram.

#### Study Protocol

**Echocardiography.** Patients were studied by echocardiography at one to two weeks, one month, and six months after AMI using a Challenge 7000 echocardiograph (Esaote Biomedica, Florence, Italy). Both end-systolic volume (ESV) and end-diastolic volume (EDV) were measured using a single-plane area-length method (10). The average of three measurements was used for each parameter. Patients were deemed to have undergone LV dilation if both  $\text{ESV}_3/\text{ESV}_1$  and  $\text{EDV}_3/\text{EDV}_1$  were higher than 1.1, or if either one of these ratios was >1.2—that is, 10% or 20% difference from baseline (11).

**PET scanning.** Patients underwent PET scanning using an ECAT 931-08/12 scanner (CTI/Siemens, Knoxville,

Tennessee) two to four weeks after AMI. After a 20-min transmission scan, the blood pool was imaged using inhaled  $\text{C}^{15}\text{O}$ . After 10 min, myocardial blood flow (MBF) was measured using  $\text{H}_2^{15}\text{O}$  (12).

Subsequently, myocardial beta-AR density was measured using CGP (13). Briefly, the first dose of CGP with high specific activity ( $159 \pm 29$  MBq;  $5.7 \pm 2.3$   $\mu\text{g}$ ) was infused intravenously over 2 min and followed, 30 min later, by a second low specific activity injection ( $300 \pm 67$  MBq;  $28.6 \pm 5.8$   $\mu\text{g}$ ) infused over 2 min. A 55-frame dynamic emission scan (12) was used to measure the temporal and spatial distribution of the tracer in vivo. Venous blood was continuously withdrawn and passed through a bismuth germanium oxide counting system to assess changes in CGP blood concentration with time. This information was used to correct the CGP scan for vascular activity. Five calibration blood samples were taken during this period and assayed for [<sup>11</sup>C]-activity in a well counter, cross-calibrated with the scanner (13).

**PET DATA ANALYSIS.** All sinograms were normalized, corrected for attenuation, and then reconstructed to provide transaxial images with a spatial resolution of 8.4 mm full width at half maximum and a slice thickness of 6.6 mm full width at half maximum. Images were resliced in short axis, and 12 slices were obtained from the mitral valve plane to the apex of the heart. Regions of interest (ROIs) were defined by dividing the LV myocardium into anterior, septal, lateral, and inferior regions, further subdivided into 16 segments (13,14). A whole-heart ROI was also created by averaging all pixels within the area between the outer and inner trace for all 12 slices. These ROIs were then applied to all emission images of the different scans. The ROIs of the myocardial territory subtended by the infarct-related artery were termed “infarcted myocardium”; the ROIs of the myocardial territory subtended by an artery reciprocal to the infarct-related artery were termed “remote myocardium.” Thus, the anterior and septal ROIs were considered “remote” with respect to an inferior infarct, and the inferior ROI was considered “remote” with respect to an anterior infarct.

**MBF MEASUREMENT.** The MBF (ml/min/g) was calculated by fitting the arterial input (obtained from a left atrial ROI) and tissue time-activity curves from the blood flow scan to a single-tissue compartment tracer kinetic model (12), which includes corrections for partial volume effect and spillover of activity from the LV chamber into myocardial ROIs.

**MEASUREMENT OF BETA-AR DENSITY.** Myocardial time-activity curves were corrected for radioactive decay and for vascular activity (13). The sections of the curve corresponding to the two slow clearance phases, which represent the dissociation of CGP bound to beta-AR, were exponentially extrapolated back to the start of the infusions. Beta-adrenoceptor density was determined as the maximum number of available specific CGP binding sites per gram of tissue ( $B_{\text{max}}$ ) in the ROIs (13). The  $B_{\text{max}}$  values were

**Table 1.** Treatment, Left Ventricular Volumes, and TIMI Flow for Each of the 61 Patients

Patient No.	Treatment	EDV1 (ml)	EDV3 (ml)	ESV1 (ml)	ESV3 (ml)	$\delta$ ESV	$\delta$ EDV	TIMI Flow A	TIMI Flow B
1	ASA+ACEI	73	127	43	67	1.56	1.74	1	1
2	ASA+ACEI+CCB	72	110	39	67	1.72	1.53	1	3
3	ASA+ACEI+CCB	101	149	58	90	1.55	1.48	1	3
4	ASA+ACEI+CCB	86	123	45	61	1.36	1.43	2	3
5	ASA+ACEI	138	120	72	60	0.83	0.87	3	3
6	ASA+ACEI+CCB	60	62	36	35	0.97	1.03	2	3
7	ASA+ACEI	103	92	55	54	0.98	0.89	1	2
8	ASA	144	112	81	58	0.72	0.78	2	3
9	ASA	93	109	44	42	0.95	1.17	1	3
10	ASA	100	71	62	38	0.61	0.71	3	3
11	ASA+ACEI+CCB	92	81	54	34	0.63	0.88	2	3
12	ASA+ACEI+CCB	100	109	53	65	1.23	1.09	1	3
13	ASA+ACEI	82	151	31	91	2.94	1.84	0	2
14	ASA+CCB	82	75	36	25	0.69	0.91	2	3
15	ASA+ACEI	59	106	35	61	1.74	1.80	1	3
16	ASA	107	112	52	55	1.06	1.05	1	3
17	ASA+CCB	93	184	55	125	2.27	1.98	2	2
18	ASA+CCB	109	106	72	62	0.86	0.97	1	1
19	ASA+ACEI	132	174	76	115	1.51	1.32	2	2
20	ASA	148	171	90	67	0.74	1.16	2	3
21	ASA+ACEI	152	194	81	84	1.04	1.28	2	3
22	ASA	124	141	63	78	1.24	1.14	2	3
23	ASA	101	109	46	53	1.15	1.08	2	3
24	ASA	109	129	59	80	1.36	1.18	0	3
25	ASA+CCB	236	278	142	167	1.18	1.18	2	3
26	ASA+CCB	79	94	39	32	0.82	1.19	2	3
27	ASA+ACEI+CCB	92	84	53	41	0.77	0.91	2	3
28	ASA	116	112	57	50	0.88	0.97	2	3
29	ASA+ACEI+CCB	135	158	67	86	1.28	1.17	2	3
30	ASA+CCB	103	108	58	67	1.16	1.05	1	3
31	ASA+CCB	114	111	55	62	1.13	0.97	1	3
32	ASA+CCB	115	108	41	55	1.34	0.94	2	3
33	ASA+CCB	101	102	49	45	0.92	1.01	3	3
34	ASA+ACEI	93	107	46	50	1.09	1.15	2	3
35	ASA+ACEI+CCB	105	101	61	54	0.89	0.96	2	3
36	ASA+ACEI+CCB	123	106	63	49	0.78	0.86	2	3
37	ASA+CCB	132	132	65	61	0.94	1.00	2	2
38	ASA+ACEI+CCB	133	201	79	119	1.51	1.51	1	3
39	ASA+ACEI	95	56	47	27	0.57	0.59	1	3
40	ASA+ACEI	138	149	94	96	1.02	1.08	0	3
41	ASA+ACEI+CCB	103	99	58	64	1.10	0.96	1	3
42	ASA	130	111	68	47	0.69	0.85	2	3
43	ASA	118	112	69	44	0.64	0.95	2	3
44	ASA+ACEI+CCB	111	96	65	55	0.85	0.86	2	3
45	ASA+ACEI	145	82	76	42	0.55	0.57	2	3
46	ASA	154	124	103	70	0.68	0.81	2	3
47	ASA+CCB	109	121	53	49	0.92	1.11	2	3
48	ASA+CCB+ACEI	198	126	99	69	0.70	0.64	2	3
49	ASA+CCB	117	112	43	60	1.40	0.96	1	2
50	ASA+ACEI	153	125	74	67	0.91	0.82	0	3
51	ASA	155	135	74	77	1.04	0.87	2	3
52	ASA+CCB	163	197	90	135	1.50	1.21	0	2
53	ASA+CCB	100	107	44	49	1.11	1.07	3	3
54	ASA+ACEI+CCB	78	114	42	53	1.26	1.46	2	3
55	ASA+CCB	172	128	117	66	0.56	0.74	2	3
56	ASA+CCB	115	107	48	56	1.17	0.93	1	3
57	ASA+ACEI	110	119	69	91	1.32	1.35	1	2
58	ASA+ACEI	132	100	68	46	0.68	0.76	1	3
59	ASA+CCB	129	144	41	79	1.93	1.12	2	3
60	ASA+ACEI	224	180	115	88	0.77	0.80	2	3
61	ASA+CCB	114	110	50	62	1.24	0.96	2	3

ASA = aspirin; ACEI = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker; ESV1 = end-systolic volume at one week; ESV3 = end-systolic volume at six months; EDV1 = end-diastolic volume at one week; EDV3 = end-diastolic volume at six months;  $\delta$ ESV =  $ESV3/ESV1$ ;  $\delta$ EDV =  $EDV3/EDV1$ ; TIMI A = Thrombolysis In Myocardial Infarction flows at baseline (after thrombolysis, but before percutaneous interventions); TIMI B = Thrombolysis In Myocardial Infarction flows after percutaneous interventions.

corrected for partial volume effect and movement using the measured values of tissue fraction (12). In infarcted regions the presence of significant tissue thinning and fibrosis might lead to erroneously lower  $B_{\max}$  owing to a dilutional effect of scar. To minimize the effect of such thinning and fibrosis, all beta-AR values were corrected for partial volume using the perfusable tissue index (15). This is derived from the  $H_2^{15}O$  scan and provides an estimate of the fraction of *viable* tissue within the volume of interest capable of exchanging rapidly the freely diffusible tracer  $H_2^{15}O$ . Therefore, beta-AR densities are reported per milliliter of perfusable and hence viable tissue.

**Plasma catecholamine assay.** Venous samples were taken after subjects had been relaxed and recumbent for 30 min. Adrenaline and noradrenaline were assayed using high-performance liquid chromatography with electrochemical detection (13).

### Statistical Analysis

Values are expressed as mean  $\pm$  SD. Analysis of variance was carried out to assess the differences in beta-AR and myocardial blood flow among the myocardial ROIs within groups, with the Scheffé test to localize the source of any differences. The two-tailed unpaired Student *t* test was used to compare the ages and the values of myocardial beta-AR between each patient group and its matched control subset. Regression analysis was performed using standard techniques. The relationship between Thrombolysis In Myocardial Infarction (TIMI) flows and changes in LV volumes at six months was assessed through ordered classification analysis (16). A *p* value of  $<0.05$  was considered significant.

## RESULTS

**Clinical outcomes.** The proportion of patients with anterior or anteroseptal infarction was 44%. The number of patients with ST-elevation infarcts was 44/61 and non-ST-elevation MI was 17/61. The peak creatine kinase levels of these groups were, respectively,  $1,798 \pm 1,557$  IU/l and  $1,233 \pm 993$  IU/l, *p* = NS. Thrombolytics were given to 93% of patients and percutaneous revascularization was attempted in 89% of patients. The TIMI flows at baseline (after thrombolysis, but prior to percutaneous interventions) and after percutaneous interventions are shown in Table 1.

Although no patient had overt CHF at enrollment, two patients developed CHF by six months (one patient [17] was in New York Heart Association functional class III and one [57] in class IV). The former patient died suddenly at home three years after the AMI.

**Hemodynamics and LV volumes.** Resting heart rate was  $63 \pm 9$  beats/min at one week and  $63 \pm 10$  beats/min at six months (*p* = NS). Systolic blood pressure was  $116 \pm 17$  mm Hg at one week and  $119 \pm 16$  mm Hg at six months (*p* = NS). Diastolic blood pressure was  $71 \pm 8$  mm Hg at one week and  $72 \pm 8$  mm Hg at six months (*p* = NS). Left ventricular volumes at one week and six months and their

ratios are reported in Table 1. The ESV2 and EDV2 data were little different from the values of ESV1 and EDV1 and have therefore been omitted. The ratios ESV3/ESV1 ( $\delta$ ESV) and EDV3/EDV ( $\delta$ EDV), as indices of LV dilation, are also reported in Table 1.

**MBF, beta-AR, and circulating catecholamines.** These data are reported in Table 2. Resting MBF in remote myocardium was significantly higher than that in the infarcted zone, although both were within the normal range (17). The whole-heart beta-AR was significantly lower in the patients compared to controls ( $6.25 \pm 0.98$  pmol/g vs.  $8.32 \pm 2.14$  pmol/g, *p* < 0.0001). This difference remained significant for the infarct-related territory ( $6.22 \pm 1.34$  pmol/g, *p* = 0.0002 vs. controls) and remote territory ( $6.70 \pm 1.17$  pmol/g, *p* = 0.0003 vs. controls), although no significant difference existed between beta-AR in the infarct-related territory and the remote myocardium within the patient group.

One month after AMI, at the time of PET, patients had lower circulating noradrenaline than controls ( $1.61 \pm 0.96$  nmol/l vs.  $2.84 \pm 1.20$  nmol/l, *p* = 0.0004), whereas the adrenaline was not different ( $0.23 \pm 0.16$  nmol/l vs.  $0.30 \pm 0.21$  nmol/l, *p* = NS).

**Interrelations of measured parameters.** The changes in LV end-systolic ( $\delta$ ESV) and end-diastolic volume ( $\delta$ EDV) are shown in Table 1. Significant inverse correlations were observed between the changes in ESV and EDV six months after AMI and beta-AR densities measured one month after AMI (Figs. 1 and 2).

Patients in whom LV volumes were unchanged or decreased showed no significant difference from those in whom there had been an increase in LV volumes in terms of beta-AR in the territory of the infarct-related artery ( $6.30$  pmol/g vs.  $6.05$  pmol/g, *p* = NS). However, for the remote myocardial territory, beta-AR was significantly lower in patients with LV dilation ( $6.15$  pmol/g) compared to those without ( $6.98$  pmol/g, *p* = 0.008) (Fig. 3). In addition, a higher TIMI flow score after percutaneous revascularization was associated with improved LV volumes at follow-up (Table 3).

No correlations were seen between circulating catecholamines and changes in LV volumes; neither were any correlations seen between circulating catecholamines and beta-AR.

## DISCUSSION

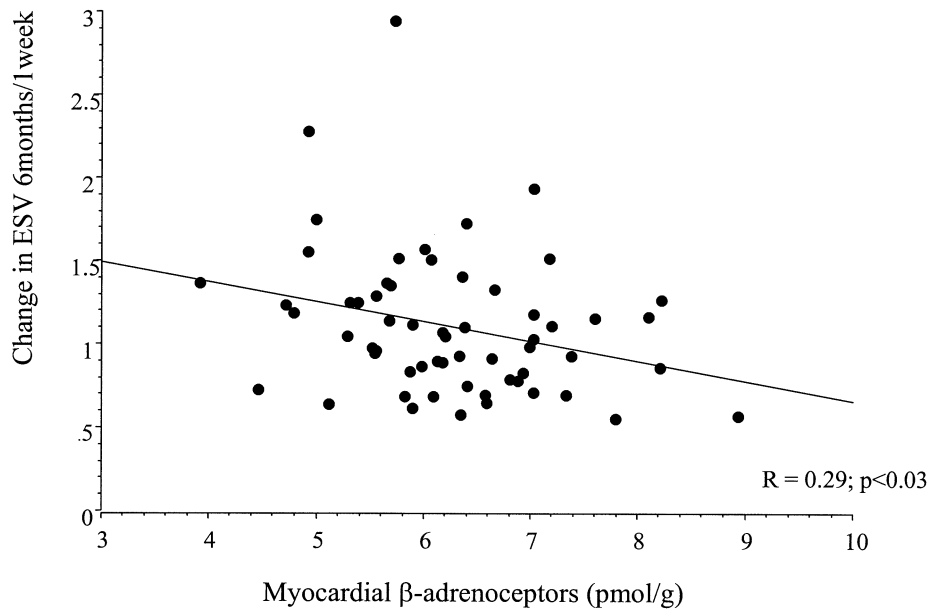
**Summary of findings.** The present study shows that 1) myocardial beta-AR is reduced in the subacute phase after AMI, in the absence of symptoms and signs of CHF; 2) the changes in myocardial beta-AR occurred in the absence of an increase in circulating catecholamines; 3) the degree of downregulation of myocardial beta-AR is predictive of later increase in LV volumes; and 4) the degree of LV volume change at six months is inversely related to the TIMI flow in the subacute phase.

**Table 2.** Myocardial Beta-AR Density and Blood Flow for Each of the 61 Patients

Patient No.	Whole-Heart Beta-AR	Infarct ROI Beta-AR	Remote ROI Beta-AR	Infarct ROI MBF	Remote ROI MBF	Whole-Heart MBF
1	6.01	6.97	5.03	0.69	1.30	0.82
2	6.40	6.19	7.93	0.69	1.11	0.91
3	4.93	3.66	4.86	0.91	1.00	0.80
4	3.92	3.49	4.54	1.00	0.83	0.98
5	5.88	5.05	8.44	1.00	1.06	1.00
6	5.53	4.77	6.82	1.15	1.57	1.28
7	7.00	6.59	8.86	0.99	0.50	0.76
8	4.47	4.59	4.56	0.70	0.94	0.86
9	5.56	5.39	7.21	1.05	0.83	0.88
10	5.91	6.74	6.57	0.86	1.61	1.19
11	5.13	5.08	5.04	1.12	0.93	1.06
12	4.73	6.03	4.81	0.92	0.64	0.83
13	5.73	5.66	5.72	0.81	1.23	1.02
14	6.59	5.68	6.95	0.96	1.25	1.03
15	5.01	5.31	5.09	0.56	0.78	0.72
16	6.18	5.98	6.48	0.84	0.81	0.82
17	4.93	4.49	6.73	0.57	0.63	0.53
18	5.99	8.61	7.52	1.55	0.43	0.79
19	5.77	5.20	7.03	0.86	0.60	0.76
20	6.41	5.12	8.00	0.81	1.08	0.90
21	5.30	4.43	5.91	1.23	1.29	1.20
22	5.32	5.3	4.99	0.60	0.93	0.82
23	7.60	7.45	8.35	1.00	0.95	0.98
24	5.66	4.55	6.77	0.88	0.78	0.80
25	4.80	4.50	5.88	0.51	0.64	0.58
26	6.94	7.44	7.05	0.81	1.10	0.97
27	6.89	9.00	6.77	0.58	1.20	0.96
28	6.19	7.00	6.13	0.76	0.81	0.82
29	5.57	7.11	5.57	0.53	0.78	0.64
30	8.11	8.63	8.33	1.06	1.04	0.93
31	5.68	4.28	6.16	0.55	0.89	0.75
32	5.70	5.11	6.99	0.60	0.86	0.69
33	6.34	5.99	7.22	1.09	0.92	0.97
34	6.39	6.38	7.36	0.96	1.36	1.24
35	6.13	6.6	5.87	0.83	0.89	0.78
36	6.81	7.82	7.45	0.67	1.02	0.94
37	5.55	2.89	3.79	0.92	0.86	1.02
38	7.18	7.38	7.94	0.55	0.63	0.61
39	6.35	6.01	7.55	1.16	1.32	1.13
40	7.03	6.14	6.43	0.99	0.78	0.90
41	7.20	7.10	8.05	1.15	1.36	1.13
42	7.34	6.71	7.79	0.66	1.11	0.80
43	6.60	7.42	6.70	0.82	0.66	0.74
44	8.21	7.46	7.59	0.87	1.42	0.93
45	7.80	12.40	8.40	0.68	0.91	0.83
46	5.83	5.48	6.71	0.72	0.53	0.67
47	7.39	6.55	6.66	1.00	1.10	1.03
48	7.04	6.77	7.20	0.89	0.73	0.82
49	6.37	8.94	5.95	0.73	1.31	1.11
50	6.64	6.20	8.39	0.83	0.63	0.73
51	6.21	8.74	4.46	1.90	1.16	1.56
52	6.08	8.80	6.73	0.82	0.77	0.82
53	5.90	6.38	6.65	0.79	1.00	0.93
54	8.22	7.92	8.73	0.86	1.42	1.04
55	8.94	6.65	8.94	1.38	1.01	1.10
56	7.04	7.95	6.49	0.79	0.87	0.86
57	6.67	8.84	6.86	0.62	0.94	0.88
58	6.10	5.44	6.52	0.73	0.84	0.79
59	7.04	8.60	8.06	0.77	0.96	0.86
60	5.79	4.58	5.50	0.24	0.90	0.84
61	5.39	4.31	6.01	1.07	1.77	1.42
Mean $\pm$ SD	6.25 $\pm$ 0.98	6.22 $\pm$ 1.34	6.70 $\pm$ 1.17	0.86 $\pm$ 0.26	0.98 $\pm$ 0.28‡	0.91 $\pm$ 0.19

‡p = 0.023 vs. MBF (ml/min/g) in infarct-related territory.

Beta-AR = beta-adrenoceptor; MBF = myocardial blood flow; ROI = region of interest.

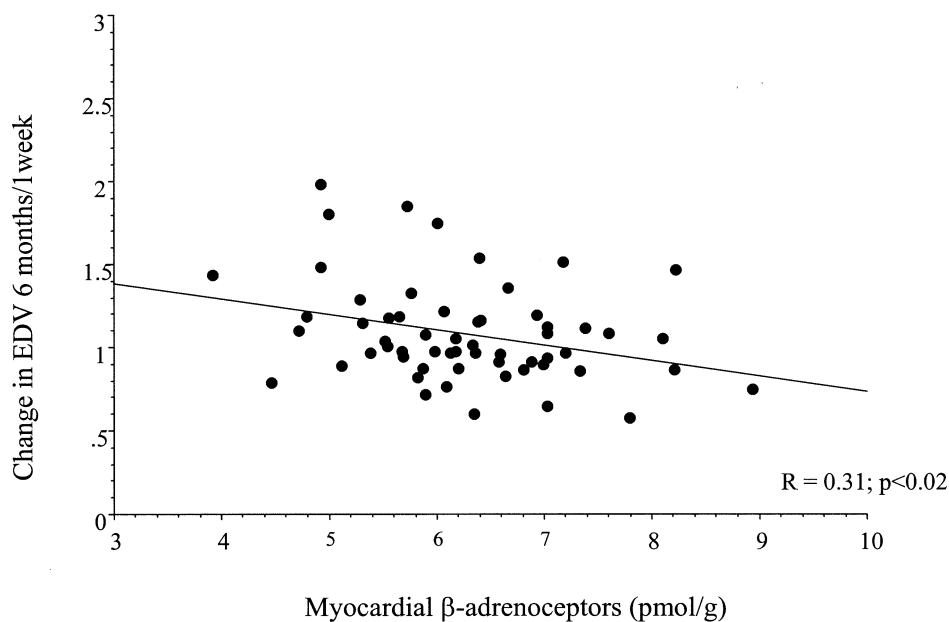


**Figure 1.** Regression line (n = 61) through individual patients' end-systolic volume change (ESV) (values at six months divided by those at one week), plotted against the respective beta-adrenoceptor density as measured by positron emission tomography, one month post-acute myocardial infarction.

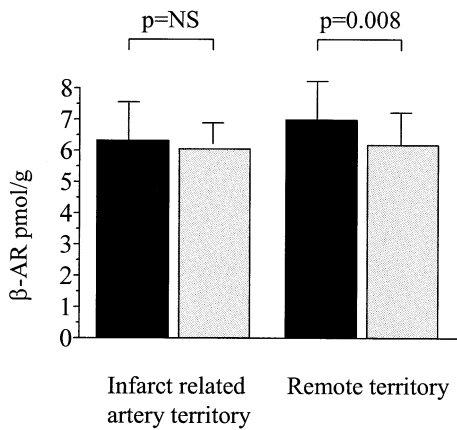
**Significance of myocardial beta-AR downregulation in the nonfailing heart.** A particular characteristic of the present study was that, on average, our patients had well preserved LV systolic function (mean ejection fraction 47%). Unlike patients with CHF (7), no significant increase in circulating catecholamines was found in our patients despite the demonstration of myocardial beta-AR downregulation. We have previously studied another condition, HCM, in which myocardial beta-AR downregulation occurs despite normal LV systolic function (13). Furthermore, we demonstrated that in patients with HCM, the degree of

myocardial beta-AR downregulation was predictive of CHF development at follow-up (9).

In a more recent PET study in patients with HCM (14), we combined the measurement of postsynaptic myocardial beta-AR density with that of presynaptic noradrenaline reuptake-1 using the catecholamine analogue [ $^{11}\text{C}$ ]-hydroxyephedrine. The data showed that beta-AR downregulation was associated with a reduced reuptake of [ $^{11}\text{C}$ ]-hydroxyephedrine by neural terminals in the myocardium. This reduced reuptake-1 leads to a less efficient disposal of catecholamines from the synaptic cleft, and we believe that



**Figure 2.** Regression line (n = 61) through individual patients' end-diastolic volume change (EDV) (values at six months divided by those at one week), plotted against the respective beta-adrenoceptor density as measured by positron emission tomography, one month post-acute myocardial infarction.



**Figure 3.** Black bars = those patients (n = 41) whose left ventricular (LV) volumes were found to be decreased six months after infarction; White bars = those patients (n = 20) whose LV volumes were found to be increased six months after infarction. Beta-AR = myocardial beta-adrenoceptor density.

this contributes to myocardial beta-AR downregulation in HCM. This supports the pathophysiologic model of Bristow et al. (18), suggesting that increases in local neurotransmitter concentrations rather than elevated circulating catecholamines are probably responsible for myocardial beta-AR downregulation (indeed, we found in the present study that patients had lower circulating noradrenaline than controls, whereas the adrenaline level was not different). Although the data from the present study do not extend that far, we hypothesize that a similar abnormality of regional (i.e., confined to the heart) catecholamine turnover is responsible for the downregulation observed in our post-AMI patients.

**Relation between beta-AR downregulation and LV remodeling.** The way in which SNS activation affects LV remodeling in the subacute phase after AMI, prior to the development of heart failure, is not fully understood. Data from studies of heart rate variability and baroreflex sensitivity (19,20) would suggest that neural drive to the heart within the first four weeks after AMI is altered in the direction of sympathetic predominance, and these indices have prognostic significance. The data from the present study are consistent with this and show that beta-AR downregulation is diffuse, involving both infarcted and remote myocardium and is predictive of LV dilation at follow-up. In addition, other factors, such as the speed and success of recanalization of the infarct-related artery (i.e.,

TIMI flow value), play an important role in determining the degree of LV remodeling, as does infarct size (21).

The short-term benefits of this regional SNS activation after infarction are apparent (e.g., in the maintenance of cardiac output). It can be appreciated, however, that the preservation of cardiac output may become dependent upon greater degrees of sympathetic drive, and this sustained and excessive activation may be maladaptive, as demonstrated in both animal (22,23) and human studies (4,24-28).

**Clinical implications.** Treatment with angiotensin-converting enzyme inhibitors has been shown to modify the relationship among infarct size, CHF, and mortality after AMI (5,25). It was suggested by the SAVE investigators (5) that the mechanism of this might be a blunting of neuro-humoral activation (29). With the recognition of the benefits for mortality of beta-blockade treatment after AMI and for established CHF (such as in the CIBIS, MOCHA, MERIT-HF, COPERNICUS, and CAPRICORN studies [30-33]), our data provide a further pathophysiological basis for the efficacy of this class of drugs.

**Methodologic considerations.** Positron emission tomography is a well-established method for the quantitative, noninvasive measurement of regional myocardial radionuclide distribution in vivo (34). This technique has been used for the quantification of regional MBF (12,17,35,37), metabolism (38,39), and autonomic function (34). The hydrophilic beta-AR antagonist S-CGP 12177 labeled with <sup>11</sup>C (S-[<sup>11</sup>C]CGP 12177) is an ideal ligand for the measurement of total beta-AR density as it has a high affinity, is nonselective and hydrophilic, does not cross the cell membrane, and therefore binds only to the functionally active cell-surface receptors (8,13). Previously, Merlet et al. (8) reported a significant correlation between LV beta-AR density measured by PET with [<sup>11</sup>C]CGP 12177 and beta-AR density measured using in vitro binding of [<sup>3</sup>H]CGP 12177 in LV endomyocardial biopsy specimens taken from patients with idiopathic dilated cardiomyopathy (r = 0.79, p = 0.019). In a previous study from our group, myocardial beta-AR was measured twice in the same patients using PET with [<sup>11</sup>C]CGP 12177, and the reproducibility of the technique was >80% (13).

Finally, it is possible that the beta-AR density on the myocytes is normal, but that the proportion of cardiac myocytes relative to the other tissue components (e.g., fibrous tissue) is reduced in infarcted myocardium. To minimize the effect of thinning and fibrosis in the infarcted areas, all beta-AR values were corrected for partial volume using the perfusable tissue index (15). This index is derived from the H<sub>2</sub><sup>15</sup>O scan and provides an estimate of the fraction of *viable* tissue within the volume of interest capable of exchanging rapidly the freely diffusible tracer H<sub>2</sub><sup>15</sup>O (15). Furthermore, beta-AR downregulation was also demonstrated in remote, noninfarcted myocardium. Thus, we consider that "dilution" of cardiac myocytes by nonmyocyte tissue could only account at most for a small

**Table 3.** Relationship Between TIMI Flows and Left Ventricular Volumes (Improved vs. Dilated) at Six Months

TIMI Flow	Improved	Dilated	Totals
TIMI 1	1	1	2
TIMI 2	2	6	8
TIMI 3	38	13	51
Totals	41	20	61

A higher Thrombolysis In Myocardial Infarction (TIMI) score predicted an improved left ventricular volume at six months (p < 0.002).

part of the observed difference between infarcted and noninfarcted regions.

**Study limitations.** The study was based on a single measurement of beta-AR soon after AMI, as obviously the occurrence of the infarct could not be predicted. However, although a baseline beta-AR scan was not obtained before AMI, by excluding patients with other potential causes of SNS activation and LV remodeling, we should have minimized the likelihood of a preexisting beta-AR downregulation.

Finally, it is increasingly clear that genetic variability (e.g., polymorphism of beta-AR, which was not assessed in the present study) accounts for clinical variability in response to a myocardial insult and adversely affects the outcome of CHF (40).

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