JACC Vol. 14, No. 3
September 1989:624–30

Acute Hemodynamic Effects of Norepinephrine Inhibition in Patients With Severe Chronic Congestive Heart Failure

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The pathophysiologic role of high levels of circulating catecholamines in patients with congestive heart failure remains unclear. To assess the hemodynamic contribution of circulating catecholamines, metyrosine (alpha-methyl-p-tyrosine), an inhibitor of catecholamine synthesis, was administered to nine patients with acutely decompensated chronic congestive heart failure. Baseline left ventricular ejection fraction averaged 23.3 ± 9.9%, whereas cardiac output averaged 3.69 ± 1.03 liters/min, with a pulmonary wedge pressure of 27.4 ± 8.5 mm Hg.

After 48 h of metyrosine administration, plasma norepinephrine concentration decreased from 919.4 ± 810.6 to 335.4 ± 143.1 pg/ml ($p < 0.05$). Plasma epinephrine concentration averaged 176.4 ± 166.0 pg/ml at baseline, and was unchanged during metyrosine administration. Despite the significant decrease in circulating norepinephrine, no significant hemodynamic changes were observed during metyrosine administration.

These results suggest that high levels of circulating norepinephrine may be more a marker of severe congestive heart failure than an important contributor to the underlying pathophysiology at this advanced stage of the disease process.

(J Am Coll Cardiol 1989;14:624–30)

Neurohumoral abnormalities are known features of congestive heart failure. The successful therapeutic application of angiotensin-converting enzyme inhibitors clearly indicates that excessive renin-angiotensin activity contributes to the manifestations of heart failure. In contrast, the role of circulating catecholamines in similar patients remains unclear. Observations that adrenergic inhibition may lessen symptoms in selected patients with heart failure and that there is a direct relation between catecholamine levels and mortality in patients with heart failure suggest that increased sympathetic nervous activity may be harmful in this setting (1–3). However, it has been suggested (4) that heightened sympathetic tone represents a desirable compensatory response to the failing heart and that withdrawal of this support could be harmful. In fact, sympathomimetic agents are commonly administered as effective treatment for acute severe heart failure.

Thus, increased circulating catecholamines may play a significant role in the pathophysiology of established congestive heart failure or they may represent a mere marker of advanced heart disease. If catecholamines do play an important role, they may be harmful through increasing afterload and metabolic demands on the failing heart or they may be beneficial by helping to maintain blood pressure and cardiac output. Correlations between circulating catecholamine levels and hemodynamics have been poor in patients with heart failure (5). Therapeutic interventions aimed at increasing or inhibiting adrenergic tone have not yielded consistent results, probably reflecting heterogeneity of patient study groups and associated pharmacologic actions of the agents employed (1,2,6–8).

The present study was designed to assess the contribution of increased circulating catecholamines to the hemodynamic abnormalities observed in patients with heart failure. The study group chosen was one with acutely decompensated severe chronic congestive heart failure because such patients are commonly treated with sympathomimetic agents and have high afterload. Thus, reduction of catecholamine levels might reasonably be expected to produce unequivocal hemodynamic improvement or worsening in these patients. The agent chosen to reduce catecholamine activity was metyrosine (alpha-methyl-p-tyrosine), whose only pharma-

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This study was supported in part by a grant from the Medical Research Service, Veterans Administration, Washington, D.C.

Manuscript received December 18, 1988; revised manuscript received February 24, 1989, accepted April 12, 1989.

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0735-1097/89/$3.50

cologic action is thought to be inhibition of catecholamine synthesis, especially that of norepinephrine (9,10).

Methods

Patient selection. The study group consisted of nine men with acutely decompensated chronic congestive heart failure requiring hospitalization. For inclusion in the study, patients had to be between 18 and 70 years of age and have a history of chronic congestive heart failure due to coronary artery disease or idiopathic dilated cardiomyopathy. Congestive heart failure was defined as a history of exercise intolerance resulting from dyspnea or fatigue only, plus at least one of the following measurements obtained within the preceding 30 days: left ventricular ejection fraction <40% by contrast or radionuclide ventriculography, cardiothoracic ratio >54% by standard chest X-ray study and left ventricular end-diastolic diameter >55 mm by M-mode echocardiography. Patients must have been experiencing increased symptoms or physical findings attributable to congestive heart failure despite treatment with at least digitalis and diuretic drugs during the preceding month.

The diagnosis of coronary artery disease was established by a history of documented previous acute myocardial infarction (serial electrocardiographic [ECG] and serum enzyme changes) or by angiographically proved coronary artery obstructive disease. Idiopathic dilated cardiomyopathy was diagnosed when no other cause of heart failure was apparent. Patients were excluded for any of the following conditions: acute myocardial infarction within the previous 3 months, primary valvular heart disease, primary pulmonary disease, hypertension requiring treatment and inability to tolerate withdrawal of vasodilator therapy.

Study protocol. Patients meeting these selection criteria gave written informed consent. The protocol was approved by the Human Studies Subcommittee of the local institutional review board. Vasodilator therapy was discontinued for at least 48 h before study, and digitalis and diuretic drugs were continued at constant doses throughout the study period. On the day of study, patients were brought to a special procedure room adjacent to the coronary care unit. A Swan-Ganz catheter was inserted percutaneously through a femoral or antecubital vein to record pulmonary artery and right atrial pressures and measure cardiac output by thermodilution. An intraarterial cannula was inserted into the brachial artery to measure intraarterial pressure. After all catheters were inserted, baseline hemodynamic measurements, including pulmonary artery occluded and phasic pressures, right atrial pressure, systemic arterial pressure, heart rate (from continuous ECG monitoring) and cardiac output in triplicate, were obtained. Pulmonary wedge pressure was taken as pulmonary artery diastolic or occluded pressure, and these variables were not interchanged in any given patient. Control hemodynamic measurements were repeated at 20 min intervals until they were stable. Stability was defined as ≤10% variation in any hemodynamic variable on two consecutive sets of measurements.

On completion of baseline hemodynamic measurements, samples of mixed venous blood were obtained for measurement of plasma catecholamines by high performance liquid chromatography (11). Plasma renin activity was measured at baseline study by radioenzymatic assay as part of the assessment of patient characteristics. Metyrosine administration was then begun and repeated every 8 h for 48 h. Hemodynamic measurements were repeated at 4, 8, 24 and 48 h after administration of the first dose of metyrosine. Mixed venous samples for plasma catecholamines were repeated at 24, 48 and 72 h after administration of the first dose of metyrosine.

Metyrosine dose titration. Because of the lack of previous experience with metyrosine and the risks of catecholamine withdrawal in patients with severe heart failure, the initial dose of metyrosine in the first two patients was 250 mg every 8 h. The dose was increased by 750 mg/day (in three divided doses) in successive pairs of patients until plasma norepinephrine was reduced ≥70% from control values in both members of the pair any time within the first 72 h after drug administration. In any case, the maximal allowable dose of metyrosine was 1,500 mg every 8 h. This dosing regimen was chosen on the basis of previous experience with metyrosine in patients with pheochromocytoma (9,10). The dose could not be increased in subsequent patients if undesirable symptoms or side effects occurred in any patient. Similarly, any striking hemodynamic change judged to be potentially harmful, with or without symptoms, precluded an increase in dose.

Data analysis. Because serial observations were made, all data were subjected to an analysis of variance, and paired *t* tests were made only if the F value was significant. Coefficients of correlation were obtained by standard linear regression analysis. A probability (p) value <0.05 was considered statistically significant for the paired *t* tests. When the Bonferroni correction was applied to the interpretation of coefficients of correlation (r), a p value <0.0015 was required for an r value to be considered statistically significant.

Results

Patient characteristics (Table 1). In the study group of nine men, heart failure was caused by idiopathic dilated cardiomyopathy in six and coronary artery disease in the other three. By protocol, all patients had symptoms for ≥3 months, with worsening during the preceding month ultimately requiring hospitalization. Symptomatic status was categorized as class III-IV (New York Heart Association criteria) in all patients despite treatment with at least digoxin and furosemide. In addition, three patients were taking other

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Table 1. Characteristics of Nine Patients With Congestive Heart Failure Given Metyrosine

Patient No.	Age (yr) & Gender	BSA (m^2)	Dx	NYHA Class	LVEF (%)	CTR (%)	LVDD (mm)	Prior Medications for CHF
1	53M	1.86	IDC	IV	—	57	65	Digoxin, furosemide, hydralazine
2	63M	1.73	CAD	IV	—	55	—	Digoxin, furosemide, spironolactone, hydralazine, isosorbide dinitrate
3	50M	1.96	IDC	IV	—	44	60	Digoxin, furosemide, nitroglycerin
4	65M	2.08	IDC	III	21	59	50	Digoxin, furosemide, hydrochlorothiazide, triamterene
5	62M	1.84	IDC	III	13	60	73	Digoxin, furosemide
6	53M	1.82	IDC	III	25	53	63	Digoxin, furosemide, hydralazine, isosorbide dinitrate
7	64M	1.76	CAD	III	35	58	65	Digoxin, furosemide
8	66M	1.62	CAD	IV	10	46	62	Digoxin, furosemide, nitroglycerin
9	64M	1.63	IDC	III	36	—	—	Digoxin, furosemide, hydrochlorothiazide, triamterene
Mean	60.0	1.81			23.3	54.0	62.6	
± SD	5.8	0.14			9.9	5.6	6.4	

BSA = body surface area; CAD = coronary artery disease; CHF = congestive heart failure; CTR = cardiothoracic ratio; Dx = diagnosis; IDC = idiopathic dilated cardiomyopathy; LVDD = left ventricular diastolic dimension; LVEF = left ventricular ejection fraction; NYHA Class = New York Heart Association functional class; SD = standard deviation.

diuretic drugs, and five were receiving vasodilator therapy. All patients had cardiomegaly with increased cardiothoracic ratio or left ventricular end-diastolic dimension, and left ventricular ejection fraction was depressed in all six patients in whom it was measured. Thus, on the basis of symptoms, cardiac size and cardiac function, all patients had severe congestive heart failure at the time of study.

Metyrosine dose (Table 2). The first dose that produced the desired responses in both members of the pair was 3,750 mg (1,250 mg three times a day), which lowered norepinephrine levels by ≥70% in both patients. For safety reasons relating to our lack of previous experience with metyrosine, the initial dose was given to both members of the first pair of patients even though the first patient did not meet the response criteria. Because the first patient in the third pair (Patient 5) did not meet the response criteria, a second patient did not receive that same dose (750 mg three times a day). In all other pairs, the first patient met the response criteria, and the second patient was given the same dose of metyrosine. No patient experienced undesirable symptoms, side effects or hemodynamic responses.

Changes in plasma catecholamines during the 72 h after administration of metyrosine (Table 3). Norepinephrine levels were reduced at 24 h, with the peak significant reduction occurring by 48 h. Circulating epinephrine levels were not significantly altered by metyrosine. The baseline values for norepinephrine were generally high, averaging 919.4 ± 810.6 pg/ml, consistent with advanced heart failure. Normal values for plasma norepinephrine by the method employed average 342 ± 30 pg/ml (11). All patients experienced a reduction in norepinephrine levels, except Patient 1, whose norepinephrine levels remained unchanged. This patient received the lowest dose of metyrosine and was also the only one with normal baseline norepinephrine values.

Table 2. Dose Titration of Metyrosine

Patient No.	Metyrosine Total Daily Dose (mg)*	Maximal % Change in Norepinephrine
1	750	−40
2	750	−66
3	1,500	−76
4	1,500	−41
5	2,250	−41
6	3,000	−82
7	3,000	−40
8	3,750	−86
9	3,750	−72

*Administered in divided doses three times daily.

Figure 1. Relation between response to metyrosine and baseline plasma norepinephrine (NE) concentration in nine patients with congestive heart failure.

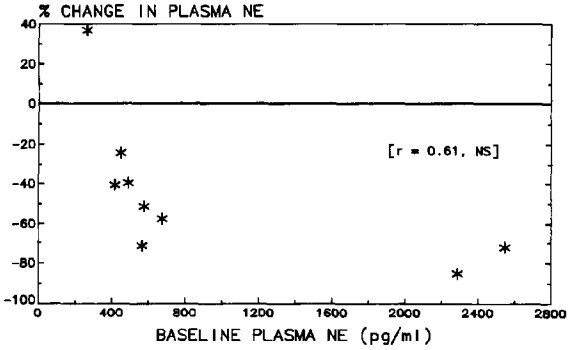

Table 3. Neurohumoral Responses to Metyrosine Administration in Nine Patients With Congestive Heart Failure

Patient No.	Norepinephrine				Epinephrine			
	C	24 h	48 h	72 h	C	24 h	48 h	72 h
1	263	203	360	158	27	11	82	7
2	577	222	281	195	117	94	162	64
3	2,548	806	708	623	708	391	474	134
4	418	308	248	336	10	46	210	60
5	448	265	339	—	53	184	241	—
6	674	124	286	—	57	62	181	—
7	492	670	297	300	88	99	156	119
8	2,288	538	339	1,018	320	539	526	482
9	567	360	161	200	186	162	133	133
Mean	919.4	388.4	335.4	404.3	174.0	176.4	240.6	142.7
± SD	810.6	218.7	143.1	289.4	209.3	166.0	145.5	145.1
p		NS	<0.05	NS		NS	NS	NS

C = control; h = hours after metyrosine administration.

The magnitude of the decrease in norepinephrine levels averaged 42.0 ± 34.3% ($p < 0.01$) and 45.1 ± 34.1% ($p < 0.01$) at 24 and 48 h, respectively, after metyrosine administration. In the seven patients whose norepinephrine levels were obtained at 72 h (that is, 24 h after cessation of metyrosine administration), norepinephrine levels were no longer significantly reduced from control values, suggesting a true drug effect rather than a spontaneous decrease in norepinephrine levels during metyrosine administration. Baseline norepinephrine values failed to correlate with the change in norepinephrine levels produced by metyrosine (Fig. 1). Furthermore, there was no significant correlation between baseline norepinephrine values and baseline plasma renin activity ($r = 0.39$, $p = NS$), which was also elevated at 6.3 ± 6.5 ng/ml per h.

Hemodynamic responses after administration of metyrosine (Table 4). Satisfactory pulmonary artery pressure tracings could not be obtained at baseline study in two patients (Patients 3 and 6). Both patients were included in the study, however, because one (Patient 3) had a very high right atrial pressure and both had low cardiac output and stroke volume. At baseline study, pulmonary wedge pressure for the group averaged 27.4 ± 8.5 mm Hg, and cardiac output was 3.69 ± 1.03 liters/min, indicating severe hemodynamic compromise. Despite these severe hemodynamic abnormalities at baseline study, no significant changes in any hemodynamic variable were observed after either 24 or 48 h of metyrosine administration. Furthermore, there were no significant correlations between norepinephrine or epinephrine plasma concentrations and any hemodynamic variable at baseline study or during metyrosine administration (Table 5).

Discussion

Role of circulating norepinephrine in heart failure. Although it is generally accepted that increased levels of

Table 4. Hemodynamic Responses to Metyrosine Administration in Nine Patients With Congestive Heart Failure

Patient No.	Heart Rate (beats/min)			Right Atrial Pressure (mm Hg)			Mean Arterial Pressure (mm Hg)			Pulmonary Wedge Pressure (mm Hg)			Cardiac Output (liters/min)			Stroke Volume (ml/beat)			Systemic Vascular Resistance (units)		
	C	24 h	48 h	C	24 h	48 h	C	24 h	48 h	C	24 h	48 h	C	24 h	48 h	C	24 h	48 h	C	24 h	48 h
1	62	66	69	11	14	12	88	90	90	42	43	43	3.06	2.69	2.66	49	41	39	25	28	29
2	81	90	100	11	8	—	73	65	72	25	21	18	2.95	4.34	3.12	36	48	31	21	13	—
3	108	100	99	22	21	18	74	66	73	—	—	—	2.38	2.43	2.91	22	24	29	22	19	19
4	78	84	81	9	9	10	88	81	81	22	23	18	5.42	4.70	4.92	69	56	61	15	15	14
5	90	93	90	11	8	15	87	90	99	26	20	34	5.24	5.06	5.11	58	54	57	15	16	16
6	111	99	108	5	9	5	87	93	87	—	—	—	3.24	4.52	3.01	29	46	28	25	19	27
7	80	84	84	8	8	4	118	100	109	25	11	10	3.29	4.05	3.54	41	48	42	33	23	30
8	98	86	81	15	14	21	101	88	85	37	28	37	3.09	4.20	3.49	32	49	43	28	18	18
9	77	66	63	6	8	4	111	103	104	15	—	7	4.54	3.63	4.88	59	55	77	23	26	20
Mean	87.2	85.3	86.1	10.9	11.0	11.1	91.9	86.2	88.9	27.4	24.3	23.9	3.69	3.96	3.74	44.0	46.8	45.2	23.0	19.6	21.9
SD	15.0	11.7	13.9	4.8	4.2	6.1	14.5	12.6	12.3	8.5	9.8	13.0	1.03	0.84	0.91	15.8	9.5	16.5	6.0	3.9	5.6
p	—	NS	NS	—	NS	NS	—	NS	NS	—	NS	NS	—	NS	NS	—	NS	NS	—	NS	NS

Abbreviations as in Table 3.

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Table 5. Relation Between Neurohumoral Factors and Hemodynamics in Nine Patients With Congestive Heart Failure Given Metyrosine

Independent Variable	Dependent Variable	r	p
Control			
Plasma NE	HR	0.65	NS
Plasma NE	MAP	0.19	NS
Plasma NE	PWP	0.34	NS
Plasma NE	CO	0.52	NS
Plasma NE	SVR	0.19	NS
Plasma E	HR	0.55	NS
Plasma E	MAP	0.25	NS
Plasma E	PWP	0.08	NS
Plasma E	CO	0.53	NS
Plasma E	SVR	0.11	NS
48 hours after metyrosine			
Plasma NE	HR	0.40	NS
Plasma NE	MAP	0.48	NS
Plasma NE	PWP	0.84	NS*
Plasma NE	CO	0.47	NS
Plasma NE	SVR	0.06	NS
Plasma E	HR	0.26	NS
Plasma E	MAP	0.41	NS
Plasma E	PWP	0.35	NS
Plasma E	CO	0.12	NS
Plasma E	SVR	0.44	NS

*$p < 0.02$; >0.01 is not significant because of Bonferroni correction requiring $p < 0.0015$. CO = cardiac output; E = epinephrine; HR = heart rate; MAP = mean systemic arterial pressure; NE = norepinephrine; NS = not significant; PWP = pulmonary wedge pressure; SVR = systemic vascular resistance.

circulating norepinephrine in patients with heart failure are indicative of augmented sympathetic nervous activity, the origin and significance of this heightened adrenergic drive are unclear (3–5,12–14). Depletion of myocardial norepinephrine stores together with normal circulating epinephrine (of adrenal medullary origin) suggests that the circulating norepinephrine in patients with heart failure derives from peripheral sympathetic nerves (12,13). Given the well known pharmacologic effects of circulating catecholamines on the cardiovascular system, the widespread use of exogenous sympathomimetic agents to improve hemodynamics in states of circulatory insufficiency and the increase in plasma catecholamine levels in response to stress, it has been logical to conclude that an increase in circulating norepinephrine levels represents a beneficial and necessary compensatory response in patients with heart failure (4,13,14). In contrast, the harmful effects of vasoconstriction on cardiovascular performance and observations that elevated plasma norepinephrine levels correlate directly with worse symptoms and a lower survival rate in patients with congestive heart failure suggest a detrimental role of excess catecholamines (3,13, 15). The cardiotoxic effects of catecholamines are well known (15,16). Finally, adding to the difficulty in interpreting the role of catecholamines in patients with heart failure are the findings that cardiac beta-receptor density and sensitivity are reduced in such patients and that these can be restored in association with clinical improvement during long-term administration of beta adrenergic blockers in some patients with chronic congestive heart failure (1,2,17,18).

Attempts to distinguish the role of circulating norepinephrine as a significant pathophysiologic determinant or mere marker of advanced coronary heart disease have relied on nonspecific pharmacologic interventions. The widespread use of sympathomimetic agents to treat acute heart failure supports the notion that circulating catecholamines provide important circulatory support, yet prolonged use of these agents has been associated with undesirable effects including arrhythmias and death (19,20). Furthermore, these agents may affect multiple dopaminergic and adrenergic receptors, and may not truly mimic the effects of endogenous catecholamines. In fact, exogenously administered norepinephrine produces blunted responses in patients with heart failure, and very large doses are required to produce even these effects (15).

Interventions intended to reduce adrenergic drive have also yielded inconsistent results. Administration of bromocriptine, which reduces circulating norepinephrine by inhibiting its release, has been associated with hemodynamic improvement in patients with chronic heart failure, but this agent may have direct vasodilating activity (21). In similar patients from the same laboratory (15), guanabenz acetate also reduced norepinephrine levels but did not affect hemodynamics. Thus, the effect of circulating norepinephrine on hemodynamics in patients with chronic congestive heart failure has not yet been clearly defined.

Significance of the present results. In this study, inhibition of norepinephrine synthesis by metyrosine resulted in a marked reduction in plasma norepinephrine levels, which decreased almost threefold to within the normal range. Despite this striking neurohumoral alteration, systemic hemodynamics were unchanged. Because the only known action of metyrosine is its inhibition of synthesis of norepinephrine in peripheral nerves (9, 10), it is unlikely that other actions of this agent could have offset any effects produced by removal of norepinephrine from the circulation. Thus, our results represent the first demonstration of the effects of "pure" norepinephrine inhibition in patients with heart failure. Not only did the reduction in plasma norepinephrine fail to alter hemodynamics, but baseline plasma norepinephrine levels were not related to any baseline hemodynamic variable or to plasma renin activity. Furthermore, the changes in norepinephrine levels and hemodynamic responses during metyrosine administration were also unrelated.

These results suggest that absolute levels or changes in

levels of circulating norepinephrine do not contribute significantly to the hemodynamic abnormalities observed in patients with moderate to severe chronic heart failure. Our observations are surprising in that the patients studied had acutely decompensated moderate to severe chronic left ventricular failure with marked hemodynamic abnormalities. In such patients, exogenous sympathomimetic agents and vasodilator drugs are commonly administered, alone or together, with resulting hemodynamic improvement. The present results indicate that such improvement is not mediated through circulating norepinephrine. Thus, it appears that the high levels of circulating norepinephrine in patients with moderate to severe congestive heart failure represent a mere marker of advanced coronary heart disease without contributing significantly to the underlying pathophysiology at that stage of the process. Similar observations have been made in conscious dogs (22).

Limitations of the study. The present results can not be extrapolated to mean that norepinephrine plays no important role in the pathophysiology of heart failure. Our observations were limited to patients with advanced coronary heart disease who were studied at rest and only over a 48 h period of observation. It is possible that circulating norepinephrine plays an important role during periods of stress such as exercise. Furthermore, it is now established (17,18) that beta-receptor density and responsiveness are reduced in chronic heart failure associated with high levels of circulating catecholamines and that antiadrenergic agents can restore beta-receptor levels and responsiveness over time. Thus, more prolonged administration of metyrosine might have resulted in significant hemodynamic changes in our study patients.

The present results might also reflect inadequate reduction of plasma norepinephrine. Although plasma norepinephrine levels decreased almost threefold to within the normal range, even this reduced level may represent an excess, given the tiny amounts needed at the neuroeffector junction. Plasma catecholamine levels are thought to represent excess amounts entering the circulation after local metabolism and reuptake (23). Nevertheless, the degree of reduction in plasma norepinephrine in the present study is comparable with that observed in states of known catecholamine dependency, such as pheochromocytoma, where both blood pressure and heart failure have been controlled by metyrosine administration (9,10,24).

Another possible explanation for the present results is that other neurohumoral factors were playing a more influential role. Plasma renin activity was increased in our patients. In addition, circulating epinephrine was not reduced by metyrosine, and it has been suggested (25) that epinephrine is a more important determinant of blood pressure than is norepinephrine. Epinephrine may also affect cardiac performance through $beta_2$-receptors (26). These receptors may assume greater importance in regulating performance of the failing heart with its reduced $beta_1$-receptor integrity (27).

The discrepancy between the present results and previous observations that alpha-receptor antagonists produce immediate vasodilation and hemodynamic improvement in patients with heart failure may relate to some of the mechanisms described herein (28,29). Thus, any amount of circulating norepinephrine may be regarded as excessive relative to the amounts required for activity at the alpha-receptor level. Furthermore, these receptors may be responding to other vasoconstrictor influences in addition to norepinephrine, or the alpha-receptor blocking agents may possess direct vasodilating activity.

Conclusions. Our results suggest that the high levels of plasma norepinephrine observed in patients with chronic congestive heart failure do not contribute significantly to the hemodynamic abnormalities observed at rest in these patients with advanced heart failure. Norepinephrine may still be important in initiating the vicious cycle of heart failure because the adrenergic nervous system is activated very early in patients after acute myocardial infarction, and the magnitude of this change relates to the extent of myocardial damage as well as to survival (30). Once the process of heart failure becomes established, other mechanisms may become more influential in the maintenance or progression of disease, and circulating norepinephrine may become more of a marker at that stage. Clarification of the ultimate role of circulating catecholamines in the pathophysiology of heart failure requires further study. In the meantime, our results support the concept that manipulation of the adrenergic nervous system as a therapeutic intervention can be safely investigated.

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