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Although recent physiologic studies suggest that increased catecholamine release in humans may in the long run represent an adverse homeostatic mechanism, this catecholamine release is acutely important in permitting human response to stress. Clinical interventions with beta-adrenergic blocking agents have showed a salutary effect on cardiac function in patients with severe heart failure; in patients with heart failure associated with myocardial infarction, these agents may help improve mortality rates. These studies indicate that the drugs are well tolerated when used carefully in these high-risk patients. (Henry Ford Hosp Med J 1986;34:184-7)

Recent clinical investigations suggest that beta-adrenergic blocking agents may have a beneficial role in the treatment of patients with heart failure. This appears paradoxical, since this class of drugs has long been known to have a negative inotropic effect. Nevertheless, a series of clinical studies suggests that these agents may be effective in certain patients with heart failure. Investigations have been carried out in two groups of patients: those with heart failure due to primary cardiomyopathy (1-5), and those who experience heart failure in association with a recent acute myocardial infarction (6-8). The investigations of beta-adrenergic blocking agents in primary cardiomyopathy have examined patients' physiologic responses to these drugs. Since the number of patients available for such studies is limited, information is not yet available regarding the long-term effect of beta-blocking agents on mortality. Clinical trials, however, are planned to explore this issue. Conversely, patients with recent myocardial infarction associated with heart failure were studied not only to examine the effects of these drugs on morbidity and mortality but also to determine whether adverse drug reactions occurred.

Norepinephrine in Heart Failure

These clinical studies, coupled with the observation that the mortality rate of heart failure appears to be directly related to norepinephrine concentration (9), have not only encouraged investigation of the neurohumoral response to heart failure but also increased our understanding of norepinephrine and its role in heart failure. Although it was recently observed that plasma norepinephrine concentration is increased in patients with heart failure, we have known for some time that the concentration of catecholamine in the myocardium is decreased (10-12).

These observations suggest that myocardial norepinephrine uptake is decreased or that the rate of norepinephrine turnover or clearance in the failing myocardial tissue is accelerated. The reflex-neurohumoral response to heart failure is usually accompanied by norepinephrine release. In the setting of a falling cardiac output, norepinephrine maintains systemic blood pressure by vasoconstriction. The decreased myocardial catecholamine concentration is thought to be caused by chronic increased sympathetic discharge which is required for the maintenance of blood pressure. The decreased myocardial norepinephrine concentration resulting from the chronic neurosympathetic activity may explain the myocardial beta-adrenergic receptor down-regulation (13). This down-regulation of beta-receptors partly explains the failure of the myocardium to respond to increased norepinephrine concentration in the blood. Studies of norepinephrine clearance in patients with heart failure indicate that the increased serum norepinephrine content is a function of both increased norepinephrine release and a decrease in regional norepinephrine clearance in the specific coronary vascular bed (14). This combination of increased norepinephrine secretion and decreased clearance is observed in cardiac and renal beds but not in the pulmonary bed. Although increased norepinephrine is critical to the early adaptation to a fall in cardiac output, in the long run beta-receptor down-regulation and decreased clearance of norepinephrine render adrenergic stimulation less important for the maintenance of cardiac homeostasis. In fact, increased serum norepinephrine concentration may be detrimental to cardiac function, leading to increased work load of the heart resulting from alpha-receptor stimulation and increased systemic vascular resistance. Continued myocardial stimulation may also lead to acceleration of myocardial degeneration (15), promoting cardiac arrhythmias and sudden death (16).

The relationships between circulatory and myocardial norepinephrine, beta-receptor regulation, and cardiac function at rest and during stress are shown in Figs 1 and 2. In the setting of heart failure, an increase occurs in circulating norepinephrine stores. This increase in circulatory norepinephrine results in an increased peripheral resistance in the setting of decreased left ventricular function (Fig 1). With stress in the failing heart, a

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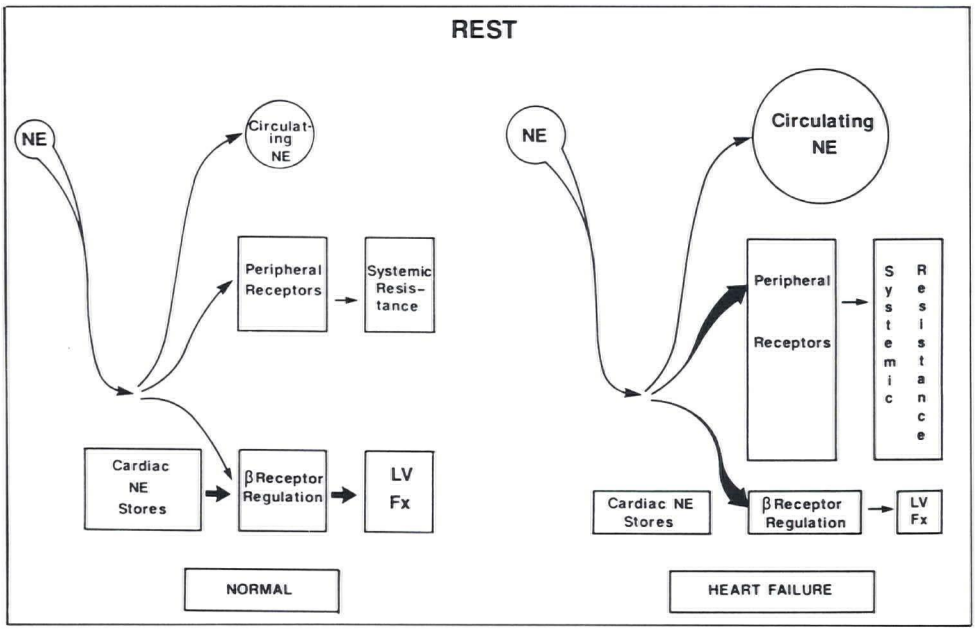

Fig 1—The relationship between circulatory norepinephrine (NE), beta-receptor regulation, peripheral resistance, and left ventricular function (LV Fx) in the normal individual and the individual with heart failure.

slight increase in left ventricular function occurs as a result of a marked increase in circulating norepinephrine, but is associated with a further exaggeration of systemic resistance (Fig 2).

Beta Blockers in Cardiomyopathy

The seminal clinical studies by Waagstein et al (1), in which metoprolol was administered to patients having heart failure predominantly due to primary cardiomyopathy, first explored the potential of this therapy. Most recently, Engelmeier and colleagues (4) examined the effect of graded doses of metoprolol on cardiac function in patients with primary cardiomyopathy. Incremental doses of metoprolol were carefully administered to patients up to when either the daily dose of 100 mg was reached or a systolic pressure of 90 mm Hg or a pulse rate of 60 was achieved. The endpoints of therapy were attained in 20 of 21 patients.

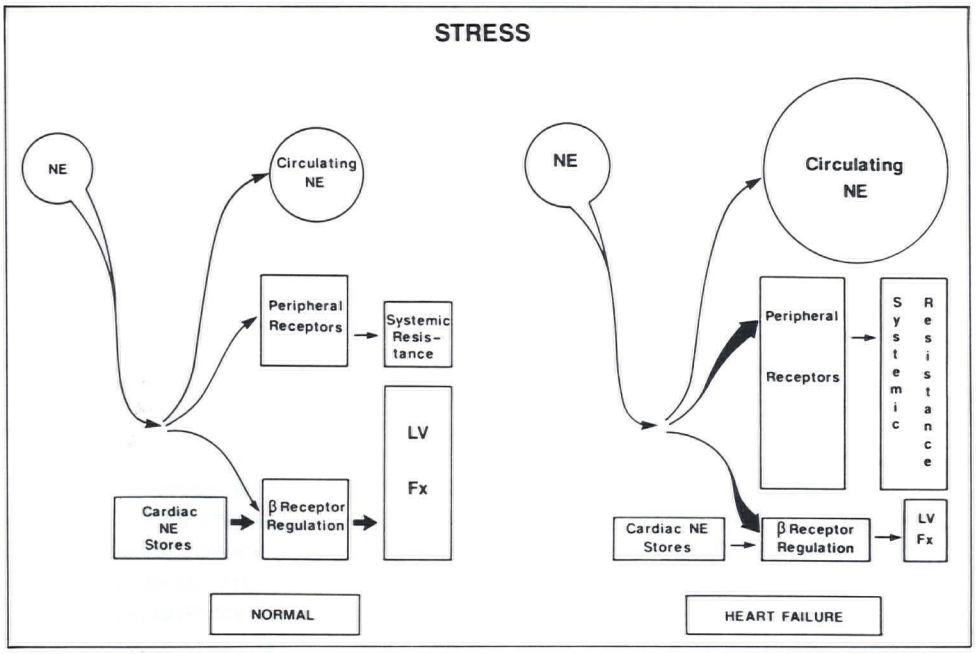

Fig 2—Similar relationship of normal individual and heart failure individual during stress.

Table
Efficacy of Beta-Blocking Agents in Heart Failure

Study	Drug	No. of Patients	Total Death Placebo	Total Death Control	Sudden Death Placebo	Sudden Death Control
Hansteen et al (6)	Propranolol	560	13.1%	9.0%	8.2%	4.0%
Australian/ Swedish study (7)	Pindolol	529	17.7%	17.1%	11.7%	10.6%
Beta Blocker Heart Attack Trial subgroup analysis (1)	Propranolol	710	18.4%	13.3%	10.4%	55.5%

Once metoprolol dosage was established, 14 of the 20 patients experienced improved exercise tolerance, and seven of 20 achieved an improvement in ejection fraction and fall of the left ventricular end-diastolic pressure to almost normal levels. The changes took place over a three-month period. Only rare, adverse effects that could not be dealt with by prolongation of dosage interval were observed. The effect of the drug appeared to be closely related to its bradycardic effect. Similar results were reported by Svedberg et al (2). Other studies of mixed patient populations with heart failure due to diverse causes failed to show a beneficial effect of metoprolol when changes were measured within one month (3,5). Engelmeier et al (4) suggest that the effect of metoprolol requires treatment for a longer duration.

These studies suggest that beta-adrenergic blocking agents may produce a beneficial effect in heart failure patients. Patient candidates include those with tachycardia and perhaps hypertension. The only drug used in these treatment programs was metoprolol, a cardioselective drug. A case can be made that these should be the most appropriate beta blockers to use, since the increased vasoconstriction occasionally observed with nonselective drugs could modify the effects of these drugs. The effects of these drugs which also result in alpha-blockade may also be modified by decreasing peripheral resistance.

Beta-Blocking Agents in Congestive Heart Failure Associated with Coronary Heart Disease

The results of beta blocker studies in postinfarction patients with heart failure are listed in the Table. The two prospective studies were not specifically designed to study the effect of these agents in postinfarction patients with heart failure alone. A Norwegian study (6) and a combined Australian/Swedish study (7) examined high-risk postmyocardial infarction individuals in whom heart failure was one of the major characteristics. Also included in these study populations, however, were patients with ventricular ectopy and serious cardiac rhythm disturbances. The Norwegian study of high-risk postmyocardial infarction patients observed that total and sudden death mortality decreased to 32% (p value not significant) and 50% ($p < 0.05$) when patients were treated with propranolol. In the combined Australian/Swedish multicenter study with pindolol, no significant beneficial effect was observed in patients treated with that beta blocker. This lack of effect may be attributed to the intrinsic sympathomimetic-stimulating activity characteristics of pindolol. The incidence of heart failure in the active treatment program in both studies was slightly higher than in the placebo group. In the Norwegian propranolol study, the occurrence of heart failure in the first two weeks of therapy was 6.5% in the propranolol group and 1.8% in the placebo group. After two weeks this adverse effect related to propranolol disappeared and was 1.4% in the propranolol group and 3.9% in the placebo group.

A retrospective subgroup analysis was conducted in the Beta Blocker Heart Attack Trial (8), examining patients who had experienced congestive heart failure prior to randomization. In this postmyocardial infarction study, the total mortality over the 25-month average follow-up in the patients with heart failure treated with propranolol was 13.3% compared to 18.4% in the placebo group; in those without heart failure, the mortality was 5.9% and 7.8%. The decrease in total mortality, 27% and 25%, respectively, was similar regardless of the history of heart failure. Patients with heart failure, however, did experience a greater absolute benefit with beta blockers because of the increase in mortality rate in general. An impressive 47% decrease in the rate of sudden death was observed in the propranolol-treated patients with a history of heart failure, compared to a 13% decrease in those without heart failure. However, a slight increase of heart failure did occur during the first 30 days of propranolol administration in patients having a history of heart failure. The overall incidence of heart failure during follow-up was similar in the placebo-treated and propranolol-treated patients regardless of whether they had previous heart failure.

The mechanism by which beta blockers modify mortality in coronary heart disease patients is not entirely clear. Patients with heart failure are known to have increased ventricular ectopy. In the Beta Blocker Heart Attack Trial (8), 19.6% of the patients with a history of heart failure had >10 ventricular premature beats/hr compared to 11.8% of those without a history of heart failure. A similar increased frequency of ventricular complex ectopy was observed in patients with heart failure (50.2%) compared to those without a history of heart failure (38.6%) ($p < 0.05$). Beta blockers have been shown to decrease ventricular ectopy in patients with coronary heart disease. This particular effect may explain the observed decrease in total mortality, particularly in view of the decreased rate of sudden death in propranolol-treated patients. However, whether this decreased frequency of ventricular ectopy is an antiarrhythmic effect or is due to the ability of beta blockers to modulate myocardial ischemia is unclear. Antiarrhythmic effects of beta blockers have been demonstrated in patients without ischemic heart disease (17). In animal models, beta blockers have been shown to decrease ventricular fibrillation threshold in both ischemic and nonischemic animals (18).

Engelmeier et al (4) suggest a number of other possible mechanisms by which beta-adrenergic blocking drugs can exert their action. They suggest that these drugs may block the cardiotoxic effects of catecholamines, restore the down-regulation of beta-adrenergic receptors, or modulate inappropriate tachyarrhythmias. The restoration of normal receptor regulation occurs as a result of chronic beta-receptor blockade, rendering these receptors more sensitive to beta stimulation. Regardless of the proposed mechanism, the demonstration of their clinical

efficacy has stimulated considerable research on how these drugs can modify both symptomatology and mortality.

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