Do ß-blockers have a role in patients with Congestive Heart Failure?

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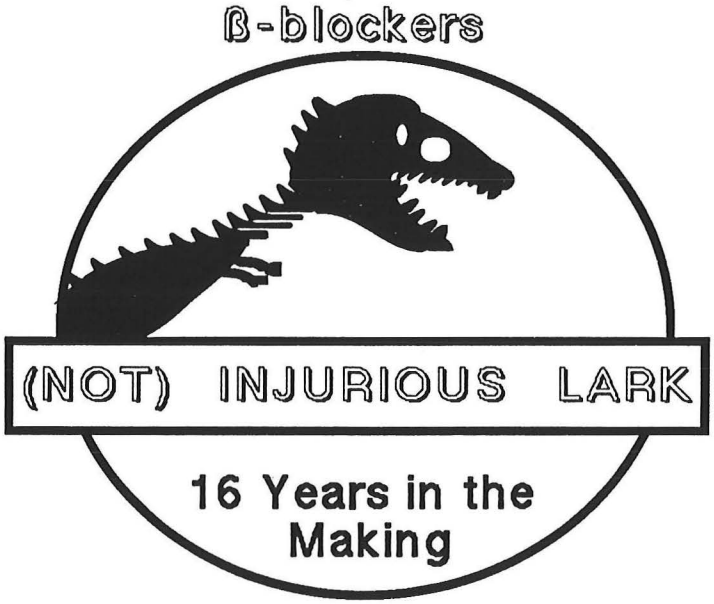

Despite the use of angiotensin converting enzyme inhibitors, digitalis, and diuretics, the 1 year mortality of patients with moderate to severe congestive heart failure remains high. The overall 1 year mortality is 26% for New York Heart Association Functional Class III and 42% for NYHA Class IV despite use of angiotensin converting enzyme inhibitors, digitalis, and diuretics (Figure 1).[1]

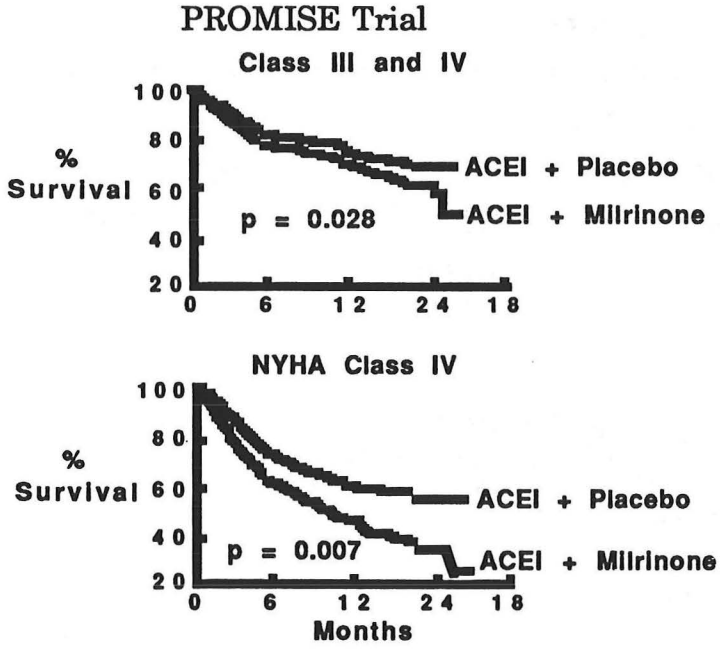

Figure 1 (from ref. 1)

Recent studies have demonstrated that these patients have progressive loss of exercise tolerance and functional ability despite maximal medical therapy.[2] As cardiac transplantation is available to only a few patients with heart failure due to a limited donor supply and large expense, prevention and medical treatment of heart failure has gained new focus. Over the last 20 years, cardiologists have searched for a therapy which would not only prolong life but also improve the quality of life of these very sick patients. While vasodilators [2-4] and angiotensin converting enzyme inhibitors [2,5-9] have clearly made an impact in this area, they have slowed but not halted the progression to death (Figure 1). Thus, newer therapies to halt or reverse the progression of heart failure are needed.

Congestive heart failure is of growing importance in the United States. A 1991 study that examined diagnosis related groups (DRGs) estimated that congestive heart failure accounts for 4.8 million hospital

days nationwide and accounted for nearly 6% of all inpatient hospital bills submitted for fiscal year 1991. This translates into a $9.1 billion expenditure for heart failure. According to the National Heart, Lung and Blood Institute, the estimated economic impact was $4.7 billion in 1987 for direct costs. Thus, a new therapy to reduce the yearly expenditure for heart failure hospitalization is needed

Heart Failure and the adrenergic balance-

Heart failure is a result of inadequate ability of the heart to maintain peripheral tissue perfusion and oxygen delivery.[10]

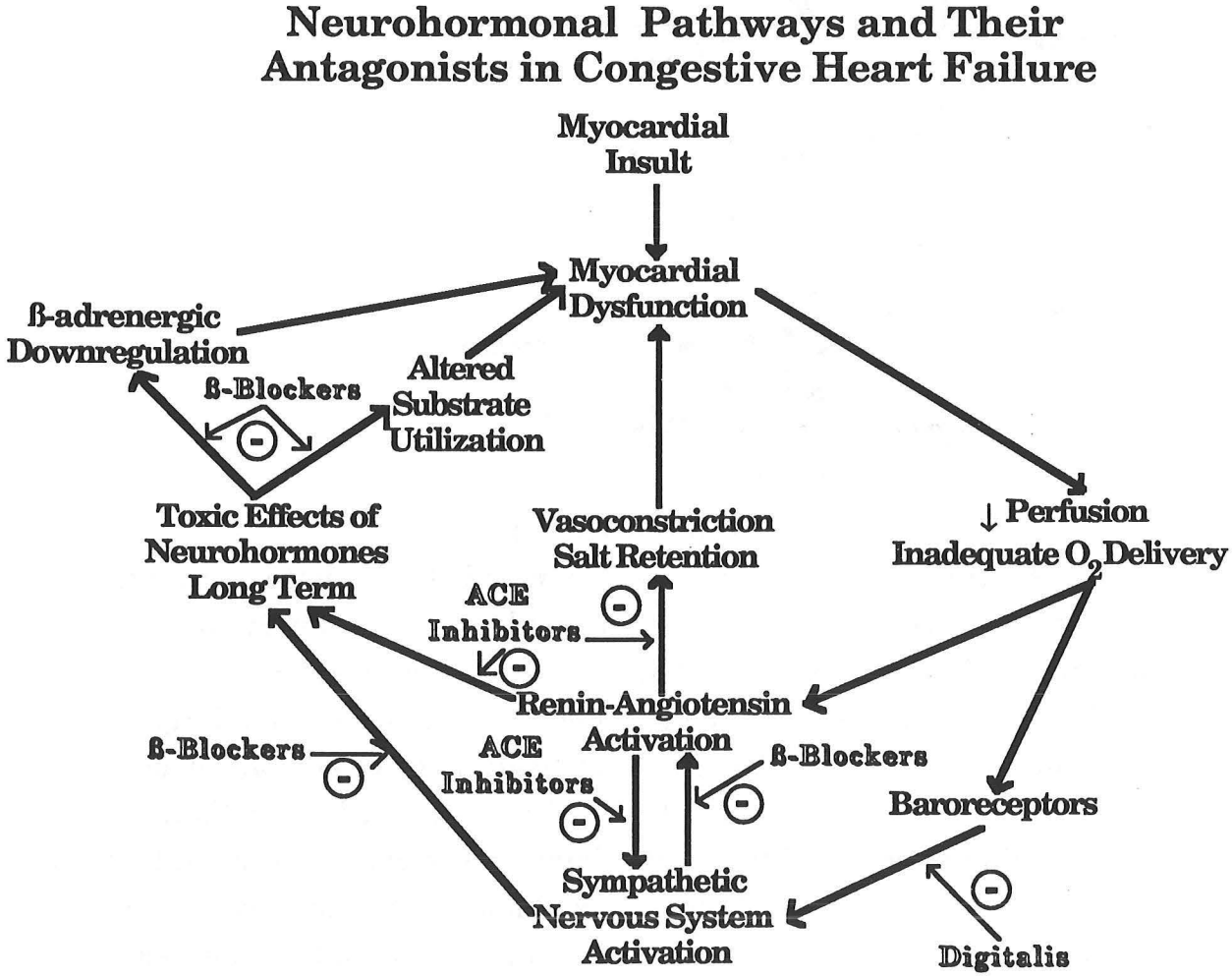

Figure 2 (from ref. 10)

When the heart fails, aortic and ventricular baroreceptors are reset allowing less inhibition of sympathetic discharge (Figure 2).[10-12] This results in heightened adrenergic tone. In addition, reduced glomerular

blood flow results in release of renin, activating the renin-angiotensin system (RAS).[13] Both the sympathetic nervous system and the RAS cross activate each other as renin release is partially mediated by β_1 stimulation of the kidney [14] and angiotensin acts at the pre-synaptic receptor to block norepinephrine reuptake.[15,16] In the short term, these compensatory mechanisms act in concert to retain fluid and inotropically support the heart and circulation. Long term, these systems may be detrimental to the heart.[10,12] Both elevated plasma norepinephrine [17] (a marker of sympathetic nervous system activation) and hyponatremia [12,18] (a marker of RAS activation) have been shown to be independent prognostic signs, independent of ejection fraction, in patients with heart failure. Figure 3 shows the relationship of plasma norepinephrine to survival in patients with heart failure. Those with the most neurohormonal activation had the poorest survival.

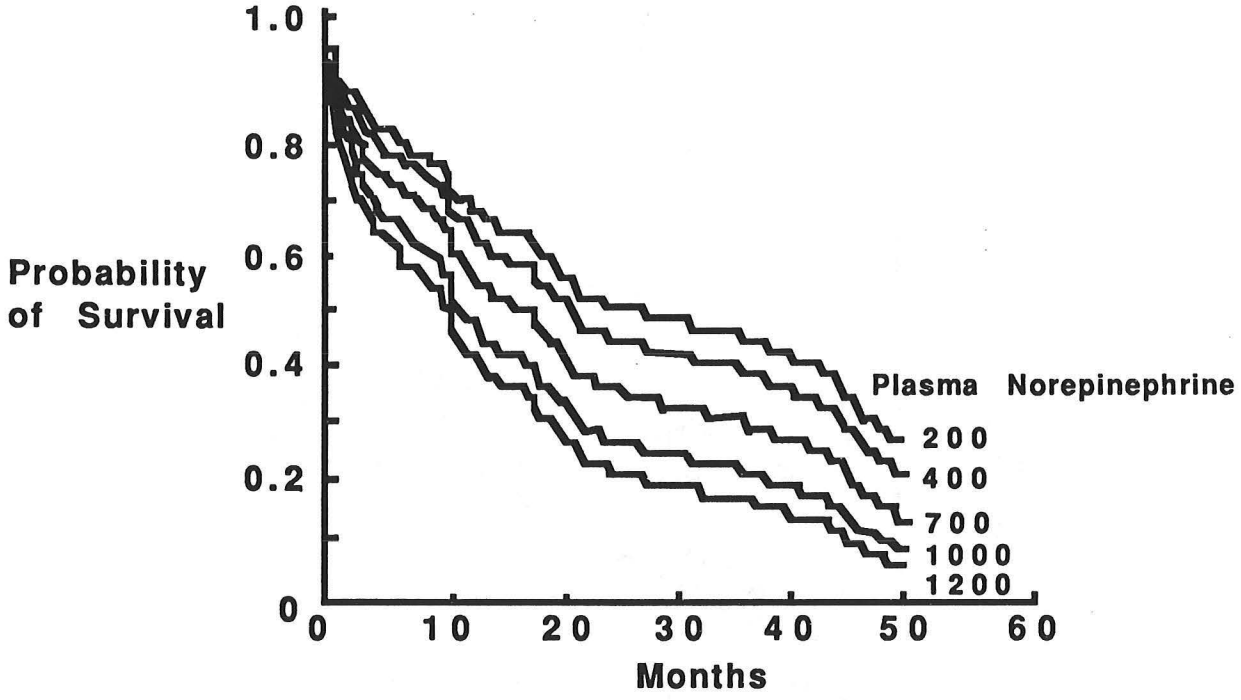

Figure 3 (from ref. 17)

In addition, the use of angiotensin converting enzyme inhibitors has been shown to improve the survival of heart failure patients more than hydralazine and isosorbide dinitrate despite greater improvement in ejection fraction and exercise tolerance with the latter agents (Figures 4 and 5).[2] Thus, ACE inhibitors have an effect on survival which exists beyond hemodynamic improvement.

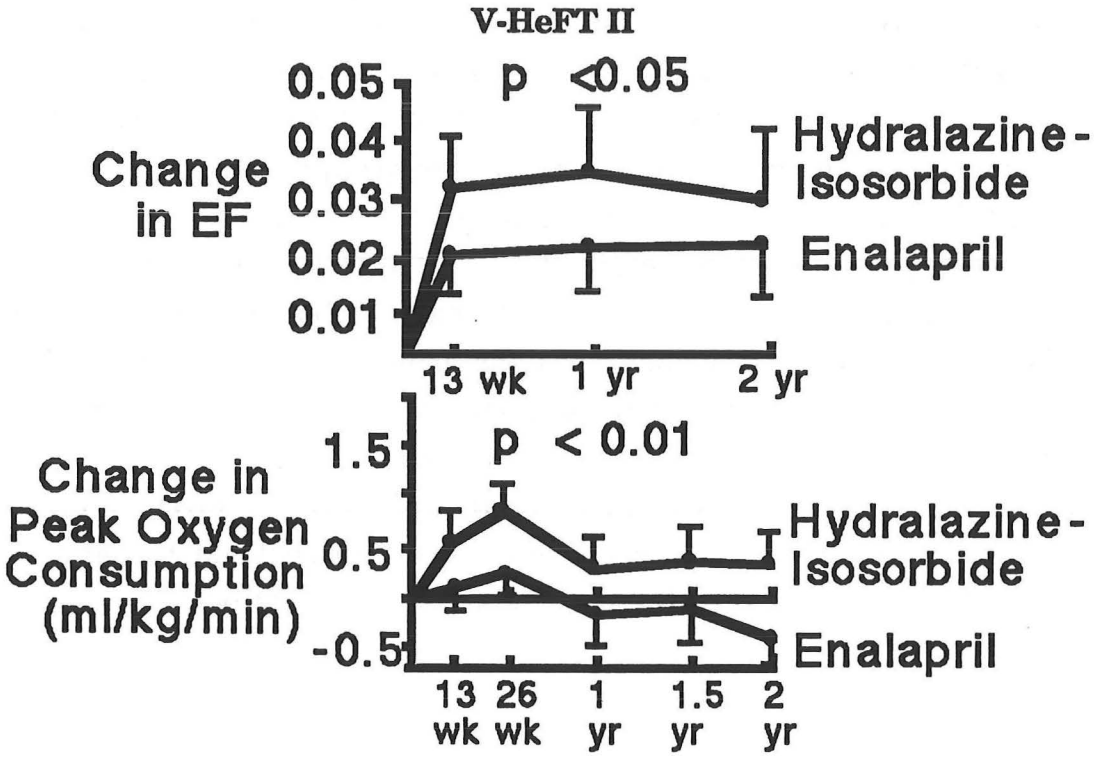

Figure 4 (from ref. 2)

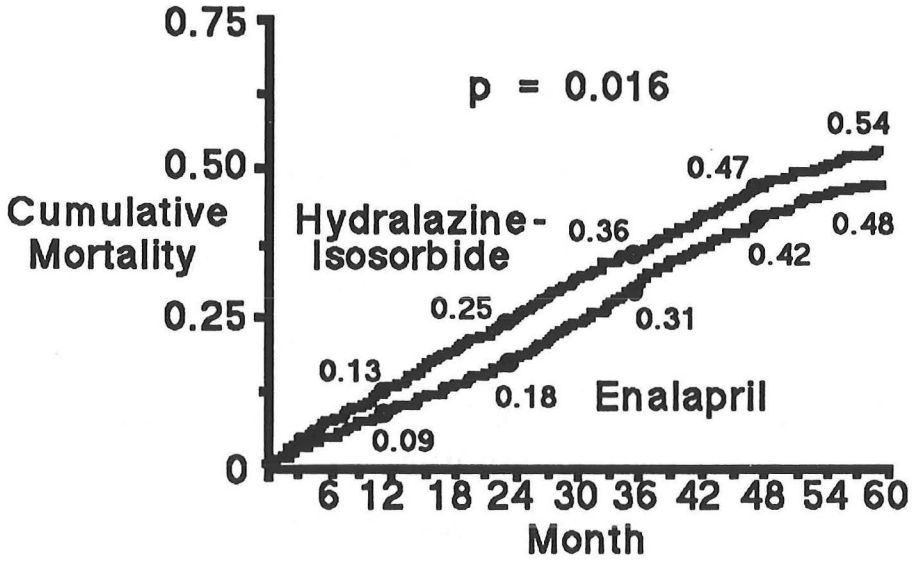

Figure 5 (from ref. 2)

Finally, both norepinephrine [19-21] and angiotensin II [22] have been shown to have direct toxic effects on the heart. While these adverse effects on the heart have not been well characterized, it is clear that long term unblocked

neurohormonal activation produces progressive myocardial dysfunction. This establishes a vicious cycle as the weakened heart thereby further activates the sympathetic nervous system and the RAS.[10]

Should we stimulate the heart in the face of high adrenergic tone?

The search for new agents to treat heart failure lead to the discovery of several inotropic agents in the 1970s and 80s. However, ß-adrenergic agonists despite some mild initial improvements resulted in patient tolerance over time and loss of initial clinical improvement.[23-28] As shown in Figure 6 much of the tolerance to ß-agonists is due to progressive downregulation of the ß-receptors in heart failure, with further downregulation after administration of the ß-agonist. Thus, the heart becomes subsensitive to ß-stimulation and ejection fraction returns to baseline despite initial improvement.

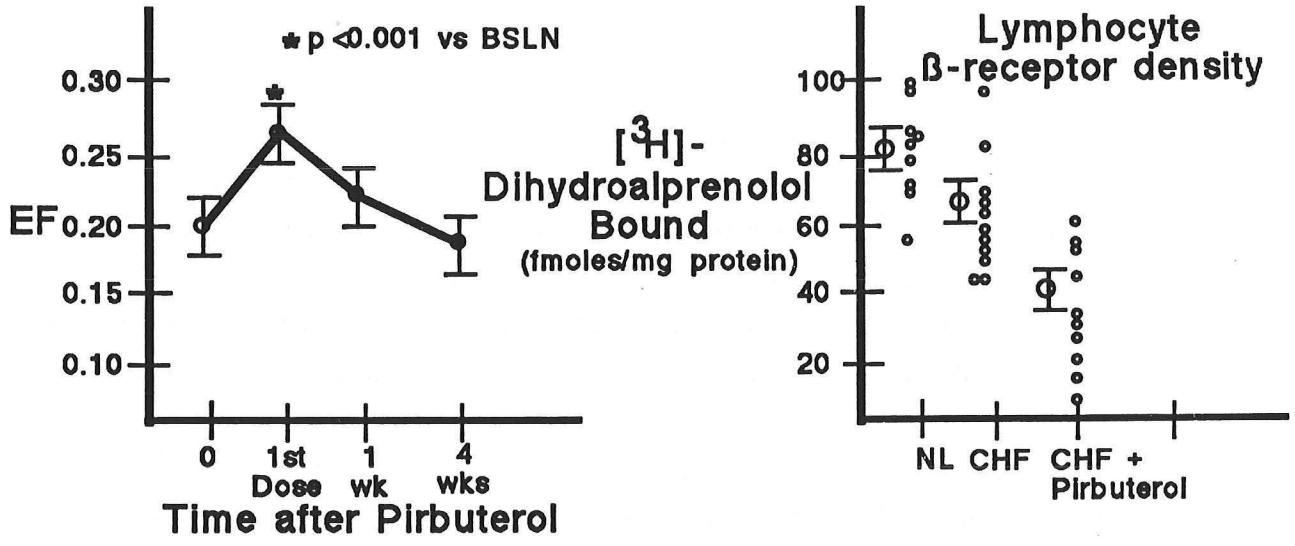

Figure 6 (from ref 28)

Additionally, moderate to high dose ß-agonists have been shown to increase mortality (Figure 7).[29,30]

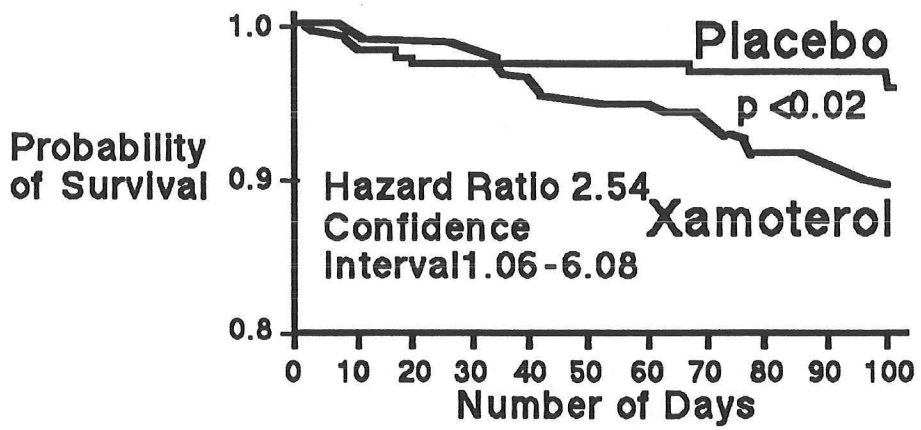

Figure 7 (from ref. 30)

Phosphodiesterase inhibitors despite leading to some modest clinical and hemodynamic improvement, did not lead to increases in ejection fraction.[31] The phosphodiesterase inhibitors also lead to increased mortality (Figure 1).[1,29] This increase in mortality appears to be due to an increase in sudden death.[32] Thus, stimulating the heart in the face of high adrenergic tone does not lead to a prolonged salutary effect and may increase mortality.

Two mild inotropes, digitalis [33-36] and visnarinone (OPC 8212) [37-40], have shown some benefit in the treatment of congestive heart failure. Digitalis, while a mild inotrope [33], probably works in heart failure as it has been shown to reduce sympathetic nerve traffic [34], and thus may act to some degree as a neurohormonal antagonist. It has also been shown to result in diastolic improvement [33], an effect which leads to reduced filling pressures [41], reduced myocardial stretch, and this ultimately results in less sympathetic activation. Thus, digitalis may act more as a neurohormonal antagonist than we realize. Visnarinone, while a mild inotrope [37-39], has been demonstrated to increase mortality at higher dosages.[40] While this increase in mortality at higher dosages may be a result of an inotropic effect, this has yet to be proven. At lower dosages, visnarinone results in reduced mortality.[39,40] The reason for this is unknown, but may be due to its special antiarrhythmic properties or improved myocardial energetics.

Thus, in general, excessive stimulation of the heart, in the face of high adrenergic tone, results in adverse effects on survival and little long term benefit.

Benefits of neurohormonal antagonism-

By contrast, when neurohormonal antagonists, such as ACE inhibitors, are administered, long term functional and hemodynamic benefit results (Figure 4).[2,6-9,35] In addition, there is a clear benefit in terms of survival in moderate to severe congestive heart failure [2,5,42] (Figures 5, 8 and 9), and a clear effect on hospitalization for recurrent heart failure in patients who have minimal to no symptoms of heart failure.[43]

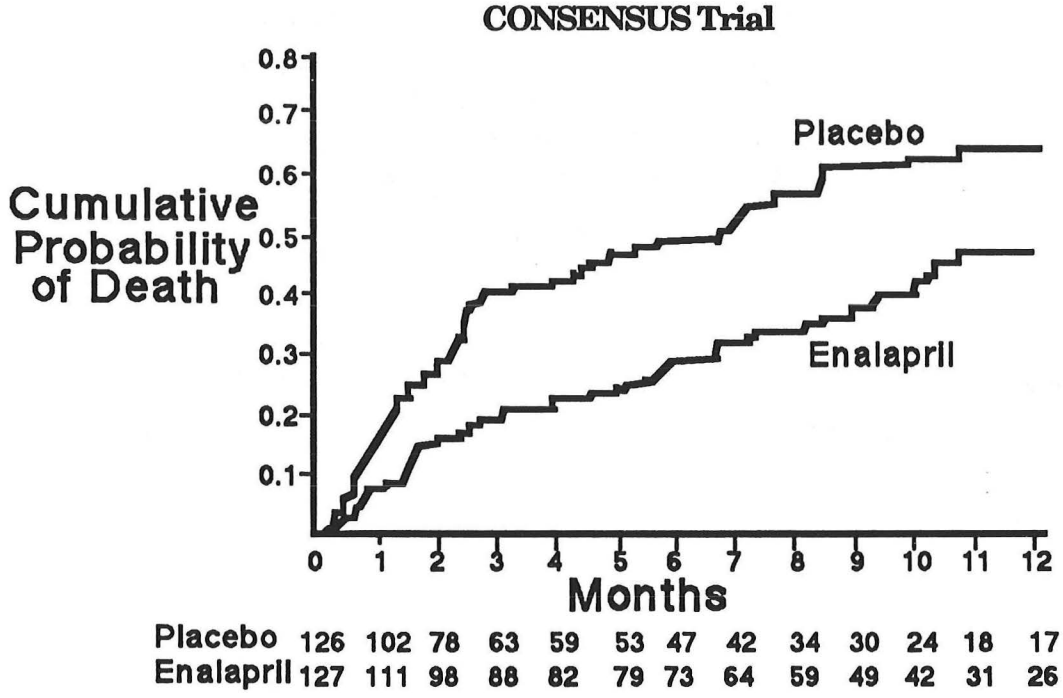

Figure 8 (from ref 42)

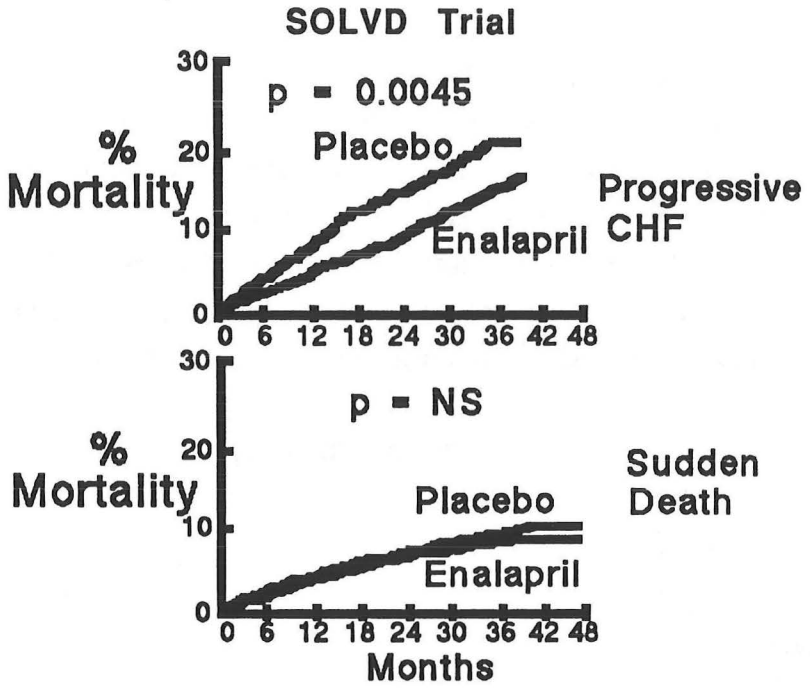

Figure 9 (from ref. 5)

However, ACE inhibitors only deactivate the RAS and incompletely deactivate the sympathetic nervous system.[44-46] Thus, the long term toxic effects of post-synaptic norepinephrine continue even after the administration of an ACE inhibitor. This was recently demonstrated in the V-HeFT II trial (Figure 10).

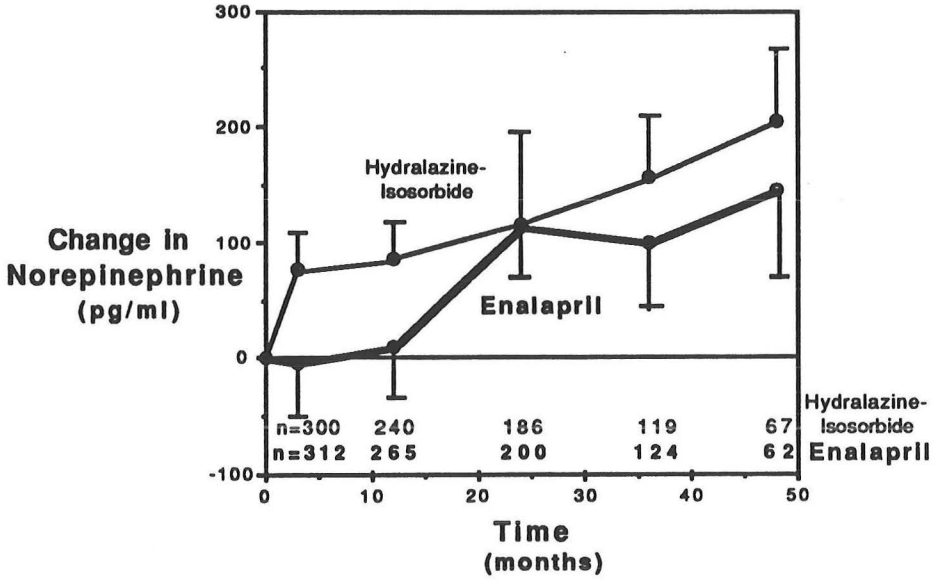

Figure 10 (from ref. 45)

The recently completed Metoprolol in Dilated Cardiomyopathy (MDC) trial demonstrated that when ß-blocking agents are given to patients with heart failure, there is a reduction in the combination of mortality and need for transplantation (Table 1).[47]

Table 1: Metoprolol in Dilated Cardiomyopathy (MDC) Trial

	Metoprolol (n=194)	Placebo (n=189)
Death	23	19
Need for Transplant	2	19
Total Morbidity/Mortality	25*	38

*p=0.058 vs placebo

In addition, retrospective analysis of a post myocardial infarction trial [48] and two small prospective trials [49,50] have suggested a survival benefit when these agents are used. As seen in Figure 11, a retrospective analysis of the Beta-Blocker Heart Attack (BHAT) Trial demonstrated a survival benefit of ß-blockers in all patients, and most especially in those patients with heart failure. ß-blockers conferred a 47% reduction in sudden death in patients with heart failure.

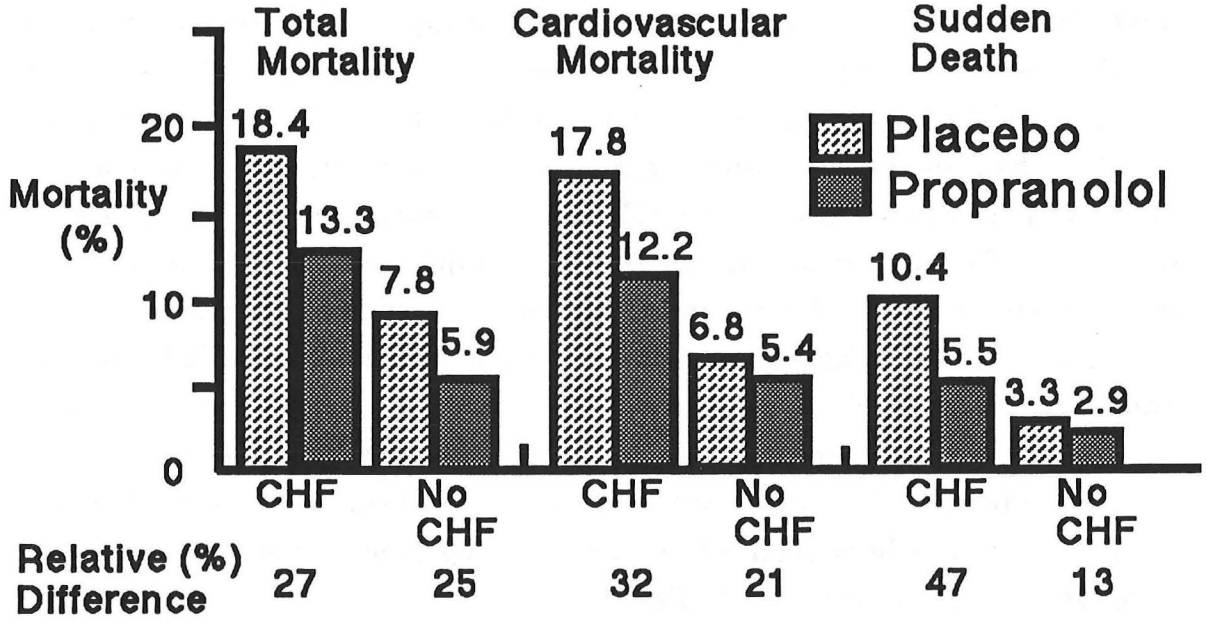

Figure 11 (from ref. 48)

ß-blockers have been shown to raise ventricular fibrillation threshold [51-53] and their use in the CAST trial lead to a reduction in sudden death and episodes of ventricular fibrillation.[54] While a survival benefit of ß-adrenergic blockers used in heart failure patients has yet to be proven in a prospective trial, these data provide substantial evidence to suggest either a beneficial effect or at worst, no effect. It is difficult to imagine, based upon the above data, that ß-blockers when used judiciously produce an increase in mortality in patients with impaired ventricular function. This is especially true as ß-blockers improve ejection fraction over time (see below) and ejection fraction is an independent predictor of mortality in congestive heart failure. A prospective, randomized, double-blind survival trial has been approved within the Veterans Administration and is under consideration at the NHLBI-NIH. This trial known as the Beta-blocker Evaluation of Survival Trial (BEST) will probably begin enrolling patients in 1994.

Evidence for a beneficial effect on ventricular function and functional class-

To date 10 metoprolol (548 patients) [47,50,55-61], 6 bucindolol (265 patients) [62-67], and 1 carvedilol heart failure studies (12 patients) [68] have been completed. This represents a collective experience of over 500 patients who have received ß-blockers for the treatment of congestive heart failure (Table 2). The results of these trials provide undeniable evidence of a hemodynamic benefit of these agents. Every ß-blocker study of 3 or more months duration has shown an improvement in left ventricular ejection fraction and a reduction in symptoms.[10] While improvement in exercise tolerance has been difficult to demonstrate [10], most studies to date have used maximal exercise instead of modified submaximal exercise as criteria for improvement. As ß-blockers blunt maximal exercise tolerance in both normal and sick patients [69], improvement in maximal exercise is not a fair assessment of improvement, especially as daily activities represent submaximal exertion. In studies where submaximal exercise is used, ß-blockers have shown a beneficial effect corroborating more subjective functional improvement noted in these studies.[66]

Table II

Change in ejection fraction, exercise tolerance, and symptom score in published studies of ß-blockade for treatment of heart failure (Mean ± S.D.)

Authors	Number of Patients	Pre-treatment LVEF	Post treatment LVEF	Exercise Improvement?	Symptom Improvement?	Agent	Follow-up time (mos.)
Waagstein et al[111]	7	.35±.17	.59±.13*	Yes	----	several	2-12
Ikram et al [72]¶	15	.47±.13	.44±.15	No	----	acebutolol	1
Engelmeier et al [55]¶	8	.13±.06	.18±.05†	Yes	Yes	metoprolol	3
Currie et al [61]¶	10	---------	---------	No	----	metoprolol	1
Heilbrunn et al [59]	14	.26±.11	.39±.11§	----	----	metoprolol	6
Waagstein et al [56]	26	.25±.06	.41±.13§	----	Yes	metoprolol	16
Anderson et al [67]	50	---------	---------	----	----	metoprolol	32
Andersson et al [57]	21	.22±.07	---------	Yes	Yes	metoprolol	14
Fischer et al [58]¶	17	.22±.08	.28±.09†	Yes	Yes	metoprolol	6
Sachdev et al [60]	12	.26±.06	.37±.11†	----	----	metoprolol	6
MDC trial [47]¶	383	.22±	.32±§	Yes	Yes	metoprolol	12-18
Eichhorn et al¶	15	.22±.10	.33±.13‡	-----	Yes	metoprolol	3
Gilbert et al [64]¶	13	.26±.07	.35±.11§	No	Yes	bucindolol	3
Eichhorn et al [62]	15	.23±.12	.29±.14‡	-----	Yes	bucindolol	3
Pollock et al [65]¶	12	.19±.07	.23±.08†	Yes	Yes	bucindolol	3
Bristow et al [66]||¶	35	.23±.07	.31±.14†	No	----	bucindolol	3
Woodley et al [63]¶							
all patients	29	.23±.08	.29±.11†	No	Yes	bucindolol	3
IDC	13	.26±.06	.35±.10†	No	Yes	bucindolol	3
ISCDC	16	.21±.08	.23±.09	No	Yes	bucindolol	3
Anderson et al [112]¶	20	.25±.08	.35±.13§	No	Yes	bucindolol	23
DasGupta et al [68]	16	.28±.09	.33±.10†	Yes	----	carvedilol	2
Wisenbaugh et al [113]¶	11	.23±.08	.33±.12†	No	----	nebivolol	3

*p<0.1; †p<0.05; ‡ p<0.01; §p<0.005 vs. pre-treatment. || Only patients at maximal daily dose compared to baseline for this table.

¶ Denotes controlled trial, either with double-blind placebo controlled parallel groups or crossover design.

IDC = Idiopathic dilated cardiomyopathy. ISCDC = ischemic dilated cardiomyopathy.

For many years we have been told that ß-blockers are negative inotropes. Thus, the finding of an increase in ejection fraction in patients with heart failure [10] has left some to wonder if ß-blockers are somehow unloading the heart by reducing vascular resistance. Studies from our laboratories has clearly demonstrated an increase in relatively load independent indices of contractility with bucindolol.[62] More recently, we have completed a prospective, randomized, double-blind, placebo-controlled trial of metoprolol in 24 patients with dilated cardiomyopathy. We found an increase in ejection fraction (Figure 12) and peak+dP/dt (Figure 13) only in the patients on active drug.

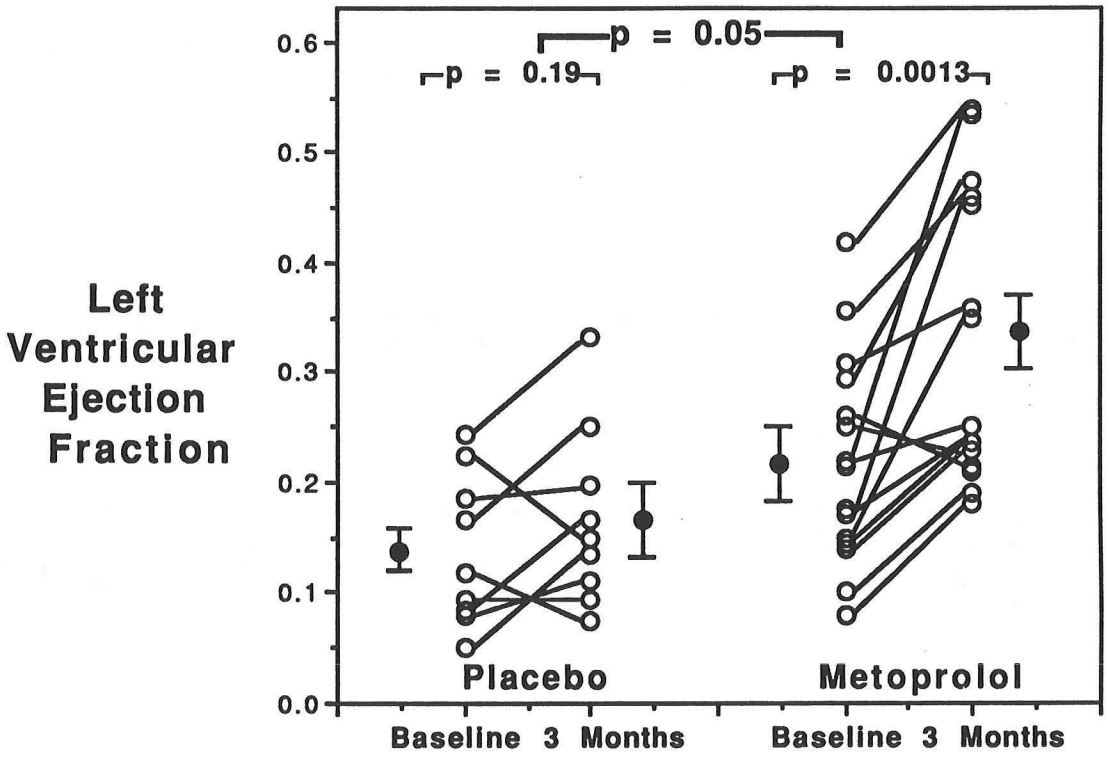

Figure 12

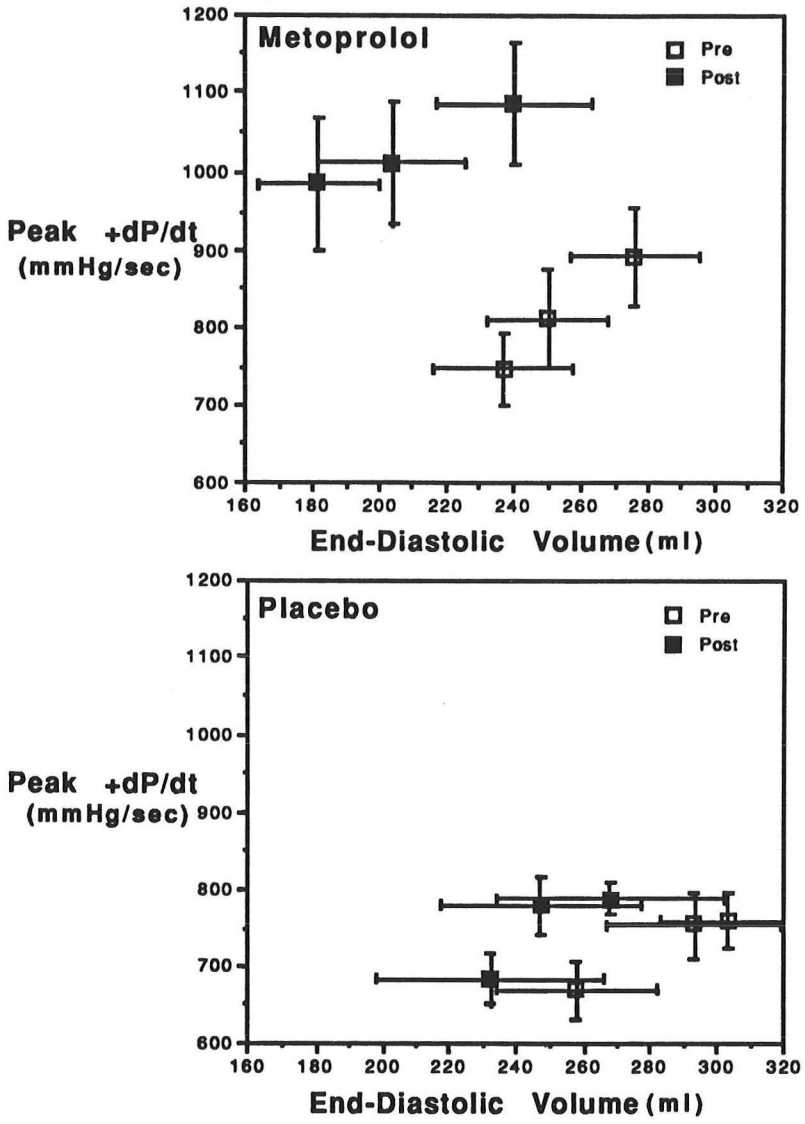

Figure 13

These data provide evidence that ß-blockers when titrated carefully are "positive inotropes" not negative inotropes (although their initial effect is a negative inotropy). This relatively heretical viewpoint is further strengthened by the finding that patients with heart failure who are withdrawn from ß-blockers often experience decompensation and deterioration.[56,70] In addition, we have demonstrated that ß-blockade with bucindolol or metoprolol results in improved myocardial relaxation and a reduction in left ventricular end-diastolic pressure.[62] As long term improvements in relaxation in patients with heart failure are closely related to reductions in left ventricular end-diastolic pressure [41] (and as ß-blockers have been shown to

not significantly increase end-diastolic pressure on therapy initiation [71]), this improvement in relaxation may be a very beneficial effect. Finally, our laboratory has demonstrated that metoprolol improves stroke work and minute work (stroke work times heart rate) while reducing myocardial oxygen consumption. Thus, metoprolol makes the failing heart more efficient (Table 3). Based on these current data, we must abandon our traditional thinking concerning these agents.

Table 3

Baseline left ventricular characteristics before and after therapy with metoprolol or placebo.

Measurement		Pre Treatment	Post Treatment	p value (M vs P)
Heart Rate (min^{-1})	P	84±10	83±19	
	M	83±17	68±17§	0.014
End-systolic	P	61±6	60±7	
Pressure (mmHg)	M	62±14	77±19*	0.023
Stroke work Index	P	17.0±5.0	20.7±10.9	
($g\text{-}m/m^2$)	M	18.7±7.8	32.9±17.5§	0.064
Minute Work Index	P	1.4±0.4	1.6±0.7	
($kg\text{-}m/m^2$)	M	1.5±0.6	2.1±0.8*	0.25
Coronary Sinus Blood	P	146±102	201±136	
Flow (ml/min)	M	178±88	115±71	0.026
Myocardial Oxygen	P	16.8±9.2	22.1±12.5	
Consumption (ml/min)	M	22.3±11.3	13.1±7.6	0.035
Myocardial Efficiency	P	7.9±3.8	9.2±6.7	
(%)	M	8.5±5.6	18.5±10.9*	0.10
Coronary Sinus	P	730±445	1114±727	
Norepinephrine (pg/ml)	M	569±426	433±357	0.025

*$p<0.05$ vs pre; § $p<0.005$ vs pre; † $p<0.05$ vs placebo pre treatment.

LVEDP = left ventricular end-diastolic pressure. M = metoprolol. P = placebo.

We have recently examined the time course of ventricular improvement with ß-blockade using serial echocardiography. As is evident in Figure 14, left ventricular function worsens mildly in the first month, only to improve substantially between months 1 and 3. These data explain why the two studies of ß-blockade [61,72] which were 1 month in duration both had negative results.

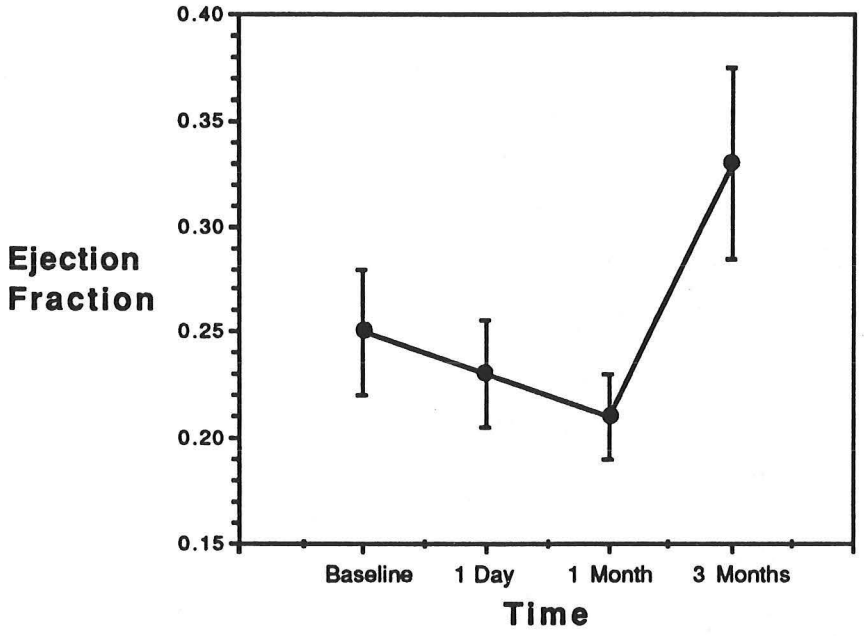

Figure 14

While a clear survival benefit has not been shown for these agents, an adverse effect on mortality is unlikely given all the retrospective [48,49,54] and small prospective trials [47,50] done to date. Thus, as these drugs produce hemodynamic and functional improvement [10], even if they produce no effect on mortality, they would be beneficial in heart failure due to their hemodynamic effects. Should they prove to prolong survival in heart failure patients, they would become standard of care. As the Food and Drug Administration has recently made a policy decision to allow drugs for the treatment of heart failure which have hemodynamic benefits and have possible adverse or unknown effects on survival, the consideration of ß-blockers as investigational agents should soon be challenged. Their lack of proper acceptance has been linked to both the reluctance of physicians to acknowledge a proven but counterintuitive therapy and the reluctance of any pharmaceutical company to pursue research on agents which they feel would not gain widespread acceptance.

Possible mechanisms of action-

Part of the reluctance of physicians to accept this therapy has been the lack of a mechanism to explain how these agents work. For several years the general thinking about how these agents work was based on the observation that β_1 cell surface receptors are downregulated in heart failure.[73-77] This is probably a result of chronic norepinephrine stimulation [73,75,78] of the heart and a feedback mechanism that allows the heart to "protect" itself from the toxic effects of norepinephrine long-term. Upregulation of these receptors (Figure 15) [56,59] and restored responsiveness to ß-agonist stimulation (Figure 16) [59] has been demonstrated after ß-blockade.

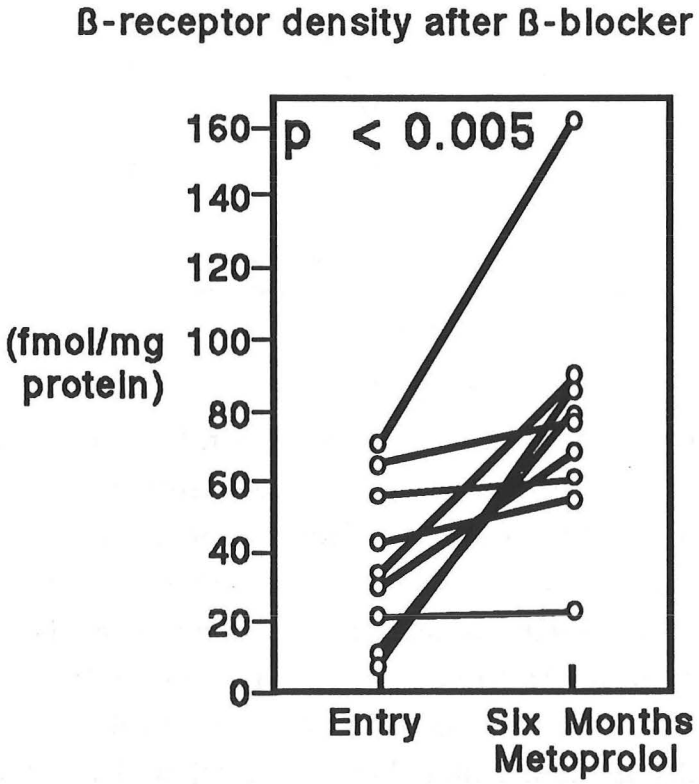

Figure 15 (from ref. 59)

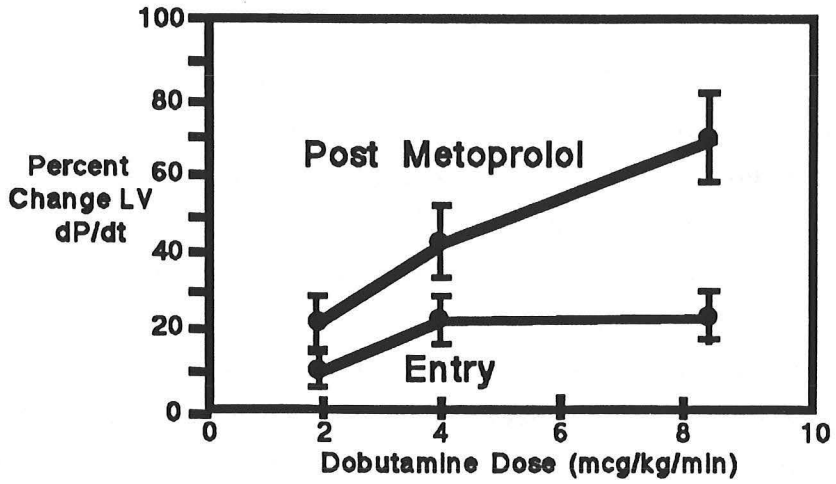

Figure 16 (from ref. 59)

While ß-receptor upregulation may explain improved submaximal exercise responsiveness, it cannot explain the improvements in resting left ventricular function for several reasons: a) despite an increase in contractility, heart rate usually falls.[10,56,59,62-64] If improved resting ventricular function were due to heightened sensitivity to agonist stimulation, then heart rate should increase, not decrease with increased contractility. b) Upregulation of beta-receptors occurs temporally more quickly than improved ventricular function (i.e the two events are temporally disparate).[79] c) Some beta-adrenergic blocking agents have been shown to improve ventricular function in the absence of beta-receptor upregulation.[80] Thus, other theories must be put forth to explain this phenomenon.

It has been previously documented in animals and man that catecholamines are deleterious to the heart.[19-21] However, the etiology of this deleterious effect is unclear. It has long been known that fatty acids and glucose provide the major substrates for myocardial energy metabolism and that excess utilization of free fatty acids by the heart increases myocardial oxygen consumption.[81-83] Fatty acid substrate utilization by the heart is therefore less efficient than glucose (as more oxygen is used per amount of mechanical work performed).[81-85] In the oxygen limited heart, high concentrations of free fatty acids depress myocardial performance.[81,84] When oxygen consumption is increased by atrial pacing or stress, myocardial oxygen consumption is increased disproportionately in the

presence of infused lipids and heparin as compared to a control state.[85] Catecholamines stimulate release and utilization of fatty acids [81,85], and inhibit insulin-induced glucose transport by skeletal muscle.[86] Conversely, propranolol increases insulin sensitivity while increasing blood free fatty acids in diabetic rat skeletal muscle.[86] This suggests ß-adrenergic stimulation plays a role in substrate utilization in heart failure. As congestive heart failure is a state of increased adrenergic stimulation, with elevated sympathetic nerve traffic and increased plasma norepinephrine levels [11,12,17,78,87,88], lipolysis and glycogenolysis are both stimulated.[82,85,89] In the dog, myocardial oxygen consumption which is increased by beta-agonist stimulation, is further increased by a beta-stimulated increase in (i.e. a shift to) fatty acid utilization.[82] We have recently examined the relation between neurohormonal activation as reflected by coronary sinus norepinephrine and substrate utilization as manifest by transmyocardial respiratory quotient. As can be seen in Figure 17, we found a relation between the change in coronary sinus norepinephrine and change in transmyocardial respiratory quotient over a 3 month period of metoprolol or placebo therapy. These data support our theory that neurohormonal activation may affect the ratio of carbohydrate to fatty acids utilized by the heart.

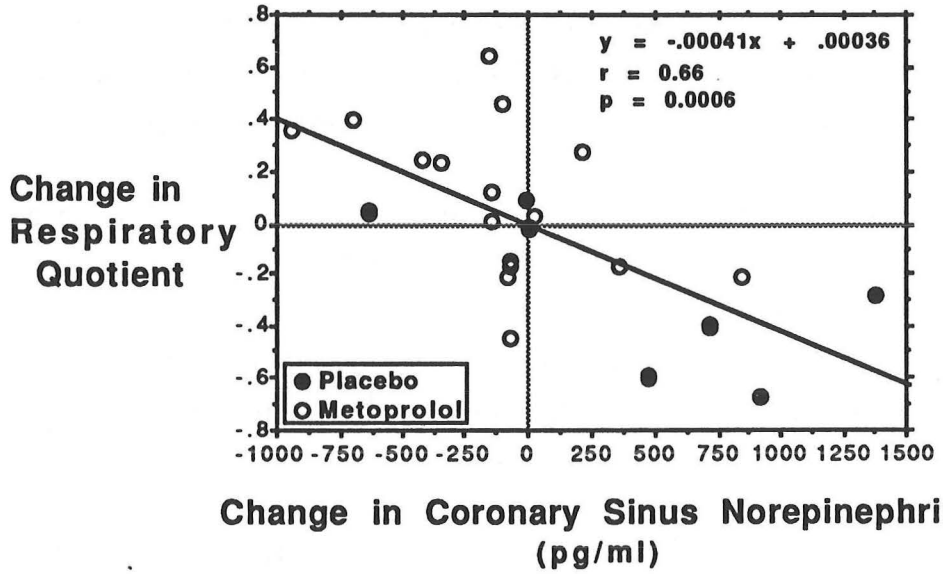

Figure 17 (from ref. 90)

As myocardial work does not change or decreases when there is a shift from glucose to fatty acid utilization, this shift represents a reduction in myocardial efficiency.[82] Indeed, a relation between degree of neurohormonal activation and substrate utilization has been established in patients with dilated cardiomyopathy.[90] Thus, the institution of ß-adrenergic blockade may reduce fatty acid utilization and shift substrate utilization to glucose and pyruvate, which are more efficient fuels. Support for this hypothesis comes from one of the early ß-blocker trials where lactate extraction increased with ß-blocker therapy.[91] Lactate uptake increases when pyruvate is being preferentially used for oxidative phosphorylation. It has been previously documented that both angina [92] and congestive heart failure [93] can be treated by dichloroacetate (an agent which activates pyruvate dehydrogenase, stimulates glucose metabolism, and inhibits fatty acid oxidation) intravenously. After dichloroacetate, stroke work and minute work are increased while myocardial oxygen consumption is reduced. This is the result of improved myocardial efficiency. Beta-blockers may improve ventricular function in a manner similar to dichloroacetate.

Other theories include: 1) Inhibition of sympathetically mediated vasoconstriction via prostaglandins and reduced renin release.[94] In addition, angiotensin II may have some direct cardiotoxic properties [22], which would be diminished by the ability of ß-blockers to reduce renin-angiotensin activation. As angiotensin (and perhaps norepinephrine) may have some potential for inducing protein synthesis and myocardial hypertrophy [95], the long term effect of ß-blockers on ventricular remodeling has yet to be elucidated. 2) Improved protein synthesis, message expression, and function within the mitrochondria and sarcoplasmic reticulum. 3) Improved calcium transport within the myocyte 4) Inhibition of other "toxic" effects of norepinephrine on the myocyte. 5) Finally, endothelin has been postulated to play a role in patients with congestive heart failure.[96-99] Endothelin is a powerful vasoconstrictor and has been shown to correlate with pulmonary artery pressures and pulmonary vascular resistance.[98] In addition, endothelin is known to stimulate proliferation of rat vascular smooth muscle cells, fibroblasts, glomerular mesangial and human carcinoma cells with the expression of protooncogenes *c-myc* and *c-fos*.[100] Thus, some mitogenic actions regulating cell proliferation and fibrosis may exist, which in concert with angiotensin II may alter the structure of the

myocardium. Endothelin is released by several factors including norepinephrine.[97] Thus, a reduction in endothelin may occur by ß-adrenergic blockade, although this has yet to be proven.

Which ß-blocker should be used?

Currently, it is unclear which is the best ß-blocker to use for the treatment of heart failure. Three beta-adrenergic blocking agents have been used extensively for the treatment of congestive heart failure, metoprolol, bucindolol, and carvedilol. The latter two have mixed actions with primarily beta-blocking effects and some vasodilator effects. Both of these agents (bucindolol and carvedilol) are non-Food and Drug Administration approved for any indications and are thus investigational agents.

Metoprolol is a beta-1 selective antagonist without vasodilator or agonist action. It is the most widely studied beta-blocker with over 500 heart failure patients in 10 completed studies placed on this agent.[47,50,55-61]

Bucindolol hydrochloride is a phenoxypropanolamine with potent non-selective ß-antagonist and mild vasodilatory properties.[101,102] Bucindolol has equipotent $ß_1$ and $ß_2$ antagonist actions as propranolol.[102] Although mild intrinsic ß-sympathomimetic activity has been demonstrated in rats and dogs [103-105], no intrinsic sympathomimetic activity has been found in human ventricular myocardium.[102] While bucindolol (and carvedilol) exhibit an "agonist" binding site modulated by guanine nucleotides in human myocardium, this does not confer agonist (adenylate cyclase) activity.[80,106] In addition, bucindolol possesses weak α_1-antagonist [101,102,107,108], weak serotonin antagonist (in animals)[103,108], and mild vasodilator action[102,103,108,109]. As compared to labetolol, the vasodilator action is not modulated by its weak α_1 antagonist action.[80,108,109] It is the vasodilator action of bucindolol which most likely makes it well tolerated in patients with congestive heart failure.

Carvedilol is a less selective ß-blocker than metoprolol, but is more selective for $ß_1$ receptors than bucindolol (i.e. carvedilol has less $ß_2$ antagonism than bucindolol but more than metoprolol).[101,106] This is shown in Table 4 below where selectivity ratios of various ß-blocking agents are shown (Data based on ^{125}[I] ICYP cold ligand competition curves in presence of 30 µM Gpp(NH)p: [106]

Table 4:

Agent	K_H ($ß_1$) (nM)	K_L ($ß_2$) (nM)	Selectivity $ß_1$:$ß_2$
Metoprolol	45.6±31.0	3345±1789	73
Carvedilol	3.37±0.75	105±6.0	31
Bucindolol	3.83±1.14	3.83±1.14	1
Propranolol	4.42±1.53	4.42±1.53	1

In addition, carvedilol has moderate vasodilator activity (as compared to bucindolol's mild vasodilator activity).[80,101,102]

As both carvedilol and bucindolol possess the atypical feature of guanine nucleotide modulatable binding [80,106,110], and as they do not upregulate ß-receptors in the same fashion as metoprolol [80,106,110], they may offer superior "protection" from the adverse long-term effects of norepinephrine on the heart. However, as bucindolol has been shown to increase contractility and relaxation, lower plasma norepinephrine, non-selectively antagonize both the $ß_1$ and $ß_2$ receptors, not upregulate ß-receptors, and is well tolerated on therapy initiation, it may well provide the perfect combination of "myocardial protection" and hemodynamic improvement. By contrast, metoprolol, does not block the $ß_2$ receptor, upregulates $ß_1$ receptors [59], and does not significantly lower plasma norepinephrine (Table 3). These effects may lead to a lack of reduction in sudden death (Table 1) [47] despite improvements in hemodynamics (Figures 12 and 13; Table 3).[60] These data suggest bucindolol is the superior agent, although a head-to-head comparison needs to be performed.

<u>Titration of ß-blocking agents</u>-

Despite the fact that these agents increase myocardial contractility over the long-term, they still act as negative inotropes during therapy initiation and titration. Thus, caution must be observed during titration. No patient should be started on ß-blockers who shows signs of hypoperfusion, significant pulmonary or systemic edema, or recent acute decompensation. In such patients, intravenous diuretics with or without short-term inotropic support should be used to bring the patient back into a compensated state. After the patient is compensated ß-blockade can be initiated. Most of the intolerance to ß-blocker therapy occurs at the time of

therapy initiation, not at the higher (target) doses. The starting dose should be determined by the severity of the heart failure. For the very ill class IV patient who has recently been on inotropic support, or who has signs of right sided failure (ascites and jugular venous distension), a lower starting dose is recommended. Metoprolol 2 or 3 mg of the intravenous solution or labetolol 3 to 5 mg of the intravenous solution can be placed in juice and given twice daily. For less sick patients, metoprolol 6.25 mg (1/8 of a 50 mg tablet) or labetolol 12.5 mg (1/8 of a 100 mg tablet) can be given twice daily as initial dosages. ß-blockers can then be increased every 5 to 7 days as tolerated, usually doubling the dose. A target dose of 50 mg BID of metoprolol or 50-100 mg BID of labetolol can be used. Labetolol may be slightly easier to titrate due to its alpha antagonist (vasodilating) properties. However, this has not been proven and its efficacy has yet to be fully established. During titration, the patient must be watched carefully for signs of weight gain, worsening edema and fatigue. If fluid retention occurs, titration can be slowed and diuretics increased. Both the physician and patient must be patient with titration, and not deem the treatment a failure if early fluid collection occurs. The patient should be warned in advance that improvements may take 6-8 weeks to occur and that he/she may actually worsen some during titration. In addition, as this therapy is still considered investigational by the Food and Drug Administration, informed consent may be necessary.

Future Directions-

A mortality study to determine if ß-blocking agents prolong survival in heart failure is being planned (ß-Blocker Evaluation of Survival Trial, BEST) as a VA-NIH cooperative trial. This study will hopefully answer the question as to whether ß-blocking agents improve survival in patients with advanced heart failure. Other questions for the future include the differential effects of selective versus non-selective ß-blockade. In addition, the significance of guanine nucleotide modulatable binding has not been completely defined. It is also not clear who will best respond to this therapy and when is the optimal time for initiation of ß-blocking agents (i.e. Is there a benefit for the asymptomatic or mildly symptomatic patient?) Finally, the mechanism(s) of benefit of these agents have not been fully defined. These questions will be answered in the next few years.

Summary-

ß-adrenergic blocking agents have been demonstrated to benefit ventricular systolic and diastolic function, improve functional class, and reduce neurohormonal activation in patients with congestive heart failure. Their effects on mortality while still unknown are unlikely to be adverse and more likely to be favorable based on prior studies. Thus, these agents are slowly gaining acceptance as a novel treatment modality for patients who have congestive heart failure.

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