REVIEW ARTICLE

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Effects of β-Blockers on Neurohormonal Activation in Patients with Congestive Heart Failure

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Contents

Abstract

The effect of β-adrenoceptor antagonists (β-blockers) on neurohormonal activation in patients with congestive heart failure has been the subject of study in numerous small clinical trials. Short term therapy with β-blockers is associated with a variable acute neurohormonal response which may be determined by the pharmacology of the agent under study and the baseline characteristics of the patient population. Long term therapy with β-blockers devoid of intrinsic sympathomimetic activity (partial agonist activity) is associated with evidence of decreased plasma markers of activation of the sympathetic nervous system, the renin-angiotensin system, and endothelin-1. β_1-Selective and nonselective β-blockers appear to be associated with evidence of decreased neurohormonal activation, with differential effects on β-adrenoceptor density. Agents with partial agonist activity appear to differ from pure antagonists, with some studies reporting evidence of increased neurohormonal activation. The mechanisms by which β-blockers reduce neurohormonal activation and the clinical relevance of changes

in adrenergic function to their use in the treatment of heart failure require further investigation.

Congestive heart failure (CHF) is a clinical syndrome characterised by a cluster of signs (elevated jugular venous pressures, rales, oedema) and symptoms (dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, fatigue) related to abnormal cardiac function. While the clinical syndrome of CHF can be the end result of virtually any type of cardiac disease, the majority of patients have clinical heart failure attributable to a primary abnormality in systolic function due to ischaemic heart disease (IHD), hypertensive heart disease, or idiopathic dilated cardiomyopathy (IDC). In patients with heart failure due to systolic dysfunction, the pathophysiology of disease progression is determined by a complex interaction of haemodynamic abnormalities and neurohormonal activation, which induce progressive changes in the structure and function of the left ventricle.[1,2] The progressive changes in ventricular structure and function appear to be the key determinants of long term morbidity and mortality (fig. 1).

Recognition of the importance of ventricular remodelling as a determinant of long term morbidity and mortality has resulted in changes in therapeutic strategies for patients with heart failure. Long term therapeutic goals in these patients are based on reduction of long term morbidity and mortality with neurohormonal antagonists that slow the progression of or reverse ventricular and vascular remodelling. Much of the long term benefit of angiotensin converting enzyme (ACE) inhibitors is derived from their properties as specific antagonists of the renin-angiotensin-aldosterone system and consequent favourable effect on ventricular remodelling.[3]

The concept of therapeutic suppression of neurohormonal activation in heart failure has been applied to the sympathetic nervous system. Heart failure is characterised by increased plasma noradrenaline (norepinephrine) levels, decreased myocardial noradrenaline content, increased sympathetic neural traffic, and adrenergic hyporesponsiveness. Decreased response to adrenergic stimulation has been attributed to down-regulation of β_1-adrenoceptors, relative up-regulation of β2-adrenoceptors, and uncoupling of β-adrenoceptors due to abnormalities in G-proteins (guanosine triphosphate regulatory binding proteins), adenylate cyclase activities, β-adrenoceptor kinase activity, and intracellular signal transduction pathways.[4-10] Chronic activation of the sympathetic nervous system contributes to progression of heart failure by promoting ventricular and vascular remodelling, promoting myocellular apoptosis and increasing interstitial fibrosis.[11,12] Clinical trials with β-adrenoceptor antagonists (β-blockers) have demonstrated short term adverse effects at the initiation of therapy related to deterioration in haemodynamic function and long term substantial reductions in morbidity and mortality in association with improved haemodynamics, favourable phenotypic myocardial changes and fa-

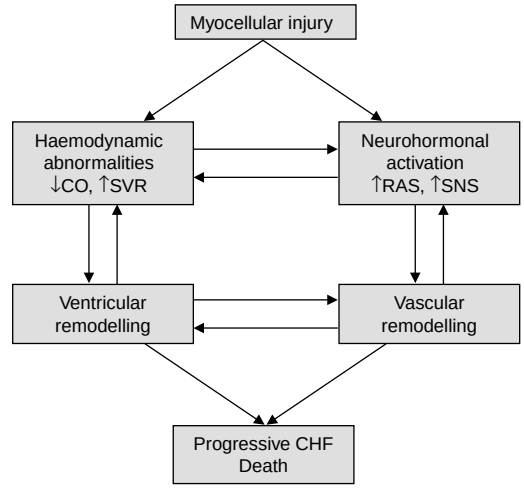


Fig. 1. Schematic representation of proposed pathophysiology of congestive heart failure. Neurohormonal activation appears to play a critical role in the progression of pathological changes in structure and function of the cardiovascular system. Suppression of neurohormonal activation is a therapeutic strategy that has led to numerous trials of β-blockers in the heart failure population. **CHF** = congestive heart failure; **CO** = cardiac output; **RAS** = renin-angiotensin system; **SNS** = sympathetic nervous system; **SVR** = systemic vascular resistance.

vourable effects on ventricular remodelling.[13-16] The rationale for the use of β-blockers in heart failure and a summary of therapeutic trials with β-blockers are the subject of recent reviews.[13,17-19]

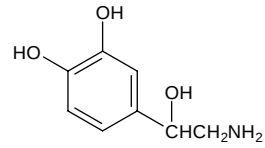
β-Blockers are a heterogeneous class of therapeutic agents (fig. 2). Their primary pharmacological action is attenuation of the effects of endogenous catecholamines via competitive antagonism of the β-adrenoceptor in cardiovascular and other tissues. In addition, β-blockers may alter activation of the sympathetic nervous system and other neurohormonal systems via direct and indirect mechanisms. Additional pharmacological properties which may influence the clinical effects of β-blockers include β_1-selectivity, lipophilicity, intrinsic sympathomimetic activity (partial agonist activity), inverse agonism and G-protein interactions.[10,20] The clinical effect of β-adrenoceptor blockade is likely to be determined by the net effect of the agent on the entire β-adrenoceptor complex, including the receptor, G-protein coupling, adenylate cyclase and β-adrenoceptor kinase activity. Third generation β-blockers such as carvedilol have unique pharmacological properties (β_1- and β_2-receptor blockade, α_1-receptor blockade, G-protein interactions) which may provide more complete suppression of sympathetic activation than first and second generation agents. Accordingly, in this review, newer agents with ancillary properties (third generation agents) are grouped separately from first and second generation agents.

This review focuses on experimental and clinical studies that have specifically investigated the effects of β-adrenoceptor blockade on neurohormonal activation in heart failure with a primary emphasis on the sympathetic nervous system, and secondary consideration of the effects on the renin-angiotensin system, endothelin-1 and natriuretic peptides when data are available. The majority of reports have relied on measurement of the level of neurohormones in plasma as an indirect index of neurohormonal activation. Plasma levels are provided in the original units reported for each study. A few studies have used more direct measures of sympathetic activity by isotopic assessment of noradrenaline kinetics and direct recording of sympathetic neural activity. Although not using a direct measurement of neurohormonal activation, studies which examined other aspects of the function of the β-adrenoceptor complex, such as changes in β-adrenoceptor density, β-adrenoceptor kinase activity and heart rate variability, are also included in the review.

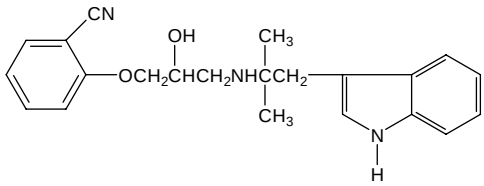
1. Experimental Studies

The acute effects of β-adrenoceptor blockade with propranolol were assessed in a bovine model of heart failure induced by progressive pulmonary hypertension after ligation of the right pulmonary artery.[21] This experimental model produces a period of compensated right ventricular hypertrophy lasting up to 6 weeks, followed by progressive heart failure. Administration of propranolol 0.2 mg/kg was associated with a deterioration in resting haemodynamics and a substantial increase in plasma noradrenaline and adrenaline (epinephrine) levels in animals with right ventricular failure, but not animals with compensated right ventricular hypertrophy or control animals. Right ventricular myocardial noradrenaline content tended to be much lower in animals with heart failure when compared with those with compensated right ventricular hypertrophy or control animals (0.11 ± 0.01 *vs* 1.16 ± 0.33 *vs* 1.48 ± 0.14 μg/g), although no formal statistical comparison is provided. The increase in plasma noradrenaline levels in response to propranolol may represent a compensatory adrenal-mediated response to maintain circulatory homeostasis, rather than a direct pharmacological action.

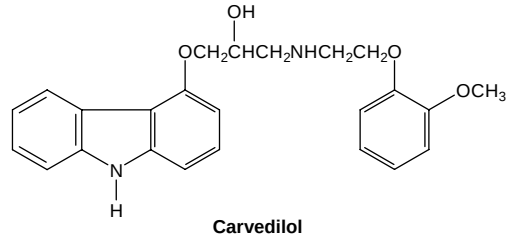
The short term effects of β-adrenoceptor blockade were assessed in a canine model of heart failure induced by rapid right ventricular pacing.[22] Four weeks of oral propranolol therapy (4 mg/kg/day) was associated with increased plasma noradrenaline levels when compared with untreated paced animals with heart failure and unpaced control animals (1100 ± 210 *vs* 720 ± 80 *vs* 270 ± 50 ng/L; $p < 0.05$). Myocardial noradrenaline content was significantly decreased in all paced animals with heart



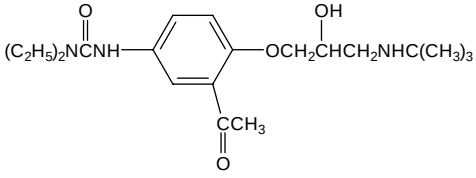
Noradrenaline (norepinephine)



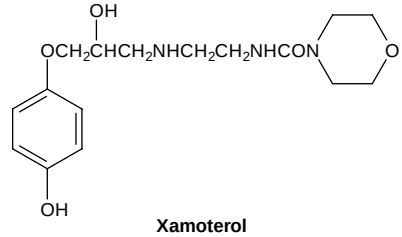
Bucindolol



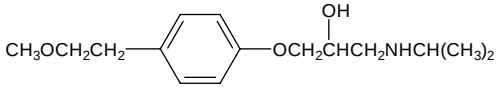
Carvedilol



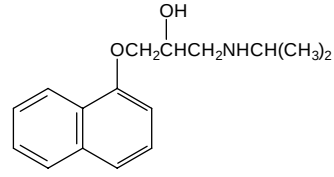
Celiprolol



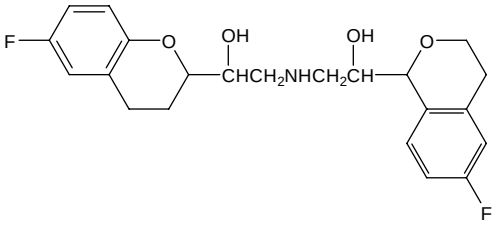
Xamoterol



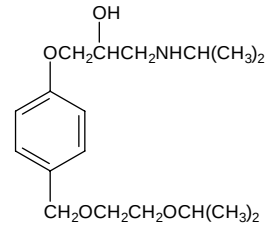
Metoprolol



Propranolol



Nebivolol



Bisoprolol

Fig. 2. Structure of noradrenaline (norepinephrine) and various β-blockers investigated in patients with heart failure.[20]

failure with or without propranolol therapy when compared with unpaced normal control animals. Plasma levels of neuropeptide Y, a parasympathetic neuroenzyme marker, in paced animals with heart failure with or without propranolol therapy did not differ from those in control animals. Myocardial neuropeptide Y content was decreased in paced animals with heart failure with or without propranolol therapy when compared with control animals. These findings are concordant with the report of the acute effects of propranolol in the right ventricular failure model in calves.[21]

The effects of β-adrenergic blockade on neurohormonal activation in a genetic model of heart failure, the BIO 53.58 strain of Syrian cardiomyopathic hamster, have been assessed by 2 groups of investigators. This experimental model is characterised by progressive left ventricular dilation, without hypertrophy, with frank CHF before 6 months of age. Yamada and colleagues[23] studied the effects of metoprolol (1 mg/kg/day) in this model. In a comparison with untreated control animals, metoprolol therapy, administered between the ages of 11 and 18 weeks, significantly decreased plasma noradrenaline level (3.39 ± 0.65 *vs* 6.02 ± 1.03 μg/L; $p < 0.05$), significantly increased myocardial noradrenaline content (10.9 ± 0.9 *vs* 6.7 ± 0.8 μg/g; $p < 0.01$) and significantly increased myocardial β-adrenoceptor density (40.0 ± 2.0 *vs* 28.8 ± 2.1 fmol/mg; $p < 0.01$). The plasma noradrenaline level, myocardial noradrenaline content and β-adrenoceptor density measured during metoprolol therapy were similar to those of a control hamster strain without cardiomyopathy. The improvements in adrenergic function were accompanied by decreased fibrosis in the left ventricle. Tomita and colleagues[24] administered arotinolol, a nonselective β-blocker, by mouth for 10 weeks (ages 14 to 24 weeks) in the same strain of Syrian hamsters. In a comparison with untreated animals, arotinolol therapy significantly decreased plasma noradrenaline level (103 ± 24 *vs* 821 ± 227 ng/L; $p < 0.05$) without change in myocardial β_1-adrenoceptor density, adenylate cyclase activity, G_s-binding protein activity or isoprenaline (isoproterenol) responsiveness.

The effects of β-adrenoceptor blockade on neurohormonal activation have been assessed by 2 groups of investigators in rats after experimental myocardial infarction. Latini and colleagues[25] studied the effects of metoprolol in rats with experimental myocardial infarction produced by coronary artery ligation. Surviving rats were treated with metoprolol 10 mg/kg/day via osmotic pump for 4 weeks, beginning 2 months after the coronary ligation procedure. Metoprolol therapy was associated with a reduction in left ventricular end-diastolic pressure when compared with untreated infarcted controls (6 ± 1 *vs* 13 ± 3mm Hg; p value not specified) but no change in left ventricular mass or myocardial collagen deposition. Plasma noradrenaline levels in metoprolol-treated rats did not differ from those in untreated infarcted controls (245 ± 37 *vs* 224 ± 53 ng/L). Warner and colleagues[26] treated rats with propranolol 500 mg/L in drinking water for 6 weeks, beginning 21 days after coronary ligation. When compared with no treatment in rats with infarction, propranolol therapy significantly increased myocardial β-adrenoceptor density (11.9 ± 1.7 *vs* 9.3 ± 0.6 fmol/mg; $p < 0.05$) but did not change adenylate cyclase activity or isoprenaline responsiveness.

Doxorubicin-induced myocardial damage is another well characterised experimental model of heart failure in which the effects of β-adrenergic antagonism have been studied.[27] When compared with no treatment in heart failure rats, metoprolol therapy (10 mg/kg/day) administered for 3 weeks starting 1 week after administration of doxorubicin (3 mg/kg 3 times weekly for 5 weeks) significantly decreased plasma noradrenaline level (1.0 ± 0.6 *vs* 2.2 ± 1.3 μg/L; $p < 0.01$), increased myocardial noradrenaline content (495 ± 87 *vs* 372 ± 92 ng/g; $p < 0.05$), and increased myocardial β-adrenoceptor density (57 ± 8 *vs* 46 ± 9 fmol/mg; $p < 0.01$).

The effects of 2 weeks' administration of atenolol (0.1 to 10 mg/kg/day) and carvedilol (10 mg/kg/day) by osmotic pump on myocardial sensitivity and β-adrenoceptor kinase activity were evalu-

Table I. Effects of second generation β-blockers on plasma noradrenaline (norepinephrine) levels in patients with heart failure

Reference	Agent	No. of patients	Duration	Plasma noradrenaline	Comments
Swedberg et al.[30]	Metoprolol	11	Short term	↑	
Nemanich et al.[31]	Metoprolol	10	8wk	↓	
Andersson et al.[32]	Metoprolol	21	6-12mo	↓	No change myocardial noradrenaline
Maisel[33]	Metoprolol	15	6-12mo	↓	p = 0.14
Santostasi et al.[34]	Metoprolol	15	6mo	↓	
Ishida et al.[35]	Metoprolol	9	6mo	↓	↑ lymphocyte β_2-adrenoceptor density
Rahman et al.[36]	Metoprolol	6	20mo	↓	↓ SNS nerve activity
Kukin et al.[37]	Metoprolol	30	3mo	↓	↓ combined with doxazosin
Andersson et al.[38] (MDC)[a]	Metoprolol	41	6mo	↓	No different from placebo at 12 months
Eichhorn et al.[39][a]	Metoprolol	24	3mo	↓	Coronary sinus blood
Paolisso et al.[40][a]	Metoprolol	10	3mo	↔	Valvular heart disease
Suwa et al.[41]	Bisoprolol	18	10wk	↓	

a Placebo-controlled study design.

MDC = Metoprolol in Dilated Cardiomyopathy trial; **SNS** = sympathetic nervous system.

ated in C57/B16 mice by Iaccarino et al.[28] In this species, 2 weeks' administration of isoprenaline (0.3 to 30 mg/kg/day) is associated with decreased myocardial β-adrenoceptor density and increased expression and activity of β-adrenoceptor kinase. Both atenolol and carvedilol administration were associated with specific decrease in β-adrenoceptor kinase expression (protein content and mRNA levels) and activity. Atenolol, but not carvedilol, was also associated with increased myocardial β-adrenoceptor density. These findings suggest that β-adrenoceptor blockade modulates adrenergic function by specifically decreasing β-adrenoceptor kinase activity independently of effects on β-adrenoceptor density. These findings may be relevant to clinical observations on the interaction of β-blocker therapy and the inotropic effects of phosphodiesterase inhibitors in patients with heart failure. Bohm and colleagues[29] reported that 6 months of β-adrenoceptor blockade with metoprolol 150mg daily increased the positive inotropic effects of the receptor-independent phosphodiesterase inhibitor, milrinone, in 15 patients with heart failure, suggesting drug-induced postreceptor enhancement of adrenergic function.

Conflicting findings in experimental studies may be due to species differences, model-specific differences or pharmacological differences. The relatively short duration of therapy in all these studies limits the ability to extrapolate the experimental findings to clinical studies of human heart failure.

2. Clinical Studies

2.1 First and Second Generation β-Blockers

The effects of first and second generation β-blockers on plasma norepinephrine levels are presented in table I.

2.1.1 Metoprolol

Metoprolol is a β_1-selective blocker which has been the frequent subject of investigation in studies in patients with CHF. The Metoprolol CR/XL Randomised Intervention Trial in Heart Failure (MERIT-HF) randomised 3991 patients with mild to severe heart failure of ischaemic and nonischaemic origin to placebo or metoprolol controlled release/extended release (CR/XL) in a single-blind fashion for 6 to 20 months (mean follow-up period was 1 year).[42] The maximum dosage of metoprolol was 200 mg/day (mean 159 mg/day). All-

cause mortality [relative risk (RR) 0.66, adjusted p value 0.0062), sudden death (RR 0.59, $p < 0.001$) and death from worsening heart failure (RR 0.51, $p < 0.01$) were all significantly reduced in patients assigned to metoprolol compared with those assigned to placebo. Neurohormonal data are not yet published from the MERIT-HF population and therefore are derived from mostly small noncontrolled studies, with a few controlled studies also available.

Noncontrolled Studies

Swedberg and colleagues[30] reported on the acute effects of intravenous metoprolol administration in 11 patients with IDC. Arterial and coronary sinus plasma noradrenaline levels were determined before and after administration of metoprolol 15mg. Arterial and coronary sinus plasma noradrenaline levels increased in response to β-adrenoceptor blockade (3.8 ± 1.6 to 5.0 ± 2.9 nmol/L and 5.0 ± 3.6 to 8.2 ±6.0 nmol/L, respectively; $p < 0.05$). As observed in experimental models, acute increases in plasma noradrenaline in response to β-adrenoceptor blockade may be attributable to a reflex response to short term deterioration in haemodynamic function. Haber and colleagues[43] reported on the acute effect of non-blind intravenous administration of propranolol and metoprolol in 24 patients with heart failure. Acute deterioration in left ventricular systolic function as determined by fall in systolic pressure, resting cardiac index and end-systolic elastance was similar for both agents.

Nemanich et al.[31] reported findings in 10 patients with CHF attributable to IHD (6 patients) and IDC (4 patients). Metoprolol was administered non-blind and titrated to a maximum dosage of 50mg twice daily. Plasma catecholamines, noradrenaline kinetics and peripheral blood lymphocyte β_2-adrenoceptor density were measured before treatment and after 8 weeks of therapy. Plasma noradrenaline and adrenaline levels were elevated at baseline but decreased significantly with treatment (613 ± 706 ng/L baseline to 303 ± 142 ng/L, and 71 ± 50 to 40 ± 21 ng/L, respectively; $p < 0.05$ for noradrenaline, $p < 0.02$ for adrenaline). There was no significant change in lymphocyte β_2-adrenoceptor density or receptor affinity with treatment. Similarly, no significant change in noradrenaline kinetics was detected in this 8-week protocol. The physiological relevance of lymphocyte β_2-adrenoceptor density measurements is uncertain, as metoprolol is a β_1-selective agent.

Waagstein and colleagues[44] studied, nonblind, 33 consecutive patients treated with metoprolol (target 50mg 3 times daily) for a mean of 16 months (range 6 to 20 months). 16 of the patients were in New York Heart Association (NYHA) class IV CHF, and 15 were in class III. Dosages of metoprolol were slowly titrated to the target. Endomyocardial biopsies were performed at the start of the protocol and at completion, for measurement of myocardial β-adrenoceptor density. Myocardial β-adrenoceptor density increased significantly from pretreatment values with metoprolol (30.3 ± 2.9 to 49 ± 7.1 fmol/mg protein; $p < 0.0.05$).

Andersson et al.[32] investigated the acute and chronic effects of intravenous metoprolol in patients with heart failure on haemodynamics, plasma noradrenaline and myocardial noradrenaline extraction. Short term non-blind administration of intravenous metoprolol (2.5 to 15mg, mean 13mg) was associated with evidence of deterioration of resting haemodynamic function (decreased ejection fraction and cardiac index) and activation of the sympathetic nervous system (increased arterial noradrenaline level and increased myocardial release of noradrenaline). Long term administration of metoprolol (mean dosage 127 mg/day) for 6 to 12 months was assessed in 21 patients (15 non-ischaemic, 6 ischaemic) in a non-blind study.[45] Arterial and coronary sinus plasma noradrenaline and adrenaline levels were determined at rest and during supine bicycle ergometry. In contrast to the acute study, arterial noradrenaline levels were significantly reduced during long term metoprolol therapy when compared with pretreatment values (3.72 ± 2.4 to 2.19 ± 3.5 nmol/L; $p < 0.02$). Myocardial noradrenaline extraction (arterial – coronary sinus noradrenaline level) trended to reduction at rest when compared with pretreatment values (–0.28 ± 0.37 *vs* –0.13 ± 0.09 nmol/L; p =

0.14). This comparison was statistically significant during exercise (–1.13 ± 1.5 *vs* –0.27 ± 0.48; $p < 0.05$), suggesting that metoprolol therapy decreases stress-induced myocardial production of noradrenaline. Plasma adrenaline levels did not change from baseline during metoprolol therapy at rest or during exercise.

Heilbrunn and colleagues[46] studied 15 patients with idiopathic CHF, 3 in NYHA Class III, 7 in NYHA Class II, and 5 in NYHA Class I. Metoprolol was titrated over 8 weeks to a mean dose of 103mg (range 75 to 150mg total daily). Myocardial β-adrenoceptor density significantly increased after 6 months of metoprolol therapy when compared with pretreatment values (39 ± 7 to 80 ± 12 fmol/mg protein; $p < 0.005$) to levels comparable to previously reported normal values,[47] indicating that metoprolol treatment could normalise (i.e. upregulate) β-adrenoceptor number in CHF. The increase in β-receptor density was accompanied by a functional improvement in the positive inotropic response to administration of a synthetic β-agonist, dobutamine.

Maisel[33] reported the results from a non-blind trial of 6 to 12 months of metoprolol therapy (mean daily dose 76mg) in 15 patients with NYHA Class II-IV heart failure symptoms, due to IHD in 10 patients and IDC in 5. A nonrandomised, age- and symptom-matched control group of 15 patients with contraindications to metoprolol therapy was also studied. Plasma noradrenaline levels tended to decrease from baseline in patients treated with metoprolol but not in untreated patients (baseline 550 ± 90 *vs* 370 ± 70 ng/L metoprolol-treated and 585 ± 100 ng/L untreated patients, $p = 0.14$). Plasma adrenaline level did not change over the course of the study.

Santostasi and colleagues[34] reported the findings of a non-blind, prospective study of the effects of 6 months of metoprolol therapy (30 to 150 mg/day, mean 78 mg/day) in 15 patients with NYHA Class II-III heart failure symptoms due to IDC. Plasma noradrenaline levels decreased significantly from baseline by 28% after 1 month of metoprolol therapy (265±115 *vs* 183 ± 84 ng/L; $p < 0.05$) but not after 6 months of therapy (272 ng/L). Changes in plasma noradrenaline level after 1 month of therapy were inversely correlated to change in left ventricular ejection fraction after 1 month of therapy.

Ishida and colleagues[35] studied the effects of 6 months of metoprolol therapy (mean dosage 46 mg/day) in 9 patients with NYHA Class II-III heart failure symptoms due to IDC. When compared with pretreatment baseline values, non-blind metoprolol therapy was associated with a significant decrease in plasma noradrenaline level (0.381 ± 0.068 *vs* 0.243 ± 0.095 μg/L; $p < 0.05$) and significant increase in lymphocyte β_2-adrenoceptor density. Changes in β_2-adrenoceptor density correlated positively with left ventricular ejection fraction ($r = 0.81$, $p < 0.0001$) and inversely with plasma noradrenaline level ($r = –0.73$, $p < 0.001$). The increased β_2-adrenoceptor density is unlikely to be directly related to the pharmacological action of metoprolol, a β_1-selective agent, but may represent a secondary effect related to changes in plasma noradrenaline level or improved haemodynamic status.

Rahman et al.[36] studied the effects of metoprolol treatment on sympathetic activity in a prospective non-blind, noncontrolled trial of 6 patients with heart failure. Muscle sympathetic nerve activity in the peroneal nerve, plasma noradrenaline and atrial natriuretic factor levels were measured before and after an average of 20 months of metoprolol therapy (mean dosage of metoprolol of 45.8 mg/day). Plasma noradrenaline and atrial natriuretic peptide levels decreased during therapy when compared with pretreatment values (2.9 ± 1.1 to 1.7 ± 0.5 nmol/L; $p = 0.07$ and 59.7 ± 14.6 to 31.6 ± 10.7 pmol/L; $p < 0.05$; respectively). Sympathetic nerve activity decreased by 50% when compared with pretreatment values, even after adjustment for lower heart rate on metoprolol ($p < 0.005$). In addition, a 62% reduction in resistance to blood flow in the calf circulation was reported, consistent with vasodilation in the skeletal muscle bed served by the peroneal nerve. These data provide direct evidence that decreased plasma noradrenaline levels in response to metoprolol are associated with decreased sympa-

thetic activity, but unfortunately lack a suitable control group.

Kukin and co-workers[37] studied the effect of combined α_1- and β_1-blockade with doxazosin (4 mg/day) and metoprolol (100 mg/day) versus metoprolol (100 mg/day) alone in 30 patients with CHF NYHA Class II-IV symptoms, due to IHD in 10 patients and IDC in 20. After 3 months of therapy, plasma noradrenaline levels decreased significantly from baseline in patients treated with metoprolol alone (567 ± 108 to 302 ± 41 ng/L; $p < 0.02$) and patients treated with metoprolol plus doxazosin (786 ± 91 to 434 ± 42 ng/L; $p < 0.01$), with no significant difference between the 2 treatment groups.

Intermediate and Long Term Placebo-Controlled Studies

The Metoprolol in Dilated Cardiomyopathy (MDC) trial randomised 383 patients with IDC to treatment with metoprolol or placebo in a double-blind fashion for 1 year.[48] The maximum dose was metoprolol 50mg 3 times a day, in a forced titration pattern. In a neurohormonal substudy of MDC, arterial and coronary sinus noradrenaline and adrenaline levels and coronary sinus blood flow were measured at study entry and at 6 and 12 months in 41 patients.[38] Of these 41 patients, 14 completed a 12-month submaximal exercise test. After 6 months, arterial plasma noradrenaline levels significantly decreased from baseline in patients treated with metoprolol when compared with the placebo group (2.94 ± 1.7 to 1.72 ± 2.3 nmol/L *vs* 2.76 ± 3.3 to 3.2 ± 2.3 nmol/L; $p < 0.03$). After 12 months, arterial plasma noradrenaline levels in the 2 treatment group were no longer different ($p = 0.16$). No significant difference between metoprolol and placebo in arterial plasma adrenaline levels was noted at either 6 or 12 months. All groups demonstrated net release of noradrenaline across the coronary circulation at rest, with no significant differences between patients treated with metoprolol and placebo. Both groups demonstrated modest extraction of adrenaline across the coronary circulation at rest which tended to decrease nonsignificantly over time.

During submaximal supine exercise, arterial plasma noradrenaline levels were significantly decreased in patients treated with metoprolol when compared with placebo at 12 months (9.16 ± 5.8 *vs* 11.8 ± 6.9 nmol/L; $p < 0.04$). Exercise arterial plasma adrenaline level was significantly lower in the metoprolol group when compared with placebo at 6 months (0.99 ± 0.84 *vs* 1.48 ± 1.3 nmol/L; $p = 0.02$), but this difference was no longer significant at 1 year. There were no significant differences in myocardial noradrenaline or adrenaline extraction during exercise at either 6 months or 1 year. Interpretation of these findings is limited, since the numbers of patients were small, and for various reasons, only limited numbers of patients completed the exercise portion of the study.

Eichhorn and colleagues[39] studied 24 men with dilated cardiomyopathy, treated for 3 months, in a double-blind placebo-controlled trial (3 : 2 metoprolol 100 mg/day to placebo randomisation ratio). Arterial and coronary sinus catecholamine levels were determined before treatment and after 3 months of blinded therapy. Coronary sinus noradrenaline levels were significantly lower in patients treated with metoprolol than in those receiving placebo (569 ± 426 *vs* 422 ± 357 ng/L pretreatment and 730 ± 445 *vs* 1114 ± 72 ng/L post-treatment, respectively; $p < 0.03$). Coronary sinus adrenaline showed a nonsignificant trend to reduction during metoprolol therapy ($p = 0.09$). After completion of the blinded study, all the patients were switched to open-label metoprolol and followed for an additional 3 months.[49] Coronary sinus noradrenaline level did not correlate with the magnitude of change in left ventricular ejection fraction.

Paolisso and colleagues[40] studied 10 patients with CHF due to either valvular or nonischaemic causes in a double-blind, crossover, randomised trial, with a target dose of metoprolol of 25mg twice daily for 3 months. Patients treated with metoprolol and placebo demonstrated no significant difference in plasma noradrenaline levels (5.11 ± 0.38 *vs* 5.38 ± 0.16 nmol/L) or plasma adrenaline level (388.9 ± 54.9 *vs* 358.4 ± 58.7 nmol/L). The results of this trial are difficult to interpret because the

cause of heart failure was related to valvular heart disease in 50% of the patients with no reported information on left ventricular ejection fraction.

2.1.2 Bisoprolol

Bisoprolol is a second generation, highly β_1-selective receptor antagonist which has been recently reported to reduce long term mortality in patients with CHF.[50] There are few published data on the effects of bisoprolol on indices of neurohormonal activation.

Suwa and colleagues[41] compared the effects of therapy with bisoprolol (5 mg/day for 10 weeks) and diltiazem (60 to 120 mg/day) in a randomised study of 18 patients with NYHA Class III and IV heart failure due to IDC. Five patients dropped out of the study because of worsening heart failure symptoms. In the remaining patients, plasma noradrenaline level decreased significantly from pretreatment values in 8 patients treated with bisoprolol (487 ± 317 to 296 ± 177 ng/L; $p < 0.05$) and also tended to decrease in 5 patients treated with diltiazem.

Additional studies reported the effects of bisoprolol on heart rate variability, an index which provides information on relative activation of the sympathetic and parasympathetic nervous systems.

The effects of bisoprolol therapy on heart rate variability were recorded in 2 reports from a substudy of 63 patients from the Cardiac Insufficiency Bisoprolol Study (CIBIS).[51,52] The CIBIS study was a double-blind, placebo-controlled study of patients with NYHA Class III and IV heart failure, with a mean follow-up of 1.9 ± 0.8 years.[53] All patients in the Holter substudy had a 24-hour recording before randomisation, and a repeat after 2 months of blinded treatment. Nine patients were not included in the analyses because of inadequate Holter recordings. All were in sinus rhythm. With bisoprolol, the average R-R interval significantly increased (representing slower heart rates). While the scatterplot length did not change, the scatterplot width increased at the 50th, 75th and 90th percentiles of R-R length. This was confirmed by Fast Fourier analysis. The interpretation of this finding is that higher heart rates (associated with higher degrees of sympathetic activation) are most affected by bisoprolol use. In addition, the Fourier analysis was able to document an increase in the high frequency heart rate variability band with bisoprolol treatment, which is thought to be an index of increased parasympathetic tone.

In summary, clinical studies of first and second generation β_1-selective blockers have yielded conflicting findings. The dosage and duration of treatment and differences in patient populations may account for some of the discordant findings. Most studies reported decreased plasma levels of noradrenaline and increases in β-adrenoceptor density.

2.2 Third Generation β-Blockers

The effects of third generation β-blockers on plasma norepinephrine levels are presented in table II.

2.2.1 Bucindolol

Bucindolol is a third generation, nonselective β-blocker with weak vasodilating effects related to an undetermined mechanism. The effects of long term bucindolol therapy were evaluated in the Beta-Blocker Evaluation Survival Trial (BEST). Preliminary reports of the results of this trial were presented at the 1999 American Heart Association Scientific Sessions.[65] 2798 patients with ischaemic and nonischaemic chronic heart failure were treated with bucindolol or matching placebo for an average of 2 years. Although plasma noradrenaline level decreased during bucindolol therapy (by 20%), bucindolol therapy was associated with a modest, nonsignificant ($p = 0.109$) 10% reduction in all-cause mortality when compared with placebo, a nonsignificant increase in left ventricular ejection fraction, and statistically significant 16% reduction in risk for hospitalisation for worsening of heart failure ($p < 0.001$).

Noncontrolled Studies

Eichhorn and co-workers[54] examined the effects of 3 months of bucindolol therapy in 15 patients with CHF (12 idiopathic and 3 ischaemic). Bucindolol was titrated in open-label fashion from 12.5mg twice daily to 100mg twice daily. Plasma

Table II. Effects of third generation β-blockers on plasma noradrenaline (norepinephrine) levels in patients with heart failure

Reference	Agent	No. of patients	Duration	Plasma noradrenaline	Comments
Eichhorn et al.[54]	Bucindolol	15	3mo	↔	PRA ↓
Gilbert et al.[55]a	Bucindolol	24	3mo	↓	
Woodley et al.[56]a	Bucindolol	51	3mo	↓	Significant only in idiopathic group
Olsen et al.[57]a	Carvedilol	60	3mo	Arterial ↔ CS ↓	
Krum et al.[58]a	Carvedilol	56	14wk	Trend ↓	Not significant *vs* placebo
Krum et al.[59]	Carvedilol	15	14wk	Trend ↓	Endothelin-1 ↓
Yoshikawa et al.[60]	Nipradolol	18	6mo	↓	↑ Lymphocyte β_2-adrenoceptor density
Virk & Davies[61]	Xamoterol	30	Acute	↔	
Sato et al.[62]	Xamoterol	10	Acute	↔	
McMurray et al.[63]a	Xamoterol	51	10 days	↔	Postmyocardial infarction
Erlemeier et al.[64]	Xamoterol	30	3mo	↔	

a Placebo-controlled study design.

CS = coronary sinus; **NS** = not significant; **PRA** = plasma renin activity; ↔ indicates no change;↑ indicates increase; ↓ indicates decrease.

noradrenaline and renin levels were measured before and after 3 months of long term therapy. In addition ^{123}I metaiodobenzylguanidine (MIBG) scanning was performed at baseline and study end. This isotope shares pharmacokinetic properties with noradrenaline, and thus its uptake reflects regional variations in noradrenaline uptake. Some patients demonstrated a decrease in plasma noradrenaline levels from baseline, but this was not a consistent finding, and no significant difference was detected in the group (403 ± 231 to 408 ± 218 ng/L). In addition, quantitative analysis of the MIBG scans showed no differences from baseline, consistent with the lack of change in plasma noradrenaline level. Plasma renin levels declined with bucindolol therapy (11.6 ± 13.4 to 4.3 ± 4.1 μg/L/h; $p < 0.05$), although the significance of this finding in patients treated with ACE inhibitors is uncertain.

Controlled Studies

Gilbert and colleagues[55] assessed the effects of bucindolol therapy in a randomised, double-blind, placebo-controlled study of 24 patients with IDC. 23 patients who tolerated an initial challenge dose of bucindolol 3.125mg were randomised to bucindolol versus placebo in a 3 : 2 ratio with weekly up-titration to a target dosage of 100mg twice daily. The total duration of therapy was 3 months, including 1 month of up-titration. Plasma noradrenaline level significantly decreased in patients receiving bucindolol when compared with patients receiving placebo (423 ± 79 to 212 ± 101 ng/L *vs* 362 ± 71 to 456 ± 272 ng/L; $p = 0.01$).

Woodley and colleagues[56] studied 51 patients stratified for ischaemic versus idiopathic cardiomyopathy, in a double-blind, placebo-controlled trial with bucindolol. This paper extended the work by the same group of investigators, discussed above,[55] with an identical study protocol for administration of bucindolol. The data from some patients are included in both reports. 50 of the 51 patients tolerated the initial bucindolol challenge dosages and 49 patients completed the 12-week protocol (22 nonischaemic and 27 ischaemic). Plasma noradrenaline levels were similar at baseline in patients with idiopathic cardiomyopathy and those with ischaemic cardiomyopathy. When the patients were grouped together without regard to the cause of cardiomyopathy, plasma noradrenaline levels tended to decrease in those treated with bucindolol when compared with placebo (427 ± 55 to 297 ± 32 ng/L *vs* 409 ± 52 to 415 ± 73 ng/L; $p = 0.09$). When groups were analysed on the basis of the cause of cardiomyopathy, plasma noradrenaline levels decreased significantly only in the group with idiopathic cardiomyopathy (idiopathic 461 ± 82 to 211 ± 39 ng/L

vs ischaemic 397 ± 76 to 374 ± 34 ng/L; $p < 0.05$). There were no significant changes in plasma noradrenaline level in the placebo group, regardless of the cause of cardiomyopathy.

2.2.2 Carvedilol

Carvedilol has a $\beta_1 : \beta_2$ selectivity profile that is slightly β_1-selective, but for clinical purposes it is considered a third generation, nonselective β-blocker. Carvedilol is also an α-blocker with vasodilating properties and may also mediate some of its antiadrenergic effects through interactions with G-proteins.[66] A meta-analysis of published clinical trials of carvedilol therapy of 6 to 12 months' duration demonstrated reductions in morbidity and mortality.[67-70] However, mortality was not the primary end-point of any of these clinical trials.

Olsen et al.[57] reported the findings of a prospective, randomised study of carvedilol in 60 patients with NYHA Class II and III CHF (43 idiopathic and 17 ischaemic in origin). Patients who tolerated a dosage of carvedilol 3.125mg twice daily for 1 week were randomised to either carvedilol or placebo in a 3 : 2 allocation, with up-titration to 25 to 50mg twice a day over 3 months. 36 patients received carvedilol and 24 were assigned to placebo. Right heart catheterisation, arterial and coronary sinus plasma noradrenaline and adrenaline levels and right ventricular endomyocardial biopsy were obtained before and after carvedilol therapy. Arterial noradrenaline level did not change, but coronary sinus plasma noradrenaline level significantly decreased during carvedilol therapy when compared with placebo (665 ± 351 to 510 ± 343 ng/L *vs* 524 ± 295 to 748 ± 756 ng/L; $p < 0.05$). There were no differences among treatment groups in adrenaline levels in arterial and coronary sinus blood. There were no differences in β-adrenoceptor density or changes in β-receptor subtype ratios from endomyocardial right ventricular biopsy tissue.

Krum et al.[58] described the results of a double-blind placebo-controlled study of carvedilol in a group of 56 patients with CHF (38 described as nonischaemic and 17 ischaemic) mostly in NYHA Class III (35 patients) or IV (6 patients). A non-blind 3-week run-in period was used to assess tolerability of the medication. 49 of the 56 patients who completed a 3-week tolerability phase of low dose carvedilol were randomised to either placebo or continued up-titration of carvedilol to 25mg twice daily in a blinded fashion. Plasma noradrenaline levels tended to decrease with carvedilol but were not statistically different from that with placebo (715 ± 135 to 588 ± 39 ng/L *vs* 580 ± 61 to 727 ± 133 ng/L; NS). Plasma adrenaline level significantly decreased with carvedilol therapy versus placebo (80 ± 28 to 49 ± 8 ng/L *vs* 56 ± 10 to 109 ± 28 ng/L; $p < 0.02$). Serum aldosterone level tended to decrease with carvedilol compared with placebo (31 ± 5 to 23 ± 4 ng/dl *vs* 25 ± 5 to 44 ± 12 ng/dl; $p = 0.065$).

In another report by Krum and colleagues,[59] plasma endothelin-1 and plasma noradrenaline and aldosterone levels were measured before and after carvedilol therapy in 15 patients (10 nonischaemic, 5 ischaemic). Plasma endothelin-1 levels decreased significantly with carvedilol therapy compared with the increases seen in the placebo group (7.6 ± 1.9 to 5.5 ± 1.4 ng/L *vs* 4.2 ± 1.8 to 6.4 ± 1.6 ng/L; $p < 0.05$). Plasma noradrenaline levels also demonstrated a substantial decrease with carvedilol (1078 ± 364 to 639 ± 176 ng/L *vs* 547 ± 80 to 923 ± 153 ng/L) but without statistical significance, possibly because of a β-error in a small patient population. Serum aldosterone levels significantly decreased in patients treated with carvedilol when compared with placebo (37 ± 11 to 18 ± 8 μg/L *vs* 19 ± 5 to 57 ± 14 μg/L; $p < 0.05$). Plasma endothelin-1 levels correlated significantly with the plasma levels of noradrenaline and aldosterone. In addition, an inverse relation between endothelin-1 level and symptomatic improvement (reduction in NYHA functional class) as well as submaximal exercise capacity was noted.

Goldsmith and colleagues[71] studied the effects of carvedilol on parasympathetic function, as assessed by heart rate variability analysis in 10 patients with CHF. When compared with pretreatment values, carvedilol therapy was associated with a significant increase in high frequency power, a correlate

of parasympathetic activity (geometric means 26 *vs* 64 ms^2; $p < 0.01$).

2.2.3 Nipradilol

Nipradilol is a nonselective β-blocker with vasodilating activity which may be related to an endothelium-dependent mechanism. Yoshikawa and co-workers[60] studied the effects of nipradilol on neurohormonal activation in 18 patients with IDC, in a nonrandomised, controlled cohort study. When compared with pretreatment values, 6 months of nipradilol therapy (mean daily dosage 5.8 mg/day) tended to decrease plasma noradrenaline level (0.53 ± 0.44 to 0.36 ± 0.22 μg/L; NS) and plasma atrial natriuretic factor level (152 ± 99 to 45 ± 42 ng/L; NS) and significantly increased lymphocyte β-adrenoceptor density (6.7 ± 1.8 to 9.8 ± 1.4 fmol/ mg protein; $p < 0.05$). No significant changes in neurohormonal levels or β_2-adrenoceptor density occurred in the control group. There were no significant differences reported in plasma levels of adrenaline, renin, aldosterone or arginine-vasopressin during the study period in either treated or control patients.

The findings from this group of investigators were extended by an additional study in 6 patients (5 idiopathic and 1 ischaemic cardiomyopathy) treated with carteolol (mean dosage 7.3 mg/day), a nonselective β-blocker with partial agonist activity.[72] Neurohumoral levels before and after 2 weeks and 6 months of therapy, in response to nipradilol or carteolol, are reported as pooled data. When compared with pretreatment values, plasma noradrenaline level significantly decreased after 2 weeks (769 ± 509 to 409 ± 315 ng/L; $p = 0.01$) and 6 months (400 ± 368 ng/L; $p = 0.0066$). Plasma atrial natriuretic factor level significantly decreased from pretreatment values after 2 weeks (156 ± 85 to 86 ± 67 ng/L; $p < 0.01$), but not after 6 months (106 ± 135 ng/L). Lymphocyte β_2-adrenoceptor density increased significantly from pretreatment values after 2 weeks of therapy (7.6 ± 3.3 to 10.2 ± 4.4 fmol/mg protein; p= 0 .05), but not after 6 months (7.8 ± 3.0 fmol/mg protein). There were no significant changes in the adrenaline, renin, aldosterone or arginine-vasopressin levels during the study. Interpretation of these data is confounded by the inclusion of data from patients treated with carteolol, an agent with partial agonist activity. As described in the following sections, agents with partial agonist activity may have effects on plasma noradrenaline level which differ from pure antagonists.

2.2.4 Pindolol

Pindolol, a nonselective β-blocker with partial agonist activity, was administered to 10 patients with IDC in an acute haemodynamic study.[73] Resting haemodynamics and catecholamine and aldosterone levels were determined before and 2 hours after administration of a single oral dose of pindolol 5mg on one day and a single oral dose of pindolol 10mg 24 hours later. There was no significant change from pretreatment values in plasma noradrenaline level after the 5mg dose, but there was a trend towards increasing noradrenaline after the single 10mg dose (455 ± 474 *vs* 572 ± 450 ng/L; $p < 0.10$). Plasma adrenaline was significantly increased from baseline with the 5mg dose (83 ± 60 *vs* 254 ± 342 ng/L; $p < 0.05$), but not with the 10mg dose (133 ± 16 *vs* 100 ± 78 ng/L; $p < 0.10$). There were no significant changes in serum aldosterone with either dose of pindolol.

2.2.5 Xamoterol

Xamoterol is a mixed β-agonist/antagonist, with approximately 43% of the agonist activity of the full agonist isoprenaline. The ratio of β-adrenoceptor antagonism to β-adrenoceptor agonism depends on sympathetic tone.[74] Xamoterol provides mild stimulation when sympathetic tone is low, and protects from overstimulation when it is high. While xamoterol binds both β_1- and β_2-adrenoceptors in animals, with β_1 affinity 10 to 100 times greater than β_2 affinity, no evidence of β_2 stimulation or appreciable antagonism has been identified in humans. However, the effects of xamoterol on β_2-adrenoceptors in human heart failure, which is characterised in part by a relative increase in myocardial β_2-adrenoceptor density, have not been determined. Clinical trials in heart failure have demonstrated improved haemodynamics and exercise

capacity in short term trials, but increased mortality during long term therapy.[75]

The acute effects of xamoterol on neurohormonal activation have been reported in 2 studies. Virk and Davies[61] investigated the acute effects of intravenous xamoterol (0.2 mg/kg) in 30 patients with NYHA Class II-III heart failure of mixed causes. Administration of xamoterol did not change plasma noradrenaline level from baseline values at rest (450 ± 46 *vs* 499 ± 54 ng/L) or during maximal exercise (1671 ± 198 *vs* 1727 ± 201 ng/L). Sato and colleagues[62] administered xamoterol 0.15 mg/kg to 10 patients with mild to moderate left ventricular dysfunction (mean left ventricular ejection fraction 0.52) secondary to mixed valvular, ischaemic hypertrophic and idiopathic causes. Six matched patients received saline control injection. Plasma noradrenaline level did not change from pretreatment values in patients receiving xamoterol (234 ± 87 *vs* 210 ± 109 ng/L) or saline. Plasma noradrenaline level significantly increased from pretreatment values at peak exercise in patients treated with xamoterol (754 ± 279 *vs* 1068 ± 551 ng/L; $p < 0.05$) but not in patients treated with saline.

The effects of short term therapy with xamoterol have been reported by 2 groups of investigators. McMurray and colleagues[63] investigated the effects of xamoterol (400 mg/day for 10 days) on neurohormonal activation after myocardial infarction in a randomised, double-blind study. Of the 51 patients in the study, 16 required diuretics for the treatment of heart failure. Plasma levels of noradrenaline and atrial natriuretic factor and plasma renin activity did not differ in patients treated with xamoterol or placebo. Erlemeier and colleagues[64] investigated the effects of xamoterol (400 mg/day for 3 months) on plasma noradrenaline level at rest and during submaximal bicycle exercise in a randomised, placebo-controlled trial of 30 patients with NYHA Class II-III heart failure secondary to IHD. When compared with pretreatment values, xamoterol therapy did not change plasma noradrenaline levels at rest (491 ± 318 *vs* 488 ± 226 ng/L) or during exercise (758 ± 336 *vs* 675 ± 325 ng/L).

In summary, the majority of clinical trials with third generation nonselective β-blockers demonstrate a decrease in plasma levels of noradrenaline. In contrast to β_1-selective agents, no increase in myocardial β-adrenoceptor density was observed, although lymphocyte β-adrenoceptor (β_2-adrenoceptor) density increased. It is important to note that many of these trials included a tolerability phase, in which individuals unable to tolerate initiation of low dose β-blockers were excluded from randomisation. The exclusion of these patients confounds comparison of the findings with those from earlier trials of first and second generation agents. The neurohormonal response to agents with partial agonist activity is distinct from that of pure receptor antagonists. Failure to suppress neurohormonal activation during long term therapy may have contributed to the adverse effects on mortality reported with xamoterol.[75]

3. Comparative Studies

Few direct comparisons of β-blockers are available. A small intermediate term clinical trial suggested that the clinical effects of metoprolol and carvedilol are distinct in patients with heart failure.[76] A long term mortality trial comparing metoprolol and carvedilol is currently in progress (COMET).[20]

Newton and Parker[77] compared the acute effects of intravenous metoprolol and propranolol on cardiac sympathetic activity in 18 patients with NYHA Class III-IV symptoms, secondary to IHD in 12 patients and IDC in 6. Systemic and coronary circulation steady-state noradrenaline kinetics were assessed with tritium-labelled noradrenaline before and after a short term intravenous infusion of either propranolol (n = 9) or metoprolol (n = 9) titrated to produce a 15% decline in heart rate, rate of change of left ventricular pressure (dP/dT) or mean arterial blood pressure, or a 5mm Hg increase in left ventricular end-diastolic pressure. A mean dose of propranolol 2mg (range 1 to 3.5mg) or metoprolol 3.6mg (range 2 to 6mg) was administered. Total body noradrenaline spillover was not affected by acute β-adrenoceptor blockade with either agent. Cardiac noradrenaline spillover was

significantly reduced after propranolol treatment (277± 55 to 262 ± 53 pmol/min; p< 0 .05) and significantly increased after metoprolol treatment (233 ± 57 to 296 ± 82 pmol/min; p < 0.05). Plasma noradrenaline levels tended to increase in response to both propranolol and metoprolol (2.5 ± 0.7 to 2.9 ± 0.8 and 2.3 ± 0.6 to 3.5 ± 0.8 nmol/L, respectively). Propranolol treatment did not induce changes in adrenaline level, whereas metoprolol was associated with a significant increase in coronary sinus adrenaline level (0.4 ± 0.3 to 0.7 ± 0.4 nmol/L; p < 0.05) and a borderline significant increase in arterial plasma adrenaline levels (0.6 ± 0.2 to 0.9 ± 0.4 nmol/L; p = 0.06).

Yamada and colleagues[78] investigated the effects of β-adrenoceptor blockade with metoprolol (mean dosage 31 mg/day) and bisoprolol (mean dosage 2.4 mg/day) on serial lymphocyte β_2-adrenoceptor density measurements in 12 patients with IDC. Pretreatment lymphocyte β_2-adrenoceptor density was decreased in patients with heart failure when compared with normal volunteers (886 ± 84 *vs* 1657 ± 108 binding sites/cell; p < 0.001). Therapy with both agents was associated with significant increases in lymphocyte β-adrenoceptor density. In the 6 patients treated with metoprolol, β_2-adrenoceptor density increased from 27% over pretreatment values after 1 week of therapy to 158% over pretreatment values after 2 years of therapy (both p < 0.01 *vs* pretreatment values). In the 6 patients treated with bisoprolol, β_2-adrenoceptor density increased from 31% over pretreatment values after 1 week of therapy to 72% over pretreatment values after 2 years of therapy (both p < 0.01 *vs* pretreatment values). A statistical comparison of the effects of the 2 treatments was not reported. In both treatment groups serial measurements revealed significant increases in β_2-adrenoceptor density after 3 months of therapy and a slow continuous increase in β_2-adrenoceptor density over the 2-year course of the study. The mechanism of change in β_2-adrenoceptor density in response to these agents is uncertain, as both metoprolol and bisoprolol are β_1-selective blockers.

Gilbert and colleagues[76] published an analysis of the findings from 2 separate prospective, placebo-controlled studies of metoprolol and carvedilol limited to the subgroup of patients with IDC. Some of the findings were previously published, as summarised above.[76] The dosage used in the studies of each of these agents (metoprolol 125 to 150 mg/day, carvedilol 50 to 100 mg/day) produced similar decreases in resting heart rate, suggesting an equivalent degree of β-adrenoceptor blockade. Plasma noradrenaline levels from coronary sinus blood decreased during therapy with carvedilol when compared with placebo (655 ± 351 to 510 ± 343 ng/L *vs* 524 ± 295 to 748 ± 756 ng/L; p < 0.05) but tended to increase from baseline during therapy with metoprolol (533 ± 327 to 610 ± 490 ng/L). A comparison of the change from baseline in coronary sinus plasma noradrenaline levels for the 2 agents showed borderline statistical significance (–155 ± 219 ng/L for carvedilol *vs* 77 ± 488 ng/L for metoprolol; p = 0.07). The transmyocardial gradient for noradrenaline decreased during therapy with carvedilol when compared with placebo (262 ± 358 to 110 ± 346 ng/L *vs* 135 ± 162 to 320 ± 400 ng/L; p < 0.05) but did not change during therapy with metoprolol. Right ventricular endomyocardial β-adrenoceptor density increased during therapy with metoprolol compared with placebo (47.8 ± 21.4 to 75.0 ± 40.5 fmol/mg *vs* 41.9 ± 23.3 to 40.0 ± 16.3 fmol/mg; p < 0.05) but did not change during therapy with carvedilol. Post-treatment β-adrenoceptor density was significantly greater in patients treated with metoprolol than in those treated with carvedilol (75.0 ± 40.5 *vs* 28.7 ± 21.5 fmol/mg; p < 0.05). Although the study design is not a true randomised comparison of metoprolol and carvedilol, these findings demonstrate different effects of these 2 agents on the β-adrenoceptor system, particularly in regard to the effect on β-adrenoceptor density. Differences in the pharmacological properties of these 2 agents (β_1-selectivity and G-protein binding) or differences in the placebo groups for the 2 studies may account for these findings.

4. Possible Mechanisms of Action

The primary mechanism by which β-blockers alter neurohormonal activation cannot be determined from available experimental and clinical studies. It has been proposed that the effect of these agents on neurohormonal activation is entirely due to reflex mechanisms secondary to drug-induced changes in cardiovascular function. Thus, early increases in neurohormonal activation are attributable to acute haemodynamic deterioration, and late decreases in neurohormonal activation are attributable to chronic improvements in haemodynamic function. However, several studies demonstrated acute decreases in neurohormonal activation which occurred before any haemodynamic improvement would be expected. In these studies, a specific pharmacological action has been postulated. In addition to reflex haemodynamic mechanisms, β-blockers could decrease neurohormonal activation by altering neuronal uptake of noradrenaline or by central inhibition of sympathetic output. Experimental studies demonstrating increased myocardial noradrenaline content in response to β-adrenergic receptor blockade suggest that increased neuronal uptake may play a role.

In addition to direct and/or indirect effects of plasma neurohormonal levels, β-blockers alter the β-adrenergic effector mechanism by increasing β-adrenoceptor density (first and second generation agents) and partially restoring functional coupling of the β-adrenoceptor with its intracellular signal transduction pathways (third generation agents). Whether changes in expression of components of the β-adrenoceptor complex are merely part of the restoration of normal myocardial phenotype or account for efficacy of β-blockers has not been established.

Although β-blockers probably mediate their effects primarily by inhibition of sympathetic adrenergic stimulation, other unidentified factors may be important. Interestingly, a placebo-controlled clinical trial of moxonidine, a centrally acting α-agonist which inhibits sympathetic outflow, lowers plasma noradrenaline levels and causes peripheral vasodilation, was prematurely terminated because of a trend towards increased mortality in patients treated with moxonidine when compared with placebo ($p = 0.20$; MOXCON trial, presented at the Heart Failure Society of America Scientific Sessions, September 1999.

5. Clinical Implications

The clinical implications of decreased activity of the sympathetic nervous system in patients receiving β-blockers, in whom the primary effector mechanism of the sympathetic neurotransmission system is blocked, is uncertain. Clinical studies have not fully assessed the effects of β-blocker therapy on the β-adrenoceptor complex inclusive of G-proteins, adenylate cyclase activity and β-adrenoceptor kinase activity. Differences among agents in their acute and chronic effects on indices of neurohormonal activation may be related to basic differences in pharmacological properties. β_1-Selectivity, lipophilicity, inverse agonist activity, partial agonist activity, G-protein binding properties, and vasodilator effects may all directly or indirectly modulate the effects on neurohormonal activation. In addition, ancillary pharmacological properties such as membrane stabilisation effects and antioxidant effects may contribute to the long term clinical effects of these agents.[79] The efficacy of a newer, third generation agent, carvedilol, may be further enhanced by down-regulation of β-adrenoceptors, and more comprehensive antiadrenergic effects by virtue of multiple receptor blockade and G-protein interactions. Cardiac noradrenaline levels are lower with bucindolol and carvedilol than with metoprolol for these reasons. However, bucindolol therapy was associated with less favourable effect on mortality (BEST trial) than therapy with metoprolol, bisoprolol or carvedilol in placebo-controlled trials.

Differences in pharmacology and haemodynamic and neurohormonal effects may not be critical to the long term clinical benefits of β-blocker therapy, as clinical trials with carvedilol, metoprolol and bisoprolol, agents with distinct pharmacology, are associated with substantial reductions in long term morbidity and mortality during long term therapy.[50,70] The ongoing COMET trial, which is

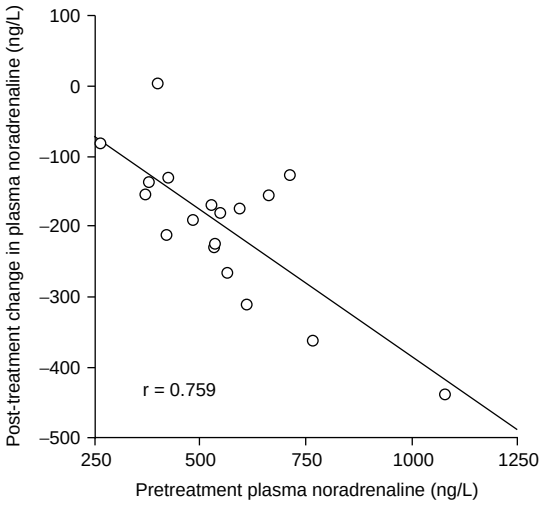


Fig. 3. Change in plasma noradrenaline (norepinephrine) level during long term β-blocker therapy is closely correlated with pretreatment plasma noradrenaline levels. Data for this figure were derived from reviewed studies that provided plasma noradrenaline levels before and after therapy with β-blockers (tables I and II). Data from the study by Paolisso et al.[34] are excluded, as this small study included many patients with valvular heart disease as the cause of heart failure and did not report ejection fraction.

a prospective, randomised comparison between carvedilol and metoprolol, may provide important data to determine whether differences in basic pharmacology are associated with differences in patient outcomes; however, the dosage of metoprolol used in this trial is only half that used in MERIT-HF.

6. Summary and Conclusions

In summary, current knowledge of the effects of β-blockers on neurohormonal activation in patients with CHF is largely derived from studies of small patient populations. Short term therapy with β-blockers is associated with a variable response which may be determined by the pharmacology of the agent under study and the baseline characteristics of the patient population. Long term therapy with β-blockers (devoid of partial agonist activity) is associated with evidence of decreased plasma markers of activation of the sympathetic nervous system, the renin-angiotensin system, and endothelin-1. First and second generation and third generation β-blockers appear to be associated with evidence of decreased neurohormonal activation, with differential effects on β-adrenoceptor density. Agents with partial agonist activity appear to differ from pure antagonists, with some studies reporting evidence of increased neurohormonal activation. The decrease in plasma noradrenaline level during intermediate and long term therapy correlates closely with the pretreatment plasma noradrenaline level (fig. 3). Whether decreased plasma noradrenaline level during long term therapy is attributable to decreased noradrenaline release (as opposed to increased neuronal uptake) is uncertain, as only one small study has directly demonstrated decreased sympathetic nervous system activity during long term therapy. Additional studies are needed to determine the underlying mechanisms of changes in neurohormonal activation during β-blocker therapy.

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