Reductions in muscle sympathetic nerve activity after long term metoprolol for dilated cardiomyopathy: preliminary observations

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Abstract

Objective—To determine whether efferent muscle sympathetic nerve activity diminishes in subjects with dilated cardiomyopathy who improve after long term treatment with metoprolol.

Methods—Microneurographic, echocardiographic, plethysmographic, and neurohumoral data were obtained immediately before and 20 months after the addition of β blockade in seven subjects with idiopathic dilated cardiomyopathy with clinical deterioration despite conventional treatment.

Results—Six subjects (three men, three women, aged 24–62 years) were restudied after a mean (SEM) of 20 (2.4) months treatment with metoprolol (45.8 (2.6) mg/d). Long term treatment was associated with decreases in left ventricular end diastolic and end systolic diameter ($P < 0.005$), left ventricular mass index ($P < 0.05$), and atrial natriuretic factor ($P < 0.05$), and increases in fractional shortening ($P < 0.05$) and mean blood pressure ($P < 0.05$). There was a 50% reduction in peroneal muscle sympathetic nerve activity (from 49.2 (10.1) to 24.5 (4.7) bursts/min; ($P < 0.005$) and a 62% decrease in calf vascular resistance (from 56.2 (4.4) to 21.2 (5.7) units; $P < 0.005$). This reduction in pulse synchronous nerve activity was not simply a function of bradycardia (heart rate fell from 94.2 (4.6) to 62.8 (5.7) beats/min; $P < 0.005$) since muscle sympathetic burst incidence also decreased (from 51 (8.7) to 37.5 (5.2) bursts/100 heart beats; $P < 0.05$). Similar haemodynamic improvement was observed in the seventh subject, who was switched to sotalol 200 mg/d and restudied after 20 months, but burst frequency was 50% higher and calf vascular resistance 93% higher.

Conclusions—Muscle sympathetic nerve activity and calf vascular resistance decrease in patients with dilated cardiomyopathy who improve after long term treatment with metoprolol. Inhibition of central sympathetic outflow may be one mechanism by which metoprolol benefits such subjects.

(Br Heart J 1995;74:431-436)

Keywords: metoprolol; dilated cardiomyopathy; sympathetic nerve activity

Sympathetic nervous system activation is an important marker for adverse outcome in congestive heart failure.¹ Although the mechanisms responsible for this disturbance have not been fully elucidated,²⁻⁴ its adverse consequences for the failing myocardium have been well documented.³⁻⁷

In 1975 Waagstein and coworkers reported symptomatic and haemodynamic improvement after short term β adrenoceptor blockade in seven patients with idiopathic dilated cardiomyopathy.⁸ These observations provided the impetus for subsequent studies of chronic β adrenoceptor blockade in selected patients. Recently, a placebo controlled multicentre trial reported a favourable impact of metoprolol on symptoms, cardiac function, and disease progression in this condition.⁹

Reversal of β adrenoceptor downregulation or uncoupling are two of the presumed benefits of chronic β adrenoceptor blockade in congestive heart failure.¹⁰ Its effects on central sympathetic outflow are not known. β Adrenoceptor antagonists might oppose the actions of catecholamines on postjunctional adrenoceptors in the heart and the peripheral circulation without attenuating sympathetic outflow to heart, kidney, and peripheral vasculature. Indeed, by reducing discharge from cardiac mechanoreceptors with inhibitory vagal afferents, the negative inotropic properties of β adrenoceptor blockers might cause a reflex increase in sympathetic nerve traffic.¹¹

Alternatively, β adrenergic antagonists might attenuate sympathetic drive to the heart and periphery through a central or reflex action. Wallin *et al*¹² observed reductions in both blood pressure and muscle sympathetic nerve burst frequency in hypertensive subjects restudied after four months of oral metoprolol. Noradrenaline release across the failing human heart may be attenuated by carvedilol.¹³ We undertook this study to test the hypothesis that efferent muscle sympathetic nerve activity diminishes in those subjects with dilated cardiomyopathy who improve after long term treatment with metoprolol.

Methods

SUBJECTS

Seven subjects with idiopathic dilated cardiomyopathy (four men, three women, mean (SEM) age 37 (5) years, range 24–62 years), were referred for this study by their attending cardiologists in anticipation of starting β adrenergic blockade treatment with metopro-

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Accepted for publication
22 May 1995

Table 1 Subject characteristics

Subject	Age (years)	Sex	Dose (mg)	Duration	Weight (kg)	BSA (m ²)	NYHA class	EF%	Treatment	SBP (mm Hg)	DBP (mm Hg)	HR (beats/min)	MSNA (bursts/min)
(A) First study: immediately before β blockade													
Subjects restudied on metoprolol													
1	29	F			48	1.454	II	15	ADFC	88	51	103	66
2	28	F			65	1.714	III	16	ADFH	89	53	81	48
3	62	F			62	1.702	III	14	ADFC	97	72	88	37
4	36	M			95	2.174	II	18	AC	95	49	84	20
5	34	M			82	2.023	II	10	ADFC	114	63	108	89
6	24	M			73	1.934	IV	10	DH	92	54	101	35
Mean	35.5				70.8			14		96	57	94	49
SD	13.7				16.5			3.3		9.5	8.8	11	25
Other subject													
7	46	M			79	1.928	III	23	ADC	101	63	85	22
(B) Second study													
Subjects restudied on metoprolol													
1			50	16	49.5	1.500	I		ADC	121	66	75	24
2			37.5	25	75	1.825	I		AF	124	67	72	30
3			50	13	62	1.702	I		ADFC	112	73	71	29
4			50	15	100	2.175	I		ADFCam	92	51	43	12
5			50	26	88	2.119	I		ADFC	118	66	69	41
6			37.5	24	73	1.934	I		ADC	103	55	47	11
Mean			45.8	20	74.6					112	63	63	25
SD			6.45	6	18					12	8.3	14	12
Other subject													
7			S	20	80	1.938	I		ADC	121	73	70	33

BSA, body surface area; NYHA, New York Heart Association functional class; EF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity; Dose, daily dose of metoprolol; Duration, months between first and second study; A, ACE inhibitors; D, digoxin; F, diuretics; C, coumarin; Am, amiodarone; H, heparin; S, sotalol (200 mg/d in this subject).

lol. All subjects had been admitted to hospital for the management of progressive congestive heart failure and met the following criteria: left ventricular ejection fraction $\leq 25\%$, marked global hypokinesia, and a short axis left ventricular end diastolic dimension (LVDD) of 60 mm or more. Coronary artery disease and active myocarditis were excluded by coronary angiography and endocardial biopsy. None had concomitant medical conditions that might otherwise alter sympathetic nerve activity. All subjects suffered progressive clinical deterioration despite sodium restriction, and several months (mean 7 (3), range 1–22 months) of chronic treatment with diuretics ($n = 4$), digitalis ($n = 6$), and angiotensin converting enzyme (ACE) inhibitors ($n = 6$). One subject (No 6) was unable to tolerate ACE inhibition because of hypotension. All were on anticoagulants (table 1). At entry, mean reported New York Heart Association functional class was 2.7 (0.3). Their ejection fractions, as assessed by radionuclide ventriculography, ranged from 10% to 23% (mean 15 (2)%). The decision to start metoprolol was made independently by the patients' own cardiologists.

PROCEDURES

Blood pressure was measured by an automatic cuff recorder (Physio Control Lifestat 200),

Figure 1 Electrocardiogram (ECG) and mean voltage neurograms of muscle sympathetic nerve activity (MSNA) of one dilated cardiomyopathy subject (No 5), studied immediately before (left panel) and after 26 months of treatment with metoprolol (right panel). Sympathetic nerve activity in this subject fell from 89 to 41 bursts/min.

and heart rate was derived from lead II of the electrocardiogram. Calf blood flow (ml/min/100 ml of calf volume) was estimated by venous occlusion plethysmography.¹⁴ Calf vascular resistance (expressed as resistance units) was calculated as the quotient of mean arterial pressure divided by the average of four to six measures of calf blood flow. Left ventricular dimensions were determined by M mode echocardiography (Ultramark 8; Advanced Technology Laboratories) with subjects in the left lateral position. Left ventricular mass and mass index were calculated using the formula of Devereux and Reichek.¹⁵ Multiunit recordings of post-ganglionic muscle sympathetic activity were obtained from the peroneal nerve.¹⁶ Sympathetic activity was expressed as bursts/min (burst frequency) and bursts/100 cardiac cycles (burst incidence). The mean interobserver variability arising from visual evaluation of the microneurographic record in our laboratory is 3.9%; the mean intra-observer variability is 4.5%.

PROTOCOL

After informed written consent, each subject underwent two identical studies, performed at the same time of the day: (1) baseline observations, immediately before starting β adrenoceptor blockade; and (2) a follow up study an average of 20 (2) months later (fig 1). Following instrumentation, subjects rested supine for 20 min before any measurements. Blood pressures were obtained every minute. Heart rate, the electrocardiogram, and the mean voltage neurogram of muscle sympathetic nerve activity were recorded continuously for 15–20 min (Gould 2800S ink recorder). Calf blood flow was measured every 15 s over the last 2 min of this period, after which venous blood was withdrawn for determination of plasma noradrenaline and atrial natriuretic factor concentrations. Echocardiographic measurements were then obtained. These investigations were approved

by our institutional human subjects review committee.

β ADRENOCEPTOR BLOCKADE

Metoprolol was started by the attending cardiologist at doses as low as 5 mg daily and gradually increased as tolerated. All subjects but one (subject No 3) were admitted to hospital for this purpose. Six subjects (Nos 1–6) were restudied after an average of 20 months on between 37.5 and 50 mg of metoprolol daily (final average dose, 45.8 (2.6) mg/d) (table 1). One subject (No 7 in table 1) was able to tolerate metoprolol 50 mg orally twice daily but because of non-sustained ventricular tachycardia was switched soon after to sotalol 200 mg/d and restudied while on that drug 20 months after his first study.

STATISTICAL PROCEDURES

Data were analysed with Systat 5.2 (Systat Intelligent Software) and are presented as mean (SEM), unless stated otherwise. Paired *t* tests were applied to compare pre-treatment and post-treatment values.

Table 2 Haemodynamic, echocardiographic, and neurohumoral variables before and after long term treatment with metoprolol. Values are mean (SEM) for 6 subjects

	Before β blocker	Follow up
Haemodynamic data		
Systolic blood pressure (mm Hg)	95.8 (3.9)	112.0 (5)*
Mean blood pressure (mm Hg)	69.8 (3.3)	79.2 (3.6)*
Diastolic blood pressure (mm Hg)	57.0 (3.6)	63.0 (3.4)
Heart rate (beats/min)	94.2 (4.6)	62.8 (5.7)†
Calf blood flow (ml/min/100 ml) ^a	1.2 (0.1)	4.9 (1)*
Calf vascular resistance (units) ^a	56.2 (4.4)	21.2 (5.7)†
Echocardiographic data		
Left ventricular end diastolic diameter (cm)	7.1 (0.3)	5.6 (0.2)†
Left ventricular end systolic diameter (cm)	6.3 (0.2)	4.5 (0.2)†
Fractional shortening (%)	10.7 (1.8)	19.8 (1.4)*
Left ventricular mass (g)	379 (49.5)	232 (34)*
Left ventricular mass index (g/m ²)	197 (20.7)	122 (13)*
Neurohormonal data		
Sympathetic nerve activity (bursts/min)	49.2 (10.1)	24.5 (4.7)†
Sympathetic nerve activity (bursts/100 heart beats)	51.0 (8.7)	37.5 (5.2)*
Plasma noradrenaline (nmol/l)	2.9 (1.1)	1.7 (0.5)
Plasma atrial natriuretic factor (pmol/l)	59.7 (14.6)	31.6 (10.7)*

^a5 subjects.
**P* < 0.05; †*P* < 0.005.

Figure 2 Plots of heart rate and mean arterial blood pressure immediately before addition of metoprolol (time 1) and after long term treatment (time 2). Average heart rate was significantly lower (*P* < 0.005), and average mean arterial pressure significantly higher (*P* < 0.05) after β blockade.

Results

Mean data from the six subjects restudied while on metoprolol (table 1), used to assess the effects of long term treatment, will be referred to as the group mean. Group means for haemodynamic, echocardiographic, and neurohumoral variables before metoprolol and on metoprolol are presented in table 2. Individual data points are presented in figs 2–4.

HAEMODYNAMIC CHANGES

Long term metoprolol treatment was associated with increases in systolic blood pressure (*P* < 0.05) and mean blood pressure (*P* < 0.05) and decreases in heart rate (*P* < 0.005) (table 2). In five subjects calf blood flow increased threefold (*P* < 0.05), and there was a corresponding decrease in calf vascular resistance (*P* < 0.005) (fig 4). In the sixth subject calf blood flow was undetectable at baseline by this technique and it was 1.5 ml/min/100 ml calf volume on restudy. There was a similar increase in blood pressure and decrease in heart rate in the one subject restudied on sotalol (table 1), but in contrast to metoprolol treated patients, calf vascular resistance rose, from 30.2 to 58.2 Units, on the β adrenoceptor blocker.

ECHOCARDIOGRAPHIC MEASUREMENTS

Left ventricular end diastolic and end systolic diameters decreased significantly in metoprolol treated subjects (table 2; fig 3). These changes were associated with significant increases in fractional shortening. Calculated left ventricular mass and mass index decreased in all six subjects. There were qualitatively similar changes in these echocardiographic variables in the sotalol treated subjects—for example, fractional shortening increased from 13% to 27%.

NEURAL AND HORMONAL CHANGES

Muscle sympathetic nerve burst frequency fell in all six metoprolol treated subjects (*P* < 0.005) (table 2, fig 4). These changes in pulse synchronous sympathetic outflow remained significant even when expressed as burst incidence, by adjusting for reductions in heart rate (*P* < 0.005). There were corresponding reductions in plasma noradrenaline concentrations (*P* ~ 0.07) and plasma atrial natriuretic factor (*P* < 0.05) (table 2; fig 4). There was no relation between the relative reduction in muscle sympathetic burst incidence and the initial heart rate of these subjects (*r* = 0.6, *P* ~ 0.18; *n* = 6).

By contrast, sympathetic nerve burst frequency increased 50% in the subject restudied on sotalol (from 22 to 33 bursts/min) and burst incidence by 81% (from 26 to 47 bursts/100 heart beats). Plasma noradrenaline concentrations were 1.5 nmol/l on both study days, and plasma atrial natriuretic factor fell from 22.5 to 15 pmol/l.

AGGREGATE DATA

There were correlations between muscle sympathetic nerve activity at baseline and changes

Figure 3 Plots of left ventricular end diastolic and end systolic diameters, fractional shortening, and left ventricular mass index immediately before addition of metoprolol (time 1) and after long term treatment (time 2). Average ventricular dimensions were significantly lower ($P < 0.005$), fractional shortening significantly greater ($P < 0.05$), and left ventricular mass significantly reduced ($P < 0.05$) on follow up.

in muscle sympathetic nerve burst frequency ($r = -0.90$, $P \sim 0.01$; $n = 7$), muscle sympathetic nerve burst incidence ($r = -0.81$, $P \sim 0.05$; $n = 7$), and plasma noradrenaline concentrations ($r = -0.76$, $P \sim 0.08$; $n = 6$) between the first and second study. There was also a correlation between changes in muscle sympathetic nerve activity and changes in plasma noradrenaline concentration ($r = 0.79$, $P \sim 0.06$; $n = 6$) between the first and second study.

Discussion

Chronic β adrenoceptor blockade might benefit patients with dilated cardiomyopathy by antagonising the adverse effects of neurally released and circulating catecholamines on β adrenergic receptors and on cardiac myocytes,³ or by attenuating efferent sympathetic traffic to the heart and peripheral vasculature. Attenuation of central sympathetic outflow should confer greater long term benefit, since peripheral β adrenoceptor blockade leaves α adrenoceptor mediated vasoconstriction and renal sodium retention unopposed, and the heart and periphery are not shielded from the vasoconstrictor actions of other neurotransmitters coreleased by noradrenergic nerves, such as neuropeptide Y.^{2,3} Moreover, such generalised sympathoinhibition could

also explain the sustained benefits achieved by the β_1 selective antagonist metoprolol, even though the failing heart has a relatively higher proportion of β_2/β_1 adrenergic receptors than the normal heart.^{5,6}

Activation of the sympathetic nervous system in heart failure has been attributed to impairment of inhibitory afferent input from arterial and cardiopulmonary mechanoreceptors, and recruitment of sympathetic excitatory afferent input from underperfused skeletal muscle.^{3,17} Muscle sympathetic nerve burst frequency in patients with heart failure appears to be positively related to pulmonary arterial diastolic pressure, and inversely related to left ventricular stroke work index.^{2,4} Consequently, any improvement in these haemodynamic indices might reduce sympathetic outflow reflexively. However, in a sub-study of 41 subjects enrolled in the metoprolol in dilated cardiomyopathy trial, those randomised to metoprolol experienced increases in ejection fraction after 12 months of treatment comparable to those of our subjects (from 21% to 34%), as well as increases in cardiac output, yet resting arterial noradrenaline concentrations at that time were no lower than values in the placebo treated group, and net myocardial noradrenaline release was similar in placebo and metoprolol treated subjects, both at rest and during exercise.¹⁸

There are limitations inherent in this indirect estimate of sympathetic nerve activity¹⁹ that are exacerbated in heart failure, a condition in which increased noradrenaline concentrations reflect both increased spillover into plasma and decreased regional or total body clearance.^{2,20} The approach used in the present study is fundamentally different: this is the first study in dilated cardiomyopathy to examine directly the effects of long term β adrenergic blockade with metoprolol on central sympathetic outflow to calf muscle, and at the same time assess a functional consequence of sympathetic nerve discharge to this bed by measuring calf vascular resistance distal to the recording electrode. Our objective was to test the hypothesis that muscle sympathetic nerve activity diminishes in subjects with dilated cardiomyopathy who improve after long term β adrenoceptor blockade. Our principal finding was that efferent postganglionic muscle sympathetic nerve activity decreases in subjects who respond to long term treatment with metoprolol. The subjects in the present study had improvement in their symptoms, increases in blood pressure, and significant improvement in their left ventricular size and function. There was a 50% reduction in sympathetic burst frequency and a 62% reduction in resistance to blood flow in the calf, the major muscle bed distal to the recording electrode. These changes contrast with the consistency of muscle sympathetic nerve activity and calf vascular resistance over time in both normotensive and hypertensive subjects.^{14,21}

The duration of follow up of our metoprolol treated patients (approximately 20 months) should be emphasised. Haemodynamic

Figure 4 Plots of muscle sympathetic burst frequency, burst incidence, calf vascular resistance, and plasma atrial natriuretic factor concentration immediately before addition of metoprolol (time 1) and after long term treatment (time 2). There were significant reductions in mean values for muscle sympathetic nerve activity ($P < 0.05$), atrial natriuretic factor ($P < 0.05$), and calf vascular resistance ($P < 0.005$) between the first and second studies.

improvements in dilated cardiomyopathy elicited by β adrenergic blockade are not always evident after two to three months.¹⁰ Indeed, the results of several short term (less than three months) placebo controlled double blind studies of β adrenergic blockade therapy in congestive heart failure have been disappointing.^{22,23}

The negative chronotropic effect of β adrenergic blockade accounts for some of the reduction in muscle sympathetic nerve burst frequency in the present study.¹² The pulse synchronous nature of muscle sympathetic nerve activity is a consequence of the restraining influence of afferent baroreceptor input on tonic sympathetic discharge. Since such input is highest during systole, and virtually absent during diastole, release of this tonic inhibition during each diastole provides the potential for a subsequent efferent burst. Nonetheless, chronic β adrenergic blockade had an effect on muscle sympathetic nerve burst frequency that was independent of, and in addition to, its negative chronotropic action, because burst incidence (burst/100 heart beats) also fell from pretreatment levels.

Although arising from a single case, data from the sotalol treated subject are nonetheless interesting. If decreased heart rate and increased arterial and cardiac mechanorecep-

tor afferent input were the principal explanation for the effects of β adrenoceptor blockade on sympathetic nerve traffic, similar sympathoinhibition should have been observed in this subject. Haemodynamic indices improved, yet burst frequency was 50% higher and burst incidence was 81% higher (and calf vascular resistance distal to the recording electrode 93% higher) on restudy. These discordant findings indicate that mechanisms related to haemodynamic improvement cannot entirely explain the reductions in muscle sympathetic nerve activity observed after chronic metoprolol treatment in our subjects. Those reductions may result from a drug specific, perhaps central sympathoinhibitory, action of metoprolol.¹²

The concordance of neurovascular coupling in these subjects has not been described to date in any group of patients treated for heart failure. Over the short term (five weeks) enalapril causes modest calf vasodilatation (+30%),²⁴ but ACE inhibitors appear to exert this effect through augmentation of endothelial function,²⁵ rather than through sympathoneural withdrawal.²⁶

As the improvement in our subjects' clinical status was temporally related to the addition of metoprolol, which was started because of progressive clinical deterioration despite hospital admission and several months of treatment, it would be implausible to attribute the haemodynamic and sympathoneural changes in our subjects either to spontaneous improvement or to a delayed response to their previous drug regimen. Transcardiac and total body noradrenaline spillover into plasma remain markedly increased despite long term treatment with digitalis, ACE inhibitors, or both.²⁶ Long term placebo controlled trials of β adrenoceptor blockade in dilated cardiomyopathy have revealed little or no change in haemodynamic variables^{9,27} or plasma noradrenaline concentrations^{18,28} in placebo treated subjects. Because the objective of this study was to test the hypothesis that muscle sympathetic nerve activity diminishes in subjects with dilated cardiomyopathy who improve after long term treatment with metoprolol, our principal conclusion, namely that efferent postganglionic muscle sympathetic nerve activity decreases in those subjects who respond to such treatment, remains intact even in the absence of a placebo treated group. The delayed nature of this sympathoneural withdrawal¹² may explain why patients do not experience haemodynamic compromise when exposed to gradually increasing doses of β blockade.

Recently, we have suggested that activation of adrenergic drive to the diseased myocardium may be a causative mechanism linking sympathetic activation to adverse outcome in left ventricular dysfunction, and proposed that interventions that selectively modulate sympathetic outflow to the heart may benefit such patients, possibly if administered early before the development of generalised sympathetic activation. The hypothesis that interventions that attenuate sympathetic

outflow to the heart will improve outcome in congestive heart failure has not been specifically addressed.³ Because there is concordance between changes in muscle sympathetic nerve activity and cardiac noradrenaline spillover,²⁹ our present demonstration, by direct microneurographic recordings, that muscle sympathetic nerve activity decreases significantly in patients with idiopathic dilated cardiomyopathy who improve after their conventional therapy is supplemented suggests that metoprolol may be one such intervention.

Supported by the Heart and Stroke Foundation of Ontario (Grants Nos B1956, T2326), the Pettit Fund of the University of Toronto, and the University of Toronto Centre for Cardiovascular Research. JSF holds a clinician scientist award from the Ministry of Health of the Province of Ontario. MAR was a recipient of a fellowship from the Medical Research Council of Canada. KH was supported by postgraduate fellowship funds from the Division of Cardiology and the Department of Medicine, University of Toronto, and by the Medical Research Council of Canada.

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