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 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 (7–7) 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 only 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.

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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.5–7

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 may be 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 al12 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 metoprolol.
Table 1  Subject characteristics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Dose (mg)</th>
<th>Duration</th>
<th>Weight (kg)</th>
<th>BSA (m²)</th>
<th>NYHA class</th>
<th>EF%</th>
<th>Treatment</th>
<th>DBP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>MSNA bursts/min</th>
</tr>
</thead>
</table>
| (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  ACE  89  51  87  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  58  94  49
SD    13.7  16.5  3.3  8.5  8.1  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  2-172  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  ADC  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 inhibitor; 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 ≤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), digoxins (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 Lifesat 200), 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. 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. Multitunit recordings of post-ganglionic muscle sympathetic activity were obtained from the peroneal nerve. 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.

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.
Significant reductions in cardiac output and left ventricular end-diastolic volume were noted in the control group (P<0.05). There were significant reductions in plasma norepinephrine 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 norepinephrine 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...
in muscle sympathetic nerve burst frequency ($r = -0.90, P < 0.01; n = 7$), muscle sympathetic nerve burst incidence ($r = 0.81, P < 0.05; n = 7$), and plasma noradrenaline concentrations ($r = -0.76, P < 0.08; n = 6$) between the first and second study. There was also a correlation between changes in muscle sympathetic nerve activity and changes in plasma noradrenaline concentration ($r = 0.79, P < 0.06; n = 6$) between the first and second study.

Discussion
Chronic $\beta$ adrenoceptor blockade might benefit patients with dilated cardiomyopathy by antagonising the adverse effects of neurally released and circulating catecholamines on $\beta$ adrenergic receptors and on cardiac myocytes, 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 $\beta$ adrenoceptor blockade leaves $\alpha$ 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. Moreover, such generalised sympathoinhibition could also explain the sustained benefits achieved by the $\beta$ selective antagonist metoprolol, even though the failing heart has a relatively higher proportion of $\beta_1/\beta_2$ adrenergic receptors than the normal heart. 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. 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. 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. 

There are limitations inherent in this indirect estimate of sympathetic nerve activity 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. 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 $\beta$ 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 $\beta$ 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. 

The duration of follow up of our metoprolol treated patients (approximately 20 months) should be emphasised. Haemodynamic
improvements in dilated cardiomyopathy elicited by β adrenergic blockade are not always evident after two to three months. 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.

The negative chronotropic effect of β adrenergic blockade accounts for some of the reduction in muscle sympathetic nerve burst frequency in the present study. 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 adrenergic receptor 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. These reductions may result from a drug specific, perhaps central sympathoinhibitory, action of metoprolol.

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%), but ACE inhibitors appear to exert this effect through augmentation of endothelial function, rather than through sympathetic nervous withdrawal.

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 digitals, ACE inhibitors, or both. Long term placebo controlled trials of β adrenergic blockade in dilated cardiomyopathy have revealed little or no change in haemodynamic variables or plasma noradrenaline concentrations 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 withdrawal 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 the discordance 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.

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