

## Effect of Digoxin on Exercise Performance in Mildly Symptomatic Patients with Idiopathic Dilated Cardiomyopathy and Sinus Rhythm

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### SUMMARY

The purpose of this investigation was to evaluate the effect of digoxin on aerobic performance in mildly symptomatic patients with congestive heart failure and sinus rhythm. Ten patients (8 men and 2 women) with idiopathic dilated cardiomyopathy (ejection fraction 17 to 33%, mean  $27 \pm 4\%$ ) who were stable and mildly symptomatic with maintenance digoxin and diuretic therapy were studied. All patients underwent maximal symptom-limited ergometer exercise with analysis of respiratory gases during maintenance digoxin therapy, 4 weeks after digoxin withdrawal, and 4 weeks after digoxin readministration. Exercise capacity was assessed by peak oxygen uptake and anaerobic threshold. Serum digoxin concentration was 1.0 to 1.8 (mean  $1.3 \pm 0.2$ ) ng/ml during digoxin therapy, and less than the detectable level after digoxin withdrawal. No patients showed clinical deterioration after digoxin withdrawal. Peak oxygen uptake after digoxin withdrawal ( $23.7 \pm 3.0$  ml/kg/min) did not differ significantly from that during maintenance digoxin therapy ( $23.8 \pm 2.5$  ml/kg/min) or after digoxin readministration ( $24.1 \pm 2.9$  ml/kg/min). The anaerobic threshold after digoxin withdrawal ( $14.9 \pm 2.5$  ml/kg/min) did not differ significantly from that during maintenance digoxin therapy ( $15.0 \pm 2.1$  ml/kg/min) or after digoxin readministration ( $14.9 \pm 2.2$  ml/kg/min). No differences in heart rate and diastolic blood pressure were observed during exercise, but systolic blood pressure during exercise was significantly higher with digoxin therapy ( $p < 0.05$ ).

These results suggest that digoxin has no effect on aerobic performance in mildly symptomatic patients with idiopathic dilated cardiomyopathy and sinus rhythm. (Jpn Heart J 35: 301–310, 1994)

**Key words:** Heart failure    Exercise test    Digitalis

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ALTHOUGH digoxin has been used in treating heart failure for more than two centuries, its value for increasing functional capacity in patients with heart failure and sinus rhythm remains controversial.<sup>1-3)</sup> Three recent large multicenter placebo-controlled trials have shown a modest increase in exercise duration with digoxin, but such improvement failed to achieve statistical significance in 2 of the 3 trials.<sup>4-6)</sup> The apparent lack of improvement in exercise capacity during digoxin therapy may be attributable to the limitations of using exercise duration in assessing exercise capacity, because a variability in patient motivation, the learning effect of repeated exercise testing and observer bias may all influence the duration of exercise independent of true changes in aerobic performance.<sup>7)</sup> In fact, the duration of treadmill exercise increased in many studies of placebo-treated patients.<sup>6,8,9)</sup>

Respiratory gas analysis has been used to evaluate the functional capacity of patients with heart failure.<sup>10,11)</sup> Peak oxygen uptake (peak  $\dot{V}O_2$ ) and anaerobic threshold (AT) determined by respiratory gas analysis are more reliable and objective parameters than is the conventional measurement of exercise capacity by exercise duration.<sup>7,10-12)</sup> However, only a few studies have used respiratory gas analysis to evaluate the effect of digoxin on exercise performance.<sup>13-15)</sup> Sullivan et al showed that both AT and peak  $\dot{V}O_2$  improved significantly with digoxin therapy in patients with moderate to severe heart failure and a third heart sound.<sup>14)</sup> However, the effect of digoxin on the aerobic performance of less symptomatic patients with severe left ventricular systolic dysfunction and sinus rhythm has not been elucidated.

Accordingly, the purpose of this study was to evaluate the effect of digoxin on exercise performance in mildly symptomatic patients with idiopathic dilated cardiomyopathy and sinus rhythm by using analysis of respiratory gases.

## METHODS

**Study patients** (Table I): Ten mildly symptomatic ambulatory patients (8 men and 2 women) aged 26 to 64 years (mean  $48.2 \pm 10.6$  years) with idiopathic dilated cardiomyopathy in sinus rhythm were studied. Coronary arteries were normal or minimally sclerotic in all patients. Left ventriculography revealed left ventricular enlargement (left ventricular end-systolic volume index: 82 to 164 ml/m<sup>2</sup>, mean  $110 \pm 24$  ml/m<sup>2</sup>) and left ventricular systolic dysfunction (ejection fraction: 17 to 33%, mean  $27 \pm 4\%$ ). Patients with significant valvular disease or a history of atrial tachyarrhythmia were excluded from the study. Five patients had a history of one or more well-documented instances of heart failure. The other patients had experienced symptoms of left-sided failure and had shown radiographic evidence of cardiomegaly, which had since been relieved with digoxin

**Table I.** Patient Characteristics and Results of Exercise Testing

Pt No.	Age & Sex	EF (%)	ESVI (ml/m <sup>2</sup> )	S <sub>3</sub>	Digoxin		Peak VO <sub>2</sub> (ml/kg/min)			AT (ml/kg/min)		
					Dose (mg/day)	Serum conc. (ng/ml)	ON 1	OFF	ON 2	ON 1	OFF	ON 2
1.	44M	33	86	—	0.25	1.0	20.0	21.3	20.0	12.5	13.6	13.0
2.	57F	31	93	—	0.18	1.4	24.4	23.0	22.8	17.6	17.1	17.5
3.	46M	28	131	—	0.25	1.3	27.6	29.2	29.5	17.5	18.9	17.0
4.	26M	27	164	+	0.50	1.4	24.2	21.1	24.6	12.7	13.0	13.4
5.	40M	29	82	+	0.25	1.3	22.0	21.9	22.5	14.4	11.3	14.0
6.	47F	26	96	—	0.125	1.2	25.3	25.5	26.5	16.6	14.4	15.0
7.	59M	24	116	—	0.25	1.8	23.0	20.6	21.3	11.8	12.4	11.3
8.	43M	17	124	—	0.25	1.3	20.4	21.4	22.5	13.8	13.6	13.0
9.	64M	29	119	—	0.25	1.5	27.5	28.8	28.3	17.3	18.5	17.9
10.	56M	29	91	—	0.25	1.0	23.7	23.7	23.8	15.6	16.1	16.8
Mean	48.2	27	110		0.26	1.3	23.8	23.7	24.1	15.0	14.9	14.9
± SD	10.6	4	24		0.09	0.2	2.5	3.0	2.9	2.1	2.5	2.2

AT = anaerobic threshold; Conc = concentration; EF = ejection fraction; ESVI = endsystolic volume index; ON 1 = during maintenance digoxin therapy; OFF = 4 weeks after digoxin withdrawal; ON 2 = 4 weeks after digoxin readministration; Peak VO<sub>2</sub> = peak oxygen uptake; Pt = patient; S<sub>3</sub> = third heart sound gallop; SD = standard deviation.

and diuretic therapy. All patients received maintenance digoxin and diuretic therapy and had been stable for at least 3 months before entering the study. Two patients had a third heart sound gallop at the time of entry. Informed consent was obtained from all patients prior to the study.

**Protocol:** Exercise tests with analysis of respiratory gases were performed during long-term maintenance digoxin therapy, 4 weeks after the withdrawal of digoxin, and 4 weeks after the readministration of digoxin. Digoxin dosage ranged from 0.125 to 0.5 mg/day (mean  $0.26 \pm 0.09$  mg/day) during maintenance therapy and after the drug's readministration. Serum digoxin concentration was within the therapeutic range (1.0 to 1.8, mean  $1.3 \pm 0.2$  ng/ml) during digoxin therapy. No patients had detectable serum digoxin levels during the period in which they were not taking digoxin.

**Exercise tests:** Patients were familiarised with the ergometer and the apparatus for respiratory gas analysis before the study. All patients underwent maximal symptom-limited exercise while seated on an electrically braked cycle ergometer. Exercise was performed 4 to 6 hours after the morning cardiac medication had been taken. After a 3-min rest period, exercise began with a 3-min warm-up period at 10 Watts and was followed by a continuous ramp protocol corresponding to increments of 20 Watts/min until the subject could no longer continue. Electrocardiography was monitored throughout the exercise and a 12-lead electrocardiogram was recorded every minute. Cuff blood pressure was measured every minute.

Respiratory gases were analyzed on a breath-by-breath basis by use of an

Aero Monitor AE-280 (Minato Medical Science, Osaka, Japan). This system consists of a hot-wire spirometer, a zirconia cell oxygen ( $O_2$ ) analyzer, and infra-red absorption carbon dioxide ( $CO_2$ ) analyzer. The system introduces a low volume of dead space into the ventilatory circuit and was calibrated before each study. Data were processed by an on-line computer system and the following parameters were calculated: expired minute ventilation ( $\dot{V}E$ ),  $O_2$  uptake ( $\dot{V}O_2$ ),  $CO_2$  output ( $\dot{V}CO_2$ ), end-tidal  $PO_2$ , end-tidal  $PCO_2$ , respiratory exchange ratio (RER:  $\dot{V}CO_2/\dot{V}O_2$ ), ventilatory equivalent for  $O_2$  ( $\dot{V}E/\dot{V}O_2$ ) and ventilatory equivalent for  $CO_2$  ( $\dot{V}E/\dot{V}CO_2$ ).

Exercise capacity was assessed by peak  $\dot{V}O_2$  and AT. Peak  $\dot{V}O_2$  was determined as the average of values obtained in the final 15 seconds of exercise. AT was determined by 2 experienced reviewers who knew nothing about the patients or their medications, by use of the V slope method,<sup>12,16)</sup> in addition to the following conventional criteria: 1)  $\dot{V}E/\dot{V}O_2$  increases after being stable or decreases while  $\dot{V}E/\dot{V}CO_2$  remains constant or decreases, 2) increase in end-tidal  $PO_2$  without a decrease in end-tidal  $PCO_2$ , 3) RER, which was stable or slowly rising, begins to rise more steeply.<sup>10,17)</sup>

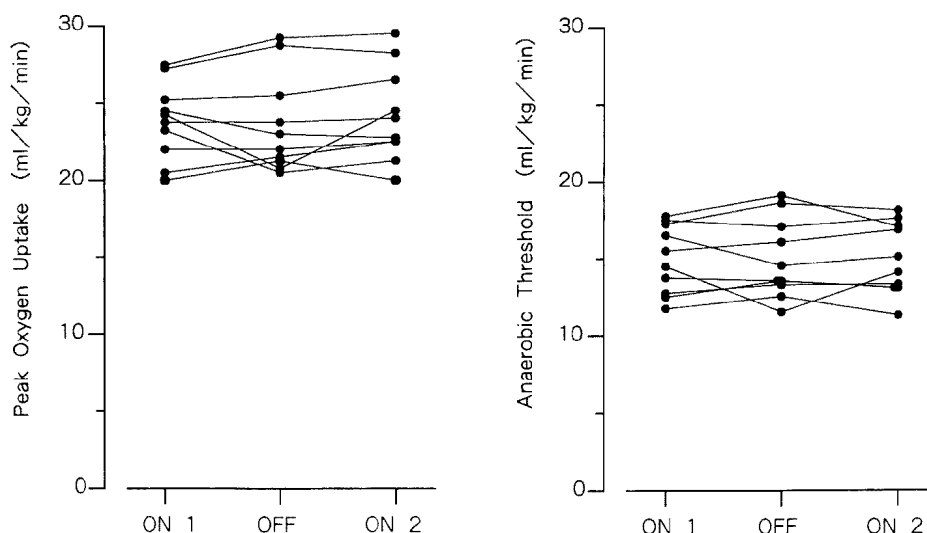
**Statistics:** Data are expressed as mean  $\pm$  SD. Comparisons of exercise capacity with and without digoxin were made by paired t-tests. Two-way analysis of variance was used to assess the significance of changes in exercise heart rate and blood pressure response in each phase. A probability value less than 0.05 was considered statistically significant.

## RESULTS

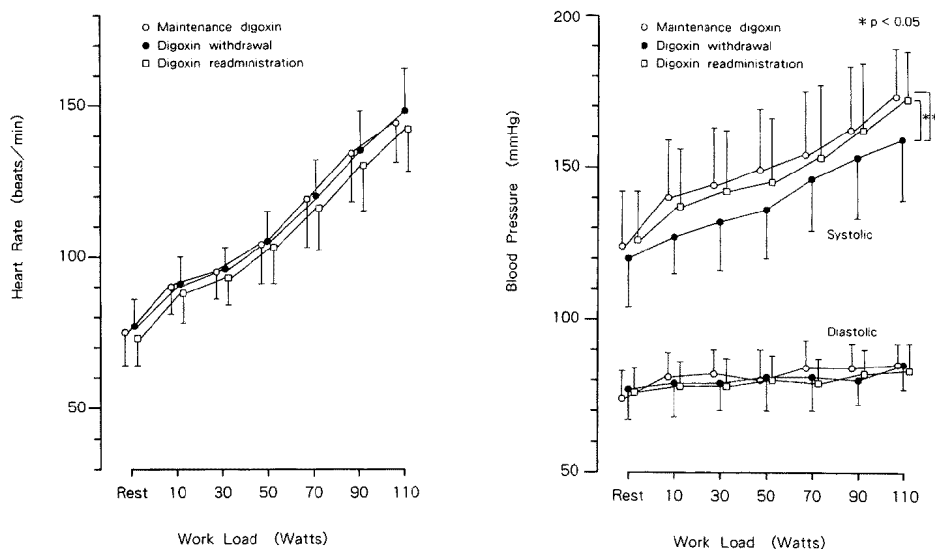
No patients showed clinical deterioration or required adjustment of diuretic dosage during the study. In all cases, exercise was limited by fatigue and dyspnea, with no complications observed during exercise testing. RER at peak exercise was  $1.20 \pm 0.07$  during maintenance digoxin therapy,  $1.21 \pm 0.09$  during digoxin withdrawal, and  $1.20 \pm 0.07$  during digoxin readministration; these results indicate near-maximal and almost identical exercise was achieved in each phase.

Peak  $\dot{V}O_2$  did not differ significantly between the three phases ( $23.8 \pm 2.5$  ml/kg/min during maintenance digoxin therapy;  $23.7 \pm 3.0$  ml/kg/min during digoxin withdrawal; and  $24.1 \pm 2.9$  ml/kg/min during digoxin readministration). AT did not change significantly after digoxin withdrawal ( $15.0 \pm 2.1$  ml/kg/min during maintenance digoxin therapy;  $14.9 \pm 2.5$  ml/kg/min during digoxin withdrawal; and  $14.9 \pm 2.2$  ml/kg/min during digoxin readministration) (Figure 1).

Heart rate and diastolic blood pressure from rest to peak exercise did not differ significantly between the three phases. Systolic blood pressure from rest to peak exercise was significantly higher with digoxin therapy ( $p < 0.05$ ) (Figure 2).



**Figure 1.** Peak oxygen uptake and anaerobic threshold with (ON 1, ON 2) and without (OFF) digoxin. No difference was noted among the three phases. ON 1 = during maintenance digoxin therapy; OFF = 4 weeks after digoxin withdrawal; ON 2 = 4 weeks after digoxin readministration.



**Figure 2.** Heart rate and blood pressure responses during exercise with and without digoxin therapy. Systolic blood pressure was significantly higher with digoxin therapy (\* $p < 0.05$ ). No differences between groups were noted in diastolic blood pressure or heart rate.

## DISCUSSION

The present study showed that digoxin had no effect on exercise performance, as determined by AT and peak  $\dot{V}O_2$  in mildly symptomatic patients with idiopathic dilated cardiomyopathy and sinus rhythm.

Digoxin has been used for treating congestive heart failure for more than 200 years, but there is still controversy about its chronic effects in patients with congestive heart failure and sinus rhythm.<sup>1-3)</sup> Although chronic maintenance digoxin therapy can be discontinued without any clinical deterioration in many patients with heart failure and sinus rhythm,<sup>3,18)</sup> some patients with the most advanced disease experienced clinical and hemodynamic deterioration after withdrawal of digoxin.<sup>19,20)</sup> Digoxin exerts a modest positive inotropic effect, but the extent of its positive inotropic action is inversely related to baseline myocardial contractility, i.e., severely depressed myocardial contractility shows a more vigorous response to digoxin.<sup>21)</sup> Gheorghiade et al reported that patients with persistent abnormal rest hemodynamics after receipt of near-maximal tolerated doses of diuretics and vasodilators responded to digoxin with an improvement in cardiac output and a decrease in filling pressure; in contrast, patients who had nearly normal hemodynamics after optimal therapy with diuretics and vasodilators failed to respond hemodynamically to digoxin.<sup>22)</sup> Other studies have shown that patients whose hemodynamics improved after digoxin administration tend to have a third heart sound and a very high pulmonary capillary wedge pressure.<sup>19,20)</sup> Digoxin seems to be effective in severe congestive heart failure even in patients in sinus rhythm.<sup>19,20,22)</sup>

Measurement of exercise capacity has been used to assess drug efficacy in patients with mild to moderate heart failure.<sup>5,6,14,15)</sup> Recent multicenter placebo-controlled trials have attempted to evaluate the effects of chronic maintenance digoxin therapy on exercise performance.<sup>4-6)</sup> These studies showed a modest increase in exercise capacity with digoxin, but the improvement in exercise capacity with digoxin was statistically significant in only one of 3 trials.<sup>4)</sup> These studies and many others used exercise duration as a measurement of exercise capacity.<sup>4-6,8,9)</sup> Although the correlation of exercise duration with oxygen uptake is reasonably good, a learning effect from repeated exercise, motivation of the patient, and observer bias may all influence exercise duration independent of true changes in oxygen uptake.<sup>7)</sup> In fact, placebo-treated patients showed improvement in treadmill exercise duration in many studies.<sup>6,8,9)</sup> Therefore, measurement of exercise duration may not be adequate for a precise evaluation of therapeutic changes in aerobic performance.

Measurement of peak  $\dot{V}O_2$  and AT by respiratory gas analysis during exercise provides more objective and accurate information about exercise capacity

and its response to therapy.<sup>10,11,14)</sup> However, only a few reports have used respiratory gas analysis to assess digoxin efficacy.<sup>13-15)</sup> Sullivan et al showed that digoxin therapy is associated with a significant improvement in exercise capacity as determined by peak  $\dot{V}O_2$  and AT in patients with heart failure and sinus rhythm, but 10 of 11 patients had a consistent third heart sound gallop.<sup>14)</sup> Peak  $\dot{V}O_2$  value of 16.7 ml/kg/min without digoxin therapy indicated a moderately depressed exercise tolerance. The rest heart rate of 102 beats/min without digoxin in their study was very fast, as compared with 76.9 beats/min in the present study. Alicandri et al showed mean maximal oxygen uptake increased significantly from 585 ml/min to 716 ml/min with digoxin, which also indicates a severely depressed baseline exercise capacity.<sup>13)</sup> In the present study, no benefits of digoxin on aerobic performance were recognized in mildly symptomatic patients (peak  $\dot{V}O_2 > 20$  ml/kg/min) with idiopathic dilated cardiomyopathy and sinus rhythm. Fleg et al recognized that the change in peak  $\dot{V}O_2$  induced by digoxin was inversely related to peak  $\dot{V}O_2$  during placebo therapy.<sup>15)</sup> In their study, none of the 5 patients with peak  $\dot{V}O_2 > 20$  ml/kg/min showed improvement in exercise capacity, but 2 of 3 patients with peak  $\dot{V}O_2 < 15$  ml/kg/min did show improvement in exercise capacity. Sullivan et al showed that all 5 patients with peak  $\dot{V}O_2 < 15$  ml/kg/min benefited from digoxin,<sup>14)</sup> making it likely that patients with more severe baseline aerobic impairment would have greater improvement with digoxin. A captopril-digoxin multicenter research group failed to demonstrate the efficacy of digoxin in increasing exercise tolerance;<sup>6)</sup> this result may be related to the mildly impaired baseline aerobic performance of the subjects, because their exercise duration of 560 seconds corresponds to about 6 metabolic equivalents (equal to approximately 21 ml/kg/min). A milrinone multicenter trial group showed that digoxin significantly increased exercise duration; the exercise tolerance of these subjects was moderately to severely impaired.<sup>4)</sup> These inconsistent results may be attributable to differences in baseline aerobic performance of the subjects. From these studies and our results, it appears that patients with less impaired exercise performance (peak  $\dot{V}O_2 > 20$  ml/kg/min) may not benefit from digoxin in terms of exercise capacity.

Systolic blood pressure from rest to peak exercise was significantly higher with digoxin therapy in the present study. Other studies have shown that digoxin produced a significant increase in both rest and exercise systolic blood pressure in patients with mild to moderate heart failure.<sup>23,24)</sup> Digoxin reduces peripheral vascular resistance in severe congestive heart failure,<sup>20,22)</sup> but in patients with a lesser degree of hemodynamic abnormality, systemic vascular resistance remains unchanged or is actually augmented by digoxin.<sup>22,25,26)</sup> Because cardiac output during exercise was not measured in the present study, we could not determine whether the increase in systolic pressure with digoxin was caused by an increase

in peripheral vascular resistance or an increase in stroke volume.

While this study included only a small number of patients, they represent a homogeneous population with mildly symptomatic idiopathic dilated cardiomyopathy and sinus rhythm. In contrast to many other trials, patients with congestive heart failure due to coronary artery disease were not included. An exercise test was performed 4 weeks after digoxin withdrawal, because previous reports had shown that deterioration of clinical condition and functional capacity was recognized at that time.<sup>27,28)</sup> Although the present study was neither placebo controlled nor double blind, a determination of AT was made by a reviewer who knew nothing about the patients or their cardiac medications. As a result, the value for AT was objective and not influenced by observer bias or patient motivation. Although a maximal  $\dot{V}O_2$ , recognized as a levelling off of  $\dot{V}O_2$  with increasing work loads is often difficult to obtain in patients with congestive heart failure, the identical and adequately elevated value of respiratory exchange ratio at peak exercise indicated that a near-maximal and identical effort was performed in each phase. Reproducibility of the values of AT and Peak  $\dot{V}O_2$  was confirmed by the exercise test performed 4 weeks after readministration of digoxin, which indicates that a learning effect from repeated exercise was not involved.

Our finding that digoxin had no effect on exercise capacity in mildly symptomatic patients with idiopathic dilated cardiomyopathy and sinus rhythm does not necessarily mean that digoxin should be reserved for use only in patients with a third heart sound or those who are moderately symptomatic, even after maximally tolerated doses of diuretics and vasodilators. Use of vasodilators can prolong survival.<sup>29,30)</sup> However, no studies have shown that digoxin can prolong life in congestive heart failure. Digoxin, however, may have a protective effect which prevents clinical manifestations of heart failure even in patients with mild to moderate heart failure.<sup>4,6)</sup> Further investigations are needed to clarify the role of digoxin in mildly symptomatic patients with congestive heart failure and sinus rhythm.

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