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Absence of excess peripheral muscle fatigue during β-adrenoceptor blockade

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1 In eight normal volunteers, the adductor pollicis (AP) was fatigued using intermittent trains of programmed, supramaximal stimulation at 1, 10, 20, 50, 100 and 1 Hz. Activity protocols were performed both with and without circulatory occlusion, both without and during propranolol 80 mg thrice daily in order to investigate the effects of β-adrenoceptor blockade on 'peripheral' fatigue mechanisms.

2 The degree of β-adrenoceptor blockade was assessed by the reduction of exercise tachycardia during cycle ergometry, e.g. pulse rates at 210 watts were reduced from 190 ± 15 to 127 ± 5 beats min^{-1} (mean ± 1 s.d.) indicating that β-adrenoceptor blockade was substantial and highly significant ($P < 0.001$).

3 Before, during and following fatiguing activity with circulatory occlusion force declines were identical during and without β-adrenoceptor blockade. During and following activity without occlusion, there were slight declines in force which were questionably significantly different at 20 Hz ($P < 0.05$).

4 The compound muscle action potential (CMAP) amplitude, measured from the skin surface over the muscle, was unaltered by β-adrenoceptor blockade before, during or after activity whether with or without circulatory occlusion.

5 The maximal relaxation rate (MRR) was not significantly reduced in previously unfatigued muscle during β-adrenoceptor blockade. During activity, both with and without circulatory occlusion, there was no evidence that MRR was reduced significantly more during β-adrenoceptor blockade.

6 The absence of a convincing effect of β-adrenoceptor blockade on peripheral fatigue mechanisms may indicate that central mechanisms are involved or that impairments of peripheral force production, of a specific nature or as a result of exacerbation of limitations of circulatory oxygen transport, though small are detected during voluntary exercise and give rise to increases in motor unit recruitment and/or firing rates, and hence increased perception of fatigue.

Keywords fatigue β-adrenoceptor blockade contractile properties

Introduction

β-adrenoceptor blockers are important antihypertensive agents. Their use however, is associated with excessive 'fatigue' which may be manifest as an increased perception of effort, during everyday activities (Stephen, 1966; Lewis *et al.*, 1984) and during exercise protocols with

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various scales rating perception of effort (Kaiser, 1984; Wilcox *et al.*, 1984), but also as reduced endurance times during maximal or submaximal exercise (Tesch *et al.*, 1984a; Wilcox *et al.*, 1984). The nature of this excess fatigue is unknown. Most of the haemodynamic and metabolic changes which occur during physical exercise involve the sympathetic nervous system and many are mediated via β-adrenoceptors. It is, therefore, perhaps not surprising that β-adrenoceptor blockade could affect skeletal muscle function. During β_1-adrenoceptor blockade there are modest reductions in blood pressure but marked reductions in heart rate causing a net reduction in cardiac output of approximately 20% (Epstein *et al.*, 1965). The consequent reductions in muscle blood flow (Smith & Warren, 1982) may thus reduce oxygen supply to exercising muscle. Local vasoconstriction, due to β_2-adrenoceptor blockade, may exacerbate this situation (Eklund & Kaijser, 1976). During exercise muscle blood flow increases in proportion to power output, indicating that metabolic demand and perfusion are closely matched (Jorfeldt & Wahren, 1971). Therefore any reduction in blood flow during β-adrenoceptor blockade might be expected to limit metabolic exchanges of blood borne substrates and thus performance. This appears of importance when it is realised that, during heavy leg exercise, blood flow may increase 10–15 times (Jorfeldt & Wahren, 1971). The potential reductions in blood flow and oxygen consumption, during β-adrenoceptor blockade, are presumably responsible for the observed reductions of maximum oxygen uptake, $\dot{V}o_2$ max. (Epstein *et al.*, 1965; Tesch & Kaiser 1983).

During β-adrenoceptor blockade impairment of energy substrate mobilisation may also occur, in addition to that as a consequence of blood flow changes. Thus impaired tissue lipolysis, by β_1-adrenoceptor blockade, may reduce the availability of free fatty acids for aerobic glycolysis (Trap-Jensen *et al.*, 1976), this being reflected by reductions in the respiratory quotient (Epstein *et al.*, 1965; Kaiser, 1984) indicating that carbohydrate metabolism may become predominant. Impairment of hepatic and muscle glycogenolysis by β_2-adrenoceptor blockade (Arnold *et al.*, 1968) may also reduce anaerobic glycolysis and explain the reported reductions of plasma lactate (Trap-Jensen *et al.*, 1976; Frisk-Holmberg *et al.*, 1977). Muscle lactate, however, is unaltered during β-adrenoceptor blockade indicating that impaired performance is not the result of lactate accumulation (Kaiser & Tesch, 1983).

It is not known whether the excess fatigue of β-adrenoceptor blockade is 'peripheral', due to impairment of the muscle at or distal to the neuromuscular junction or 'central', due to impairment of motivation, spinal transmission and motor-unit recruitment, or indeed a combination of these factors. The extensive data outlined above appear to suggest that the impairment is within muscle, and due to impairment of oxygen and substrate supply. The present study therefore examines peripheral fatigue mechanisms, without and during β-adrenoceptor blockade, by using stimulated contractions of the adductor pollicis muscle. Preliminary results of this study have been presented to the Physiological Society (Cooper *et al.*, 1987).

Methods

Experimental subjects

Eight normal subjects (seven male, one female) gave their informed consent for participation in this study which was approved by the Mersey Regional Health Authority Research Committee. There was no history of muscle weakness or drug ingestion, and no medical contraindication to β-adrenoceptor blockade on history or examin-

Table 1 Personal details of volunteer subjects, serum propranolol concentrations and reductions of heart rate during maximal cycle ergometry

Volunteer subject	*Sex*	*Age (years)*	*Weight (kg)*	*Serum propranolol during ergometry (ng ml^{-1})*	*Reduction in maximal heart rate (beats min^{-1})*
RC	M	33	73	45	70
MS	F	30	50	136	74
JC	M	31	72	84	80
MH	M	29	70	99	56
MJ	M	34	86	60	80
HG	M	25	64	103	68
AW	M	33	78	65	76
PS	M	30	84	39	78
Mean ± 1 s.d.		31 ± 3	72 ± 12	79 ± 33	73 ± 8

ation, in any of the volunteer subjects whose personal details are seen in Table 1.

Contractile properties of adductor pollicis (AP)

At the commencement of all experiments, muscle temperature was standardised, by warming the hand and forearm in a water bath at 45° C for 10 min, the temperature was then maintained with a lamp, to give a standard muscle temperature of 35–36° C throughout the experiment (Edwards *et al.*, 1977; Wiles & Edwards, 1982). Stimulated twitches (1 Hz) were used to locate the optimum electrode site and voltage for supramaximal stimulation of the ulnar nerve at the wrist. The stimulator (Devices 3072), which was computer driven (Apple II), then delivered trains of stimuli (pulse width 50 μs) in a set pattern of frequencies *viz.* 1, 10, 20, 50, 100 and 1 Hz for 1 s each (10 Hz for 2 s). The isometric force produced by AP during stimulation was measured by a strain gauge connected to the proximal phalanx of the thumb *via* an inextensible band in analogous fashion to that of Merton (1954). The force signal was amplified and displayed on an oscillograph and was also electronically differentiated with respect to time to produce a force differential signal which was used to calculate the maximal relaxation rate (MRR, maximal % force loss in 10 ms) after stimulation at 100 Hz (Wiles & Edwards, 1982).

Surface electromyography (EMG) over AP (Mills, 1982) was used to measure the compound muscle action potential (CMAP) amplitude. This signal was displayed on the oscillograph together with the force signals. Simultaneous recordings of force, force differential and CMAP amplitude were termed the programmed stimulation electromyogram or 'PSEM'. The appearance of the PSEM from previously unfatigued AP is seen in Figure 1, together with the changes seen during activity and recovery.

This stimulated method examined contractile properties of AP during fatiguing activity protocols both with and without circulatory occlusion.

Experimental protocols

Activity with arterial occlusion In each subject, a control PSEM was obtained from previously unfatigued ('fresh') muscle. A sphygmomanometer cuff was then inflated around the upper arm to 100 mmHg above systolic blood pressure to occlude arterial circulation. A 3 min period of ischaemic rest followed by which time 50% oxygen depletion occurs thus minimising oxidative metabolism at the commencement of activity (Harris *et al.*, 1975). Fatiguing activity then commenced and consisted of 15 PSEMs, with an interval of 23 s between each one. The cuff was then deflated and aerobic recovery monitored using the PSEM at intervals of 0.5, 1, 2, 3, 5, 10 and 15 min after the end of activity. This ischaemic protocol was performed in each subject without and during β-adrenoceptor blockade.

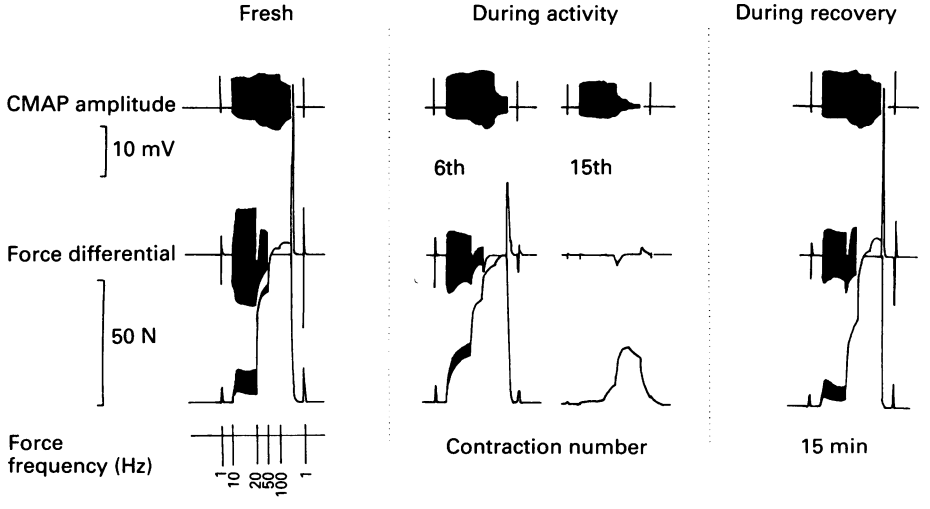

Figure 1 Simultaneous recordings of force, CMAP amplitude and force differential termed the programmed stimulation electromyogram or 'PSEM'. The appearance of the PSEM prior to activity is demonstrated together with changes seen during the protocol with arterial occlusion and at 15 min of recovery. Note 10 Hz force potentiation during activity and low-frequency fatigue in recovery.

Activity without arterial occlusion A control PSEM was obtained from previously unfatigued muscle and a 3 min period of rest followed. Fatiguing activity then commenced and consisted of 50 PSEMs with an interval of 5 s between each one. The larger number of PSEMs at shorter intervals was found necessary to induce sufficient force failure for reliable measurement. Aerobic recovery was monitored using the PSEM at intervals of 0.5, 1, 2, 3, 5, 10 and 15 min after the end of activity. This unoccluded protocol was also performed in each subject without and during β-adrenoceptor blockade.

These protocols were performed in *random* order and at least 1 week apart to ensure full recovery of adductor pollicis. In order to ensure steady state blood concentrations during the β-adrenoceptor blocked protocols, subjects received propranolol 80 mg three times daily for 72 h prior to stimulation procedures which were always performed 2–3 h following the last dose.

Assessment of β-adrenoceptor blockade

It was important to establish whether all subjects had comparable degrees of β-adrenoceptor blockade during the protocols with β-adrenoceptor blockade. Serum for propranolol concentrations was therefore withdrawn from each subject immediately on completion of protocols both with and without circulatory occlusion, during β-adrenoceptor blockade. The degree of β-adrenoceptor blockade was also assessed clinically by reductions of heart rate and blood pressure after 10 min supine rest, immediately on standing and after 2 and 5 min standing on one occasion, and by reductions in heart rate during cycle ergometry (Coltart & Shand, 1970) on the other occasion. Ergometry commenced at 110 watts and increased every 3 min by 40 watt increments. The heart rate was monitored at the end of each increment and immediately prior to exhaustion.

Analysis

During stimulated activity of AP, the force and CMAP amplitude at each frequency was measured and expressed as a percentage of the equivalent part of the control PSEM from fresh muscle. The MRR after 100 Hz was also calculated. These measures were compared, without and during β-adrenoceptor blockade, using the paired-*t* test. Data and statistical analysis was made using a Minitab statistical package (Minitab Inc). All of the results stated in the text and tables are mean ± 1 s.d. A double-blind cross-over, placebo *vs* propranolol, trial design was thought unnecessary since force, CMAP and MRR were all compared using supramaximal stimulation techniques thus excluding potential changes due to volition. Serum propranolol concentrations were measured by ICI Pharmaceuticals Division, Macclesfield.

Results

Assessment of β-adrenoceptor blockade

Heart rates during β-adrenoceptor blockade were significantly reduced after supine rest, from 70 ± 10 to 49 ± 7 ($P < 0.001$) and when standing (Figure 2). The systolic blood pressure was significantly reduced after supine rest, from 121 ± 11 to 101 ± 8 ($P < 0.01$) and during standing (Figure 2). The diastolic blood pressure was not significantly reduced after supine rest but was significantly reduced during standing (Figure 2). Heart rates during β-adrenoceptor blockade were significantly reduced during cycle ergometry at all work rates (Figure 3), e.g. at 210 watts; 190 ± 15 compared with 127 ± 5 ($P < 0.001$). The work rates attained and performance times without and during β-adrenoceptor blockade were rather similar, with only one subject stopping early during β-adrenoceptor blockade due to exhaustion (Figure 3). Serum propranolol concentrations are documented in Table 1. The β-adrenoceptor blockade was of similar degree in all subjects despite the marked variability in drug levels (Figure 4).

Activity with arterial occlusion

During stimulated activity of AP, the degree of force loss clearly depended on stimulation frequency, being greater at low than at high frequencies (Table 2). These declines in force were not associated with equivalent declines in CMAP amplitude since, in contrast to force, excitation declined more at high than at low frequencies (Table 2; Figure 5a). There were no significant differences, comparing results without and during β-adrenoceptor blockade, in force loss or excitation changes at any frequency (Table 2). The force at 10 Hz was initially variably potentiated, reaching 170 ± 57% (143 ± 34% during β-adrenoceptor blockade) before declining. During recovery, force at high frequencies rapidly returned to normal while at low frequency (1, 10 and 20 Hz) force loss persisted at 15 min. The CMAP amplitude at all frequencies had returned to normal by 15 min. There were no significant differences, comparing results without and during β-adrenoceptor blockade in the

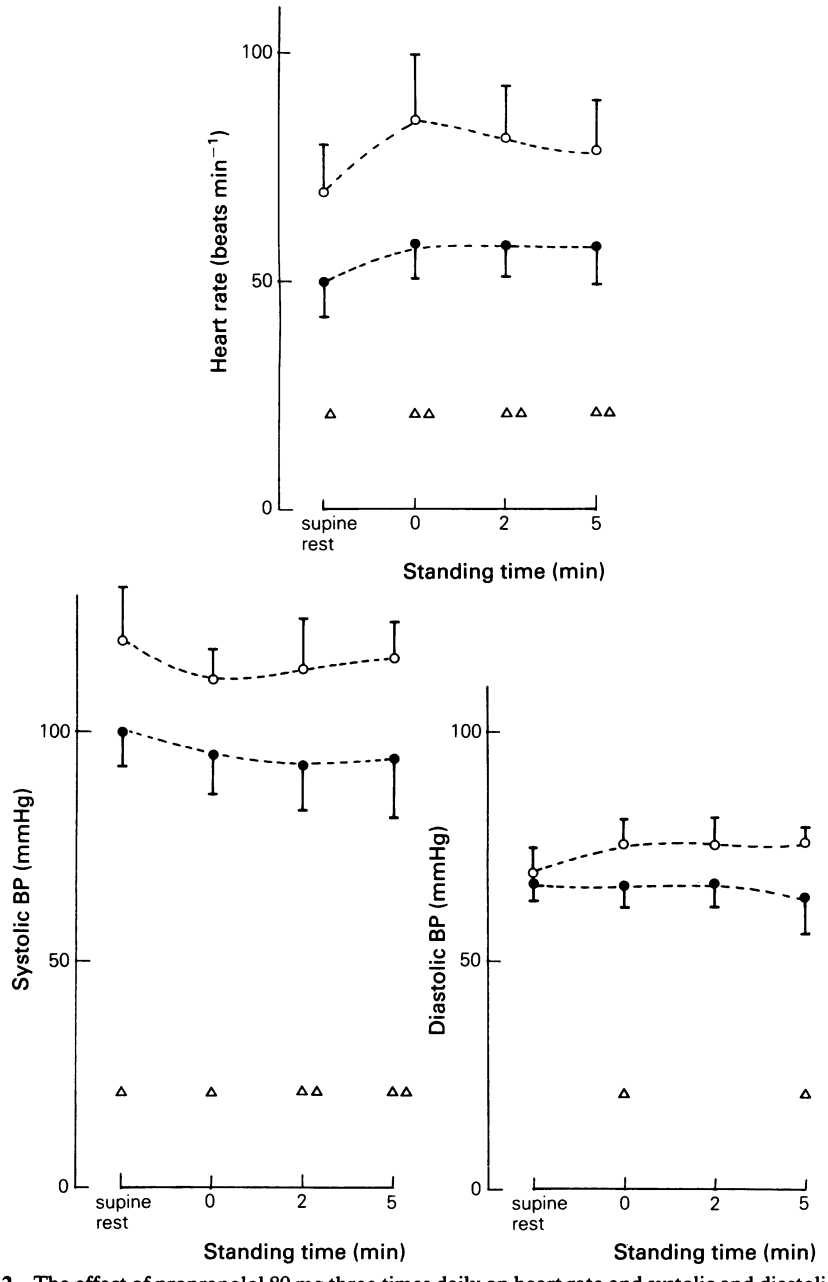

Figure 2 The effect of propranolol 80 mg three times daily on heart rate and systolic and diastolic blood pressures after 10 min supine rest, immediately on standing and at 2 and 5 min after standing. ○ control, ● during β-adrenoceptor blockade. △ $P < 0.01$, △ △ $P < 0.001$.

rate of recovery of force or excitation at any frequency (Table 3).

The MRR in previously unfatigued AP was slightly, but not significantly, reduced from 12.3 ± 0.8 to 11.6 ± 0.8 during β-adrenoceptor blockade. During activity the MRR declined to 1.7 ± 0.5 without β-adrenoceptor blockade and to very similar values during β-adrenoceptor blockade, 1.6 ± 0.2. There were no significant differences during recovery, the MRR having returned to control values by 15 min, 11.9 ± 1.2 without, and 11.2 ± 0.4 during β-adrenoceptor blockade.

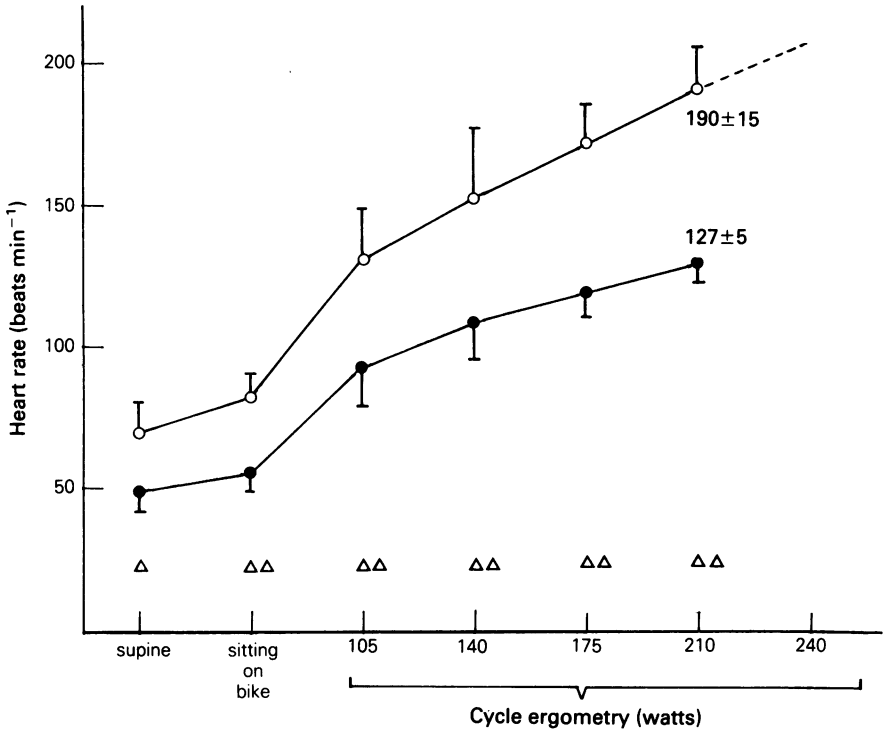

Figure 3 Heart rates at rest and during cycle ergometry in eight normal subjects. The results demonstrate that β-adrenoceptor blockade significantly reduced heart rate at rest ($P < 0.01$) and at all stages of ergometry, e.g. at 210 W: rate 190 ± 15 but 127 ± 5 beats min^{-1} during β-adrenoceptor blockade ($P < 0.001$). Only one subject performed more exercise before, compared with during β-adrenoceptor blockade (hence ------). ○ control, ● during β-adrenoceptor blockade. △ $P < 0.01$, △ △ $P < 0.001$.

Table 2 Declines of force and CMAP, at end of activity with and without circulatory occlusion without and during β-adrenoceptor blockade in eight subjects

Stimulation frequency (Hz)	*Force (% of fresh) without*	*during β-adrenoceptor blockade*	*Statistical significance*	*CMAP (% of fresh) without*	*during β-adrenoceptor blockade*	*Statistical significance*
Activity with arterial occlusion						
1	13 ± 4	13 ± 6	NS	70 ± 15	77 ± 11	NS
10	18 ± 7	15 ± 9	NS	68 ± 15	72 ± 17	NS
20	19 ± 7	18 ± 5	NS	57 ± 15	66 ± 23	NS
50	40 ± 16	42 ± 11	NS	21 ± 8	27 ± 17	NS
100	35 ± 17	34 ± 12	NS	15 ± 6	18 ± 8	NS
1	10 ± 5	9 ± 4	NS	75 ± 18	81 ± 19	NS
Activity without arterial occlusion						
1	71 ± 15	65 ± 18	NS	81 ± 22	77 ± 11	NS
10	93 ± 31	81 ± 25	NS	90 ± 18	90 ± 11	NS
20	66 ± 7	56 ± 7	< 0.05	91 ± 11	91 ± 9	NS
50	76 ± 5	71 ± 5	NS	68 ± 19	67 ± 15	NS
100	72 ± 7	68 ± 8	NS	42 ± 9	44 ± 11	NS
1	49 ± 9	49 ± 10	NS	73 ± 19	80 ± 14	NS

Activity without circulatory occlusion

During stimulated activity of AP, the declines in force were clearly less than during ischaemic activity but demonstrated a similar frequency dependance (Table 2; Figure 5b). At 10 Hz, there was marked potentiation of force such that at the end of activity, force remained similar to that of fresh muscle, 93 ± 31% (Table 2). The declines in force tended to be greater during β-adrenoceptor blockade but these differences were not significant except at 20 Hz where force declined to 66 ± 7% without, but to 56 ± 7% during β-adrenoceptor blockade ($P < 0.05$). However, the declines in force at 20 Hz were not significantly greater at all stages of activity, during

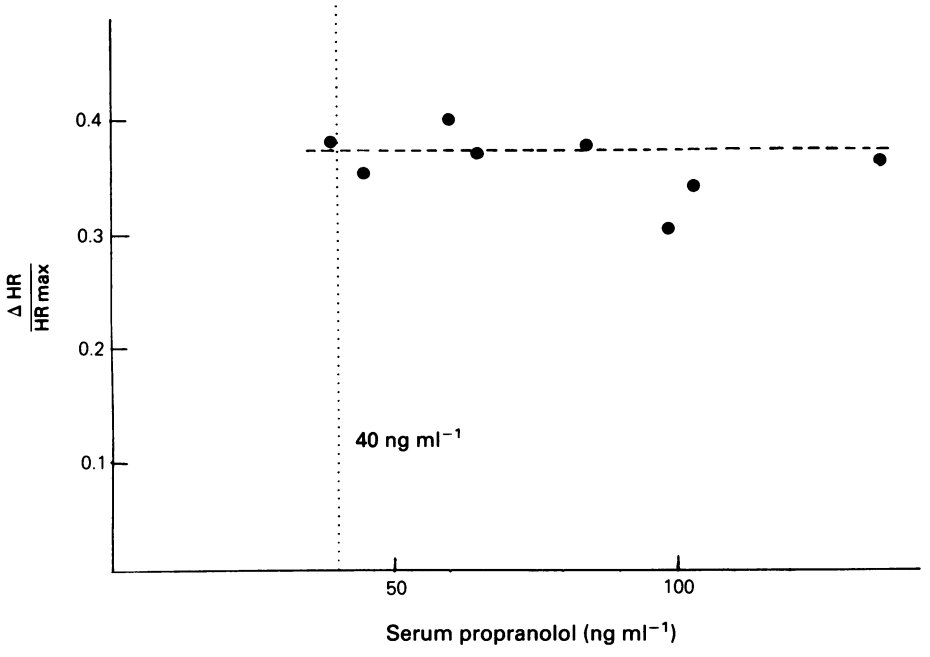

Figure 4 The ratio of β-adrenoceptor blockade induced reduction in maximal heart rates (Δ HR) and maximal heart rates (HRmax) are compared with serum propranolol concentrations. Despite a large range of drug levels, the ΔHR/HRmax ratio was similar in all subjects indicating that β-adrenoceptor blockade was complete.

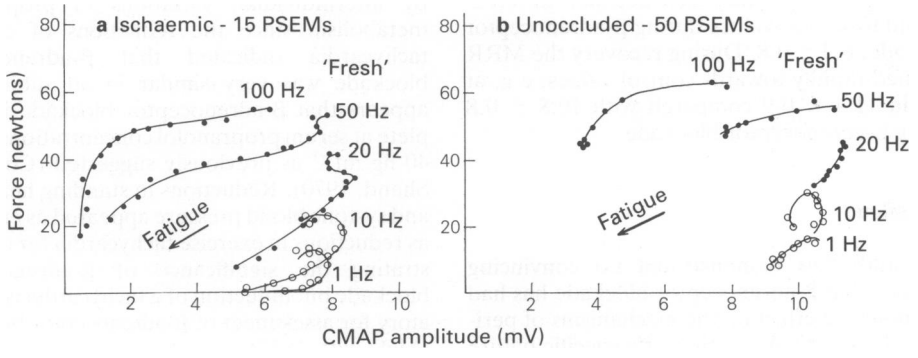

Figure 5 Declines in force (newtons) and CMAP amplitude (mV) during activity with and without circulatory occlusion. These results are in absolute values, rather than normalised and expressed as a % of fresh for clarity of presentation. They are from one experimental subject but are highly representative of results from all subjects. The declines in force and CMAP are clearly dependent on stimulation frequency. It can be seen that the pattern of changes is similar for both protocols but changes were of greater degree during ischaemia. At 1 and 10 Hz there was potentiation of force and CMAP amplitude during activity.

Table 3 Recovery in force and CMAP amplitude, 15 min after the end of activity with and without circulatory occlusion without and during β-adrenoceptor blockade in eight subjects

Stimulation frequency (Hz)	*Force (as % of fresh)*		*Statistical significance*	*CMAP (as % of fresh)*		*Statistical significance*
	without	*during β-adrenoceptor blockade*		*without*	*during β-adrenoceptor blockade*	
After activity with arterial occlusion						
1	67 ± 6	61 ± 6	NS	103 ± 11	100 ± 14	NS
10	61 ± 6	62 ± 16	NS	103 ± 8	101 ± 12	NS
20	71 ± 7	65 ± 8	NS	104 ± 6	101 ± 7	NS
50	95 ± 3	91 ± 4	NS	99 ± 4	101 ± 9	NS
100	94 ± 6	97 ± 4	NS	103 ± 14	116 ± 17	NS
1	61 ± 15	64 ± 9	NS	104 ± 13	101 ± 6	NS
After activity without arterial occlusion						
1	60 ± 13	47 ± 13	NS	87 ± 15	93 ± 15	NS
10	81 ± 29	50 ± 18	NS	95 ± 13	100 ± 11	NS
20	53 ± 7	47 ± 7	< 0.05	95 ± 10	99 ± 11	NS
50	77 ± 6	78 ± 6	NS	95 ± 12	98 ± 13	NS
100	84 ± 6	87 ± 4	NS	87 ± 11	92 ± 20	NS
1	45 ± 7	47 ± 10	NS	88 ± 15	91 ± 12	NS

β-adrenoceptor blockade. During recovery, force at high frequencies rapidly returned towards normal while at low frequencies (1, 10 and 20 Hz) force loss persisted at 15 min. There were no significant differences in the rates of recovery of force except at 20 Hz where force at 15 min was reduced to 53 ± 7% without, but to 47 ± 7% during β-adrenoceptor blockade ($P < 0.05$) (Table 3). The force at 20 Hz was not, however, significantly reduced at all stages of recovery during β-adrenoceptor blockade. In similar fashion to changes seen during activity with arterial occlusion, CMAP declined more at high than at low frequencies (Table 2; Figure 5b). There were no significant differences, comparing results without and during β-adrenoceptor blockade, in CMAP amplitude at any frequency during activity or recovery (Table 3).

During activity, the MRR declined to 6.6 ± 0.5 and to similar values during β-adrenoceptor blockade, 6.3 ± 0.8. During recovery the MRR returned rapidly towards control values, e.g. at 15 min 11.4 ± 0.9 compared with 10.8 ± 0.8 during β-adrenoceptor blockade.

Discussion

This study has demonstrated no convincing evidence that β-adrenoceptor blockade has had a pronounced effect on the mechanisms of peripheral fatigue of AP, either of a specific nature or as a result of circulatory impairment. The supramaximal stimulation techniques ensured that central mechanisms were excluded. The results, however, do demonstrate that changes in force generation and excitation are markedly dependent on stimulation frequency. Since perfusion is clearly important with regard to genesis of fatigue, this was the rationale for stimulated activity protocols with and without circulatory occlusion. The potential changes in fatiguability, due to β-adrenoceptor blockade, were expected to be encompassed between the extremes of total ischaemia and normal perfusion. Fatigue was obviously more pronounced with ischaemia as seen previously (e.g. Merton, 1954).

During the protocol with circulatory occlusion, there were no significant differences in force generation at any stimulation frequency with or without β-adrenoceptor blockade. During the protocol without circulatory occlusion forces were reduced during β-adrenoceptor blockade but not significantly so, with the possible exception at 20 Hz. The significance of this result at 20 Hz is rather debatable since the force was not reduced at all times throughout activity or recovery. The lack of a convincing effect on peripheral fatigue mechanisms could not be explained by interindividual variations in propranolol metabolism since the reductions of exercise tachycardia indicated that β-adrenoceptor blockade was very similar in all subjects. It appears that β-adrenoceptor blockade is complete at serum propranolol concentrations above 40 ng ml^{-1} as previously suggested (Coltart & Shand, 1970). Reductions in standing heart rate and systolic blood pressure appeared as effective as reductions in exercise tachycardia for demonstrating the significance of β-adrenoceptor blockade but induction of a tachycardia is mandatory for assessment of β-adrenoceptor blockade (McDevitt, 1977).

Peripheral fatigue mechanisms during β-adrenoceptor blockade have been assessed previously in the triceps surae (TS) using standard surface stimulation techniques (after Edwards *et al.*, 1977), before and following stimulated activity (Hughson *et al.*, 1987), and in double blind fashion comparing placebo with proprandolol 80 mg twice daily. Significantly greater low frequency (10 and 20 Hz) fatigue was detected

during β-adrenoceptor blockade apparently indicating that contractile function had been adversely affected. However, during a 90 min treadmill exercise protocol, when ratings of perceived exertion were significantly elevated and performance times obviously reduced during β-adrenoceptor blockade, contractile properties of TS, assessed immediately on stopping exercise, were not significantly altered (Alway *et al.*, 1987).

Some of the inconsistencies demonstrated in these studies may be explained since only part of the TS muscle underwent supramaximal surface stimulation. The technique of programmed supramaximal stimulation of the motor nerve ensures complete activation of the muscle and produces highly repeatable changes during fatiguing activity (Cooper *et al.*, 1987, 1988). Despite using this very quantitative method, significant excess peripheral fatigue was not clearly demonstrated during β-adrenoceptor blockade in the present study of AP even though this muscle consists of predominantly type I fibres (Round *et al.*, 1984). Animal studies clearly demonstrate that the catecholamine response of a muscle is dependent on fibre type (Bowman & Nott, 1969). Thus, fusion of low frequency tetani is reduced in type I (slow twitch) muscle fibres, and mean force falls, but is increased in type II (fast twitch) muscle fibres, and mean force rises. Furthermore, slow twitch muscles may have greater densities of β-adrenoceptors (Williams *et al.*, 1984) and hence be more liable to β-adrenoceptor blockade changes than fast twitch muscles.

The β_2-adrenoceptor may regulate sarcolemmal Na^+/K^+ ATPase (Bowman, 1981; Clausen & Flatman 1977). Extracellular K^+ accumulation could reduce resting membrane potential (Kwiecinski *et al.*, 1984) thereby reducing the action potential amplitude (Hodgkin & Katz, 1949). A reduction in membrane propagation could also increase the duration of the action potential. These changes might be expected to alter the electromyogram (EMG). However, previous studies have demonstrated conflicting results regarding the EMG during various activity protocols with β-adrenoceptor blockade (Tesch *et al.*, 1984b) and the present study demonstrated no significant differences in the rates of change of CMAP amplitude during β-adrenoceptor blockade.

The effect of β-adrenoceptor blockade on muscle relaxation is unclear. During activity, MRR slowing results in increases in fusion, and hence mean force, of low frequency tetani. Thus, slowing may counteract fatigue (Jones, 1981; Bigland-Ritchie *et al.*, 1983) and may explain the 10 Hz force potentiation seen in the present study. Clinical myotonia is reported during β-adrenoceptor blockade, with improvement following cessation of such therapy (Blessing & Walsh, 1977). However, stimulated twitch ½ relaxation times were not increased in previous studies (Hughson *et al.*, 1987; Alway *et al.*, 1987) and in the present study reductions in MRR during β-adrenoceptor blockade were not significant. It appears that β-adrenoceptor blockade has no important effects on muscle relaxation.

Excess fatigue during β-adrenoceptor blockade has been demonstrated previously during submaximal or maximal treadmill, running or ergometry exercise to exhaustion (Kaiser, 1984; Tesch *et al.*, 1984a). The limiting point in many of these protocols was not 'locally specific' exhaustion, e.g. of legs, but 'general' exhaustion. This 'general' exhaustion appears to have been reached when the increasing perfusion requirements of exercising muscle could not be met by cardiorespiratory oxygen transport. Clearly, if maximum cardiac output was reduced by 20% during β-adrenoceptor blockade (Epstein *et al.*, 1965) then a reduction in maximum performance might also be expected. The use of AP in the present study might be questioned since such a small muscle could be exercised to exhaustion but the maximum local blood flow required would clearly remain within the cardiac reserve, despite β-adrenoceptor blockade. However, since local requirements of a small muscle would not dictate alterations in cardiac output, it follows that the blood supply to AP in the present study would be reduced in line with reductions in cardiac output as previously demonstrated (Smith & Warren, 1982). Despite this reduction in local blood supply impairments in force production during the perfused protocol were small and mostly insignificant even though the muscle underwent considerable fatiguing activity. The use of a larger muscle, such as quadriceps, would require supramaximal stimulation of the femoral nerve which is both painful and potentially dangerous due to risk of patellar dislocation.

What then is the interpretation of these results? The absence of excess peripheral fatigue during β-adrenoceptor blockade may indicate impairments of central fatigue mechanisms. An alternative is that any impairments of peripheral muscle function during β-adrenoceptor blockade, of a specific nature or related to blood flow changes, though small are detectable during voluntary exercise and give rise to increased central activity i.e. increased motor unit recruitment and/or firing rates, and hence increased perception of fatigue.

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References

Alway, S. E., Hughson, R. L., Green, H. J., Patla, A. E. & Frank J. S. (1987). Contractile properties of the human triceps surae following prolonged exercise and β-blockade. *Clin. Physiol.*, **7**, 151–163.

Arnold, A., McAuliff, J. P., Colella, D. F., O'Connor, W. V. & Brown, T. G. (1968). The β_2-receptor mediated glycogenolytic responses to catecholamines in the dog. *Arch. int. Pharmacodyn.*, **176**, 451–457.

Bigland-Ritchie, B., Johansson,R., Lippold, O. C. J. & Woods, J. J. (1983). Contractile speed and EMG changes during fatigue of sustained maximal voluntary contractions. *J. Neurophysiol.*, **50**, 313–324.

Blessing, W. & Walsh, J. C. (1977). Myotonia precipitated by propranolol therapy. *Lancet*, **i**, 73.

Bowman, W. C. (1981). Adrenergic activators and inhibitors. In *Handbook of Experimental Pharmacology*, ed Szekeresh, E., **54**, part 2, pp. 47–128.

Bowman, W. C. & Nott, M. W. (1969). Actions of sympathomimetic amines and their antagonists on skeletal muscle. *Pharmac. Rev.*, **21**, 27–72.

Clausen, T. & Flatman, J. A. (1977). The effect of catecholamines on Na-K transport and membrane potential in rat soleus muscle. *J. Physiol.*, **270**, 383–414.

Coltart, D. J. & Shand, D. G. (1970). Plasma propranolol levels in the quantitative assessment of β-adrenergic blockade in man. *Br. med. J.*, **3**, 731–734.

Cooper, R. G., Edwards, R. H. T., Gibson, H. & Stokes, M. (1987). Human muscle fatigue: effects of ischaemia, perfusion and β-adrenergic blockade. *J. Physiol.*, **390**, 156P.

Cooper, R. G., Edwards, R. H. T., Gibson, H. & Stokes, M. (1988). Human muscle fatigue: frequency dependence of excitation and force generation. *J. Physiol.*, **397** (in press).

Edwards, R. H. T., Young, A., Hosking, G. P. & Jones, D. A. (1977). Human skeletal muscle function: description of tests and normal values. *Clin. Sci. mol. Med.*, **52**, 283–290.

Eklund, B. & Kaijser, L. (1976). Effect of regional and β-adrenergic blockade on blood flow in the resting forearm during contralateral isometric handgrip. *J. Physiol.*, **262**, 39–50.

Epstein, S. E., Robinson, B. F., Kahler, R. L. & Braunwald, E. (1965). Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man. *J. clin. Invest.*, **44**, 1745–1753.

Frisk-Holmberg, M., Jorfeldt, L. & Juhlin-Dannfelt, A. (1977). Influence of alprenolol on haemodynamic and metabolic responses to prolonged exercise in subjects with hypertension. *Clin. Pharmac. Ther.*, **21**, 675–684.

Harris, R. C., Hultman, E., Kaijser, L. S. & Nordesjö, L-O. (1975). The effect of circulatory occlusion on isometric exercise capacity and energy metabolism of the quadriceps muscle in man. *Scand. J. clin. lab. Invest.*, **35**, 87–95.

Hodgkin, A. L. & Katz, B. (1949). The effect of sodium ions on the electrical activity of the giant axon of the squid. *J. Physiol.*, **108**, 37–77.

Hughson, R. L., Green, H. J., Alway, S. E., Patla, A. E. & Frank, J. S. (1987). The effects of β-blockade on electrically stimulated contraction in fatigued human triceps surae muscle. *Clin. Physiol.*, **7**, 133–150.

Jorfeldt, L. & Wahren, J. (1971). Leg blood flow during exercise in man. *Clin. Sci.*, **41**, 459–473.

Jones, D. A. (1981). Muscle fatigue due to changes beyond the neuromuscular junction. In *CIBA Foundation Symposium*, No 8, pp 178–196. London: Pitman Medical.

Kaiser, P. (1984). Physical performance and muscle metabolism during β-adrenergic blockade in man. *Acta physiol. Scand.*, **Suppl 536**, 1–53.

Kaiser, P. & Tesch, P. A. (1983). Muscle lactate accumulation during exercise following β-adrenergic blockade. *Acta physiol. Scand.*, **117**, 149–151.

Kaiser, P., Tesch, P. A., Frisk-Holmberg, M., Juhlin-Dannfeldt, A. & Kaijser, L. (1986). Effect of β_1-selective and non-selective β-blockade on work capacity and muscle metabolism. *Clin. Physiol.*, **6**, 197–207.

Kwiecinski, H., Lehmann-Horn, F. & Rudel, R. (1984). The resting membrane parameters of human intercostal muscle at low, normal, and high extracellular potassium. *Muscle and Nerve*, **7**, 60–65.

Lewis, R. V., Jackson, P. R. & Ramsay, L. E. (1984). Quantification of side effects of β-adrenoceptor blockers using visual analogue scales. *Br. J. clin. Pharmac.*,**18**, 325–330.

McDevitt, D. G. (1977). The assessment of β-adrenoceptor blocking drugs in man. *Br. J. clin. Pharmac.*, **4**, 413–425.

Merton, P. A. (1954). Voluntary strength and fatigue. *J. Physiol.*, **123**, 553–564.

Mills, K. R. (1982). Power spectral analysis of electromyogram and compound muscle action potential during muscle fatigue and recovery. *J. Physiol.*, **326**, 401–409.

Round, J. M., Jones, D. A., Chapman, S. J., Edwards, R. H. T., Ward, P. S. & Fodden, D. L. (1984). The anatomy and fibre type composition of the human adductor pollicis in relation to its contractile properties. *J. neurol. Sci.*, **66**, 263–292.

Smith, R. S. & Warren, D. J. (1982). Effect of acute oral beta adrenergic blockade on muscle blood flow in man. *Cardiovasc. Res.*, **16**, 205–208.

Stephans, J. A. & Taylor, A. (1972). Fatigue of maintained voluntary muscle contraction in man. *J. Physiol.*, **220**, 1–18.

Stephen, S. A. (1966). Unwanted effects of propranolol. *Am. J. Cardiol.*, **18**, 463–472.

Tesch, P. A. & Kaiser, P. (1983). Effects of β-adrenergic blockade on O_2 uptake during submaximal and maximal exercise. *J. appl. Physiol.*, **54**, 901–905.

Tesch, P. A., Kaiser, P. & Kaijser, L. (1984a). Isometric muscle endurance during acute β-adrenergic blockade. *Acta physiol. Scand.*, **120**, 71–75.

Tesch, P. A., Kaiser, P. & Komi, P. V. (1984b). Effects of β-adrenergic blockade on EMG signal characteristics during progressive exercise. *Acta physiol. Scand.*, **121**, 189–191.

Trap-Jensen, J., Clausen, J. P., Noer, I.., Larsen, O. A., Krogsgaard, A. R. & Christensen, N. J. (1976). The effect of beta-adrenoceptor blockers on cardiac output, liver blood flow and skeletal muscle blood flow in hypertensive patients. *Acta physiol. Scand.*, **Suppl 440**, 30.

Wilcox, R. G., Bennett, T., MacDonald, I. A., Herbert, M. & Skene, A. M. (1984). The effects of acute or chronic ingestion of propranolol or metoprolol on the physiological responses to prolonged sub-maximal exercise on hypertensive men. *Br. J. clin. Pharmac.*, **17**, 273–281.

Wiles, C. M. & Edwards, R. H. T. (1982). The effect of temperature, ischaemia and contractile activity on the relaxation rate of human muscle. *Clin. Physiol.*, **2**, 485–497.

Williams, R. S., Caron, M. C. & Daniel, K. (1984). Skeletal muscle β-adrenergic receptors: variations due to fibre type and training. *Am. J. Physiol.*, **246**, E160–E167.

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