Heart-rate response to sustained hand grip: comparison of the effects of cardiac autonomic blockade and diabetic autonomic neuropathy

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Summary

1. The heart-rate response during sustained hand grip was studied in four normal subjects before and after intravenous atropine, propranolol and combined cardiac autonomic blockade with both drugs. The results suggest that the increase in heart rate during the first 30 s is due to parasympathetic withdrawal, whereas the further increase between 30 s and 180 s is probably mediated by a combination of parasympathetic withdrawal and sympathetic stimulation.

2. The increases in heart rate during each minute of sustained hand grip were compared in 26 normal subjects, 37 diabetic subjects without and 24 diabetic subjects with proven autonomic neuropathy. In the diabetic subjects with autonomic neuropathy the increase in heart rate during the first minute was impaired, whereas the increases during the second and third minutes were similar in all three groups.

3. The initial increase in heart rate over the first 30 s of hand grip and the later increase between 30 s and 180 s were compared in nine normal subjects, ten diabetic subjects without and six diabetic subjects with autonomic neuropathy. The increase during the first 30 s was impaired in the diabetic subjects with autonomic neuropathy, whereas the later phase of the response was similar in all three groups.

4. It is concluded that impairment of the heart-rate response to sustained hand grip in diabetic autonomic neuropathy is mainly due to impairment of the early parasympathetic phase, but that the presence of cardiac sympathetic damage can also be detected.

Key words: autonomic blockade, diabetic autonomic neuropathy, heart rate, sustained hand grip.

Introduction

The normal reflex cardiovascular response to sustained hand grip is characterized by increases in heart rate and blood pressure (Donald, Lind, McNicol, Humphreys, Taylor & Staunton, 1967). The increase in heart rate occurs in two phases (Petrofsky & Lind, 1975) with an initial rapid increase due to the withdrawal of cardiac parasympathetic activity followed by a slower increase which is probably mediated by cardiac sympathetic stimulation (Martin, Shaver, Leon, Thompson, Reddy & Leonard, 1974).

The heart-rate response to sustained hand grip is impaired in some diabetic subjects, and this is thought to be due to damage to the autonomic pathways mediating the response (Ewing, Campbell, Burt & Clarke, 1973; Nazar, Tatan, Chwalbinska-Moneta & Brzezinska, 1975). We have now attempted to establish the relative importance of sympathetic and parasympathetic involvement in the impaired heart-rate response to sustained hand grip in diabetic autonomic neuropathy.
Subjects and methods

The study was performed in three parts. The effect of cardiac autonomic blockade on the heart-rate response to sustained hand grip in normal subjects was first assessed. Secondly the increase in heart rate during each of the first 3 min of sustained hand grip was compared in normal subjects and in diabetic subjects with and without autonomic neuropathy. Finally the early phase of the heart rate response was examined, by comparing the increase between the first 30 s of hand grip with the increase between 30 and 180 s. Sustained hand grip was carried out by using a dynamometer with a comfortable, shaped hand grip (model HMZ, Tephcotronics Ltd, 5 Hillview Drive, Edinburgh, U.K.), containing a linear displacement transducer which provides an electrical output as a linear function of the applied force, in the range 0–75 kg, and allowing subsequent readings to be displayed as a percentage of the initial force.

For each subject the maximal voluntary contraction (MVC) was first determined as the highest of three brief maximal hand grip contractions. The subject was then asked to maintain 30% maximal hand grip contraction for 3 min or more, as described by Ewing, Irving, Kerr, Wildsmith & Clarke (1974), while heart rate was recorded by an electrocardiogram.

Effect of diabetic autonomic neuropathy

The subjects for these studies were all males. The diabetics without autonomic neuropathy had a normal Valsalva ratio and blood pressure response to sustained hand grip, whereas the diabetics with autonomic neuropathy had one or more clinical features (postural hypotension, abnormal sweating, gastric atony, diarrhoea, hypoglycaemic unawareness) and also an abnormal Valsalva ratio and impaired blood-pressure response to sustained hand grip (Ewing et al., 1973). None of the subjects had clinical evidence of cardiovascular or respiratory disease.

Study B

There were 26 normal subjects aged 28–52 (mean 41) years (group B1), 37 diabetic subjects without autonomic neuropathy aged 24–64 (mean 46) years (group B2) and 24 diabetics with autonomic neuropathy aged 29–63 (mean 48) years (group B3). Heart rate was recorded before, at 60 s, 120 s and 180 s during hand grip, and 120 s after release.

Study C

There were nine normal subjects aged 30–60 (mean 46) years (group C1), ten diabetics without autonomic neuropathy aged 21–65 (mean 44) years (group C2) and six diabetic subjects with autonomic neuropathy aged 28–65 (mean 44) years (group C3). Heart rate was recorded before, 30 s and 180 s after starting hand grip, and 120 s after release.

Statistical analysis

The results are expressed as the group mean ± SD. The data from the drug study were subjected to analysis of variance in the form of a factorial design problem (Armitage, 1971). The effect of one drug was assessed both by comparing the response after that drug alone with the response before autonomic blockade and by comparing the response after combined blockade with the response after the second drug alone.

Statistical comparison of the normal and diabetic groups in studies B and C was by one-way analysis of variance. Student's unpaired t-test was applied when the analysis of variance indicated that the differences between the groups were statistically significant.
Results

Effect of cardiac autonomic blockade (Study A)

As the heart-rate changes recorded during the two control periods were not significantly different, the results given are the mean of the changes on the 2 days.

The mean increase in heart rate during the entire 180 s period of hand grip before autonomic blockade (15.5 beats/min) was not significantly different after atropine (14.7 beats/min), but was slightly and significantly decreased after propranolol (9.7 beats/min) \((P < 0.01)\). After combined autonomic blockade with both drugs the response was considerably lowered, with an increase of only 2.7 beats/min \((P < 0.01)\) (Fig. 1).

During the first 30 s of the contraction the mean increase in heart rate was 7.3 beats/min before autonomic blockade. This was significantly reduced after atropine alone (1.5 beats/min) and in combination with propranolol (1.2 beats/min) (both \(P < 0.05\)). Propranolol alone had no effect, the mean increase after the drug being 5.5 beats/min.

Between 30 s and 180 s of hand grip the mean increase in heart rate before autonomic blockade was 8.2 beats/min. The larger increase after atropine (13.2 beats/min) was not significantly greater than before autonomic blockade, whereas the reductions after propranolol alone (4.2 beats/min) and after combined autonomic blockade (1.5 beats/min) were significant (both \(P < 0.01\)).

Effect of diabetic autonomic neuropathy

Study B (Table 1 and Fig. 2). The mean increases in heart rate both during the first 60 s and the full 180 s of hand grip in the diabetic subjects with autonomic neuropathy (group B3) were significantly less than in the normal subjects (group B1) and the diabetic subjects without autonomic neuropathy (group B2) \((P < 0.001)\). There were no significant differences between the two latter groups (B1 and B2). In contrast, the increases in heart rate during the second and third minutes of hand grip were not significantly different in the three groups. Fig. 2 shows the loss of the initial rapid phase of the heart-rate increase in the diabetic subjects with autonomic neuropathy (group B3).

Study C (Table 2). The mean increase during the first 30 s of hand grip was significantly less in the diabetic subjects with autonomic neuropathy (group C3) than in the normal subjects (group C1) \((P < 0.01)\) and the diabetic subject without autonomic neuropathy (group C2) \((P < 0.05)\), whereas the further increase between 30 s and 180 s

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Table 1. Effects of sustained hand grip on heart rate (beats/min), in normal and diabetic subjects (study B)

was similar in all three groups. The mean heart-rate changes in the normal subjects (C1) and the diabetic subjects without autonomic neuropathy (C2) were not significantly different.

**Discussion**

The effects of pharmacological autonomic blockade on the heart-rate changes during sustained hand grip in this study agree in several respects with previous findings in normal subjects. Our study confirms that the tachycardia in the initial 30 s of hand grip is not influenced by propranolol but is largely inhibited by atropine, supporting the view that the heart-rate response to sustained hand grip is initiated by the withdrawal of cardiac parasympathetic tone (Freyschuss, 1970; Martin et al., 1974). The present results also confirm that atropine alone has no effect on the total heart-rate increase during 180 s of sustained hand grip (Martin et al., 1974) as the greater heart-rate increase between 30 s and 180 s offsets the reduction of the first 30 s. This is presumably due to increased cardiac sympathetic stimulation. Our results also confirm that combined parasympathetic and β-adrenoreceptor blockade almost completely abolishes the tachycardia during hand grip (Martin et al., 1974).

In this study propranolol alone was shown to reduce significantly the total heart-rate increase by inhibiting the later phase between 30 s and 3 min. This finding disagrees with previous studies in which β-adrenoreceptor blockade alone had no effect on the heart-rate changes during a similar level and duration of sustained hand grip (MacDonald, Sapru, Taylor & Donald, 1966; Martin et al., 1974). The observation that atropine had no effect on the total heart-rate increase, whereas combined cardiac autonomic blockade virtually abolishes the response, has previously been interpreted to show that cardiac sympathetic stimulation only contributes to the heart-rate increase if withdrawal of cardiac parasympathetic activity is not sufficient as, for example, after parasympathetic blockade (Martin et al., 1974). The modest, but significant, effect of propranolol alone on the total increase in heart rate suggests that in normal, 'unblocked' subjects the heart-rate increase in the later stages of sustained hand grip is due to a combination of both parasympathetic withdrawal and cardiac sympathetic stimulation.

The results of study B show that the heart-rate increase during the first minute of hand grip is significantly reduced in diabetic subjects with autonomic neuropathy, when compared with normal subjects and diabetic subjects without autonomic neuropathy. In study C the impairment of the

![Changes in heart rate (beats/min)](image)

**FIG. 2. Study B. Heart-rate changes during sustained hand grip in normal and diabetic subjects. Each point represents group mean result. x, Group B1 normal subjects, n = 26; o, group B2 diabetic subjects without autonomic neuropathy, n = 37; ■, group B3 diabetic subjects with autonomic neuropathy, n = 24.**

**Table 2. Effect of sustained hand grip on heart rate (beats/min) in normal and diabetic subjects (study C)**

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early phase of the heart-rate response in diabetic subjects with autonomic neuropathy was shown to occur within the first 30 s of the contraction, which corresponds to the phase of parasympathetic withdrawal in normal subjects (Martin et al., 1974). In both studies the later phase of the heart-rate response to hand grip was similar in all three groups.

These observations show that the smaller heart-rate increase during sustained hand grip which has previously been described in diabetic subjects with autonomic neuropathy (Ewing et al., 1973) is due mainly to impairment of the parasympathetic phase of the response, and lend support to the view that impaired parasympathetic function is a common and prominent feature of diabetic autonomic neuropathy (Bennett, Hosking & Hampton, 1975; Lloyd-Mostyn & Watkins, 1975).

If, however, the abnormal heart-rate response was due entirely to parasympathetic denervation the pattern of response should resemble that seen in normal subjects after atropine. Our study shows that this is not the case. After parasympathetic blockade in the normal subjects the heart-rate increase during the later stages of the contraction was greater than before autonomic blockade, and consequently the total increase in heart rate remained unchanged. In contrast, in the diabetic subjects with autonomic neuropathy this greater heart-rate increase did not occur during the later stages of hand grip, so that the total increase in heart rate was less. This probably reflects the presence of cardiac sympathetic nerve damage, as well as parasympathetic denervation, in diabetic autonomic neuropathy.

Acknowledgments

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References


