Br. J. clin. Pharmac. (1977), **4**, 275–281

INDIRECT BLOOD PRESSURE AND HEART RATE MEASURED QUICKLY WITHOUT OBSERVER BIAS USING A SEMI-AUTOMATIC MACHINE (AUTO-MANOMETER)— RESPONSE TO ISOMETRIC EXERCISE IN NORMAL HEALTHY MALES AND ITS MODIFICATION BY β-ADRENOCEPTOR BLOCKADE

G. NYBERG*

Astra Chemicals Pty Ltd, Box 131, P.O., North Ryde, New South Wales 2113, Australia

1 In a double-blind crossover study, six volunteers performed sustained handgrip at 50% of maximal voluntary contraction before and 90 min following oral administration of 0, 25 and 100 mg metoprolol tartrate, a β_1 selective adrenoceptor blocking agent. Blood pressure and heart rate were measured with the Auto-Manometer, an electronic semi-automatic device based on the principles of the London School of Hygiene and Tropical Medicine sphygmomanometer. It eliminates observer and digital bias completely, and also records heart rate at the same time as blood pressure is recorded.

2 Resting heart rate fell 15% after 25 mg, 21% after 100 mg and was unchanged after placebo. Systolic blood pressure fell 6% on both doses and was unchanged on placebo. Diastolic pressure did not change with any of the doses.

3 At 1 min of handgrip, heart rate was significantly lower after 25 and 100 mg than before drug or after placebo. There was no difference between the blood pressure levels attained before or after any of the dose levels. The rise of heart rate tended to be somewhat dampened after 100 mg only. The rise in blood pressure was unchanged after any dose compared with before.

Introduction

Isometric exercise is a potent stimulus to elevation of systolic and diastolic blood pressure, and heart rate (Krayenbuehl & Rutishauser, 1973). Isometric exercise is commonplace in daily life, and since the time-averaged arterial pressure level in hypertensive patients is probably related to the incidence and seriousness of complications, it seems important to learn about the magnitude of these changes and the way antihypertensive therapy influences them.

In recent years, β-adrenoceptor blocking agents have become increasingly popular in the treatment of hypertension as well as many other conditions such as ischaemic heart disease, arrhythmias, anxiety, migraine, and in preventing complications after a myocardial infarction (Doyle, 1974; Harrison, 1974; Vedin, Wilhelmsson & Werkö, 1975; Whitlock & Price, 1974). The present study was undertaken to investigate the effects of isometric exercise (sustained handgrip), before and after two dose levels of a β_1-selective adrenoceptor blocking agent, metoprolol (Åblad, Borg, Carlsson, Ek, Johnsson, Malmfors & Regårdh, 1975), on heart rate and blood pressure in healthy males.

* Present address: Medical Department 1, Sahlgrenska Hospital, S–143 45 Goteborg, Sweden.

Methods

Heart rate and blood pressure measurements were taken with an Auto-Manometer® (Electronic Research Research and Development, Dunedin, New Zealand), which can be described as an electronic modification of the principle on which the London School of Hygiene and Tropical Medicine sphygmomanometer is based. It enables indirect recording of blood pressure to be made in the normal clinical way without the risk of observer or digital bias.

The Auto-Manometer® (Figure 1) is dependent on an external source of compressed air and electric power. The cuff inflation rate is constant and cuff deflation is automatically induced through decrease in cuff pressure variations when pressure has risen above

Figure 1 Front view of the Auto-Manometer. The air inlet, and an outlet for connection to a mercury manometer for calibration are on the back. The cuff inlet is on the right side. The lever to the left is used to determine inflation pressure level. When the inflation-deflation switch is flicked to inflation, INF lights up in the display window. Inflation pressure is increased manually whilst Korotkov sounds are auscultated, and when systolic level has been surpassed, the switch is flicked to deflation; DEF then lights up in the display window.

Deflation rate is regulated by the knob. During deflation, the light above the heart rate switch follows the pulse and indicates what is actually counted—any artefacts can thus easily be recognized. When Korotkov sounds are heard respectively disappear, switches 1–4 can be used to store corresponding pressure values, thus giving ample room for both mistakes and phase IV and V readings.

When the recording cycle is over, the far right switch is depressed, END then shows in display. Should this switch be depressed before the heart rate counting has ended (takes 30 s from start of deflation), HOL lights up on display and deflation continues at preset rate. Only when heart rate counting is finished does END light up automatically and deflation occurs rapidly.

When pressure and heart rate switches are depressed, the figures light up on the display.

The Vigorimeter is shown on top of the Auto-Manometer.

the systolic level. A later modification makes manual regulation of the inflation pressure level possible (cf. text under Figure 1). This mechanism can be overridden manually and it is often preferable to listen to the Korotkov sounds during inflation and switch to deflation when they have ceased. This avoids excessive inflation which can easily happen in subjects with a thick arm.

The deflation rate is constant and can be varied from 1–4 mmHg/s. There are four switches for storing pressure values during deflation. The device also counts heart rate from pressure changes in the cuff over the first 30 s from start of deflation. The values are displayed digitally when the corresponding switches are again depressed once the recording cycle is over. The whole recording sequence takes 45–75 s. A mercury manometer can easily be attached to check calibration.

The protocol given in Table 1 was used, taking blood pressure in the left arm in sitting subjects. All recordings were done with as little delay as possible between the different sections of the protocol, and the sequence usually took 15–20 min, depending on the blood pressure level. Sustained handgrip at 50% of maximal voluntary contraction was performed for about 1 min with a Vigorimeter (Gebrueder Martin, Tuttlingen, Germany), which consists of a rubber balloon and an aneroid manometer. The rises in both blood pressure and heart rate are virtually linear from the start of handgrip, for at least 1 min (Ewing, Irving, Kerr & Kirby, 1973). Therefore the exact times after start of handgrip are noted for systolic and diastolic blood pressure measurements and end of heart rate counting, and values are extrapolated to 1 min.

Mental arithmetic was done by continuously subtracting 17 from a four-digit number as fast as possible, for about 5 min. The subjects wrote down the answers on a standardized form ruled into columns, and were asked to start a new column each minute. The results from the mental arithmetic test will be reported in a separate paper.

Subjects

Seven healthy males, age ranging from 23–45 years (mean 34.6) took part. None of them had a previous history of hypertension, cardiac disease or bronchial disease. They gave their informed consent to participation in the study.

After a training session, the subjects performed the protocol twice on three different days, once before and once 90 min after intake of tablets of either placebo, 25 mg or 100 mg metoprolol tartrate. Tablets of 50 mg were used together with identical placebos, and made up so that the doses were blind to both subjects and investigator. The different doses were given in randomized order in a Latin square design. The subjects were allowed a light breakfast in the morning; the studies were done 2–4 h postprandially. The subjects carried on with their usual clerical activity between sessions and rested in the sitting position for five minutes before each session. The first two test days were consecutive, whereas the final one was 3 days later. (This may have affected the results slightly—c.f. **Results**).

Because of temporary faults in the equipment, one patient could not be assessed on placebo and another could not be assessed on the 100 mg dose. Therefore, the results will give paired comparisons of placebo *v.* 25 mg for six subjects and paired comparisons for 25 *v.* 100 mg in six. Five of the subjects in these two comparisons are common to both.

For statistical calculation, Student's paired *t*-test has been used, two-tailed.

Results

Resting values

Average resting values before and after tablet are given in Table 2. After tablets, no significant changes were seen when placebo was used. With metoprolol (25 mg), heart rate fell by 14.8% ($P < 0.01$). Systolic blood pressure fell by 6.5% ($P < 0.05$).

With metoprolol (100 mg), heart rate fell by 20.6% ($P < 0.001$), which is significantly ($P < 0.01$) more than with 25 mg. Systolic blood pressure fall was equal to that on metoprolol (25 mg), 6.4% ($P < 0.10$).

When post-tablet values of placebo *v.* metoprolol (25 mg) are compared, it is found that heart rate ($P < 0.01$) and systolic blood pressure ($P < 0.05$) are significantly lower on 25 mg. There are no significant differences between the 25 mg and 100 mg doses.

Rise of blood pressure and heart rate during isometric exercise

Average rises during the first and second isometric tests are given in Table 2. Mostly, the rises are slightly greater at the second test compared with the first test; however, no statistically significant differences are seen between tests, neither before nor after tablets.

Comparing post-tablet values, only one statistically significant difference is seen: the heart rate rise during Test 2 after tablets is greater with 25 mg (12.4 beats/min) than with 100 mg (6.7 beats/min), ($P < 0.05$).

Extrapolated levels of blood pressure and heart rate at 1 min of isometric exercise

Table 3 gives values for systolic, diastolic and mean blood pressure (mean being the diastolic + 1/3 the pulse pressure), and heart rate at 1 min of isometric exercise (values extrapolated to 1 min, rounded figures, as stated in **Methods**).

Heart rate but not blood pressure is significantly lower after tablets compared with before. In all instances except one, heart rate and blood pressure reached higher levels at the second test: these differences are not statistically significant.

When post-tablet values of placebo *v.* metoprolol (25 mg) are compared, it is seen that the level of heart rate is significantly ($P < 0.02$) lower on the 25 mg dose.

Comparing 25 mg with 100 mg, heart rate at the second test (but not the first) is significantly ($P < 0.05$) lower on the 100 mg dose than on the 25 mg dose. Blood pressure levels were not significantly different in any of the comparisons.

Day to day variation

In Table 4, the mean values for blood pressures and heart rate are given for each successive day before tablets in the six subjects who completed all pre-drug sessions. The coefficients of variation over the 3 days for each individual are summarized and given as median and range. The coefficient of variation rarely exceeded 10% and was around 5% for systolic blood pressure and heart rate and a little greater for diastolic blood pressure.

The tendency to a lower systolic blood pressure at rest and in the first handgrip test on Day 2 may be due to some hangover effect from the 100 mg dose taken

Table 1 Protocol for tests of isometric exercise and mental arithmetic

Approximate time (min)	
0	Patient seated
1–5	Three successive blood pressure readings
6	First isometric test
7	Post-exercise reading
8	Second isometric test
9	Post-exercise reading
10–16	Mental arithmetic Five blood pressure readings
17	Post-exercise reading

The whole procedure can take from 15–20 min, depending on the blood pressure level.
Resting value reported in Tables 2–4 is the mean of all five resting recordings before the mental arithmetic.
Mental arithmetic value is the mean of five recordings during the test.

on the previous day (c.f. **Methods**). For the two patients who took the 100 mg dose on the first day, the mean resting blood pressure on the second day before drug was 9 and 7 mm lower than on the first day. This was greater than for the remaining four subjects (average mean resting pressure 1.5 mm lower). At the first handgrip test, the first two patients' mean blood pressure was 21 and 23 mmHg lower on the second day than on the first day, and the average for the four remaining was 2 mm lower.

Discussion

The changes in heart rate and blood pressure in the present study are of the same magnitude as in previously reported studies, utilizing the same methodology (Nyberg, 1976b). The blood pressure response (but not the heart rate response) is greater in hypertensives in absolute values; less so on a percentage basis (Nyberg, 1976b).

Both doses of metoprolol caused falls in heart rate (dose-dependent) and systolic blood pressure (dose-independent) at rest; diastolic blood pressure was unchanged. These changes probably result from a fall in resting cardiac output, previously demonstrated in invasive haemodynamic studies (Stenberg, Wasir, Amery, Sannerstedt & Werkö, 1975).

The increase in blood pressure during handgrip was not affected by metoprolol, whereas the heart rate increase during the second test was blunted by the 100 mg dose. This agrees with previous investigations

Table 2 Mean (± s.d., $n=6$) heart rate (HR) and blood pressures (BP) before and after 0, 25 mg and 100 mg of metoprolol: resting values and rises during handgrip

			Metoprolol	
	Placebo	*25 mg*	*25 mg*	*100 mg*
Resting				
Before tablet				
BP	120.8/79.2	119.3/75.5	118.8/75.3	120.2/76.5
	(6.40) (7.96)	(10.39) (8.48)	(9.95) (8.26)	(10.59) (4.85)
HR	74.3	73.5	72.5	77.7
	(6.89)	(2.59)	(1.38)	(8.09)
After tablet				
BP	119.8/78.7	112.0/75.3	113.7/78.3	112.5/78.2
	(6.24) (5.05)	(8.83) (7.0)	(10.89) (11.69)	(11.43) (6.79)
HR	73.7	62.8	63.0	61.7
	(7.55)	(2.64)	(3.03)	(6.92)
Rise during isometric I				
Before tablet				
BP	18.2/25.8	26.2/22.8	26.4/28.2	27.3/23.3
	(7.91) (11.48)	(6.65) (12.02)	(6.86) (13.29)	(12.83) (7.97)
HR	7.8	9.3	11.0	11.3
	(3.66)	(7.99)	(7.16)	(9.31)
After tablet				
BP	22.8/26.0	28.7/28.6	30.2/28.8	30.5/27.8
	(7.22) (14.44)	(8.09) (11.85)	(7.65) (11.60)	(17.97) (14.08)
HR	8.7	9.3	9.2	8.0
	(6.28)	(9.50)	(9.64)	(8.30)
Rise during isometric II				
Before tablet				
BP	31.0/22.7	26.8/29.3	34.2/38.3	19.2/31.8
	(11.92) (8.98)	(9.22) (14.65)	(19.82) (17.45)	(9.22) (16.93)
HR	10.7	13.3	15.3	11.7
	(8.55)	(9.73)	(8.31)	(8.76)
After tablet				
BP	31.8/28.3	32.2/31.2	35.5/36.5	36.2/33.2
	(13.78) (10.93)	(12.70) (15.80)	(13.07) (11.15)	(14.25) (7.94)
HR	14.3	12.5	12.3	6.7
	(8.02)	(9.16)	(9.31)	(6.93)

The two columns for 25 mg give values from six different subjects, five of whom are common to both groups—c.f. **Methods**.

by Freyschuss (1970) of the mechanism behind the cardiovascular changes during isometric exercise. She found that cardio-acceleration is due mainly to vagal withdrawal and to a lesser extent to an increase in cardiac sympathetic tone, and the blood pressure increases mainly due to increased neural sympathetic discharge of noradrenaline, causing vasoconstriction through α-adrenoceptor stimulation.

β-adrenoceptor blockade would then be expected to dampen the heart rate, but not the blood pressure

Table 3 Mean ($n=6$) heart rate (HR) and blood pressure (BP) levels at 1 min of handgrip before and after 0, 25 and 100 mg metoprolol

	Placebo	*Metoprolol*		
		25 mg	*25 mg*	*100 mg*
Before tablet				
Test I				
Systolic/diastolic BP	139/105	145/98	145/104	148/100
Mean BP	116	114	117	116
HR	82	83	84	89
Test II				
Systolic/diastolic BP	152/102	146/105	153/114	139/108
Mean BP	119	119	127	115
HR	85	87	88	89
After tablet				
Test I				
Systolic/diastolic BP	143/105	141/103	144/107	143/106
Mean BP	118	116	118	118
HR	82	72	70	70
Test II				
Systolic/diastolic BP	152/107	144/107	149/115	149/111
Mean BP	122	119	126	124
HR	88	75	75	68

Standard deviations were all very similar to those in Table 2. The two columns for 25 mg give values from six different values, five of whom are common to both groups—c.f. **Methods**.

Table 4 Day-to-day variation of test before tablet

	Rest	*Handgrip I*	*Handgrip II*
Mean values before tablet			
Day 1			
Systolic/diastolic BP	122/80	151/102	146/107
HR	76	88	88
Day 2			
Systolic/diastolic BP	*119/76	141/98	145/102
HR	74	84	87
Day 3			
Systolic/diastolic BP	124/77	145/99	146/107
HR	75	83	86
Median and range of coefficients of variation			
Systolic	3.5 (1.0–5.1)	7.3 (3.5–9.4)	5.3 (0.8–11.1)
Diastolic	6.1 (2.6–10.0)	9.3 (4.7–17.3)	5.6 (4.2–12.7)
Heart rate	4.8 (2.8–9.9)	6.3 (2.0–16.4)	3.0 (1.3–10.8)

* Significantly lower than on Day 3 ($P<0.05$).
Average and median respectively of six patients who performed all three pre-tablet tests.

response, as was found in this study. Indeed, if vascular (i.e., β_2–) receptors are also blocked, the α-constrictive response could even be enhanced. Sangvik, Stokkeland, Lindseth-Ditlefsen & Nyberg (1976) who compared intravenous propranolol and metoprolol did in fact demonstrate that both systolic and diastolic blood pressure were higher after propranolol (5 mg) than after metoprolol (10 mg) at 1 min of handgrip. The absolute differences in mmHg were small however, and in other pilot studies of different groups of hypertensive patients investigated before and 1.5 h after their normal morning dose of different β-adrenoceptor blocking drugs including metoprolol, (having previously withdrawn treatment for 24–36 h) no significant differences were seen in the cardiovascular reaction to handgrip between the drugs (Nyberg, 1976a).

In normal man, propranolol usually decreases cardiac output but blood pressure stays unchanged (systolic may go down but diastolic goes up) (Forsberg & Johnsson, 1967), and total peripheral resistance goes up. This could be due to an effect on vascular β_2-adrenoceptors, as well as (as is usually proposed) to a bradycardiac reflex increase of sympathetic discharge through the baroreceptor reflex arc. This increase in total peripheral resistance is also seen with metoprolol in normal man at rest, but not during dynamic exercise (Sternberg *et al.*, 1975).

The dose-dependent decrease of resting heart rate by 14.6% after 25 mg and 20.6% after 100 mg are in close accordance with previously found reductions of resting heart rate in healthy subjects (Johnsson, Regårdh & Sölvell, 1975).

There was unfortunately no opportunity in this study to collect blood for blood levels of metoprolol. However, Regårdh, Johnsson, Jordö & Sölvell (1975) found that the time for peak values after a single dose of metoprolol (100 mg) in tablet form was on the average 87 min, with a range of 40–90 min for five out of six subjects, the sixth peaking at 160 min after intake. On examination of individual resting heart rates in the present study, it was found reasonable to conclude that all subjects would have reached peak plasma levels, and hence, peak β-adrenoceptor blockade, by 90 min.

It is essential in studies like these to use a device which reduces observer bias maximally; the Auto-Manometer does this and is much more convenient to use than e.g. alternative instruments such as the London School of Hygiene and Tropical Medicine sphygmomanometer, which requires more time for each recording, and does not record heart rate at the same time as blood pressure. The disadvantages are those inherent in all methods of measuring blood pressure by cuff and Korotkov sounds: the relation to the true pressure can be quite different in different patients and the vascular characteristics, which determine the quality of the Korotkov sounds, can change depending on the drug given. More research is needed to establish whether indirectly recorded blood pressures reflect the true pressure under different conditions. The character of the Korotkov sounds were, in these studies, occasionally found to change considerably when a drug had been given; mostly however, they appeared the same to the ear.

I thank the volunteers for participating, and Miss Elizabeth Berky for excellent secretarial aid.

References

ÅBLAD, B., BORG, K.O., CARLSSON, E., EK, L., JOHNSSON, G., MALMFORS, T. & REGÅRDH, C-G. (1975). A survey of the pharmacological properties of metoprolol in animals and man. *Acta pharmac. tox.*, **36**, Suppl. V., 7–23.

DOYLE, A.E. (1974). Use of β-adrenoreceptor blocking drugs in hypertension. *Drugs*, **8**, 422–431.

EWING, D.J., IRVING, J.B., KERR, F. & KIRBY, B.J. (1973). Static exercise in untreated systemic hypertension. *Br. Heart J.*, **35**, 413–421.

FORSBERG, S-Å. & JOHNSSON, G. (1967). Hemodynamic effects of propranolol and H 56/28 in man—a comparative study of two β-adrenergic receptor antagonists. *Acta pharmac. tox.*, **25**, suppl. 2, 75–83.

FREYSCHUSS, U. (1970). Elicitation of heart rate and blood pressure increase on muscle contraction. *J. appl. Physiol.*, **28**, 758–760.

HARRISON, D.C. (1974). The pharmacology and therapeutic use of β-adrenergic receptor blocking drugs in cardiovascular disease. *Drugs*, **7**, 1–7.

JOHNSSON, G., REGÅRDH, C-G. & SÖLVELL, L. (1975). Combined pharmacokinetic and pharmacodynamic studies in man of the adrenergic β_1-receptor antagonist metoprolol. *Acta pharmac. tox.*, **36**, suppl. V, 31–44.

KRAYENBUEHL, H.P. & RUTISHAUSER, W. (1973). Hemodynamic consequences and clinical significance of the handgrip test. *Eur. J. Cardiol.*, **1**, 5–9.

NYBERG, G. (1976a). Effect of β-blockers on heart rate and blood pressure in dynamic and isometric exercise. *Drugs*, **11**, suppl. 1, 185–195.

NYBERG, G. (1976b). Blood pressure reaction to isometric exercise and mental arithmetic in normotensive and hypertensive subjects. *Clin. Sci. mol. Med.*, **51**, suppl. 3, 681s–685s.

REGÅRDH, C-G., JOHNSSON, G., JORDÖ, L. & SÖLVELL, L. (1975). Comparative bioavailability and effect studies on metoprolol administered as ordinary and slow-release tablets in single and multiple doses. *Acta pharmac. tox.*, **36**, Suppl. V., 45–58.

SANGVIK, K., STOKKELAND, M., LINDSETH-DITLEFSEN, E-M. & NYBERG, G. (1976). Circulation reaction at rest and during isometric and dynamic exercise in hypertensive patients: influence of different adrenergic β-adrenoceptor antagonists. *Pharmatherapeutica*, **1**, 71–83.

STENBERG, J., WASIR, H., AMERY, A., SANNERSTEDT, R. & WERKÖ, L. (1975). Comparative hemodynamic studies in man of adrenergic β_1-receptor blocking agents without (H 93/26 = metoprolol) or with (H 87/07) intrinsic sympathicomimetic activity. *Acta pharmac. tox.*, **36**, Suppl. V, 76–84.

TAYLOR, S.H. (1975). Pathophysiology of hypertension. *Aust. fam. physician*, **4**, 41–47.

VEDIN, A., WILHELMSSON, C. & WERKÖ, L. (1975). Chronic alprenolol treatment of patients with acute myocardial infarction after discharge from hospital. *Acta med. scand.*, supplement 575, 7–56.

WHITLOCK, F.A. & PRICE, J. (1974). Use of β-adrenergic receptor blocking drugs in psychiatry. *Drugs*, **8**, 109–124.

(Received August 13, 1976)