COMPARISON OF INTRA-ARTERIAL AND INDIRECT BLOOD PRESSURES AT REST AND DURING ISOMETRIC EXERCISE IN HYPERTENSIVE PATIENTS BEFORE AND AFTER METOPROLOL

S. HUNYOR & G. NYBERG*

N.H. and M.R.C. Unit for Cardiovascular Research and the Hypertensive-Renal Clinic, Royal North Shore Hospital, St Leonards (Sydney), NSW 2065, Australia

- 1 Blood pressure was measured both directly and indirectly in seven hypertensive patients before and after a single oral dose of 100 mg metoprolol, at rest and during sustained handgrip.
- 2 Intra-arterially measured systolic and diastolic blood pressure increased linearly with time during sustained handgrip at 50% of maximal voluntary contraction. This linearity persisted for 60 s or more in most cases. Heart rate increased linearly for the first 30 s.
- 3 Indirectly measured blood pressure using an observer bias minimizing Auto-Manometer®, under-read systolic and over-read diastolic pressure both at rest and during handgrip.
- 4 By exact timing of recorded values during handgrip and linear extrapolation (or interpolation) from base-line readings, mean values at 30 and 60 s of handgrip were calculated. The relationship between direct and indirect values remained the same at base-line and 30 s of handgrip. At 60 s of handgrip, this was true only for diastolic pressure. For systolic pressure, indirect and direct values almost coincided.
- 5 After metoprolol, directly recorded blood pressure fell slightly (7–12 mm Hg, $0.02 < P < 0.10$), both at rest and during handgrip, and heart rate fell by 15–18 beats/min ($P < 0.01$). The systolic blood pressure and heart rate effect of metoprolol at 1 min handgrip correlated with peak plasma drug levels. Indirectly measured blood pressure did not change significantly.
- 6 The rate of rise in heart rate and blood pressure from base-line to 60 s of handgrip was not significantly influenced by metoprolol.

Introduction

The blood pressure response to isometric exercise in the form of sustained handgrip has been studied in normotensive and hypertensive subjects using an Auto-Manometer® (Nyberg, 1976a,b, 1977a,b). This electronic instrument is based on the principle of the London School of Hygiene sphygmomanometer (Rose, Holland & Crowley, 1964).

The purpose of the present study was to compare blood pressure values obtained by the Auto-Manometer with intra-arterial values. This also gave the opportunity to assess often quoted assumptions concerning linearity of blood pressure response with static exercise. In addition, the relationship of metoprolol on heart rate and blood pressure changes during static exercise were analysed. Metoprolol, a β_1 -selective adrenoceptor antagonist (Åblad, Borg,

Carlsson, Ek, Johnsson, Malmfors & Regårdh, 1975) was given as a single oral dose of 100 mg.

Methods

Seven hypertensive patients, three women aged 35, 45 and 46 years (one with analgesic nephropathy), and four men aged 40, 45, 46 and 51 years, signed a form of informed consent and partook in the study. Two of them had had no previous treatment, and five had been off previous treatment for 2–7 days. Indirect BP was checked in both arms prior to the study and only those patients were accepted in whom this difference was less than 5 mmHg. The pressure on any one side did not systematically differ from that in the other.

The patients came to the laboratory at 09.00 h in a post-absorptive state. Intra-arterial (direct) blood pressure was measured after percutaneous insertion of a soft 17 gauge teflon cannula (Dwellcath, Tuta Laboratories, Lane Cove, Australia) into the right brachial artery. The arterial cannulation was

* Present address and address for reprints: Medical Department 1, Sahlgrenska Hospital, S-413 45 Göteborg, Sweden.

performed under local anaesthesia (Lidocaine 2% plain), and a short line connected the cannula to a Siemens (Model 746) pressure transducer. Frequency response of the direct pressure recording system was 22 Hz with a damping factor of 0.18. Zero reference level was taken as the level of the fourth intercostal space at the sternal edge in the sitting position. The arterial pressures and calibration signals were recorded on a Siemens-Elma Mingograph recorder (model 804) and the values were read directly from the trace by an observer unaware of the cuff readings. Instantaneous heart rate values were obtained from the tachograph record obtained by feeding the arterial pulse signal into a Philips ECG amplifier (Type XV 1503). Other heart rate measurements were obtained by counting from the ECG record.

Indirect blood pressures were recorded from the left arm using an Auto-Manometer (Electronic Research & Development, Dunedin, New Zealand) which is an electronic modification of the London School of Hygiene sphygmomanometer. It enables recording of both heart rate and blood pressure while minimizing observer bias or digit preference. Phase V Korotkov sounds were chosen as the diastolic end point, since all life insurance morbidity/mortality data, as well as that from Framingham is based on Phase V diastolic. All major significant therapeutic trials e.g. VA studies and US-HDFP, Australian National BP Study as well as UK MRC Trial have settled on Phase V as end point. Recordings were made twice at rest before handgrip ('base-line'), then during sustained handgrip of the right hand squeezing a balloon connected to a manometer (Vigrometer, Gebrüder Martin, Tuttlingen, Germany) at 50% of maximal voluntary contraction. The handgrip test was performed twice ('runs I and II'). The methodology for establishing maximal voluntary contraction and other aspects has

been described in detail elsewhere (Nyberg, 1977a).

After two initial handgrip tests, the patients swallowed a 100 mg tablet of metoprolol (Betaloc) together with 150 ml of water. The patients then rested until 75 min after tablet intake when the handgrip protocol was repeated. Blood samples for metoprolol blood levels were taken at 45, 60, 72 and 90–110 min after tablet intake.

On the basis of previous reports (Ewing, Irving, Kerr & Kirby, 1973; Hoel, Lorentzen & Lund-Larsen, 1970) the rise of both systolic and diastolic pressures, and of heart rate during static exercise was linear with time. Extrapolation of the values (accurately timed) to 60 s has been done, both for indirectly and directly obtained pressures. These extrapolated values have been compared with the actually recorded intra-arterial values. Comparisons of direct-indirect values, as well as of before-after drug values, were analysed using the paired Student's *t*-test. Since there may be doubts concerning the use of a parametric test on this kind of data (Siegel, 1956), the results have also been analysed using the Wilcoxon matched-pairs signed-ranks test. If the confidence level with the latter test has been found to be lower than that of the *t*-test for any comparison, this has been specially noted.

Results

Comparison of indirect and direct blood pressures

Table 1 gives average base-line values, based on the average of two readings for each occasion with each patient.

The Auto-Manometer (AM) value of systolic pressure was lower than the intra-arterial (IA) value

Table 1 Base-line values for blood pressure and heart rate (mean and s.e. mean) in seven patients before and after metoprolol

	Auto-Manometer (AM)	Intra-arterial (IA)	AM-IA	<i>t</i>
<i>Off drug</i>				
Systolic (mmHg)	162 (10.1)	171 (9.8)	-9 (1.4)	6.20***
Diastolic BP (mmHg)	105 (5.7)	96 (6.1)	9 (2.9)	2.96*
Mean BP (mmHg)†	124 (6.3)	121 (6.8)	3 (2.7)	1.09
Heart rate (beats/min)	69 (0.8)	71 (4.2)	-2 (2.2)	1.01
<i>On drug</i>				
Systolic BP (mmHg)	154 (10.6)	160 (9.9)	-5 (3.7)	1.43
Diastolic BP (mmHg)	102 (6.4)	89 (7.4)	13 (2.8)	4.51**
Mean BP (mmHg)*	119 (5.9)	112 (7.9)	7 (2.2)	3.11*
Heart rate (beats/min)	57 (3.3)	57 (4.7)	0 (1.8)	0.11

† Mean blood pressure = diastolic + 1/3 of the pulse pressure.

* = $P \leq 0.05$; ** = $P \leq 0.01$; *** = $P \leq 0.001$.

but was statistically significant only before metoprolol (-9 mmHg, $P < 0.001$). For diastolic pressure the AM value was significantly higher than the IA value; $+9$ mmHg ($P < 0.05$) off metoprolol and $+13$ mmHg ($P < 0.01$) on metoprolol. Heart rates did not differ for the two different methods of measurement.

Table 2 gives average values during handgrip, at the exact times of recording. Again, the AM value for systolic pressure was lower than the IA value, both off metoprolol (-12 mmHg, $P < 0.001$) and on metoprolol (-7 mmHg, $P < 0.10$). As at rest, AM diastolic pressures were higher than IA pressures: off

metoprolol by $+8$ mmHg ($P < 0.01$) and on metoprolol by $+14$ mmHg ($P < 0.01$). Heart rates did not differ.

The extrapolated values at 1 min of handgrip (Figure 3), maintained the same relationship between AM and IA readings as the results given in Tables 1 and 2.

Effect of metoprolol

Table 3 gives the mean difference off drug-on drug. Heart rate and IA blood pressures are considerably

Table 2 Blood pressure and heart rate values recorded during handgrip (mean and s.e. mean) in seven patients

	<i>Auto-Manometer (AM)</i>	<i>Intra-arterial (IA)</i>	<i>AM-IA</i>	<i>t</i>
<i>Off metoprolol</i>				
Systolic BP (mmHg)	178 (10.0)	190 (10.1)	-12 (1.5)	8.19***
Diastolic BP (mmHg)	121 (8.0)	114 (7.0)	8 (3.5)	2.19†
Heart rate (beats/min)	83 (2.5)	83 (3.6)	0	
<i>On metoprolol</i>				
Systolic BP (mmHg)	173 (8.7)	181 (10.0)	-7 (3.2)	2.30
Diastolic BP (mmHg)	121 (5.8)	107 (7.2)	14 (3.3)	4.17**
Heart rate (beats/min)	67 (2.4)	66 (4.1)	1 (2.1)	0.48

† $P = 0.01$, Wilcoxon matched-pairs test.

** $P \leq 0.01$; *** $P \leq 0.001$.

Table 3 Difference in blood pressure and heart rate (off metoprolol minus on metoprolol)

	<i>Auto-Manometer (AM)</i>	<i>t</i>	<i>Intra-arterial (IA)</i>	<i>t</i>
<i>1. Base-line</i>				
Systolic BP (mmHg)	7 (5.1)	1.37	12 (3.8)	3.01*
Diastolic BP (mmHg)	3 (3.7)	0.81	7 (3.0)	2.23
Mean BP (mmHg)	4 (3.9)	1.10	9 (3.3)	2.60*
Heart rate (beats/min)	12 (2.1)	5.63**	15 (3.7)	4.08**
<i>2. Actual isometric values</i>				
Systolic BP (mmHg)	4 (3.4)	1.18	8 (3.9)	2.15
Diastolic BP (mmHg)	1 (3.7)	0.27	7 (2.1)	3.26*
Mean BP	not calculable			
Heart rate (beats/min)	16 (2.4)	6.60***	17 (3.8)	4.56**
<i>3. 1 min extrapolated values</i>				
Systolic BP (mmHg)	6 (6.9)	0.87	10 (9.4)	1.06
Diastolic BP (mmHg)	0 (4.3)	0	7 (3.1)	2.30
Mean BP (mmHg)	1 (4.6)	0.22	9 (5.1)	1.76
Heart rate (beats/min)	17 (3.5)	4.87**	18 (5.3)	3.35*

Mean BP = diastolic + $1/3$ of the pulse pressure.

* $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$.

Figure 1 Intra-arterial blood pressure changes during handgrip, for individual patients in the second run before metoprolol. Unbroken lines start at 'base-line' values at time 0. Broken lines show examples of considerable differences between actually recorded values at time 0, and the previously recorded 'base-line' values. These help to shift the start of the average curve upwards, as indicated by the thick point-broken lines. Numbers identify individual patients studied.

and significantly reduced, whereas AM blood pressure values are not.

The rate of rise in blood pressure and heart rate from base-line to 1 min of handgrip was not influenced by metoprolol.

Validity of extrapolation procedure

Figures 1 and 2 give the actual intra-arterial recordings of systolic and diastolic pressure for each patient, together with the means, for the second run without (Figure 1) and with (Figure 2) metoprolol. The average curve has been constructed from means of values at 0, 30 and 60 s as they appear on the graphs. These average curves are somewhat bent and seem to indicate that the pressure rise is not linear during the handgrip. This is also apparent from some of the individual tracings. However, this is probably due to a change in pressure from 'base-line' to 'start' of handgrip, as is indicated in the figures by the thick point-broken line; this has been drawn from actually recorded values at time 0 s ('start' values) (see also legend to Figure 1).

In Figure 3 the average intra-arterial curves (constructed as in Figures 1 and 2) have been compared with the Auto-Manometer values (base-line and 1-min-extrapolated values). The 1-min-extrapolated systolic values come closer to actual systolic values than at base-line. For heart rate, extra-

Figure 2 Intra-arterial blood pressure changes during handgrip for each patient in the second run after metoprolol. Symbols as in Figure 1.

polation seems to overrate it compared with real (i.e. instantaneous) heart rate. For diastolic pressure, the deviation is roughly the same at 1 min as at base-line.

It should be noted that if extrapolation is done to 30 s instead of 60 s, the deviation of AM values from actual IA values is very much the same as at base-line for all three parameters.

If intra-arterial readings are extrapolated in the same manner as AM readings, the curves will run roughly parallel for all three parameters.

Endurance time

Mean $\pm$ s.d. endurance time was 106 ± 14.9 s off metoprolol and 99 ± 16.8 s on metoprolol. It was shorter in the second run: 89 ± 12.4 s off metoprolol ($P < 0.05$) and 88 ± 17.1 s on metoprolol (NS). The differences off-on drug are not significant.

Discussion

In this study, indirect systolic blood pressure was under-read and diastolic blood pressure was over-read, compared with intra-arterial readings. This is in accordance with some reports in the literature (Breit & O'Rourke, 1974; Edwards, Bannister, Goldberg & Raftery, 1976), whereas others have found systolic pressure to be over-read by indirect methods (Holland & Humerfeldt, 1964; Raftery & Ward, 1968). This makes the indirect method more insensitive, and one could predict that when within-patient changes of the effect of, for example, antihypertensive therapy are measured, some real changes may be missed by

Figure 3 ——— Average intra-arterial values calculated as in Figures 1 and 2 (mean of both runs).
 ----- Average intra-arterial values going from 'start' values actually recorded at time 0 (mean of both runs).
 Average Auto-Manometer values going from base-line to 1 min extrapolated values (mean of both runs). a off metoprolol, b on metoprolol.

indirect readings. Or, in other words, if significant changes as measured indirectly do occur, the real changes behind them are probably greater. Indeed, in this study the intra-arterial values were mostly significantly lowered by metoprolol, whereas the indirect values were not.

Although several reports state that the change in blood pressure during isometric exercise is roughly linear with time, there seem to be some individuals who do not show this linearity, as is seen in Figures 1 and 2. A possible explanation for this finding may lie in the slight slackening of effort by those subjects who do not continue to raise blood pressure linearly, although such was not observed by us at the time of the study. It is interesting that only subject 6 after metoprolol showed an upward linear blood-pressure trend, whereas an element of fatigue would tend to increase the % MVC exerted with time. However, it is seen from Figure 3 that if extrapolation (or interpolation) is made to 30 s instead of 60 s, the relation to real values on the average is the same as at base-line. Therefore, the conclusions drawn from previous studies are still qualitatively valid (Nyberg, 1976a,b; 1977a), but the reservation must be made that 60 s extrapolated values do not accurately reflect true blood pressure values.

The results are in accordance with results previously obtained with the same method in untreated patients (Nyberg, 1976b) or in previously treated patients, e.g. in 13 patients who received 100 mg of metoprolol orally (Nyberg, 1976a). The blood pressure at 1 min of handgrip was not significantly lower after metoprolol, as in the present study. However, by intra-arterial readings the pressure did go down, systolic by 8 mmHg ($P < 0.10$) and diastolic by 7 mmHg ($P < 0.02$).

The fact that both base-line and handgrip systolic and diastolic pressures (as recorded intra-arterially) fell by 7 to 12 mmHg (statistical significance varying

from $P < 0.02$ to $P < 0.10$) may, of course, to some extent be a result of the rest. No firm conclusion can therefore be drawn from these data as to the acute blood pressure lowering effect of metoprolol.

The fact that there was a significantly lower diastolic pressure during handgrip (intra-arterial values, cf. Table 3), which was not significant by Auto-Manometer readings, indicates that the indirect method is less sensitive. Thus, false differences are not likely to be detected between e.g. different treatments; rather, small but real differences might well be missed. If differences are in fact detected, as in a comparison performed of the antihypertensive effect of metoprolol and propranolol (Nyberg, 1977b), they are likely to be real.

The underrating of systolic pressure and the over-rating of diastolic pressure with the indirect method of measurement seem to be slightly less pronounced on metoprolol (cf. Tables 1 and 2). This could to some extent be a consequence of drug influence on cardiac output, dp/dt or peripheral vessels, so that the conditions for producing Korotkov sounds change. On several occasions, we have formed the impression that Korotkov sounds after β -adrenoceptor blockade become considerably weaker. It would therefore be worthwhile to study more systematically the relation between direct and cuff blood pressures in patients with different antihypertensive therapy. This could lead to different limits for optimal therapeutic effect for different drugs, or, in other words, one patient may be as well-controlled on drug A with indirectly measured blood pressure of 150/80 mmHg as with drug B at 130/70 mmHg.

This reasoning supports the use of mean blood pressure in assessing the therapeutic efficacy of drugs, since this parameter is less likely to vary from the true intra-arterial value than is systolic or diastolic pressure.

While the β -adrenoceptor blockade slightly

alleviated the heart rate response at 1 min of handgrip (from 15 to 13 beats/min), this was not a significant effect and may indicate that a strong parasympathetic component can compensate for any lack of sympathetic chronotropic influence during handgrip. The failure of metoprolol to significantly inhibit the exercise heart rate increase may be unduly influenced by the results in one patient who showed a far greater rise in heart rate with than without metoprolol.

Blood levels of metoprolol were measured in these patients. Peak levels were noted at 45–102 min after intake (median 45 min) and varied from 93–881 ng/ml (0.35–3.3 $\mu\text{mol/l}$). Using Spearman Rank

correlation, the decrease both in heart rate and systolic blood pressure produced by the drug at 1 min of handgrip (real intra-arterial values as obtained in Figures 1 and 2) correlated to peak blood level ($R_s=0.829$, $P<0.05$ for heart rate and $R_s=0.714$, $P<0.05$) for systolic blood pressure). This could indicate that handgrip may prove useful in titrating the optimal dose of metoprolol in the individual hypertensive patient.

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