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Effect of Beta-Blocker Versus Combined Alpha- and Beta-Blocker on Blood Pressure Response Under Static Exercise and Cold Pressor Test

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Abstract

The effect of a single oral dose of β_1-blocker (Metoprolol) versus combined α - and ß-blocker (Labetalol) was evaluated in two groups of patients; control (C) normotensive and hypertensive (H) group with mild to moderate elevation of blood pressure. Each group consisted of ten subjects. The study comprises monitoring the heart rate (HR) and blood pressure (BP) response to two tests; hand grip test (HCT) and cold pressor test (CPT). These tests were performed before and after the drugs on separate sittings. The BP and HR response to HGT before drugs was linear for the two groups while the CPT showed insignificant rise of HR. The results at rest before and after medications in both groups showed a decrease in HR and BP. It was statistically insignificant in C-group only after labetalol. In C-group metoprolol was more effective in lowering the pressor response than labetalol while in the H-group labetalol was more potent in reducing BP specially during CPT.

Introduction

THE treatment of primary or essential hypertension involves many drug-regimens separately or in combiration. Beta-blockers are recently introduced drugs for the treatment of hypertension. They lower the blood pressure by several mechanisms; reducing cardiac output [1], supressing the release of renin from the kidney [2] or by a central action on the cerebral ß-receptors which mediate vasoconstriction [3] or blocking the feedback mechanism for these receptors [4 & 5].

To test the effectiveness of ß -blockers, sympathetic pressor tests are used to elevate the blood pressure as the hand grip test with its beta-and alpha-receptor stimulation with an ultimate rise of the mean blood pressure and heart rate [6] and cold pressor test which stimulates alpha-receptors only with an increase in peripheral vascular resistance and blood pressure with insignificant effect on heart rate [7].

In our study, the effect of two drugs metoprolol a ß1-blocker and labetalol with combined α-and ß-blocking property [8] were used to compare their effect with the hand grip test and cold pressor test on normotensive subjects and those with mild to moderate uncomplicated essential hypertension.

Material and Methods

Patient groups:

Two groups of ten patients were selected for this study; a control (C) normotensive group and a hypertensive group (H).

The subjects were selected after complete history and clinical examination. An ECG, chest roentgenogram and laboratory investigation of urine, serum urea and serum electrolytes were measured.

The control group (C) was normal without any complaint or manifestations of systemic diseases. The hypertensive group (H) was those with mild to moderate essential hypertension and no contraindication to the use of ß-blockers as symptoms and signs of heart failure, diabetes mellitus, chronic obstructive airway disease or bronchial asthma, peripheral vascular disease, ECG-conduction defects or arrhythmias as proved from history taking, clinical examination and laboratory investigations.

Test protocol:

The subjects were instructed about the drugs used in the trial and the dates of the tests. They were asked to refrain from tobaco or caffein containing beverages for at least 12 hours prior to test time and to take a light meal at least 3 hours before the test.

The protocol of the study was planned for three settings; before treatment, labetalol trial and metoprolol trial separated by 2 to 3 days interval. In the last two visits each drug was taken as a single oral dose of 100 mg 3 hours before the trial.

In each visit the subject was asked to lay supine comfortably. The electrodes of the monitoring electrocardiogram were attached in the usual manner and a sphygmomanometer cuff was fixed over the left arm. He was left for 15 min in complete rest and the last 5 min. was monitored. A complete surface ECG was then performed.

The heart rate and BP were measured three times after the resting period and an average of the three readings was calculated.

The hand grip test (HGP) and cold pressor test (CPT) were then performed separated by 10 min rest period. During these tests the subjects were instructed to

breath normally and not to perform valsalva manouver.

Hand grip test (HGT):

An initial training about how to carry out the test was performed. The maximum voluntary contraction was determined by asking the subject to compress as forcibly as he can an inflated sphygmomanometer cuff and an average of two maximal trials was recorded. The subject was asked to maintain 30% of the level of M. V. C. steadily as possible for the duration of 3 min by his right hand. The BP and heart rate were measured and the ECG was monitored at the end of each minute.

The subject was asked to relax for 10 min and the HR and BP were measured after 5 and 10 min to insure the return of the readings to the rest value.

Cold pressor test (CPT):

It was performed by immersing the right hand in ice-cold water up to his rest for 3 min. Similar measurements to those of the HGT were repeated. Immediately after the end of CPT the subject right hand was immersed in warm water. The subject was allowed to rest for 15 min and final measurements were taken up to the control values.

Results

The mean age of the control (C) group was 28.3 ± 0.45 years, weight 81.4 ± 3.17 Kg and height 174.5 ± 2.3 cm.

The clinical examination of the two groups was normal apart from elevated BP in H-group. The laboratory investigations, ECG and chest X-ray were normal in the two groups.

The results of this study were classified into four parts; the base line readings of blood pressure and heart rate for the two groups before medications and stress test, before drugs, effects of drugs at rest and lastly the effects of drugs under stress tests.

Statistical analysis of the data obtained was done by calculating the mean value, the standard deviation and the standard error of mean S. E. The Student's paired *t-test* for paired observations was used (when required) for comparison within groups where *p*-values below 0.05 were taken as significant. For comparison between groups the independent *t*-test was performed.

BP and heart rate (HR) in the two groups before medications:

i- C-groups: the mean systolic blood pressure (SBP) was 116.5 ± 2.0 mmHg and the mean heart rate (HR) 78.1 ± 2.8 b/min.

ii- H-group The mean SBP was 153.0 ± 4.2 mmHg ($p < 0.001$), DBP 101.0 ± 0.7 mmHg ($p < 0.001$) and HR of 82.8 ± 5.1 b/min.

The stress test before medication:

A- Hand grip (HG) test

There was significant increase in SBP and DBP and HR at the end of the third minute of the test.

i- C-group: the mean increase of SBP was 34 ± 1.8 mmHg and DBP 28 ± 1 mmHg. ($p < 0.001$). The HR increased by 8.3 ± 0.8 b/min ($p < 0.01$).

ii- H-group: the mean SBP increased by 35 ± 2.6 mmHg ($p < 0.001$) and DBP by 29 ± 3.5 mmHg ($p < 0.001$). The HR increased by 17.6 ± 0.6 b/min ($p < 0.001$)

B- cold pressor (CP) test:

There was significant increase in both blood pressures under the test for both groups with insignificant heart rate changes.

i- C-group: the SBP increased by 29.5 ± 0.2 mmHg and DBP by 22.5 ± 0.9 mmHg ($p < 0.001$).

ii- H-group: SBP increased by 19.5 ± 1.7 mmHg and DBP by 22.5 ± 0.9 mmHg ($p < 0.001$).

ii- H-group: SBP increased by 19.5 ± 1.7 mmHg and DBP by 17.5 3.8 mmHg ($p < 0.001$). These results are summarised in table (1) and Figure (1).

Effects of drugs at rest: (Table-2 & Fig-2)

A- Labetalol:

The percentage dectrease in SBP for the C-group was 0%, while in the H-group it was 19.3%. The percentage reduction in DBP was 4.4% for the C-group and 17.8% for the H-group. The HR was reduced by 1.3% for the C-group and 13.3% for the H-group.

B- Metoprolol:

The percentage decrease in SBP was 6.9% for the C-group and 17.3% for the H-group; while the DBP was reduced by 6.3% for the C-group and 21.1% for the H-group.

Table (1): The Effects of Hand Grip Test and Cold Pressor Test on the Blood Pressure and Heart Rate of the Control and Hypertensive Groups.

	basic			HGT			CPT		
	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR
C	116.5 ± 2.0	80.0 ± 1.8	80.0 ± .1.8	150.5 ± 3.8	108.0 ± 2.8	86.4 ± 3.6	146.0 ± 2.2	102.5 ± 2.7	73.0 ± 3.16
H	153.0 ± 4.2	101.0 ± 0.7	101.0 ± 0.7	188.0 ± 6.8	130.0 ± 4.2	100.4 ± 5.7	171.5 ± 5.9	118.5 ± 4.5	81.7 ± 6.7

HFT = hand grip test, CPT = cold pressor test, C = control group, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate and H = hypertensive group.

Table (2): The Response to Hand Grip Test after Labetalol and Metoprolol for both Groups.

	Labetalol						Metoprolol					
	SBP (mm Hg)		DBP (mm Hg)		HR (b / min.)		SBP (mm Hg)		DBP (mm Hg)		HR (b / min.)	
	Basic	3rd m	Basic	3rd m	Basic	3rd m	Basic	3rd m	Basic	3rd m	Basic	3rd m
C	116.5 ± 2.1	145.5 ± 5.8	76.5 ± 1.8	101.0 ± 4.0	77.2 ± 3.2	83.2 ± 8.3	108.5 ± 1.8	138.0 ± 4.4	76.5 ± 1.8	101.0 ± 4.0	65.5 ± 2.0	71.8 ± 2.0
H	123.5 ± 4.0	160.0 ± 5.8	83.0 ± 2.6	110.5 ± 3.6	71.5 ± 2.6	87.1 ± 3.6	126.5 ± 5.2	163.5 ± 7.8	83.0 ± 2.6	110.5 ± 3.0	65.5 ± 3.0	77.5 ± 4.0

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, 3rd m = third minute of the test, C = control group and H = hypertensive group.

Table (3): The Response to Pressor Test after Labetalol and Metoprolol for both Groups.

	Labetalol						Metoprlol					
	SBP (mm Hg)		DBP (mm Hg)		HR (b / min.)		SBP (mm Hg)		DBP (mm Hg)		HR (b / min.)	
	Basic	3rd m	Basic	3rd m	Basic	3rd m	Basic	3rd m	Basic	3rd m	Basic	3rd m
C	116.5 ± 2.0	138.5 ± 4.0	76.5 ± 3.0	98.0 ± 4.0	77.3 ± 3.0	77.6 ± 3.0	108.5 ± 1.8	131.0 ± 3.0	75.0 ± 2.0	95.0 ± 3.0	65.7 ± 3.0	65.7 ± 3.0
H	123.5 ± 4.0	143.5 ± 5.0	82.5 ± 3.0	94.5 ± 4.0	70.7 ± 3.0	73.4 ± 3.0	125.5 ± 5.0	147.5 ± 6.0	85.5 ± 3.0	105.5 ± 3.0	64.3 ± 2.0	63.0 ± 3.0

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, 3rd m = third minute of the test, C = control grou

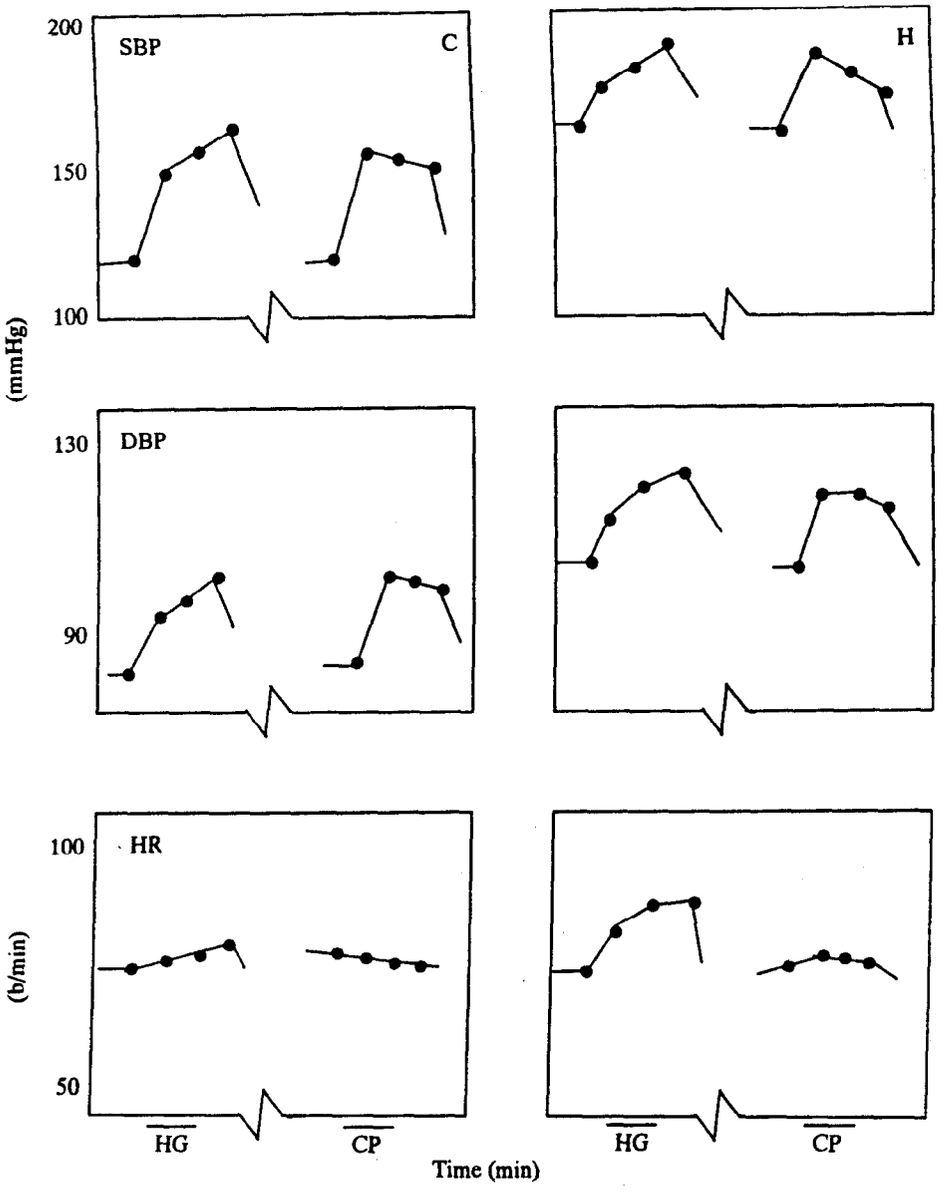

Fig. (1): Effect of H.G.T. and C.P.T. on blood pressure and heart rate responses before medications for the two groups.

C = control group, H = hypertensive group, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, HG = hand grip test and CP = cold pressor test.

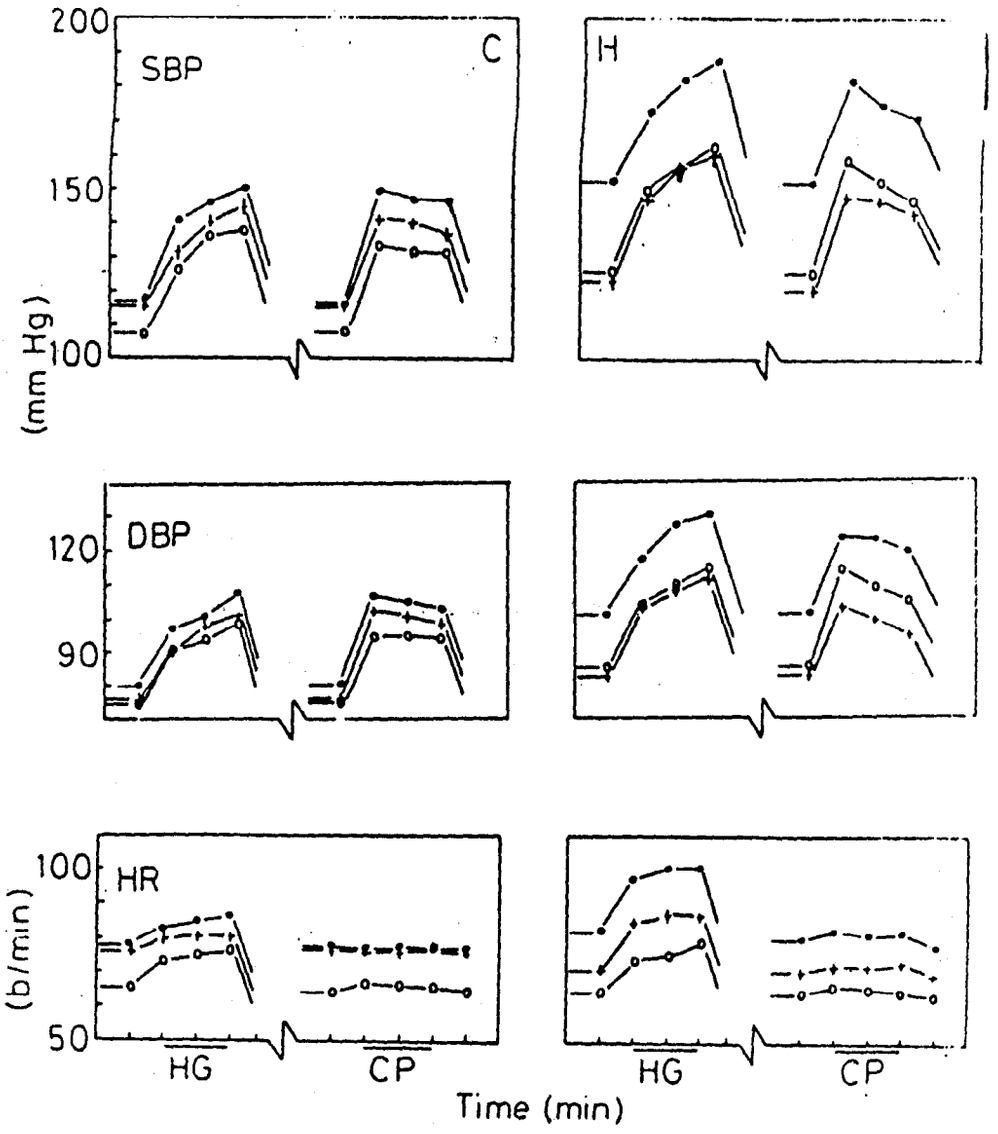

Fig. (2): Complete whole responses for the two tests for both groups; at rest and after medications.

C = control group, H = hypertensive group, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, HG = hand grip test and CP = cold pressor test.

(• = before medication, o = Metoprolol & + = Labetolol)

Effects of drugs under stress test:

The two drugs used before the test were effective in lowering the SBP and DBP durign the HG and CP tests more than that obtained before medications. The HR did not change much with labetalolol in the C-group during the two tests and it was less effective than metoprolol in reducing the HR in the H-group.

A-Hand grip (HG) test (Table -2 & Fig.2):

i- Labetalol; the increase in SBP and DBP for the C-roup was 28.5 ± 3.7 and 24.5 ± 1.1 mmHg ($p < 0.001$) and the increase for the H-group was 26.5 ± 0.8 and 27.5 ± 0.4 mmHg ($p < 0.005$) respectively.

ii- Metoprolol; the increase in SBP for the C-group was 29.5 ± 2.6 mmHg, and 37.0 ± 2.6 mmHg for H-group ($p < 0.001$). The increase in DBP for the C-group was 24.5 ± 4 mmHg and 27 ± 0.8 mmHg for H-group ($p < 0.001$). The increase in HR for the C-group was 6.3 ± 3.8 b/ min and 12.0 ± 1 b/min for the H-group ($p < 0.001$).

B- Clod pressor (CP) test (Table-3 & Fig-2):

In the C-group the HR showed no significant changes before and after using the two drugs, while SBP and DBP were more affected by the medications specially with metoprolol. In the the H-group the HR, SBP and DBP were less elevated than before using the drugs.

i- Labetalol; the increase in SBP for the C-group was 22 ± 2 mmHg and 2 ± 1 mmHg for the H-group ($p < 0.001$). The increase in DBP for C-group was 21 ± 2 mmHg and 12 ± 1 mmHg for the hypertensive group ($p < 0.001$).

ii- Metoprolol; the increase in SBP for the C-group was 22.5 ± 1.2 mmHg and 21 ± 1 mmhg for the H-group ($p < 0.001$). The increase in DBP for the C-group was 20 ± 1 mmHg and 19.5 ± 0 mmHg for the H-group ($p < 0.001$).

Discussion

The hypertensive response to static exercise and cold pressor test is often used to test the circulatory responses to sympathetic stimulation as well as the effectiveness of antihypertensive therapy [6, 7, 9].

The circulatory responses to static exercise differ from dynamic exercise. In the former a considerable increase in mean arterial blood pressure and heart rate occurs while dynamic exercise increases the heart rate and systolic blood pressure alone without any change in the mean blood pressure [6]. The increase in blood pressure with static exercise is related to an increase in cardiac output due to increase in heart rate and generalised vasoconstriction with increase in systemic vascular resistance [10].

The hemodynamic response to cold pressor test is marked increase in blood pressure due to an increase in total peripheral vascular resistance secondary to marked peripheral vascular constriction mediated through an increased

alpha-adrenergic receptors activity. The heart rate usually does not change; this can be explained by the increase in plasma catecholamines during the test that is counterbalanced by reflex inhibition of sinus node activity [9]. Thus cold pressor test can be used to test mainly alpha-adrenergic blocking drugs

In our study we can notice that before the use of the two drugs the systolic and diastolic blood pressure were elevated with the hand grip and cold pressor tests in both groups while the heart rate did not show significant increase during the cold pressor test.

The behaviour of systolic and diastolic blood pressure and heart rate after a single dose of metoprolol and labetalol at rest before the stress test was different.

In case of metoprolol the three parameters in the control group decreased and it was more exaggerated in the hypertensive group; while labetalol showed insignificant changes in the control group and a moderate effect in the hypertensive group. Such effects have been reported by other workers [8,11-15].

The difference in hemodynamic response to both drugs at rest can be explained according to their pharmacological effects. In case of metoprolol, a β_1-blocker, the heart rate is reduced and hence the cardiac output and blood pressure will be reduced. Labetalol, an α- and ß-blocker, will block the post-synaptic alpha-receptors causing a decrease in total peripheral vascular resistance that decreases the blood pressure leaving the heart rate and cardiac output unaffected significantly. The ß-blocking effect will counterbalance the reflex baroreceptor tachycardia due to decreased peripheral resistance and blood pressure; thus it does not have an apparent effect on pressor response in the control group compared to the hypertensive group [11, 15-24].

The stress testing (hand grip and cold pressor test) after giving each drug shows a less pressor response for both systolic and diastolic blood pressures than before the medication. But, compared to the initial lower values of blood pressures at rest, the percentage increase in blood pressures remains unchanged, i.e. the behaviour response to stress tests does not change but starts at a lower level or base line than before medication. These observation are also reported by Balosubramanian et. al. [11], Frishman and Halprin [17] and Koch et. al [19].

With hand grip test a linear correlation can be found between the heart rate values and both blood pressures, but with a lower heart rate values for metoprolol (Fig. 2). This is reported by other workers [8, 12, 14].

As seen from our results, the effect of the two drugs is different as regard to the pressor responses after the cold pressor test which is particularly significant in the hypertensive group than the control group.

The effect of labetalol is more pronounced than metoprolol especially on the diastolic blood pressure. This is explained by the fact that the main mechanism of the pressor response to the cold pressor test is alpha-adrenoceptor stimulation as mentioned before.

From our study we can conclude that the use of a single oral dose of either a beta-blocker or a combined alpha-and beta-blocker showed a comparative response of lowering of systolic blood pressure both at rest and during static exercise for both the control and hypertensive groups but with a lower heart rate values after ß-blocker (metoprolol); this is due to the pressor output and peripheral vascular resistance. In contrast the cold pressor test has only one mechanism mediated through alpha-adrenergic receptors with an increase in the periphetrl resistance without any change in the heart rate. So, the cold pressor test is an excellent test to assess alpha-blocker drugs. This is why labetalol was more effective than metoprolol on the hypertensive group, especially on the diastolic blood pressure. The difference in the control group, however, was not apparent.

Beta-blockers are used successfully to reduce the blood pressure at rest and during stressful situation in hypertensive patients. The main modifying or limiting factor on their dose administration is the degree of bradycardia produced by them. So, the adding of alpha- to beta-blocker seems to be of advantage causing a decrease in pressor response to stresstest with a lesser effect on the heart rate and hence the amount used of these drugs can be modified easily according to the blood pressure alone.

References

1. FROHLICH E. D., ARAZI . C. and DUSTAN H. P.: Re-examination of the hemodynamics of hypertension. Am. J. Med., 257: 9, 1969.

2. BUHLER F. R., LARAGH J. H., RAUGHN E. D., BRUNNER H. R., GAVROS H. and BAER L.: The antihypertensive action of propranolol: Specific antirenin responses in high and normal renin in essential, renal, renovascular and malignant hypertension, Am. J. Cardiol., 39 : 511, 1973.

3. DOLLERY C.T. and LEWIS P. J.: Central hypotensive effect of propranolol in the rabbit. Br. J. Pharmacol., 45: 343, 1973.

4. SEGAWA K., TATLOR A. E. and GUYTON A. C.: Dynamic performance and stability of cerebral ischemic response. Am. J. Physiol., 201: 1164, 1961.

5. SLEIGHT P.: What is hypertension? Recent studies in neurogenic hypertension. Br. Heart J., 33 (Supp): 109, 1971.

6. GROSSMAN W., McLAURIN L. P., SALTZ S. B., PARASKOS J. A., DALEN J. E. and DEXTER L.: Changes in the inotropic state of the L. V. during isometric exercise. Br. Heart J., 35: 697, 1973.

7. HINES E. A. JR., and BROWN G. E.: The cold-pressor test for measuring the

reactivity of the BF.: data concerning 571 normal and hypertensive subjects. Am. Heart J., 11: 9, 1936.

8. McNEIL J. J. and LOUIS W. J.: A double-blind crossover comparison of pindolol, metoprolol, atenolol and labetalol in mild to moderate hypertension. Br. J. Clin. Pharmacol., 8 (supp. 2) : 1635, 1979.

9. CUDDY R. P., SMULYAN H., KEIGHLEY J. F., MARKASON C.R. and EICH R. H.:Hemodynamic and catecholamine changes during a standard cold-pressor test. Am. heart J., 71 (4): 446, 1966.

10. LIND A. R. and McHICOL G. W.: Muscle factors which determine the cardiovascular responses to sustained and rhythmic exercise. Can. Med. Ass. J., 96: 706, 1967.

11. BALOSUBRAMANIAN V., MANN S., MILLARCAING M. W. and RAFTERY E. B.: Effect of labetalol in hypertensive during exercise and postural changes. Br. J. clin. Pharmacol., 8 (supp. 2): 955, 1979.

12. COLLSTE P, HGLUND K. and VON BAHR G. : Plasma level and effects of metoprolol after single and multiple oral doses. Clin. Pharmacol. Therap., 27: 421, 1980.

13. MYERS M. G. and THIESSEN J. J.: Metoprolol kinetics and dose response in hypertensie patients. Clin. Pharmacol. Therap., 27; 756, 1980.

14. BENGET E., KARLBERG O. N., TOLOEN K., NITELIUS E. and WAERN U.: Once daily metoprolol in primary hypertension. Clin. Pharmacol. Therap., 25: 399, 1979.

15. BOLLI P., WALL-MANNING H.J., WOOD A. J. and SIMPSON F. O.: Experience with labetalol in hypertension. Br. J. Clin. Pharmacol., 3 (supp. 3): 765, 1976.

16. FICK M. H. and POSRTI P.: Combined alpha- and beta-adrenoceptor blockade with labetalol in hypertension. Br. Med. J., 1: 1046, 1976.

17. FRISHMAN W. and HALPRIN S.: Clinical pharmacology of new ß-adrenoceptor blocking drugs. Part 7. New horizone in ß-adrenoceptor blockade therapy: Labetalol. Am. Heart J., 98: 660, 1979.

18. KANE J., GREG I. and RICHARDS D.: A. double-blind trial of labetalol. Br. J. Clin. Pharmacol., 3 (supp. 3): 737, 1976.

19. KOCH G.: Combined alpha-and beta-adrenoceptor blockade with oral labetalol in hypertensive patients with reference to hemodynamic effects at rest and during exercise. Br. J. Clin. Pharmacol., 3 (supp. 3): 729, 1976.

20. McNEIL J. J., ANDERSON A. E., LOUIS W. J. LOUIS W. J. and MOGAN D. J. : Pharmacokinetics and pharmacodynamic studies of labetalol in hypertensive subjects. Br. J. Clin. Pharmacol., 8 (supp. 2): 1575, 1979.

21. MEHTA J. and COHN J.: Hemodynamic effects of labetalol, an alpha-and

beta-adrenergic blocker agent, in hypertensive subjects. Cairo., 55: 370, 1977.

22. RICHARDS D. A. and PRICHARD B. N. C.:Clinical pharmacology of labetalol. Br. J. Clin. Pharmacol., 8 (supp. 2): 89, 1979.

23. RICHARDS D. A. TUCKMAN J, and PRICHARD B. N. C: Assessment of α- and ß-adrenoceptor blocking actions of labetalol. Br. J. Cli. Pharmacol. Therap., 31: 8, 1982

24. SERLIN M. J., ORME M. C. L. E., MACIVER M., GREEN G. J., MACNEE C. M. and BECKENBRIDGE A. M.: Rate of onset of hypotensive effect of oral labetalol. Br. J. Clin. Pharmacol., 7: 165, 1979.