

# Antihypertensive and Hemodynamic Properties of the New Beta Adrenergic Blocking Agent Timolol

By JOSEPH A. FRANCIOSA, M.D., EDWARD D. FREIS, M.D.,  
AND JAMES CONWAY, M.D.

## SUMMARY

The antihypertensive activity of timolol, a new beta adrenergic blocking agent, was assessed in hypertensive patients. In hospitalized patients timolol, 5 mg orally every 8 hr for one week, resulted in a significant although mild reduction of blood pressure with diastolic pressure falling from a mean of 101 mm Hg to 91 mm Hg. Heart rate and cardiac output fell while total peripheral resistance increased. The Valsalva response, the reflex tachycardia following inhalation of amyl nitrite and the cardiovascular responses to infusion of isoproterenol were significantly inhibited. Timolol also was compared to propranolol in a randomized double-blind outpatient trial. The antihypertensive and bradycrotic effects of the two drugs were similar. Heart rate was reduced 18% by both drugs ( $P < 0.05$ ). Supine diastolic pressure fell 9% ( $P < 0.05$ ). Unlike the short term effects of timolol, and in contrast to propranolol, cardiac output did not remain reduced after five weeks of continuous treatment with timolol. It is concluded that timolol merits further investigation as an antihypertensive agent.

## Additional Indexing Words:

Hypertension    Propranolol    Sympathetic blockade    Amyl nitrite

**T**IMOLOL [( - )-3-morpholino-4-(3-tertbutylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate] is a new beta adrenergic blocking agent which within one hour of a 5 mg oral dose reduces heart rate and cardiac output by 20%. It also diminishes the sympathetic reflex responses to the Valsalva maneuver and amyl nitrite inhalation.<sup>1</sup> Like propranolol it does not reduce arterial pressure acutely and does not possess intrinsic sympathomimetic activity.

Beta blocking agents can effectively lower blood pressure in properly selected patients without orthostatic hypotension or other important side effects.<sup>2-6</sup> The present study was designed to assess the antihypertensive properties of timolol and to

observe its hemodynamic effects following continued administration of the drug.

## Methods

The study was performed in two parts, the first consisting of hemodynamic observations in hospitalized patients with mild essential hypertension, the second being a comparison of timolol and propranolol in hypertensive outpatients.

## Part I

Six male volunteers ranging from 46 to 56 years of age with previously untreated mild essential hypertension (diastolic blood pressure 90 to 110 mm Hg) were selected for study. All patients had initial laboratory studies including hemogram, urinalysis, fasting blood sugar, serum electrolytes, blood urea nitrogen, serum creatinine, chest X-ray, electrocardiogram, urinary catecholamines, and intravenous pyelogram. Patients with any of the following were excluded: history of severe heart failure or myocardial infarction, resting heart rate below 50 beats per minute, insulin-requiring diabetes mellitus, hepatic disease, bronchial asthma or emphysema or renal failure defined as a serum creatinine level of 2 mg % or higher or abnormal function on intravenous pyelogram. All subjects were hospitalized at least three days prior to study during which time blood pressures were recorded three times daily. Blood pressures were recorded following 10 min in the supine position and 3 min after standing erect. A

From the Veterans Administration Hospital and the Department of Medicine, Georgetown University, Washington, D. C.

Supported in part by a research grant from Merck Sharp & Dohme, West Point, Pennsylvania.

Address for reprints: Dr. Edward D. Freis, Senior Medical Investigator, VA Hospital, 50 Irving Street, N.W., Washington, D. C. 20422.

Received December 21, 1972; revision accepted for publication February 16, 1973.

diastolic blood pressure averaging 90 mm Hg or above in the supine position during this period was used as the criterion for entrance into the study.

Hemodynamic measurements were carried out following the three to six day pretreatment control period. A Teflon needle was inserted into the brachial artery and PE 50 tubing was advanced via an antecubital vein into the right atrium. Arterial and venous pressures were recorded using a P23Db Statham pressure transducer and a Honeywell Visicorder. Cardiac output was determined by the dye dilution technique using indocyanine green. The Valsalva maneuver was performed by having the patient blow forcibly into a closed tube while maintaining a pressure of 40 mm Hg for 10–15 sec. Maximal blood pressure overshoot and heart rate during the period of reflex bradycardia were measured to quantitate the response. Amyl nitrite inhalation was carried out by having the patient take two deep breaths from a vial containing 0.3 ml of the substance. The maximum fall in diastolic blood pressure and peak tachycardia were used to quantitate the response. Isoproterenol was infused intravenously starting at 1  $\mu\text{g}/\text{min}$  and titrating upward until a 25% increase in heart rate was obtained or to a maximum of 4  $\mu\text{g}/\text{min}$ .

Following these control determinations 5 mg of timolol was given orally and one hour later the hemodynamic measurements were repeated. Continuous treatment with timolol was then initiated at 5 mg every 8 hr and maintained for seven days. Dosage was adjusted to maintain a heart rate of 50–70 beats/min in the supine position. Half of the patients remained on the initial dose and half were increased to 10 mg every eight hours. On the final day of treatment the morning dose was omitted and the patient was brought to the laboratory where the hemodynamic measurements were repeated before and one hour after the 5 or 10 mg dose of timolol.

**Part II**

From an outpatient clinic population 28 male volunteers with a previous diagnosis of essential hypertension were selected. The same exclusions described in part I were applied to these patients. All antihypertensive medications were discontinued at least three weeks prior to entry into the study; in the case of Rauwolfia derivatives this was extended to six weeks. The patients selected were those whose diastolic blood pressure ranged between 90 and 125 mm Hg during this period of no treatment. Placebo, two capsules t.i.d., was given during the first two weeks of the trial. Patients were then randomly assigned, double blind, to either propranolol, 80 mg (2 capsules) t.i.d. or timolol 10 mg (2 capsules) t.i.d. Treatment with active drug lasted for five weeks, after which all patients were again given placebo for two more weeks.

All patients were seen by the same physician at weekly intervals at which time they were weighed; heart rate and blood pressure were recorded after 10 min supine and 3 min standing, and signs and symptoms of heart failure or other complications were looked for. If the diastolic blood pressure was not reduced to normal or 10 mm Hg lower than had been

present the preceding week, the dose of active drug was increased by one capsule t.i.d. to a maximum of double the starting dose. Dosage was not increased if the heart rate was below 60 beats per min and was decreased by one capsule t.i.d. if the heart rate was below 50 beats per min.

In consenting individuals hemodynamic measurements were made just before and at the end of the five week active drug treatment period. Cardiac output, intraarterial and venous pressures were recorded and amyl nitrite inhalation was performed employing the same techniques as described in part I. Patients were instructed to take their usual morning dose of medication 1–2 hr prior to reporting to the laboratory and measurements were made under the same general conditions in both treatment groups.

**Results**

**Part I**

*Blood Pressure and Heart Rate*

Changes in heart rate and blood pressure are summarized in table 1. Every patient experienced a fall in blood pressure without orthostatic hypotension. The average daily supine blood pressures and heart rates for all patients are shown in figure 1. Treatment with timolol (5 mg every 8 hr) was begun on day seven and continued through day 13. A definite reduction in blood pressure was evident by the second day of treatment and became more pronounced with continuation of therapy. In the posttreatment period blood pressure returned toward pretreatment levels suggesting that the observed fall in blood pressure was not due to a placebo effect. The fall in blood pressure seemed to correspond with the decline in heart rate and likewise when treatment was stopped blood pressure rose parallel with the heart rate suggesting that the change in blood pressure was closely related to

**Table 1**

*Mean Values of Heart Rate and Blood Pressure in Six Hospitalized Hypertensive Patients Treated with Timolol for One Week*

	Control	Treated	% Reduction
Supine			
Heart rate (per min)	82	72	12.9
Systolic blood pressure (mm Hg)	139	129	7.2
Diastolic blood pressure (mm Hg)	101	91	9.9
Standing			
Heart rate (per min)	98	80	18.6
Systolic blood pressure (mm Hg)	139	129	7.2
Diastolic blood pressure (mm Hg)	108	100	7.4

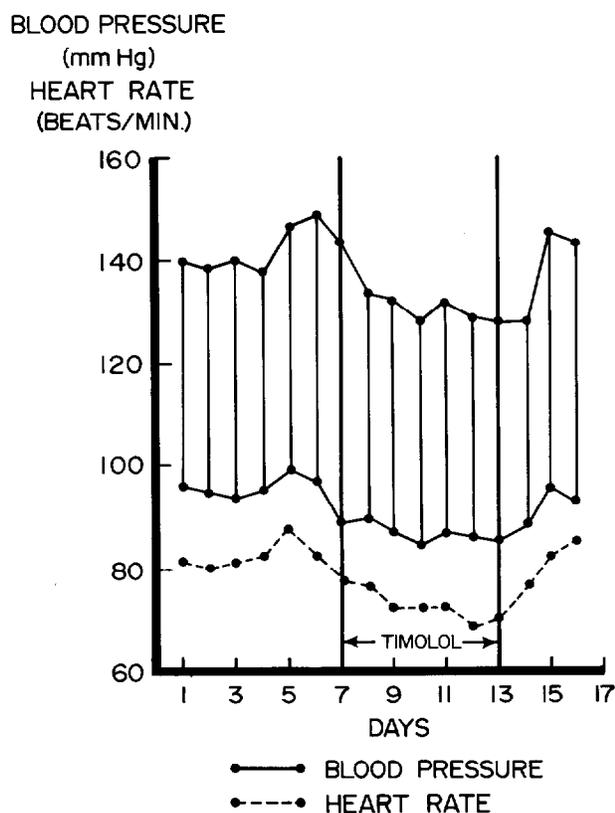


Figure 1

Blood pressure and heart rate responses of six hospitalized patients during continuous administration of timolol for one week. Points plotted are mean values for the whole group.

the level of beta blockade. It should be noted that these patients had predominantly diastolic hypertension, as the mean pretreatment systolic pressure for the group was only 139 mm Hg.

#### Hemodynamics

Prior to treatment the mean cardiac output for the entire group was 5.43 liters/min. This fell by 21% to 4.29 liters/min one hour after the first dose of timolol (fig. 2). Reduced cardiac output was still present after one week's treatment. Since blood pressure was reduced to a lesser degree than cardiac output, total peripheral resistance was increased by timolol. Stroke volume and central venous pressure were not significantly changed.

#### Sympathetic Reflex Activity

During the control period inhalation of amyl nitrite produced a mean fall of 36.3 mm Hg in diastolic blood pressure while heart rate increased by a mean of 37.8 beats per min. After the first dose of timolol diastolic pressure still fell 38.8 mm Hg, but heart rate rose only 12.5 beats per min. One

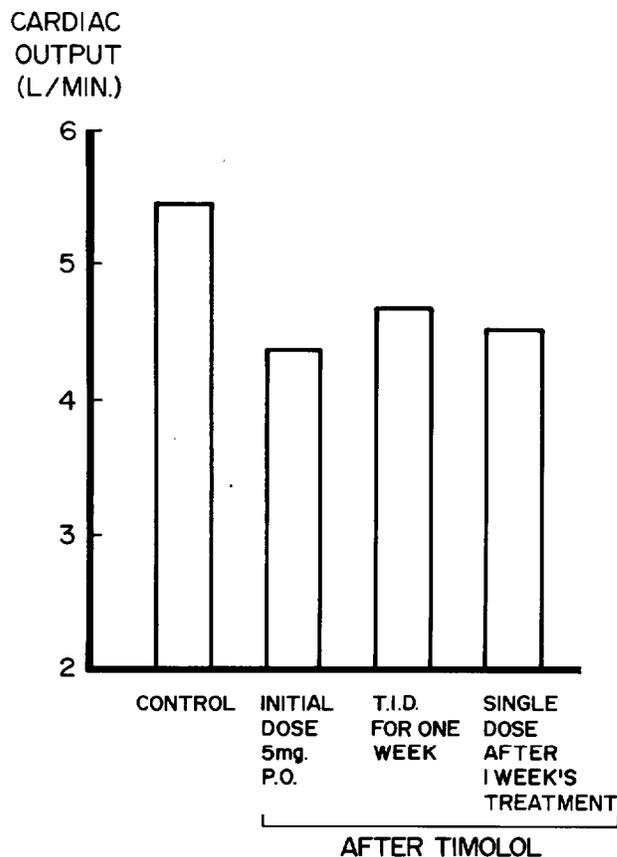


Figure 2

Effect of timolol on cardiac output in six hospitalized patients.

week later, blood pressure fell about the same amount, but the heart rate response was still significantly reduced by about 50% (fig. 3).

With respect to the Valsalva maneuver in the control period the mean increase of blood pressure during the post-Valsalva overshoot was 22.5 mm Hg systolic and 23.2 mm Hg diastolic. Heart rate fell 10.5 beats/min. After timolol, the pressure overshoot was reduced to 3.8 mm Hg systolic and 7.5 mm Hg diastolic, while heart rate fell only 1.2 beats/min. This response remained unchanged after one week of treatment.

The effects of isoproterenol infusion on heart rate and blood pressure were virtually abolished by timolol. Prior to treatment isoproterenol lowered diastolic pressure by an average of 12.3 mm Hg and increased heart rate 29 beats/min. After timolol there was essentially no response to isoproterenol infusion (fig. 4). This same response persisted after one week of therapy.

Since the morning dose of timolol was withheld prior to the second hemodynamic study, patients

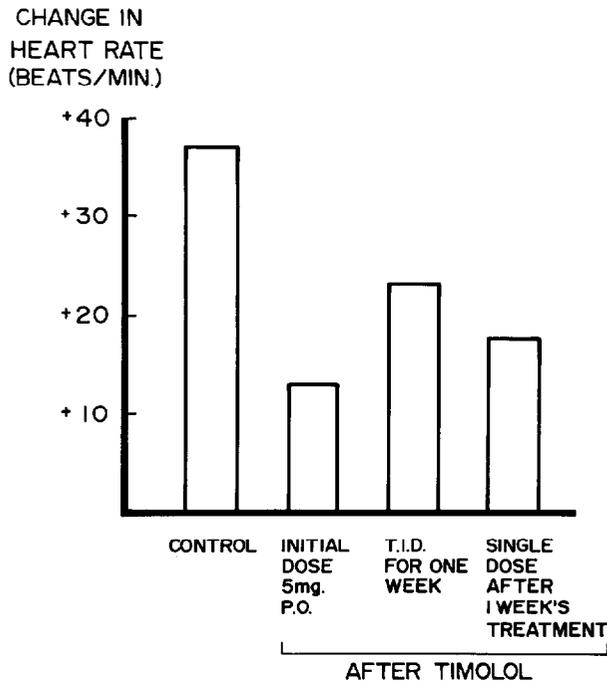


Figure 3

Effect of timolol on amyl nitrite-induced tachycardia in six hospitalized patients.

were untreated for 12-16 hr. Nevertheless, the beta adrenergic blocking effects of timolol on the reflex responses as well as cardiac output and heart rate were still present before drug administration and became more pronounced afterward (see column labelled "t.i.d. for one week" in figs. 2, 3, 4) suggesting that timolol has a prolonged duration of action or a cumulative effect.

**Part II**

*Clinical Data*

Of a total of 28 patients entering, 24 completed the outpatient trial. Among the four who were dropped, one sustained a nonfatal cerebrovascular accident at the end of the first placebo period, while two others were dropped because of failure to adhere to the protocol. Treatment was terminated in the fourth patient because of an episode of acute laryngeal edema. However, he was receiving ampicillin concurrently as treatment for a urinary tract infection.

Of the 24 patients completing the trial, 13 received propranolol and 11 received timolol. The propranolol-treated patients averaged 48.1 (range 35-60) years of age while the age of those on timolol averaged 43.6 (range 30-53) years. None of the patients had greater than Group II hypertensive retinopathy by the Kieth, Wagener, and Barker

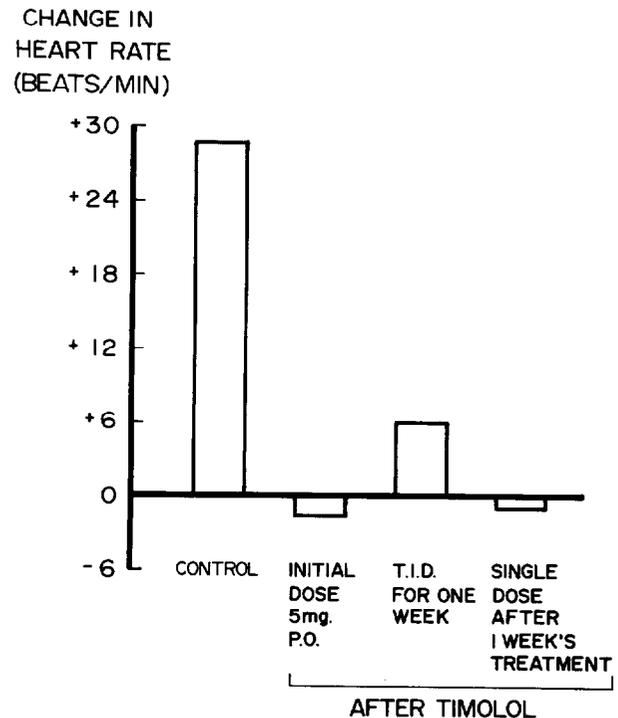


Figure 4

Effect of timolol on isoproterenol-induced tachycardia on six hospitalized patients.

criteria. In the propranolol group, 9 of 13 had Group II changes, and 6 of 11 timolol-treated patients had similar changes. Electrocardiographic or radiographic evidence of left ventricular hypertrophy was present in five patients taking timolol and in seven receiving propranolol. Three patients in the propranolol group had a history of exertional dyspnea. In one the dyspnea was unchanged during treatment, one improved, and the other patient noted transient worsening of symptoms, which was relieved by decreasing the dosage of medication. Another patient in this group developed signs and symptoms of left ventricular failure during the treatment period but responded quickly to a reduction of propranolol dosage. No patient receiving timolol developed symptoms of heart failure or noted change in preexisting symptoms. No significant weight change occurred in either group.

The average total daily dose of drug was 333 mg for the propranolol group, and 50 mg for the timolol group.

*Blood Pressure and Heart Rate*

The changes in heart rate and blood pressure are summarized in table 2. Control values were

Table 2

Comparative Effects of Propranolol and Timolol on Mean Values of Heart Rate and Blood Pressure During Out-patient Trial with 24 Patients

	Timolol				Propranolol			
	Control	Treated	% reduction	Posttreatment	Control	Treated	% Reduction	Posttreatment
Heart rate (per min)								
Supine	78	64	17.9	77	75	62	17.3	76
Standing	85	69	18.8	88	85	69	18.8	86
Systolic blood pressure (mm Hg)								
Supine	169	164	2.8	161	168	155	7.7	167
Standing	168	161	4.8	159	172	149	13.4	158
Diastolic blood pressure (mm Hg)								
Supine	112	102	8.9	109	111	101	9.0	109
Standing	117	108	5.4	113	111	104	6.3	113
Amyl nitrite tachycardia								
Increase/min	+37.8	+15.3	59.5	—	+28.5	+13.5	52.7	—

calculated from the average of three readings at weekly intervals including the preplacebo reading as well as the two weeks of placebo preceding administration of active drugs. The averages of readings during the final two weeks of active drug treatment, when peak effects were observed, were used to derive the mean values of the active treatment period.

Blood pressure fell promptly and was already significant ( $P < 0.01$ ) after the first week of treatment in both groups. In the propranolol treated group diastolic pressure fell from 111 mm Hg to 105 mm Hg after the first week of treatment, and eventually dropped to 101 mm Hg at the end of five weeks of treatment. For timolol treated patients, diastolic blood pressure was reduced from 112 to 108 mm Hg after one week and fell further to 102 mm Hg after five weeks. The degree of diastolic pressure reduction was not significantly different between the two groups, but systolic pressure was significantly lowered only in the propranolol-treated group. Both diastolic blood pressure and heart rate returned to, or was very near to pretreatment values in each group during the final two weeks of placebo administration, but systolic pressure tended to remain below control levels, especially in timolol-treated patients.

The changes in heart rate and the degree of inhibition of amyl nitrite induced tachycardia were virtually identical in the two groups suggesting that the degree of beta blockade achieved was the same with either drug (table 2).

#### Other Hemodynamic Responses

Although the two drugs yielded similar results with respect to heart rate and blood pressure, they

had markedly different effects on cardiac output (fig. 5). Although not significantly changed by timolol, cardiac output was reduced 23.1% after five weeks of propranolol treatment. This result was somewhat surprising since in Part I of the study cardiac output was reduced after one week of timolol therapy. Conclusions regarding the apparent difference between the two drugs should be regarded as preliminary since cardiac outputs were obtained in only a small sample of six timolol patients as opposed to 11 receiving propranolol. However, despite the disparity in the size of these two subgroups, the difference between them was statistically significant ( $P < 0.01$ ). The reduction in cardiac output observed in the propranolol-treated patients could explain the greater reduction in systolic blood pressure noted in this group (table

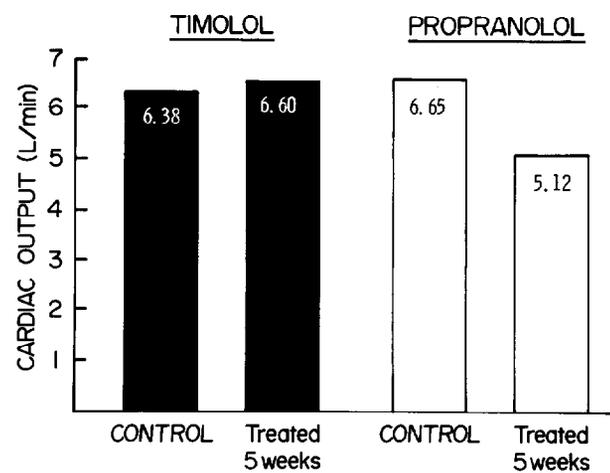


Figure 5

Comparative effects of five weeks of continuous administration of propranolol (11 pts.) and timolol (6 pts.) on cardiac output.

2). Because of the differences in cardiac output responses, total peripheral resistance fell slightly in timolol patients, but increased by 21.4% in propranolol-treated subjects.

Disturbing side effects including orthostatic symptoms were not observed in these patients. No changes were noted in the hemogram, urinalysis, blood chemistries, electrocardiogram, or chest X-ray.

#### Discussion

The present results confirm our previous observations regarding the activity of MK-950.<sup>1</sup> Cardiac output and heart rate are reduced by about 20% and cardiac sympathetic reflex activity is diminished by a single oral dose. These effects persist with continued administration of the drug, although the cardiac output tends to return to pretreatment levels over the course of several weeks.

The usual method of evaluating effectiveness of beta adrenergic blockade is to measure an agent's ability to inhibit the effects of isoproterenol infusion. Isoproterenol, however, is not the normal cardiac sympathetic stimulator and it seems physiologically more correct to assess the degree of blockade by quantitating responses to reflex sympathetic stimuli. The data from Part I of this study show that timolol inhibits the blood pressure overshoot and bradycardia following release of the Valsalva maneuver; the same has been demonstrated with propranolol.<sup>6</sup> However, because of difficulty in recording the transient changes the Valsalva response is not a practical test for clinical use in assessing the degree of blockade. Inhalation of amyl nitrite is a more easily applicable test in this regard. The fall in blood pressure is unaffected by beta adrenergic blockade, but the reflex tachycardia is 50% inhibited. Similar results can be obtained by using nitroglycerin instead of amyl nitrite.<sup>7</sup> It must be kept in mind, however, that the sympathetic blockade produced by the available blocking drugs is not complete and stimuli of sufficient magnitude such as acute emotional stress or extreme exercise can overcome it.<sup>8, 9, 10</sup>

Our data show that timolol possesses antihypertensive activity comparable to that produced by propranolol. A reduction in blood pressure is seen within one week of treatment with both drugs, and even within the first 24–48 hr in some patients. This contrasts with the results of Prichard and Gillam<sup>4, 6</sup> who observed that several weeks were required to obtain an antihypertensive effect with propranolol. However, these authors began treatment with very

small doses of propranolol which were gradually increased over the course of several weeks until levels comparable to our initial doses were attained. If a response is defined as a fall in diastolic pressure of greater than 6 mm Hg, then 67% of our patients (8 of 13 on propranolol and 8 of 11 on timolol) responded. This is within the range of 50–80% reported in other series employing beta adrenergic blocking agents.<sup>3–6, 8, 11</sup>

The mechanism of the hypotensive action of beta adrenergic blocking drugs is not known. Prichard states that there is a "resetting" of the baroreceptors<sup>2</sup> and a central action of beta blockers has also been postulated.<sup>12</sup> Other authors feel that the decrease in cardiac output is responsible.<sup>13, 14</sup>

Although the present study was not constructed to elucidate the mechanism of the blood pressure lowering effect of the beta adrenergic blocking drugs, our data argue against the concept that reduced cardiac output is the important factor during long term treatment. Blood pressure was lowered by the same amount with both drugs, but cardiac output was reduced only in the propranolol-treated group. In the nonresponders treated with propranolol, the cardiac output actually fell further 7.16 liters/min to 5.03 liters/min, than in the responders who fell from 6.23 liters/min to 5.19 liters/min. In the timolol group neither responders nor nonresponders changed their cardiac outputs significantly. It can be concluded from these data that the hypotensive effect is not related to a reduction in cardiac output. A similar lack of correlation between cardiac output and blood pressure has recently been reported by Tarazi and Dustan. They found that cardiac output was reduced in 45 of 48 patients, but blood pressure fell in only 26 patients.<sup>8</sup>

It is not clear why propranolol produced a sustained lowering of cardiac output and timolol did not, especially since the degree of beta blockade appeared equal. Because of the small number of patients involved, especially in the timolol group, additional data should be obtained with timolol in order to confirm this preliminary observation. Other observers have found that propranolol tends to sustain a chronic reduction in cardiac output.<sup>2, 8, 13, 15</sup> Studies with other beta adrenergic blocking drugs have yielded results similar to ours. Practolol does not lower cardiac output to the same degree as propranolol.<sup>16</sup> However, this may be due to the intrinsic sympathomimetic properties of practolol which would counteract the negative inotropic effect of beta blockade.<sup>17</sup> Such an

explanation does not apply in the present case, however, since neither propranolol nor timolol possesses intrinsic sympathomimetic activity.

#### References

1. ULRYCH M, FRANCIOSA J, CONWAY J: Comparison of a New Beta Adrenergic Blocker (MK-950) and Propranolol in Man. *Clin Pharmacol Ther* 13: 232, 1972
2. PRICHARD BN, SHINEBOURNE E, FLEMING J, HAMER J: Hemodynamic Studies in Hypertensive Patients Treated by Oral Propranolol. *Brit Heart J* 32: 236, 1970
3. ZACHARIAS F, COWEN K: Controlled Trial of Propranolol in Hypertension. *Brit Med J* 1: 471, 1970
4. PRICHARD B, GILLAM P: Treatment of Hypertension with Propranolol. *Brit Med J* 1: 7, 1969
5. PATERSON J, DOLLERY C: Effect of Propranolol in Mild Hypertension. *Lancet* 2: 1148, 1966
6. PRICHARD BN, GILLAM PM: Propranolol in Hypertension. *Amer J Cardiol* 18: 387, 1966
7. FITZGERALD JD: A New Test of the Degree of Adrenergic Beta Receptor Blockade. *Internat J Clin Pharmacol* 4: 125, 1971
8. TARAZI RC, DUSTAN HP: Beta Adrenergic Blockade in Hypertension. *Amer J Cardiol* 29: 633, 1972
9. ULRYCH M: Changes of General Hemodynamics During Stressful Mental Arithmetic and Non-stressing Quiet Conversation and Modification of the Latter by Beta-adrenergic Blockade. *Clin Sci* 36: 453, 1969
10. NICOTERO JA, BEAMER V, MONTSOS SE, SHAPIRO AP: Effects of Propranolol on Pressor Responses to Noxious Stimuli in Hypertensive Patients. *Amer J Cardiol* 22: 657, 1968
11. ZACHARIAS FJ, COWEN KJ, PRESTT J, VICKERS J, WALL BG: Propranolol in Hypertension: A Study of Long Term Therapy, 1964-1970. *Amer Heart J* 83: 755, 1972
12. MURMANN W, ALMIRANTE L, SACCANI-GUELFU M: Central Nervous System Effects of Four Adrenergic Blocking Agents. *J Pharm Pharmacol* 18: 317, 1966
13. LYDTIN H, KUSUS T, DANIEL W, SCHIERL W, ACKENHEIL M, KEMPTER H, LOHMÖLLER G, NICKLAS M, WALTER I: Propranolol Therapy in Essential Hypertension. *Amer Heart J* 83: 589, 1972
14. DORPH S, BINDER C: Evaluation of the Hypotensive Effect of Beta-adrenergic Blockade in Hypertension. *Acta Med Scand* 185: 443, 1969
15. FROHLICH ED, TARAZI RC, DUSTAN HP, PAGE IH: The Paradox of Beta-Adrenergic Blockade in Hypertension. *Circulation* 37: 417, 1968
16. TARAZI RC, SAVARD Y, DUSTAN HP, BRAVO EL: Cardioselective Beta Adrenergic Blockade in Hypertension. *Clin Pharmacol Ther* 13: 154, 1972
17. FITZGERALD JD, WALE JC, AUSTIN M: The Hemodynamic Effects of Propranolol, Dexpropranolol, Oxprenolol, Practolol, and Sotalol in Anaesthetised Dogs. *Eur J Pharmacol* 17: 123, 1972