Sotalol-Induced Beta Blockade in Cardiac Patients

By Harold Brooks, M.D., John Banas, Jr., M.D., Steven Meister, M.D., Murrill Szucs, Jr., M.D., James Dalen, M.D., and Lewis Dexter, M.D.

SUMMARY
Sotalol (MJ 1999), a beta-adrenergic blocking agent found to have no significant intrinsic myocardial depressant effects, was administered intravenously to 20 patients with heart disease. Eight of the patients had clinical and hemodynamic evidence of chronic heart failure. Doses ranged from 0.2 to 0.6 mg/kg.
In all studies, heart rate decreased significantly, accompanied by comparable decreases in cardiac index and tension-time index. There were, however, no significant changes in stroke index, mean blood pressure, or left ventricular end-diastolic pressure—even in those patients with advanced heart failure, indicating that the changes noted were primarily rate-related and could not be ascribed to myocardial depression. To confirm this, further studies were performed in which heart rate was held constant by atrial pacing in normal and catecholamine-depleted dogs. Sotalol, at doses much higher than the minimal beta-blocking dose, did not change stroke index, blood pressure, left ventricular end-diastolic pressure, or estimated maximal velocity of isotonic shortening (V_max), confirming that myocardial contractility was unaffected.
It is concluded that sotalol-induced beta blockade had no observable myocardial depressant action in dogs or adverse hemodynamic effects in cardiac patients, even when advanced chronic heart failure was present.

Additional Indexing Words:
Beta-adrenergic influences in heart failure
Force-velocity relationship in intact circulation
Myocardial depression

The effects of beta-adrenergic blockade on cardiovascular dynamics have been documented by numerous studies in animals and in man. In addition to the beta-blocking effect, however, propranolol and certain other structurally similar agents have been shown to have a quinidine-like, myocardial depressant or negative inotropic effect in isolated cardiac muscle preparations1-5 and to cause hemodynamic changes in the intact animal4-6 and in man7-10 indicating a depression of ventricular function. For this reason, beta blockade has generally been held to be relatively contraindicated in patients with significant heart failure.

Beta-adrenergic blockade induced by a more recently synthesized agent, sotalol* (MJ 1999), a methanesulfonanilid-substituted isopropylphenylethylamine11 (fig. 1) has been reported to be essentially free of associated myocardial depressant or negative inotropic effects, as determined by studies in isolated cardiac muscle.2,12 This study assesses the hemodynamic responses to sotalol of resting

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**Hemodynamic Effects of Sotalol-Induced Beta Blockade in Resting Cardiac Patients**

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*Paired t-test.

Abbreviations: AS = aortic stenosis; AR = aortic regurgitation; MS = mitral stenosis; MR = mitral regurgitation; TR = tricuspid regurgitation; CAD = coronary artery disease; NSR = normal sinus rhythm; 2°Bk = second degree A-V block, Wenckebach phenomenon; PE = acute pulmonary embolism; SAS = hypertrophic subaortic stenosis; S/D/M = systolic/diastolic, mean; S/ED = systolic/end-diastolic; NYHA = New York Heart Association classification; AF = atrial fibrillation; AFI = atrial flutter.

_Circulation, Volume XLII, July 1970_
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In this section, the authors discuss the selection of patients for the study. They mention that the experiments were conducted in intact, closed-chest dogs to elucidate more critically its effects upon myocardial contractility within the intact circulation.

**Methods**

**Selection of Patients**

Twenty patients, ranging in age from 23 to 67 years, were studied in the postabsorptive state during diagnostic cardiac catheterization. Premedication, consisting of a single intramuscular injection of 10 mg of diazepam, was used in 14 patients to allay apprehension. The latter drug has been shown to cause only minimal and transient hemodynamic changes. In all instances, the premedication preceded the measurement of the experimental data by at least 2 hours.

The patients’ diagnoses and their functional classification, as defined by the New York Heart Association, are shown in Table 1. All patients were symptomatic from their heart disease. Thirteen of the patients were moderately or severely symptomatic, being either class III or class IV. Fourteen of the patients were on digitalis at the time of the study. Informed consent to use the drug was obtained before each study.

**Hemodynamic Technics**

All pressure, rate, and flow measurements were made simultaneously. Cardiac output was determined by either the direct Fick method or by the indicator-dilution technic using indocyanine green injected into the pulmonary artery and sampling from a peripheral artery. During determination of the cardiac output, the following were measured: (1) heart rate and rhythm by the electrocardiogram; (2) systemic arterial, right heart, and pulmonary arterial pressures, by means of cardiac catheters attached to Statham P23D pressure transducers, with zero pressure at the level of the mid-right atrium, and (3) in 14 of the patients, left ventricular pressures were measured via the retrograde brachial approach; (4) systemic and pulmonary arterial blood saturation and capacity were determined spectrophotometrically; (5) systemic arterial blood $P_{O_2}$, $P_{CO_2}$, and pH, by an electrode blood-gas analyzer, utilizing duplicate

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*Figure 1*

The chemical structure of sotalol is shown here and is compared to two other important beta-adrenergic blockers, propranolol and dichloroisoproterenol (DCI). Isoproterenol, the prototype of the beta agonist, is also shown for comparison. Sotalol differs from DCI primarily in the substitution of the methanesulfonanilid side chain in the p para position. It differs from propranolol primarily by the absence of the naphthyl nucleus.

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*Model DU-2, Beckman Instruments, Inc., Palo Alto, California.
†Instrumentation Laboratory, Inc., Boston, Massachusetts.*

*Circulation, Volume XLII, July 1970*
samples and correcting for temperature; and (6) oxygen consumption, by collecting expired air for 3 min, utilizing a Douglas bag, with minute ventilation determined by use of a Tissot spirometer.

The following hemodynamic variables were derived:
1. Stroke index, in ml/beat/m² by using the formula:
   \[ CI/HR \]
   where \( CI = \) cardiac index in L/min/m²
   \( HR = \) heart rate in beats/min.
2. Left ventricular minute work index, in kg-m/min/m², by using the formula:
   \[ LVWI = \frac{(LVSPm - LVEDP) \times CI}{1,000} \]
   where \( LVSPm = \) mean left ventricular systolic pressure in mm Hg
   \( LVEDP = \) left ventricular end-diastolic pressure in mm Hg
   \( CI = \) cardiac index in L/min/m²
   13.6 = conversion factor for the specific gravity of Hg
3. Tension-time index, in mm Hg sec/min by using the formula:
   \[ TTI = LVSPm \times HR \times SEP \]
   where \( LVSPm = \) mean left ventricular systolic pressure in mm Hg (mean arterial systolic pressure substituted in cases without aortic stenosis)
   \( HR = \) heart rate in beats/min
   \( SEP = \) systolic ejection period in sec/beat
4. Peripheral resistance, in dynes sec cm⁻⁵ by using the formula:
   \[ P.Res. = \frac{mBA \times CO}{79.92} \]
   where \( mBA = \) mean arterial pressure in mm Hg
   \( CO = \) cardiac output in L/min
   79.92 = conversion factor (mm Hg/L/min to dynes sec cm⁻⁵).

After control measurements were recorded, sotalol was administered intravenously, in doses of 0.2, 0.4, or 0.6 mg/kg of body weight—doses considerably higher than that of 0.06 mg/kg, previously shown to cause in man a significant blockade of the tachycardia produced by 20μg isoproterenol, intravenously.¹⁴ Each dose was injected at a constant rate over a 4-min interval, and measurements were made 10 min after the midpoint of the injection. Lead II of the electrocardiogram and systemic arterial and venous pressures were measured continuously during the 30 to 90-min period of observation involved in the study.

Blood samples were taken just before and 1 week after each study and were analyzed to detect any significant changes in the hemogams or liver and renal function tests.

**Experimental Canine Studies**

To study more critically the effects of the drug on myocardial contractility, experiments were performed on two groups of healthy mongrel dogs of both sexes, ranging in weight from 15 to 23 kg. The animals were anesthetized intravenously with a warm solution of alpha-chloralose (80 mg/kg), after induction of anesthesia with a small intravenous injection of thiopental. Additional supplementary doses of the chloralose solution were given during the study to maintain a relatively uniform state of anesthesia, as judged by depression of corneal reflexes. However, no anesthetic agent was given after control measurements began. Respiration was maintained at a steady rate by a Harvard respiratory pump connected to a cuffed endotracheal tube, with steady supplemental oxygen administered to maintain optimal arterial blood oxygen saturation throughout the experiment.

Left ventricular pressure was measured through a short (4 in) 14-T gauge, semi-rigid Teflon needle* inserted percutaneously into the left ventricular apex and connected directly to a Statham P23Db pressure transducer without intervening tubing. The first derivative of left ventricular pressure (LV dp/dt) was computed electronically by means of an operational amplifier and a resistance-capacitance differentiating circuit with a time constant of 0.05 msec and a frequency response which is linear to 150 cycles/sec. The circuit was calibrated for each experiment in terms of mm Hg/sec. Aortic blood pressure was measured at the arch of the aorta through a 13-gauge Teflon needle inserted into the right carotid artery. All recordings were made on an Electronics for Medicine, 8-channel photographic recorder.

**Group 1. Three Dogs**

To assess any changes produced by the drug upon myocardial contractility, the following technics were employed, analyzing the isovolumic portion of the left ventricular pressure trace and its simultaneously computed first derivative, taken from high speed (200 mm/sec) recordings. This method is based upon technics recently developed¹⁵–²² and allows a valid estimate of the contractile state of the heart within the intact circulation independent of changes in pre-load or after-load. Analysis of the isovolumic portion of systole was made using the calculation:

\[ \frac{LV \ dp/dt}{kp}, \ in \ sec^{-1} \]

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*Becton, Dickinson and Company, Rutherford, New Jersey.
†Model EP85AU, Philbrick Nexus Co., Boston, Massachusetts.
where \( p \) = left ventricular pressure in mm Hg

\( \text{LV} \frac{dp}{dt} \) = simultaneously measured rate of rise

of pressure in mm Hg/sec

\( k \) = predetermined series elastic constant,

28, based on isolated muscle studies\(^{28}\) and

observations in the intact heart.\(^{24}\)

A force-velocity curve was then determined by

plotting the above quantity, at 4-msec intervals,

against simultaneously measured left ventricular

pressure, from the onset of ventricular contraction

to the opening of the aortic valve. An index of the

contractile state of the myocardium could then be

determined either by extrapolation of the iso-
volumic segment of the force-velocity curve back

to zero pressure load \((V_{\text{max}})\) or by visual

comparison of the two force-velocity curves before

and after administration of the beta-blocking

agent. In this group, 1.0 mg/kg of sotalol was

used.

Group 2. Three Dogs

To assess any changes produced by the drug

upon myocardial contractility in dogs independent

of the basic, resting, intrinsic adrenergic drive, three dogs were pre-treated with 1.0

mg/kg reserpine, intravenously, 18 to 24 hr prior

to the experiment. Force-velocity curves were
determined, as in group 1, before and after

graded doses of sotalol up to a maximum dose of

6.0 mg/kg.

In both groups of dogs, heart rates were held
constant throughout each experiment by means of

a unipolar pacing catheter introduced into the

mid-right atrium.

Results

Studies in Man

The effects of graded doses of sotalol upon

resting hemodynamics are shown, for all

patients, in table 1. Figures 2 to 4 show

graphically the changes in selected hemody-
namics produced by the drug. The dose used

in each patient is indicated according to the

key in each figure, with the averages for the

drure doses (before and after beta blockade)

shown in the respective margins. Patients in

heart failure are indicated by dotted lines.

Heart rate (fig. 2) decreased significantly in

all patients and at all doses. The average

change for the 0.2 mg/kg dose was approximately

15% below control level and for the 0.4

mg/kg dose, 20% below control, with no

further decrease being caused by the 0.6

mg/kg dose. Cardiac index likewise decreased

in similar proportions in all patients except

Figure 2

Decreases in cardiac index and heart rate induced in resting patients by intravenous admin-
istration of sotalol. The dose used in each patient is indicated by the key shown in the panel
on the right. The average values for each dose are shown as solid symbols in each margin.
Patients in heart failure are indicated by the dotted lines.
The effects of intravenously administered sotalol on stroke index and left ventricular end-diastolic pressure (LVEDP). The symbols are the same as in figure 2. There was, with one exception (see Discussion), no significant change in either of these two variables indicating that there was no essential change in ventricular function even in the eight patients with moderate to severe heart failure (dotted lines).

One in whom it remained essentially unchanged.

Changes in stroke index (fig. 3), however, were small and insignificant, indicating that the above-noted decrease in cardiac output was due to the associated drop in heart rate, and that flow per beat had been maintained.

Eight of the 20 patients had unequivocal elevation of left ventricular end-diastolic pressure (15 mm Hg or more) prior to administration of the beta blocker. The upper limit for normal in this laboratory is 12 mm Hg.
Hg. As seen in table 1, these patients had other hemodynamic evidence of left heart failure and all were either moderately or severely symptomatic (class III or IV). The effect upon left ventricular end-diastolic pressure following sotalol is shown graphically in figure 3. Note that in all but one of the patients there was no significant increase.

Arteriovenous oxygen difference widened in all of the 11 patients in whom it was measured, indicating an increased oxygen extraction. Changes in oxygen consumption were small and variable, and the average change at all doses was insignificant.

Mean arterial pressure was not significantly altered at any of the three dose levels of the drug. Systolic pressure decreased in almost all of the patients with a significant average decrease for all patients.

Changes in tension-time index and left ventricular minute work are shown graphically in figure 4. There were significant decreases in both parameters consistent with a reduction in myocardial oxygen consumption.

Figure 5 is a composite graph showing the average hemodynamic changes produced by sotalol-induced blockade, plotted in terms of percent change from control at each of the three dose levels. Heart rate, cardiac index, and tension-time index fell significantly to a maximum decrease of approximately 20% below control at the 0.4 mg/kg dose, beyond which there was no further change. Peripheral resistance rose uniformly in an equal amount after the 0.4 mg/kg dose, and there was no further effect by the 0.6 mg/kg dose. These data show that although significant beta blockade occurred at the 0.2 mg/kg dose, the peak hemodynamic effect of sotalol in humans was obtained by 0.4 mg/kg.

Changes in pulmonary artery pressures were small and variable. In three patients (J.B., F.B., and M.S.), all of whom had predominantly mitral stenosis, pulmonary capillary wedge pressure was measured. In all three, there was a slight decrease in wedge pressure. This was, however, accompanied by small increases in calculated pulmonary vascular resistance (380 to 460, 290 to 410, and 650 to 800 dynes sec cm⁻⁵, respectively), which was related to the reduction of cardiac output. There were no significant changes in right atrial pressure in any of the patients. The patient with the highest right atrial pressure (L.K., 19 mm Hg) received 0.6 mg/kg of sotalol. No change in right atrial pressure was detected.

\[\text{Figure 5}\]

A composite graph showing the average hemodynamic effects of sotalol-induced beta blockade, plotted in terms of per cent change from control at each of the three dose levels used. Peak hemodynamic effects on heart rate (HR), cardiac index (CI), peripheral resistance (P.Res.), and tension-time index (TTI) were reached at the 0.4 mg/kg dose with no further change at the larger dose. There was no significant effect on left ventricular end-diastolic pressure (LVED) or stroke index (SI).

\[\text{Circulation, Volume XLII, July 1970}\]
liver or renal function tests over the 1-week period following administration of the drug.

**Experimental Canine Studies**

Figure 6 is a composite graph showing a series of force-velocity curves in six dogs, comprising the paced-normal dogs (group 1) in the panel on the left and the paced-reserpinized dogs (group 2) on the right. The open symbols represent various doses of sotalol as indicated in the key. In all studies there was no downward shift in the force-velocity relationship, even at doses far above the beta-blocking dose—indicating no measurable basic change in the contractile state of the intact heart at controlled heart rates.

**Discussion**

These data extend to the intact circulation and to cardiac patients the previous findings on isolated cardiac muscle showing that sotalol-induced beta-adrenergic blockade is not accompanied by myocardial depressant effects. In the 14 patients in whom left heart catheterizations were performed, including eight patients with left heart failure, stroke output, mean arterial pressure, and left ventricular end-diastolic pressure remained essentially unchanged. No measurable deleterious effect upon resting cardiac dynamics was indicated, even in those patients who had far-advanced heart failure. The one exception was a patient (D.B.) in the group without heart failure, with isolated aortic regurgitation, in whom the left ventricular end-diastolic pressure rose from 10 to 14 mm Hg.

In the experimental canine studies it was possible to examine more critically any changes in ventricular contractility during sotalol-induced beta blockade. By maintaining a constant heart rate with atrial pacing, it was possible to evaluate the contractile state without associated rate-related changes. The use of the force-velocity relationship allowed an evaluation of the effect of the drug independent of subtle changes in ventricular pre-load or after-load. Use of these technics in both normal and reserpinized dogs made it possible to draw conclusions regarding effects on the normal and catecholamine-depleted...
myocardium. In each case there was no downward shift in the force-velocity curve, indicating that no change had been induced in the contractile state of the myocardium by beta blockade with this agent.

These results with sotalol are in sharp contrast to several studies reported in the literature using pronethalol or propranolol, in which beta blockade in man caused significant increases in filling pressures\(^7,8\) and decreases in stroke output.\(^7-9,25\) The beta-blocking potency ratio of propranolol to sotalol has been found to be approximately 5:1 in the intact dog.\(^6\) Assuming that this ratio holds true in man, the larger doses of sotalol used in these studies are equipotent to the doses used in most of the propranolol studies in man. The explanation for the important difference in hemodynamic response between sotalol and propranolol may be the presence of the negative inotropic or myocardial depressant effects of the latter. Levy and Richards,\(^12\) studying the structure-activity relationship of beta-adrenergic antagonists, noted that those compounds containing the naphthyl nucleus within their chemical structure had a potent myocardial depressant effect as well as local anesthetic action. Because of this depressant effect, understandably, there are no comparable studies in which propranolol has been given intravenously to patients with severe congestive heart failure, so that comparison of propranolol and sotalol in this circumstance is not possible. Epstein and Braunwald\(^26\) gave propranolol orally to patients in clinical heart failure, while on a controlled sodium diet. They found that over a period of weeks, increasing doses of propranolol caused sodium and water retention and worsened the heart failure. It was not determined, however, whether the observed sodium retention was due to the intrinsic myocardial depression of propranolol, its interference with the beta-adrenergic drive on the heart, or actual blockade of the sodium excretory function of the nephron.

The data in this study raise the important question regarding the actual role of circulating catecholamines in maintaining the failing myocardium from further decompensation. Several recent studies have shown that with heart failure, important alterations occur in the normal relationship between intrinsic catecholamines and the contractile response of the heart. It has been shown that early in the course of heart failure, myocardial stores of norepinephrine become diminished.\(^27\) Norepinephrine release in response to adrenergic neural stimulation also decreases.\(^28\) Plasma levels of norepinephrine increase,\(^27,29\) and the myocardium becomes more sensitive to exogenous catecholamines.\(^30\) It is not clear, however, to what extent the chronically failing myocardium—relatively late in its course, and already operating at a chronically elevated ventricular filling pressure and reduced stroke volume—depends on these increased resting levels of plasma catecholamines to maintain its remaining contractile integrity. Our data do not support the assumption that the heart depends greatly on this resting catecholamine drive. The eight patients with chronically failing hearts underwent beta blockade with a significant drop in heart rate and cardiac output. They were apparently able to tolerate this through increased oxygen extraction and further widening of arteriovenous oxygen difference. The most striking example of this was patient M.S. (table 1) who had an extremely low resting cardiac index of 1.4 L/min/m\(^2\). In spite of an already marked arteriovenous oxygen difference of 100 ml/L, beta blockade produced an even further widening of the oxygen difference to 121 ml/L with no change in left or right ventricular filling pressure, stroke index, or mean arterial pressure. The marked widening of arteriovenous oxygen difference was not accompanied by discernible untoward symptoms. Furthermore, in the reserpinized dogs whose ventricular contraction characteristics are similar to those of the failing myocardium,\(^31\) beta blockade produced no significant change in the force-velocity relationship when ventricular rates were held constant. It may be argued that since beta blockade is a simple one-to-one competitive inhibition at the receptor site, larger doses of blocking agent would be required to override the higher catecholamine

Circulation, Volume XLII, July 1970
levels in the patient with heart failure. Our data do not support this assumption since peak hemodynamic effects occurred at the 0.4 mg/kg dose rather than the 0.6 mg/kg dose.

It appears evident from these studies with sotalol that acute beta blockade—in the absence of associated nonspecific myocardial depression—does not sufficiently impair cardiac function to produce observable deleterious changes in the resting hemodynamics of patients with advanced chronic heart failure. The findings suggest also that the heart in advanced chronic failure may not depend heavily on intrinsic resting catecholamine drive to maintain its contractile response.

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