Vasodilator Administration in the Presence of Beta-Adrenergic Blockade

WILLIAM J. MROCZEK, M.D., WON RO LEE, M.D., MICHAEL E. DAVIDOV, M.D.,
AND FRANK A. FINNERTY, JR., M.D.

SUMMARY To explore the possibility that the presence of propranolol-induced beta-adrenergic blockade might have an adverse effect upon homeostatic circulatory reflexes activated by the administration of a potent vasodilator agent, arterial blood pressure and pulse rate response to rapid intravenous diazoxide injection was monitored before and after pretreatment with propranolol in ten hypertensive patients. It appeared that beta-adrenergic blockade had no clinically significant effect on the magnitude of hypotension or the degree of heart rate acceleration induced by the administration of the potent vasodilator diazoxide. This reflex vasodilator-induced cardiovascular acceleration after propranolol administration could be the result of incomplete blockade of endogenously released neurotransmitter, inhibition of the parasympathetic nervous system, or a direct pharmacologic action of diazoxide. Diazoxide administration to hypertensive patients in the presence of beta-adrenergic blockade was not associated with any clinically significant hemodynamic consequences.

THE RELATIVE CONTRIBUTIONS of the autonomic components to the reflex cardioacceleration that result from baroreceptor hypotension remain controversial.1-3 The reflex cardioacceleration that results from baroreceptor hypotension has been documented to be the result of an increase in beta-adrenergic stimulation as well as a withdrawal of parasympathetic tone.1, 2, 4, 5 In theory then, an impaired adrenergic nervous system response to the administration of a potent vasodilator compound might be hazardous; indeed, some practicing physicians have hesitated to administer the potent vasodilator agent diazoxide in the presence of beta-adrenergic blockade since one of the compensatory homeostatic mechanisms supporting the blood pressure had been rendered inoperative. The objective of the present study was to evaluate the cardiovascular effects of diazoxide injection in hypertensive patients before and after pretreatment with propranolol to determine if there were any clinically significant hemodynamic consequences of this combination of potent pharmacologic agents.

Methods and Materials

Ten patients with previously documented essential hypertension were selected from the hypertension clinic at the District of Columbia General Hospital. Informed consent was obtained from all patients. Two patients were male and all patients were black. The ages ranged from 35 to 46 years. None of the patients had received any antihypertensive or diuretic medications for the preceding two weeks. After arriving in the cardiovascular laboratory at 8 A.M., the patients were allowed to become acclimated to their surroundings and repeated measurements of blood pressure and heart rate were determined until a steady baseline value was obtained. Arterial pressure was determined by the auscultatory method with a mercury sphygmomanometer utilizing disappearance of the Korotkoff sounds as the diastolic pressure. The mean arterial pressure was calculated as the diastolic pressure plus one-third of the pulse pressure. Heart rate was determined from the cardiac apex or from a simultaneously recorded electrocardiogram.

After a stable baseline period, the patients received diazoxide, 300 mg injected rapidly intravenously in less than ten seconds. Heart rate and blood pressure were determined immediately after diazoxide administration and after 2, 5, 10, 15, and 30 minutes. The patients were continued on no antihypertensive therapy and were divided into two groups. The first group consisted of five patients who returned to the laboratory after three to seven days and received propranolol in a dose of 0.2 mg/kg intravenously prior to the administration of diazoxide. The second group of five patients received daily oral doses of propranolol, from 240 to 320 mg, for 14 days and then had diazoxide administered intravenously. The adequacy of beta-adrenergic blockade was verified by the graded infusions of isoproterenol with a Harvard infusion apparatus before and following the beta blockade in four subjects (two patients of the intravenous propranolol group and two patients of the oral propranolol group). Under control circumstances, isoproterenol infusion (4 mcg/ml) was given with a starting dose of 0.368 mcg/min and was gradually increased up to 9.16 mcg/min. The infusion lasted for 1½ minutes at each dose level. The average increases of heart rate were 12 beats/min at 1.84 mcg/min, 30 beats/min at 3.68 mcg/min, and 45 beats/min at 9.16 mcg/min. Following the previously stated doses of propranolol, the same sequence of isoproterenol infusion produced less than a 6% increase in heart rate in all patients. Furthermore, even with a higher dose of isoproterenol, 18.4 mcg/min, the average increase in heart rate ranged from 0 to 5% in the four subjects tested.

Results

The intravenous administration of diazoxide resulted in a 21% average fall in mean arterial pressure from 134 ± 16.3 to 106 ± 16.6 (+ standard deviation [SD]) mm Hg. Associated with the fall in arterial pressure was a 32% average increase in heart rate from 75 ± 10.0 to 99 ± 13.7 (± SD) beats/min. Intravenous administration of propranolol (0.2 mg/kg) in five patients did not result in an appreciable change in mean arterial pressure. The average mean arterial pressure was 135 ± 26.0 mm Hg before propranolol and was 136 ± 27.7 mm Hg after intravenous propranolol administration. Following pretreatment with intravenous propranolol, the average heart rate decreased from 78 ± 14.6 to 61 ± 11.6 beats/min. Diazoxide administra-
**TABLE 1. Arterial Blood Pressure and Heart Rate Responses to Diazoxide before and after Beta-Adrenergic Blockade**

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*Patients 1-5 returned on a second day for intravenous propranolol administration whereas patients 6-10 were receiving oral propranolol when they returned for the second administration of diazoxide.*

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**Figure 1.** The effect of diazoxide administration on average arterial pressure and mean arterial pressure in hypertensive patients. Administration of diazoxide resulted in a 17% average decrease in arterial pressure in patients who received intravenous propranolol pretreatment and a 34% average increase in pulse rate. Administration of diazoxide resulted in a 15% average decrease in arterial pressure in patients who received intravenous propranolol pretreatment. Diazoxide administration resulted in an 18% average decrease in arterial pressure and a 15% average increase in pulse rate. Analysis of the response to diazoxide.
administration before and after chronic oral propranolol failed to reveal any significant differences in the increment in heart rate or in the decrement in systolic, diastolic, or mean arterial pressure (table 1).

Combining the patients with oral and intravenous propranolol pretreatment, diazoxide injection after beta-adrenergic blockade resulted in a 22% average decrease in mean arterial pressure (from 134 ± 21.3 to 104 ± 21.1 mm Hg) and a 39% average increase in pulse rate (from 61 ± 8.4 to 85 ± 10.3 beats/min). The average changes in the absolute values of mean arterial pressure and heart rate to diazoxide injection, before and after beta-adrenergic blockade, are depicted graphically in figure 1 for both the patients who received the intravenous and the oral propranolol administration.

In figure 2, the average percent change in systolic arterial pressure is plotted against the average percent change in heart rate. This graph demonstrates that the baroreceptor reflex remained functional when diazoxide was injected following pretreatment with propranolol.

Discussion

Previous studies from this laboratory have documented the effectiveness of intravenous diazoxide as a hypotensive agent in patients with hypertension.6,7 Since reflex beta-adrenergic stimulation might have an important role in maintaining circulatory homeostasis after administration of a potent vasodilator agent, the possibility of circulatory instability or collapse was evaluated in ten hypertensive patients who received diazoxide administered before and after beta-adrenergic blockade.

The observation that the percent increase in heart rate after vasodilator administration before and after propranolol pretreatment was 39% and 32%, respectively, documents that the reflex cardioacceleration after vasodilator injection is maintained in the presence of beta-adrenergic blockade. When the heart rate response is expressed as a percent change and related to the percent change in systolic blood pressure, the resultant slope expresses the baroreceptor response, and in figure 2 it can be seen that the baroreceptor response is comparable before and after beta-adrenergic blockade.

Although there are no comparable studies in humans, several investigations with animals shed light on the mechanisms of baroreceptor-induced cardioacceleration in the presence of beta-adrenergic blockade. Thames and Kontos4 demonstrated that propranolol administration reduced, but did not abolish tachycardia in response to hypotension. In a canine study of hypotension induced by either nitroglycerin or inferior vena cava occlusion, Vatner et al.4 concluded that the reflex tachycardia induced by hypotension was not due solely to sympathetic stimulation or to a withdrawal of parasympathetic tone but rather to a combination of both effects.

Since the vasodilator-induced increases in heart rate were not totally dependent upon beta-adrenergic stimulation, several explanations for the cardioacceleration after vasodilator injection in the presence of beta-adrenergic blockade must be considered. With diazoxide administration a resting vagal restraint through the baroreceptor reflex arc, including central mechanisms may be withdrawn, as suggested by Pickering et al.9 The degree of beta-adrenergic blockade may have been insufficient to prevent a reflex sympathetic breakthrough of the propranolol induced beta-adrenergic blockade. Since the doses of the beta-blocking agent used in the present study appear to be adequate, as documented by isoproterenol infusion up to the level of 18.4 mcg/min, it seems improbable that the reflex stress can break through such a high level of pharmacologic blockade. However, we cannot completely rule out this possibility since we did not directly measure the degree of the baroreceptor reflex stress induced by diazoxide. It is also possible that a strong reflex neural drive may result in an endogenous release of neurotransmitter which may then break through the beta-adrenergic blockade that was documented to be adequate by the level of isoproterenol infusion. Although a direct cardio-stimulatory effect of diazoxide cannot be ruled out, this possibility is unlikely on the basis of previously reported evidence.10

The fall in systolic pressure and in mean arterial pressure in response to diazoxide injection was increased after intravenous propranolol pretreatment (P < 0.05). Diazoxide injection resulted in a 21% average reduction in mean arterial pressure in the control state, a 26% average reduction in mean arterial pressure after intravenous propranolol pretreatment, and an 18% average reduction in mean arterial pressure after chronic oral propranolol pretreatment. In terms of blood pressure reduction, the results of the present study are comparable to those of Gilmore and associates9 who used a different dosing regimen with an oral vasodilator and propranolol in hypertensive patients.

In the present study, rapid diazoxide injection after intravenous propranolol administration produced a further decrease in arterial pressure than did diazoxide alone; however this fall was not great enough to be likely to cause

![Figure 2. The baroreceptor response is depicted by the slope of the line relating the average percent change in heart rate to the average percent change in systolic pressure after diazoxide injection prior to beta blockade (unfilled circles) and after intravenous beta blockade (filled circles).](http://circ.ahajournals.org/Content/98/1/987/F2.large.jpg)
serious impairment or breakdown of the circulatory system (fig. 1). None of the patients studied revealed any deleterious circulatory responses.

It was therefore concluded that given the proper clinical circumstances in which the potent vasodilator diazoxide might be administered, previous propranolol administration would not be a contraindication.

References

Noninvasive Detection of Intracardiac Thrombosis
131-I Fibrinogen Cardiac Survey

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ERNEST M. BARSAMIAN, M.D., AND ALFRED F. PARISI, M.D.

SUMMARY Cardiac survey following administration of 131-I autologous fibrinogen is a noninvasive technique for the detection of intracardiac thrombosis. Fibrinogen is isolated from plasma by a rapid salting-out method with ammonium sulfate and is iodinated with chloramine T. The purity of 131-I fibrinogen, expressed as clottable radioactivity, is greater than 90%. Cardiac survey consisting of serial gamma camera imaging or rectilinear scanning after intravenous administration of 131-I fibrinogen was conducted in dogs with freshly induced thrombosis of the left atrial appendage. An accumulation of radioactivity was detectable in the area of the left atrium and confirmed in each of nine dogs sacrificed. Similarly, 20 patients with heart disease predisposing to intracardiac thrombosis were surveyed. Eight of nine patients with positive studies and 11 of 11 with negative studies were confirmed subsequently at surgery or autopsy. Cardiac survey with 131-I fibrinogen is a simple and noninvasive method of detecting intracardiac thrombosis.

IN THE COURSE OF CLINICAL PRACTICE intracardiac thrombosis (ICT) is usually recognized subsequent to a peripheral embolic event. Such retrospective diagnosis is not necessarily helpful to a patient, particularly if he has sustained a major stroke or had to undergo emergency surgery for an ischemic limb. Empirically, anticoagulation can be employed to prevent ICT and embolic events1-3 in high risk groups such as patients with mitral stenosis, myocardial infarction, and ventricular aneurysm.4-6 However, considerable uncertainty exists in the management of individual patients, many of whom may be unnecessarily exposed to the risk of bleeding with anticoagulation. In this light a rapid noninvasive method of documenting ICT would provide an objective basis for instituting prophylactic anticoagulation.

Contrast angiography is the current method for documenting anticoagulation of an intracardiac thrombus. This method requires cardiac catheterization, carries some risk, is not easily repeated, and may not be entirely reliable.7-8 While radioisotopic cardiac angiography is a more convenient procedure and has been reported for the detection of intracardiac myxoma, it has not been used for the detection of intracardiac thrombosis, presumably due to its lack of necessary resolution.9,10 This report outlines the use of tracer 131-I fibrinogen for the detection of intracardiac thrombosis by labeling the thrombotic process. This radiopharmaceutical, used as an autologous preparation, is produced with reasonable simplicity in one hour, has a minimum purity of 90% clottable radioactivity and a normal in vivo survival time in normal subjects.10

Methods
Preparation of Radioactive Autologous Fibrinogen
This technique, recently described in detail,10 is summarized below. The entire procedure is conducted at room temperature. Twenty ml of blood are collected in Vacutainers (Becton, Dickinson Corp., Lincoln, Neb.) containing ethylenediaminetetraacetic acid. Plasma is separated
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