# New Drugs Annual: Cardiovascular Drugs

*Volume 1*

Editor

Alexander Scriabine, M.D.

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# Preface

This volume of *New Drugs Annual: Cardiovascular Drugs* is the first in a series of reviews of new cardiovascular drugs that were recently introduced to the U.S. market or can be expected to be introduced in the near future. It provides in a concise form the most important up-to-date information on the pharmacology, pharmacokinetics, metabolism, toxicology, and clinical studies of new cardiovascular drugs. This and forthcoming volumes will be useful to physicians and scientists involved in drug development, teaching, or medical practice. The series will provide a better reference source than standard pharmacology texts on the specific properties or side effects of cardiovascular drugs. This will be particularly true for the more recently developed drugs that are usually not covered by the textbooks.

Each chapter in this volume of *New Drugs Annual: Cardiovascular Drugs* is devoted to a specific drug rather than to an organ or a mechanism of action. This approach is designed to facilitate the search for specific information and not to replace the organ- or system-related approach of classical pharmacology. The drugs in this volume are classified in accordance with their anticipated major clinical use even though many cardiovascular drugs are often used for more than one indication.

Many chapters in this volume are written by industrial pharmacologists who were directly involved in the development of the drug described. The authors are therefore qualified to provide the reader with first hand or even unpublished data on these drugs. Although it may be sometimes difficult for a discoverer to be completely impartial to his discovery, the information provided can be very important for the assessment of the potential therapeutic value of a drug.

A chapter on regulatory aspects of drug development is likely to become a permanent feature of this series. In this volume, Dr. F. Wolff, previously with the Food and Drug Administration, describes his views on the requirements and functions of the agency. His ideas and recollections will certainly be of interest to scientists and managers in the pharmaceutical industry.

The inclusion or omission of a particular drug in *New Drugs Annual: Cardiovascular Drugs* is not solely dependent on its chemical or pharmacological novelty. The amount of obtainable information on a given drug and the availability of the most knowledgeable contributors are additional considerations for inclusion. It is anticipated that the second volume of this series will contain information on additional important new drugs.

This volume is an indispensable reference for all clinicians who treat cardiovascular diseases, and a valuable information source for pharmacologists and toxicologists involved in the evaluation of new cardiovascular drugs.

*New Haven, Connecticut*
*January 1983*

A. SCRIABINE, M.D.

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## REGULATORY ASPECTS OF DRUG DEVELOPMENT

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# Bucindolol

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β-Adrenoceptor antagonists and vasodilators are effective drugs for treating hypertension. However, there are some possible limitations associated with the use of these two classes of drugs when administered separately. For example, β-antagonists provide a lesser hypotensive capacity than some other antihypertensive agents and cause an initial increase in total peripheral resistance, whereas tachycardia and fluid retention are side effects usually associated with vasodilator therapy. In recent years antihypertensive therapy consisting of β-adrenoceptor antagonists and vasodilators administered in combination has gained acceptance in clinical practice. The contrasting modes of action of these drugs minimize the liabilities of each agent when used alone and provide a more powerful therapeutic approach to a greater percentage of hypertensive patients (6,13,16–19).

The concept of combining the activities of both β-adrenoceptor blockade and vasodilation within a single molecule is a logical extension of combination therapy. This is the research approach of several pharmaceutical companies, and several drug candidates have emerged (1,11,12,14,15). Bucindolol HCl (MJ 13105-1), a drug synthesized at Bristol Myers Company, is one agent of this type under clinical investigation (2,4,5,7,8). The objective of this chapter is to provide a current review of bucindolol including its chemistry, animal pharmacology, drug disposition, toxicology, and available clinical experience.

## CHEMISTRY

Bucindolol is a member of a series of indolyl-*tert*-butyl substituted phenoxypropanolamines (7,8). Chemically, it is 2-[2-hydroxy-3[[2-(3-indolyl)-1,1-dimethylethyl]amino]propoxy]-benzonitrile hydrochloride, and has a molecular formula of $C_{22}H_{25}N_3O_2 \cdot HCl$. Its structural formula is shown in Fig. 1. Bucindolol is a water soluble, nonhygroscopic, white crystalline powder with a molecular weight of 399.9 and a corrected melting point of 185–187°C (dec). The pKa of bucindolol is 8.86 as determined by a potentiostatic titration method and its partition coefficient between chloroform and a 0.01 M phosphate buffer is 83.4 and 361 at pH 7.19 and 7.78, respectively.

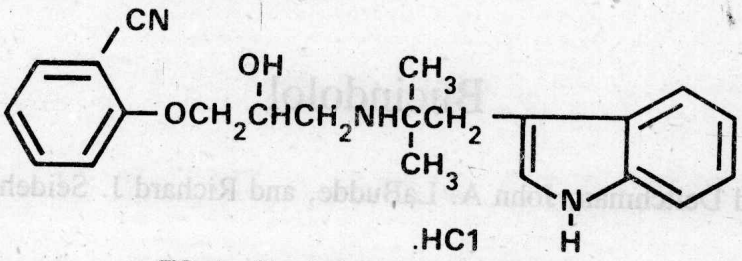


FIG. 1. Chemical structure of bucindolol.

TABLE 1. *Acute effect of oral bucindolol on blood pressure and heart rate of hypertensive and normotensive rats and dogs*

| Species | Model | N | Dose (mg/kg) | Arterial blood pressure[a] (mm Hg) Control | Arterial blood pressure[a] (mm Hg) Change | Heart rate (bpm) Control | Heart rate (bpm) Change |
|---|---|---|---|---|---|---|---|
| Rat | SHR | 7 | 30 | 218 ± 4[b] | −55 ± 9[c] | 466 ± 12 | −97 ± 9[c] |
| | DOCA-salt hypertensive | 34 | 30 | 195 ± 3 | −28 ± 2[c] | 446 ± 9 | −36 ± 8[c] |
| | Normotensive | 8 | 25 | 127 ± 4 | −6 ± 4 | 494 ± 8 | −83 ± 13[c] |
| Dog | Renal hypertensive | 5 | 3 | 200 ± 9 | −57 ± 8[c] | 67 ± 6 | 89 ± 10[c] |
| | Normotensive | 7 | 3 | 102 ± 4 | −6 ± 6 | 81 ± 7 | 63 ± 10[c] |

[a]All blood pressures were monitored from an indwelling arterial catheter.
[b]Mean ± SEM.
[c]$p < 0.01$

## PRECLINICAL PHARMACOLOGY

### Blood Pressure

Bucindolol produced a dose-dependent decrease in the systolic blood pressure of both spontaneous and desoxycorticosterone acetate (DOCA)-salt hypertensive rats at doses ranging from 12.5 to 50 mg/kg (4). Mean arterial blood pressure (MABP), measured in both models with indwelling arterial catheters, declined 55 ± 9 and 28 ± 2 mmHg, respectively, in response to bucindolol at 30 mg/kg orally (Table 1). In dogs with perinephritic hypertension (cellophane wrap and contralateral nephrectomy) and fitted with indwelling arterial catheters, bucindolol (3 mg/kg, p.o.) lowered systolic and diastolic blood pressures from hypertensive (200 ± 9/112 ± 7 mmHg) to normotensive (144 ± 11/70 ± 3 mmHg) levels. Bucindolol, in contrast to its effect in hypertensive animals, had no significant effect on the blood pressure of conscious normotensive rats and dogs (Table 1).

In the intact anesthetized rat and dog and in the reserpine-pretreated anesthetized dog, bucindolol, at doses ranging from 0.03 to 3 mg/kg, produced a dose-dependent lowering of blood pressure (4,9,10). As a hypotensive agent in barbiturate-anesthetized rats, bucindolol was approximately 38, 19, and 3.5 times more potent than

diazoxide, labetalol, and hydralazine, respectively (9). Bucindolol retained nearly 50% of its hypotensive activity after ganglionic blockade with pentolinium (10), and lowered the angiotensin-supported blood pressure of chlorisondamine-treated rats 26 ± 3% (3,8).

To study the effect of bucindolol on erect blood pressure, dogs were rotated on a special tilt table through 90° from the supine to the vertical head-up position. This maneuver reflexly increased systolic and diastolic blood pressure. Following the oral administration of an antihypertensive dose of bucindolol (3 mg/kg), systolic blood pressure in the erect position was about 35 mmHg lower than predrug values (Fig. 2). However, blood pressure in the erect position was still maintained at a level that was higher than blood pressure in the supine position, suggesting that the compensatory reflex response to this postural change was still operative (2).

## Heart Rate

Bucindolol elicited a variable heart rate response in animals. The response depended upon the species, presence or absence of anesthesia, and level of sympathetic tone to the heart. In conscious intact rats bucindolol decreased heart rate following oral administration. In contrast, heart rate increased in the conscious dog following bucindolol by intravenous or oral route (Table 1). If vagal tone was abolished by atropine, heart rate still increased and to the same degree as before atropine (2). In barbiturate-anesthetized and vagotomized dogs (4) and in barbiturate-anesthetized

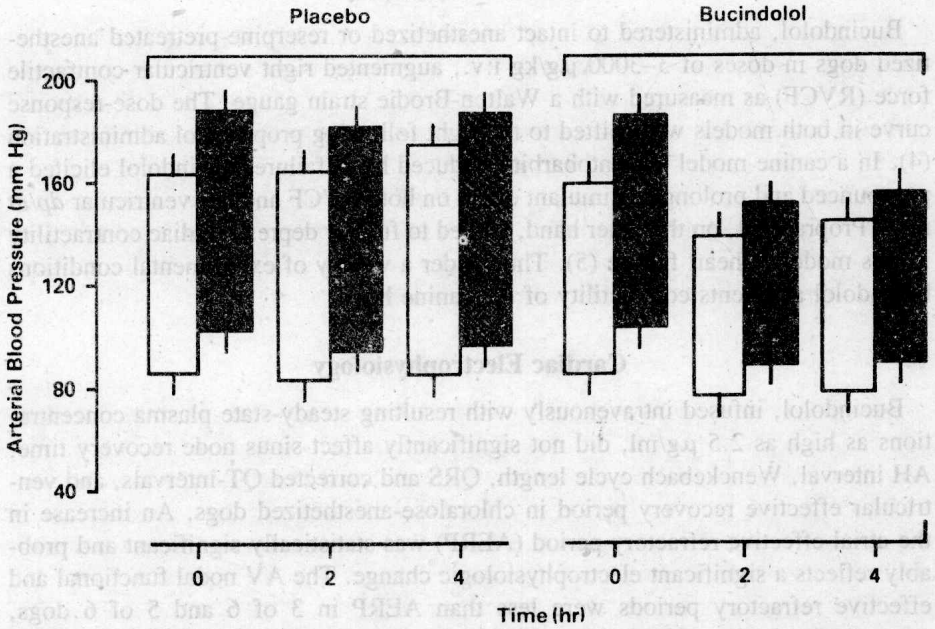


**FIG. 2.** Effects of bucindolol (3 mg/kg, p.o.) on supine *(open column)* and erect *(solid column)* systolic and diastolic blood pressure of 5 conscious, normotensive dogs. *Vertical bars* indicate SE.

rats (10) heart rate tended to slightly increase or decrease, respectively. If sympathetic tone to the heart was abolished by chlorisondamine (rat) or reserpine (rat and dog), then bucindolol caused a marked increase in heart rate. A similar bucindolol-induced tachycardia was seen in animals pretreated with propranolol at a dose that virtually abolished the response to 1 μg/kg isoproterenol. Propranolol shifted the bucindolol dose-response curve to the right in animals pretreated with reserpine (4).

The mechanism of the bucindolol-induced chronotropic response is not clear. The species difference can probably be explained in terms of existing sympathetic tone. Thus in the intact rat with its high level of sympathetic tone, the β-antagonist property prevails (see below) and heart rate tends to decline. By contrast, in the resting conscious dog with low sympathetic, high vagal tone, a stimulant action prevails and bucindolol increases heart rate. Vagal withdrawal cannot explain this tachycardia, since heart rate still increases in response to bucindolol following cholinergic blockade, and bucindolol in anesthetized dogs has no effect on cardiac slowing evoked by electrical stimulation of the right vagus nerve. A portion of the positive chronotropic response does appear to be β-mimetic, since propranolol partially antagonizes the response in reserpinized animals. Conversely, the inability of propranolol to block the response in conscious dogs suggests an additional bucindolol-evoked stimulant action that is non-β-mediated.

## Cardiac Contractility

Bucindolol, administered to intact anesthetized or reserpine-pretreated anesthetized dogs in doses of 3–3000 μg/kg i.v., augmented right ventricular contractile force (RVCF) as measured with a Walton-Brodie strain gauge. The dose-response curve in both models was shifted to the right following propranolol administration (4). In a canine model of pentobarbital-induced heart failure, bucindolol elicited a pronounced and prolonged stimulant effect on both RVCF and left ventricular *dp/dt* max. Propranolol, on the other hand, tended to further depress cardiac contractility in this model of heart failure (5). Thus under a variety of experimental conditions bucindolol augments contractility of the canine heart.

## Cardiac Electrophysiology

Bucindolol, infused intravenously with resulting steady-state plasma concentrations as high as 2.5 μg/ml, did not significantly affect sinus node recovery time, AH interval, Wenckebach cycle length, QRS and corrected QT-intervals, and ventricular effective recovery period in chloralose-anesthetized dogs. An increase in the atrial effective refractory period (AERP) was statistically significant and probably reflects a significant electrophysiologic change. The AV nodal functional and effective refractory periods were less than AERP in 3 of 6 and 5 of 6 dogs, respectively, in the control phase, and 6 of 6 dogs during infusion of drug. There was no evidence on the recorder tracing of echo beat development after premature stimuli following drug administration (D. C. Harrison, *personal communication*).

Bucindolol, at an intravenous dose level of 3 mg/kg, did not alter the QRS duration of the corrected QT-interval of normal conscious dogs, indicating a lack of a significant effect on either ventricular conduction or repolarization. Heart rate was increased and the PR-interval correspondingly shortened. A significant but brief (<15 min) narrowing of the P wave was observed following the bolus (1 min) injection of 3 mg/kg bucindolol. Infusion of the same dose over a 10-min interval was without effect (2). These studies demonstrate that intravenous infusions of bucindolol cause only minimal electrophysiologic changes in cardiac muscle and the specialized conducting system of the canine myocardium.

## Vascular Resistance

Bucindolol lowered total peripheral vascular resistance (TPR) of open-chest, anesthetized dogs instrumented with a flow probe to record aortic blood flow. In this model aortic blood flow tended to increase or remain the same, whereas MABP was decreased. Under conditions of β-adrenoceptor blockade (propranolol) bucindolol still effected an increase in aortic blood flow that was coupled to a greater decrease in MABP and TPR (4) (Fig. 3). In contrast, propranolol and pindolol neither increased aortic blood flow nor significantly reduced TPR. Intravenous infusion of bucindolol also decreased TPR in dogs with pentobarbital-induced heart failure (5).

Bucindolol caused a dose-dependent fall in perfusion pressure in the constant flow, pump-perfused hind limb of the anesthetized dog. This effect was seen following either direct infusion into the extracorporeal circuit or intravenous injection. Further, the vasodilator response was not blocked by prior administration of either propranolol, sotalol or pindolol. In contrast, infusion of pindolol directly into the extracorporeal circuit was without effect on perfusion pressure (4).

## β-Adrenoceptor Blocking Effects

Bucindolol is a potent antagonist of cardiac and vascular β-adrenoceptors. It blocked the positive chronotropic and vasodepressor responses to isoproterenol in both anesthetized dogs (4) and rats (10), and conscious dogs (2). In the anesthetized dog intravenous bucindolol was 8.7 and 4 times, respectively, more potent than propranolol in blocking cardiac ($\beta_1$) and vascular ($\beta_2$) responses to isoproterenol (Fig. 4). In anesthetized, pentolinium-treated rats, Oates et al. (10) reported that bucindolol was 32 and 4 times more potent than propranolol in blocking these same responses to isoproterenol. Thus bucindolol appears to possess some measure of cardioselectivity as compared with propranolol.

Increases in heart rate elicited by cardioaccelerator nerve stimulation, bilateral carotid occlusion, or tyramine injection were blocked equally by a 30 μg/kg dose of bucindolol administered intravenously to anesthetized dogs. Vasodilator responses to isoproterenol injected directly into the extracorporeal circuit of the canine pump-perfused hind limb were blocked by intraarterial or intravenous administration

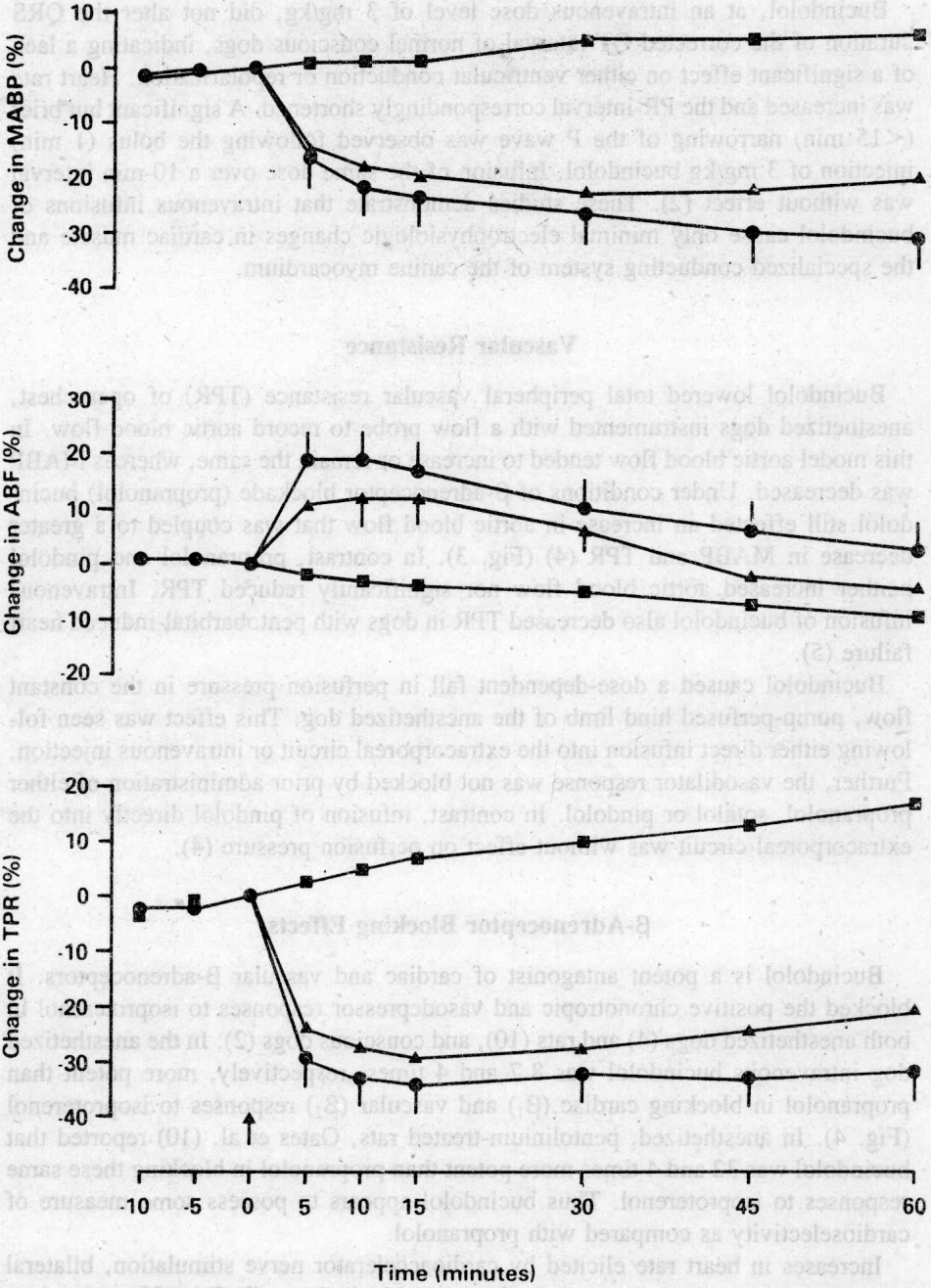


**FIG. 3.** Effect of saline *(squares)* or bucindolol (16.6 μg/kg/min i.v.) in the absence *(circle)* or presence *(triangle)* of propranolol (1 mg/kg + 1 mg/kg/hr) on mean arterial blood pressure (MABP), aortic blood flow (ABF), and total peripheral resistance (TPR) of anesthetized, vagotomized dogs (6/treatment). Symbols and vertical bars represent a mean value and SE, respectively.

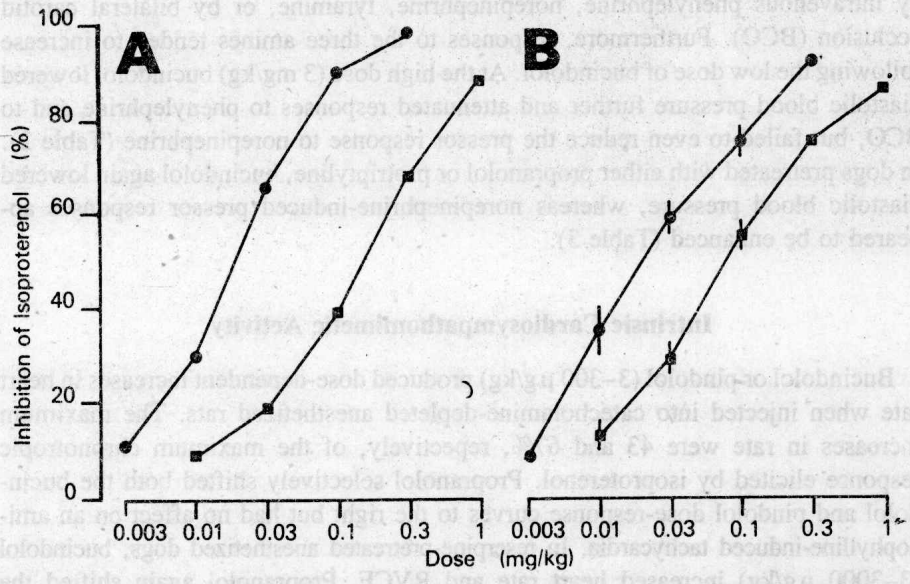


**FIG. 4.** Comparative α-adrenoceptor antagonist activities of propranolol *(squares)* and bucindolol *(circles)* in anesthetized, vagotomized dogs. Eight dogs were used for each compound. Heart rate **(A)** and diastolic blood pressure **(B)** responses to i.v. isoproterenol (1 μg/kg) were obtained before and 15 min after i.v. administration of each indicated dose of drug. Symbols and vertical bars represent a mean value and SE, respectively.

of bucindolol. In contrast, vasodilator responses elicited by acetylcholine, nitroglycerin, and histamine were unaffected (2).

## α-Adrenoceptor Blocking Effects

Bucindolol antagonized the pressor response elicited by phenylephrine in ganglion-blocked, anesthetized rats at doses equal to or greater than 1.5 mg/kg. A dose of 3.5 mg/kg was required to effect a 5-fold shift in the phenylephrine dose-response curve (4). By comparison, phentolamine caused a 5-fold shift to the right at a dose of 0.16 mg/kg. Thus in this anesthetized, ganglion-blocked rat model, bucindolol was approximately 0.05 times as potent as phentolamine as an inhibitor of the phenylephrine-induced pressor response. In comparison with phentolamine, bucindolol had a lesser capacity to block the pressor response mediated by exogenously administered norepinephrine (4) or epinephrine (10).

In the pump-perfused hind limb of sotalol-treated dogs, bucindolol, at 3 mg/kg i.v., caused a 6.5-fold shift in the dose-response curve elicited by intraarterial injections of graded doses of phenylephrine, whereas the norepinephrine-induced increase in perfusion pressure was shifted to the right only slightly (1.5-fold). Under identical conditions, phentolamine (3 mg/kg) effected a 28- and 20-fold shift in the phenylephrine and norepinephrine dose-response curves, respectively (4).

In the anesthetized dog, bucindolol, at 0.3 mg/kg, decreased diastolic blood pressure significantly but had no affect on the diastolic pressor response elicited

by intravenous phenylephrine, norepinephrine, tyramine, or by bilateral carotid occlusion (BCO). Furthermore, responses to the three amines tended to increase following the low dose of bucindolol. At the high dose (3 mg/kg) bucindolol lowered diastolic blood pressure further and attenuated responses to phenylephrine and to BCO, but failed to even reduce the pressor response to norepinephrine (Table 2). In dogs pretreated with either propranolol or protriptyline, bucindolol again lowered diastolic blood pressure, whereas norepinephrine-induced pressor responses appeared to be enhanced (Table 3).

## Intrinsic Cardiosympathomimetic Activity

Bucindolol or pindolol (3–300 μg/kg) produced dose-dependent increases in heart rate when injected into catecholamine-depleted anesthetized rats. The maximum increases in rate were 43 and 67%, repectively, of the maximum chronotropic response elicited by isoproterenol. Propranolol selectively shifted both the bucindolol and pindolol dose-response curves to the right but had no affect on an aminophylline-induced tachycardia. In reserpine-pretreated anesthetized dogs, bucindolol (3–3000 μg/kg) increased heart rate and RVCF. Propranolol again shifted the positive chronotropic and inotropic responses approximately one log unit to the right (4).

TABLE 2. *Effects of bucindolol on diastolic blood pressure and the peak increase in diastolic blood pressure elicited by the indicated α-adrenoceptor stimuli in the anesthetized dog*

| Stimulus | Bucindolol dose (mg/kg)[a] | Diastolic blood pressure (mm Hg)[b] | Stimulus response (Δ mm Hg)[b] |
|---|---|---|---|
| Phenylephrine (20 μg/kg) | 0 | 109 ± 4[c] | 79 ± 2 |
| | 0.3 | 84 ± 9[d] | 94 ± 8 |
| | 3 | 64 ± 6[e] | 45 ± 4[e] |
| Norepinephrine (1 μg/kg) | 0 | 107 ± 4 | 62 ± 3 |
| | 0.3 | 79 ± 4[e] | 84 ± 5 |
| | 3 | 61 ± 3[e] | 75 ± 5 |
| Tyramine (200 μg/kg) | 0 | 95 ± 3 | 76 ± 5 |
| | 0.3 | 69 ± 4[e] | 84 ± 5 |
| | 3 | 55 ± 3[e] | 59 ± 11 |
| Bilateral carotid occlusion (45 sec) | 0 | 115 ± 4 | 77 ± 4 |
| | 0.3 | 81 ± 6[e] | 74 ± 7 |
| | 3 | 62 ± 4[e] | 36 ± 8[e] |

[a]Bucindolol was administered intravenously over a 3-min interval in a volume of 1 ml/kg.
[b]15 min after indicated dose of bucindolol.
[c]Mean ± SEM.
[d]$p < 0.05$, significantly less than zero dose value.
[e]$p < 0.01$, significantly less than zero dose value.