

Dobutamine

DEVELOPMENT OF A NEW CATECHOLAMINE TO SELECTIVELY INCREASE CARDIAC CONTRACTILITY

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ABSTRACT

We systematically modified isoproterenol's chemical structure to reduce chronotropic, arrhythmogenic, and vascular side effects. Experiments on dogs showed that the resulting drug, dobutamine, had an inotropic efficacy as great as that of epinephrine due to a direct action on β_1 cardiac receptors. However, unlike epinephrine, dobutamine's effect on α and β_2 vascular receptors was slight. At equivalent inotropic doses, dobutamine had less than a fourth of the chronotropic effect of isoproterenol. Desmethyl-imipramine (DMI), which blocks the sympathetic nerve fiber uptake mechanism, had no effect on dobutamine's actions. In contrast, DMI antagonized dopamine's inotropic effect, and marked chronotropic and pressor responses occurred when we used doses of dopamine large enough to elicit a direct inotropic effect. Dobutamine increased the contractility of isolated cat papillary muscles more but the automaticity less than did isoproterenol. In ischemic dog hearts, dobutamine lacked significant arrhythmic activity, whereas dopamine, norepinephrine, and isoproterenol caused severe ectopic activity. In dogs with experimentally induced low cardiac contractility, low cardiac output, and hypotension, dobutamine produced dose-related increases in cardiac contractility and output, restored arterial blood pressure, and reduced total peripheral resistance slightly. In contrast, isoproterenol failed to restore blood pressure, had only a meager effect on cardiac contractility and output, caused extreme tachycardia, and lowered peripheral resistance more than did dobutamine. Norepinephrine, which did not increase cardiac contractility or output as much as dobutamine, excessively elevated peripheral resistance and arterial blood pressure.

KEY WORDS
cardiogenic shock
norepinephrine

adrenergic receptors
isoproterenol
cat papillary muscles

arrhythmias
myocardial infarction
dopamine
dogs

■ Isoproterenol has great inotropic efficacy; moreover, it does not cause the vasoconstriction and the rise in arterial blood pressure associated with the naturally occurring catecholamines, norepinephrine, epinephrine (1) and dopamine, if a narrow dose range is exceeded (2-6). However, the therapeutic value of isoproterenol for the treatment of acutely depressed cardiac contractility is limited by its chronotropic activity. Isoproterenol administration like that of the naturally occurring catecholamines involves a considerable risk of arrhythmia (7). Moreover, the strong activity of isoproterenol on the β_2 receptors (1) of the peripheral vasculature is disadvantageous because these receptors predominate in skeletal muscles, which constitute nearly half of the body's mass. Consequently, vig-

orous stimulation of β_2 receptors wastefully diverts a large portion of the cardiac output to skeletal muscle, lowers peripheral resistance to the point of reducing diastolic pressure, and hence lowers effective coronary perfusion pressure (8).

To attenuate these undesirable features, we systematically modified isoproterenol's chemical structure. First, we determined that removal of the side-chain hydroxyl group differentially altered the effects on cardiac automaticity and contractility. Experiments on cat papillary muscles showed that the desoxy analogue of isoproterenol, isopropyl-dopamine, increased contractility more than did isoproterenol, because it induced automatic beating less readily than did isoproterenol. We then synthesized several more dopamine derivatives (9) and found that for an equivalent inotropic effect none of the derivatives induced automaticity in papillary muscles as frequently as did isoproterenol. These in vitro results suggested that dopamine derivatives have less arrhythmogenic activity than do catecholamines containing the side-chain hydroxyl groups.

After the papillary muscle experiments, we as-

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This work was included in an Investigational New Drug Application to the FDA in December, 1971. Since then multilith summaries have been sent to 51 investigators along with samples of dobutamine.

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sessed the effects of these and other dopamine derivatives on cardiac contractility, heart rate, and blood pressure in open-chest dogs. These experiments indicated that dobutamine had the attenuated chronotropic and vascular effects we were seeking. We then made certain that dobutamine did not retain the norepinephrine-releasing action of dopamine (2, 10, 11), which is undesirable for two reasons. First, norepinephrine is arrhythmogenic. Norepinephrine release may be responsible for the high arrhythmogenic activity of dopamine that we have found and that has been reported by others before us (2, 12). Second, a drug that exerts part or all of its inotropic effect by releasing norepinephrine may produce unreliable responses among patients with different catecholamine stores, e.g., patients whose cardiac norepinephrine is depleted by heart failure (13, 14) or patients taking norepinephrine-depleting antihypertensive drugs. After these experiments, dobutamine's vascular and arrhythmogenic properties were compared with those of the naturally occurring catecholamines and isoproterenol.

Methods

EXPERIMENTS ON ISOLATED CAT PAPILLARY MUSCLES

We anesthetized cats of either sex with ether, immediately removed their hearts, and suspended four papillary muscles from the right ventricle in individual organ baths. A platinum hook secured the bottom end of the muscle to an electrode mounted in the bottom of the bath, and a silk thread attached the tendon to a Statham isometric transducer. The baths contained Krebs-Henseleit solution (36°C, bubbled with a 95% O₂-5% CO₂ mixture) of the following millimolar composition: NaCl 118, KCl 4.5, CaCl₂ 2.5, KH₂PO₄ 1.1, MgSO₄ 1.2, NaHCO₃ 25, and glucose 11.

A base-line tension of 1.5 g was applied to each muscle. Square-wave pulses (5.0 msec in duration, three times threshold voltage) delivered through the hook electrode and a second electrode positioned near the top of the muscle evoked 12 contractions/min, which were recorded on a Grass polygraph. After the muscles had equilibrated for 60 minutes, we adjusted the recorder gain so that the pen deflected 10 mm. Increases in contractility were tabulated as millimeters of pen deflection in excess of the base value.

To relate the dopamine derivatives to each other, we used isoproterenol as a standard agonist. The experiments were done on a crossover design so that half of the muscles were tested first with isoproterenol and the other half with one of the dopamine derivatives. After the first test the muscles were washed and allowed 60 minutes to return to control level. Then, the muscles that were first tested with isoproterenol were tested with the derivative and vice versa. We obtained the dose-response curves in a continuous fashion as shown in Figure 1. Note that the agonist concentrations shown in the figure indicate the amount added at each arrow rather than the cumulative concentration. The maxi-

mum increase in contractility that occurred before automaticity supervened was recorded for the concentration that induced automaticity and for all supra-automatic concentrations. The increases in contractility caused by the derivatives are expressed in Figure 2 as a percent of the increase caused by isoproterenol. Figure 2 also expresses the incidence of automaticity caused by each derivative as a percent of the incidence of automaticity caused by isoproterenol.

EXPERIMENTS ON DOGS

We used mongrel dogs of either sex ranging in weight from 7 kg to 14 kg. In most experiments, anesthesia was induced with sodium thiopental (15 mg/kg, iv) and maintained with sodium phenobarbital (100 mg/kg, iv). In one group of dogs (section IID), we caused myocardial infarction by ligating the left anterior descending coronary artery in two stages as described by Harris (15). For these experiments, sodium pentobarbital (30-35 mg/kg, iv) was the anesthetic and the vagus nerves were left intact. In all other experiments, the vagus nerves were cut at the level of the larynx.

A positive-pressure pump was used to ventilate the dogs through an endotracheal tube (18 strokes/min, 20 ml/kg stroke⁻¹), and a heating pad kept the body temperature at 37-38°C. Femoral arterial blood pressure was measured through a polyethylene catheter filled with heparin solution (16 units/ml) and connected to a Statham pressure transducer. Cardiac output was recorded from an electromagnetic flow probe around the aortic root.

A strain-gauge arch sutured to the right ventricle of the heart measured cardiac contractility. We adjusted tension on the gauge to 50 g and set the gain of the recorder (Beckman dynograph) so that 50 g caused a 10-mm pen deflection; cardiac contractile tension is reported as either millimeters of pen deflection or grams. Rapid intravenous injection of 50 ml of 5% dextran and mechanical compression of the aorta showed that the contractility measurements were independent of changes in preload and afterload.

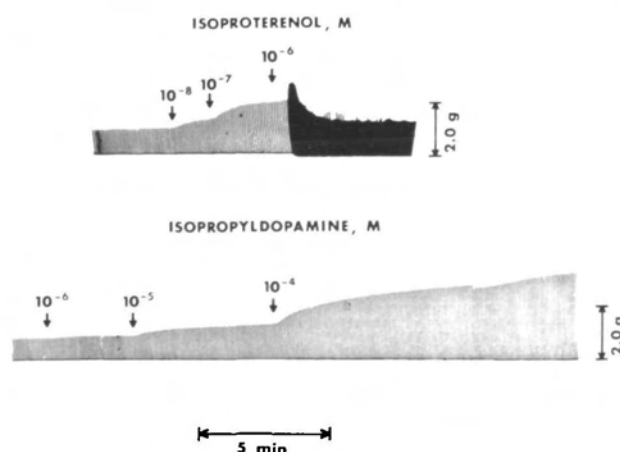


FIGURE 1

Recordings from isolated cat papillary muscles comparing the effects of isoproterenol and isopropyl-dopamine on contractility and automaticity. The solid black area in the upper tracing shows the occurrence of automatic beating.

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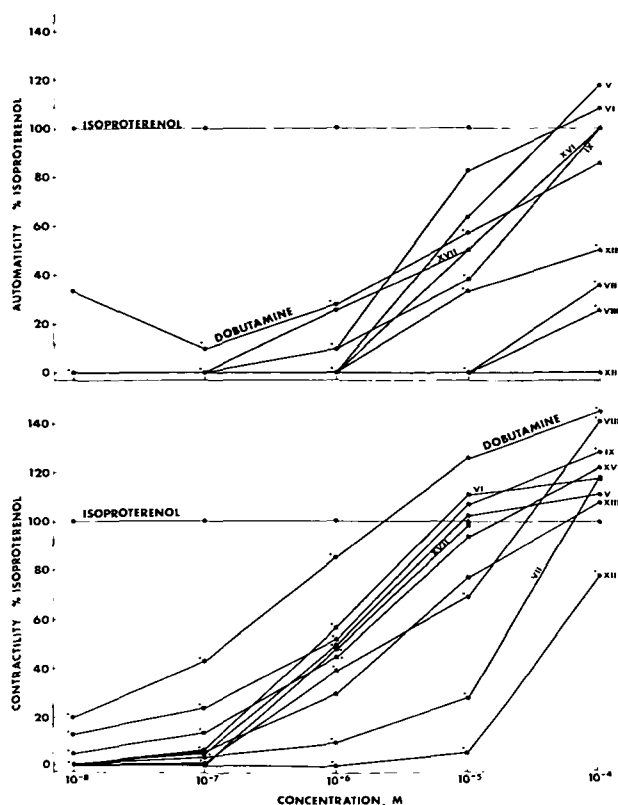


FIGURE 2

Effects of the dopamine derivatives on cat papillary muscle contractility and automaticity. Automaticity ordinate = (incidence of automaticity [derivative])/(incidence of automaticity [isoproterenol]), $\times 100$; contractility ordinate = (increase in contractility [derivative])/(increase in contractility [isoproterenol]), $\times 100$. An asterisk indicates a value that is statistically different from isoproterenol ($P < 0.05$).

DRUGS

All of the experimental agonists were catecholamines with a brief duration of action. This fact permitted testing of several agonists in each dog, but the agonist order was varied among the dogs to prevent an order effect from influencing the mean results. The agonists were given via the femoral vein by either bolus injection or pump-controlled infusion.

l-Norepinephrine and *l*-epinephrine were used as the bitartrate salts. All other catecholamines were used as hydrochloride salts. We synthesized the dopamine derivatives and proved their structures and purity by nuclear magnetic resonance spectrometry and elemental analysis. Isoproterenol and all of the synthesized compounds that contained an asymmetric center were tested as racemic mixtures. The doses of all of these drugs are expressed as the free base ($\mu\text{g/kg}$), except in the experiments on cat papillary muscles for which molar concentrations are given.

The doses of sodium phenobarbital, sodium pentobarbital, sodium thiopental, desmethylinipramine hydrochloride, and propranolol hydrochloride are given as weights of the salts (mg/kg).

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STATISTICS

Tests of statistical significance between groups of animals were done by Student's *t*-test. Within animals and papillary muscles the *t*-test for paired data was used (16). To determine the statistical significance between the difference in incidence of papillary muscle automaticity caused by isoproterenol and the dopamine derivatives, a chi-square test was used.

Results

PART I: CHEMICAL DEVELOPMENT OF DOBUTAMINE

A. Experiments on Papillary Muscles.—We compared the effects of isoproterenol and isopropyl-dopamine on contractility and induction of automaticity on 16 cat papillary muscles to see whether the β -hydroxyl group (R_1 , Table 1) of isoproterenol had a differential effect on contractility and automaticity. On a molar basis isoproterenol was more than 100 times more potent than isopropyl-dopamine. Most pertinent, however, with incremental increases in concentration isopropyl-dopamine increased contractile tension more than did isoproterenol before rapid and erratic automatic beating supervened (Fig. 1). Isoproterenol (10^{-8}M) and isopropyl-dopamine (10^{-4}M) caused the same incidence of automaticity (25%), but at these concentrations isopropyl-dopamine increased contractility by more than 2.5 times as much as did isoproterenol (7.2 ± 0.1 vs. 2.8 ± 0.7 mm, $P < 0.001$).

Thus, these experiments indicated that removing the β -hydroxyl group selectively reduced the effect on automaticity. To determine whether the low automaticity remained when the nitrogen substituent (R_3 , Table 1) was varied, we synthesized dopamine derivatives containing various alkyl and aralkyl nitrogen substituents. Of these, we compared the effects of compounds V–IX, XII, XIII, XVI, XVII, and XX (Table 1) with those of isoproterenol on papillary muscles.

All of the dopamine derivatives were less potent than isoproterenol and only two (V and VI) induced automaticity as readily as isoproterenol. All but the least potent, secondary-butyl-dopamine (compound XII), produced a greater maximum increase in contractility than did isoproterenol. Thus, these experiments demonstrated that the favorable contractility-automaticity ratio held with a wide variety of nitrogen substituents (Fig. 2).

B. Structure-Activity Relationships on Contractility, Rate, and Pressure.—In open-chest dogs we obtained dose-response curves on cardiac contractile tension, heart rate, and blood pressure for each derivative. Tables 2 and 3 show how, for an equivalent inotropic effect, the chronotropic and blood pressure activity varied among the com-

pounds. The columns headed "Contractile potency" in Table 2 show the dose of each compound required to increase contractile tension by 50% (CT₅₀) and 100% (CT₁₀₀). Table 3 shows the changes in heart rate and blood pressure at the CT₅₀ and CT₁₀₀ doses.

As in papillary muscles, high potency occurred with the hydroxylated aralkyl compounds XVI-XX. Moreover, the chronotropic activity of these compounds was low. However, compounds XVI-XVIII caused vasodepression and compound XIX had marked pressor activity. So, dobutamine (com-

TABLE 1

Chemical Structures of the Catecholamines Studied









Compound		Structures		
		R ₁	R ₂	R ₃
I	(norepinephrine)	OH	H	H
II	(epinephrine)	OH	H	CH ₃
III	(isoproterenol)	OH	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH} \\ \\ \text{CH}_3 \end{array}$
IV	(dopamine)	H	H	H
V	(methyl-dopamine)	H	H	CH ₃
VI	(ethyl-dopamine)	H	H	CH ₂ CH ₃
VII	(propyl-dopamine)	H	H	CH ₂ CH ₂ CH ₃
VIII	(isopropyl-dopamine)	H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH} \\ \\ \text{CH}_3 \end{array}$
IX	(α -methyl-isopropyl-dopamine)	H	CH ₃	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH} \\ \\ \text{CH}_3 \end{array}$
X	(α -ethyl-isopropyl-dopamine)	H	$\begin{array}{c} \text{CH}_2 \\ \\ \text{CH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH} \\ \\ \text{CH}_3 \end{array}$
XI	(cyclopropyl-dopamine)	H	H	$\begin{array}{c} \text{CH}_2 \\ / \quad \backslash \\ \text{CH} \quad \text{CH} \\ \backslash \quad / \\ \text{CH}_2 \end{array}$
XII	(secondary-butyl-dopamine)	H	H	$\begin{array}{c} \text{CHCH}_2\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$
XIII	(phenyl-ethyl-dopamine)	H	H	CH ₂ CH ₂ - 
XIV	(phenyl-isopropyl-dopamine)	H	H	$\begin{array}{c} \text{CHCH}_2 \\ \\ \text{CH}_3 \end{array}$ 
XV	(phenyl-secondary-butyl-dopamine)	H	H	$\begin{array}{c} \text{CHCH}_2\text{CH}_2 \\ \\ \text{CH}_3 \end{array}$ 
XVI	(hydroxyphenyl-ethyl-dopamine)	H	H	CH ₂ CH ₂ - 
XVII	(hydroxyphenyl-isopropyl-dopamine)	H	H	$\begin{array}{c} \text{CHCH}_2 \\ \\ \text{CH}_3 \end{array}$ 
XVIII	(hydroxyphenyl-ethyl- α -methyl-dopamine)	H	CH ₃	CH ₂ CH ₂ - 
XIX	(hydroxyphenyl-propyl-dopamine)	H	H	CH ₂ CH ₂ CH ₂ - 
XX	(dobutamine)	H	H	$\begin{array}{c} \text{CHCH}_2\text{CH}_2 \\ \\ \text{CH}_3 \end{array}$ 

TABLE 2

Cardiac Potency of the Dopamine Derivatives in Dogs

Compound	N	Contractile potency ($\mu\text{g/kg}$)	
		CT ₅₀	CT ₁₀₀
I	5	0.24 \pm 0.05	0.72 \pm 0.08
III	10	0.10 \pm 0.02	0.29 \pm 0.05
IV	20	14 \pm 2	27 \pm 3
V	8	22 \pm 5	52 \pm 8
VI	8	25 \pm 4	56 \pm 7
VII	4	487 \pm 154	2350*
VIII	14	58 \pm 5	224 \pm 27
IX	4	12 \pm 2	31 \pm 14
X	4	420 \pm 125	1300 \pm 575
XI	4	218 \pm 35	1600*
XII	8	666 \pm 218	2000 \pm 362
XIII	8	179 \pm 32	691 \pm 102
XIV	8	122 \pm 18	416 \pm 51
XV	8	48 \pm 6	128 \pm 40
XVI	12	7 \pm 2	19 \pm 3
XVII	4	8 \pm 2	29 \pm 9
XVIII	4	6 \pm 2	23 \pm 7
XIX	4	6 \pm 1	18 \pm 2
XX	16	3 \pm 1	8 \pm 2

Values are means \pm SE. CT₅₀ = dose required to increase cardiac contractile tension by 50%, CT₁₀₀ = dose required to increase cardiac contractile tension by 100%, and N = number of dogs tested.

*Maximum dose was given before CT₁₀₀ was reached.

pound XX) was the best choice. Although it caused a slight rise in blood pressure, we thought dobutamine would have little pressor potential, because its blood pressure dose-response curve was not steep: between the CT₅₀ and CT₁₀₀ doses there was a pressure difference of only 11 mm Hg.

At equally effective inotropic doses (CT₅₀ and CT₁₀₀), dobutamine had significantly less chronotropic effect than did isopropyl-dopamine (compound VIII) ($P < 0.01$). Compared with isoproterenol (compound III) at the CT₅₀ dose, the chronotropic effect was reduced more than fourfold ($P < 0.001$).

PART II: PHARMACOLOGY OF DOBUTAMINE

A. The Role of the Adrenergic Nerve Fibers and Norepinephrine Release in the Actions of Dobutamine and Dopamine.—Because dobutamine was a dopamine derivative, it was important to determine whether release of endogenous norepinephrine contributed to its effects. In six dogs, we obtained cardiac contractile tension, heart rate, and blood pressure dose-response curves for dobutamine and dopamine before and after administration of 5 mg/kg of desmethylinipramine (DMI). DMI blocks uptake by adrenergic nerve fibers and

thus prevents release of endogenous norepinephrine by indirect-acting agonists that require active uptake into the fibers (17).

Figure 3 shows that DMI had no significant effect on any of the responses to dobutamine, indicating that dobutamine is not taken up by adrenergic nerve fibers. We conclude that dobutamine is a direct-acting agonist whose effect is independent of endogenous norepinephrine.

In contrast to its lack of effect on dobutamine, DMI markedly reduced the inotropic response to dopamine. The CT₅₀ for dopamine increased from 14.7 \pm 0.5 to 55 \pm 5 $\mu\text{g/kg}$ ($P < 0.001$) in the presence of DMI. Although antagonized, the chronotropic effect of dopamine was affected less than the inotropic response; thus, there was a marked decrease in the relative inotropic-chronotropic ratio. Before administration of DMI, at the CT₅₀ the heart rate increased 1 \pm 3 beats/min. After administration of DMI, at CT₅₀ the rate increased 30 \pm 3 beats/min ($P < 0.001$). There was a similar shift in the relative inotropic-pressor responses to dopamine. Before DMI administration, at CT₅₀ pressure rose 22 \pm 6 mm Hg; afterward, it rose 75 \pm 6 mm Hg. The difference in these pressor responses was statistically significant ($P < 0.001$).

TABLE 3

Heart Rate and Blood Pressure Responses at Equivalent Inotropic Doses in Dogs

Compound	Heart rate increase (beats/min)		Blood pressure change (mm Hg)	
	CT ₅₀	CT ₁₀₀	CT ₅₀	CT ₁₀₀
I	16 \pm 9	38 \pm 18	22 \pm 2	47 \pm 4
III	33 \pm 3	64 \pm 4	-19 \pm 6	-32 \pm 6
IV	6 \pm 4	21 \pm 6	27 \pm 3	44 \pm 3
V	15 \pm 6	48 \pm 6	53 \pm 8	83 \pm 11
VI	9 \pm 6	35 \pm 9	18 \pm 4	37 \pm 5
VII	21 \pm 14	85*	57 \pm 8	127*
VIII	19 \pm 3	53 \pm 5	-12 \pm 3	-23 \pm 4
IX	16 \pm 3	31 \pm 7	-20 \pm 4	-32 \pm 5
X	13 \pm 5	33 \pm 6	-28 \pm 10	-45 \pm 10
XI	32 \pm 6	110*	120 \pm 9	244*
XII	19 \pm 3	51 \pm 7	-9 \pm 4	-28 \pm 3
XIII	28 \pm 4	74 \pm 6	-12 \pm 2	-24 \pm 4
XIV	34 \pm 6	71 \pm 7	-19 \pm 3	-31 \pm 4
XV	36 \pm 5	82 \pm 7	-2 \pm 4	-20 \pm 4
XVI	14 \pm 3	32 \pm 3	-1 \pm 4	-2 \pm 5
XVII	18 \pm 3	49 \pm 10	-14 \pm 3	-31 \pm 3
XVIII	19 \pm 3	54 \pm 9	-40 \pm 5	-49 \pm 6
XIX	9 \pm 5	29 \pm 6	88 \pm 3	154 \pm 5
XX	8 \pm 2	26 \pm 3	16 \pm 3	27 \pm 2

Values are means \pm SE. See Table 2 for definition of abbreviations.

*Maximum dose was given before CT₁₀₀ was reached.

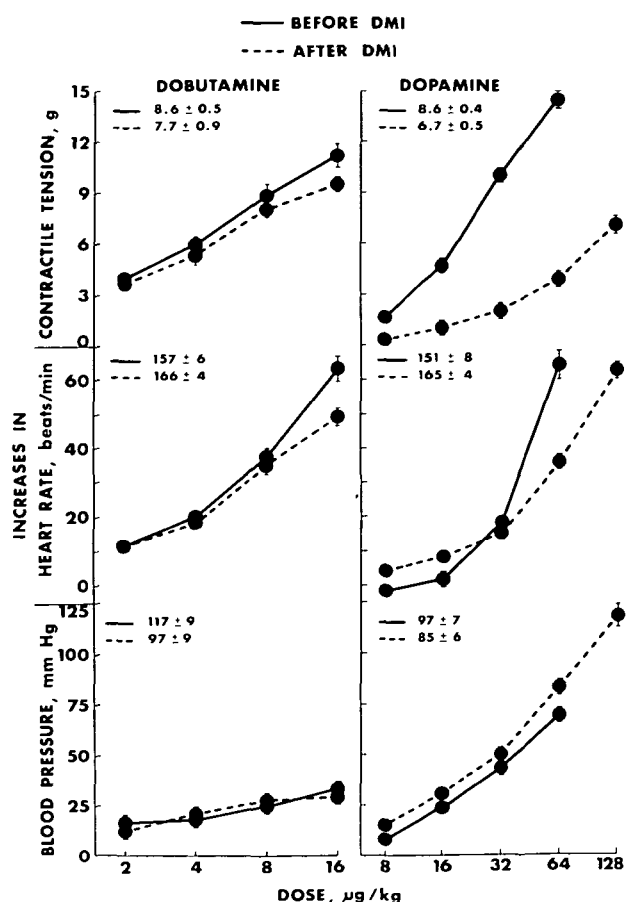


FIGURE 3

Effect of sympathetic nerve fiber uptake block by desmethyl-imipramine (DMI) on dobutamine and dopamine. The numbers at the top of each graph show the control values and bars indicate ± 1 SE.

At low doses and in the absence of DMI, dobutamine and dopamine had similar inotropic-pressor ratios. At 4.0 $\mu\text{g/kg}$ of dobutamine and 16 $\mu\text{g/kg}$ of dopamine, there were no significant differences in the inotropic or pressor responses of the agonists. But with increasing doses, the greater pressor action of dopamine appeared, and in the presence of DMI the contrast in the inotropic-pressor ratio of dobutamine and dopamine became striking. After DMI administration, at the highest doses given dobutamine increased contractility somewhat more than did dopamine. But dopamine increased pressure by 118 ± 10 mm Hg, whereas dobutamine increased it by only 29 ± 5 mm Hg ($P < 0.001$).

B. Assessment of Dobutamine's Peripheral Adrenergic Effects.—As currently classed, β_1 receptors mediate the cardiac effects of adrenergic drugs, α receptors mediate vasoconstriction, and β_2 receptors mediate vasodilation (18). To assess the relative activity of dobutamine on these different receptors, we obtained dose-related responses for

dobutamine and epinephrine on cardiac contractility and blood pressure in two groups of four dogs before and after selective adrenergic blockade. In the first group, α receptors were blocked by phenoxylbenzamine (5.0 mg/kg). In the second group, propranolol (0.5 mg/kg) blocked β_1 and β_2 receptors. We chose epinephrine as the reference agonist because of its strong activity on all three types of receptors.

The dose-response curves in Figure 4 show that the doses of epinephrine and dobutamine used were equally effective in increasing cardiac contractility but that the blood pressure curves were not similar in either slope or magnitude. Before α blockade, blood pressure rose steeply with each epinephrine dose. With dobutamine, the only sharp increase in pressure occurred with the first dose; with increasing doses, the curve flattened. At the highest doses used, dobutamine and epinephrine caused equal increases in cardiac contractility, but epinephrine increased pressure 110 ± 6 mm Hg and dobutamine increased it only 40 ± 5 mm Hg—a difference of 70 mm Hg ($P < 0.005$).

After α blockade, the β_2 -mediated vasodepressor component of each agonist was unmasked. Again epinephrine and dobutamine caused similar inotropic responses, but even the lowest dose of epinephrine caused a 20 ± 6 -mm Hg fall in pressure that was significantly greater ($P < 0.05$) than the pressure fall caused by any of the dobutamine doses.

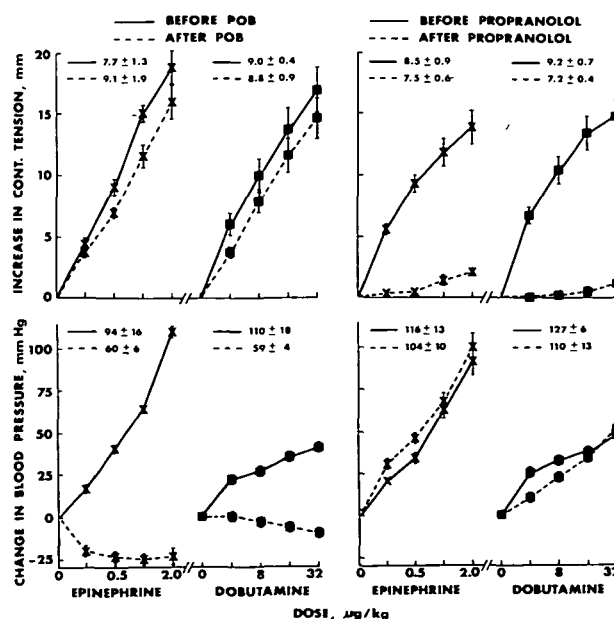


FIGURE 4

Effect of α - and β -receptor blockade on epinephrine and dobutamine. POB = phenoxylbenzamine

The right side of Figure 4 shows that inotropic responses to the two agonists were blocked by propranolol. The pertinent aspect, however, is that blockade of β_2 receptors did not reveal an unforeseen pressor response to dobutamine. In fact, propranolol slightly reduced the pressor response to dobutamine as opposed to the slight enhancement of epinephrine's pressor action.

Since α blockade failed to unmask depressor activity as great as epinephrine's and β blockade failed to unmask any additional pressor activity, we concluded that in contrast to its strong β_1 inotropic effect, dobutamine's activity on vascular α and β_2 receptors was modest.

C. Comparison of Dobutamine, Norepinephrine, and Isoproterenol in Dogs with Experimentally Induced Hypotension and Low Cardiac Output.—Daniell et al. (8) have shown that in the presence of hypotension isoproterenol fails to exert its positive inotropic effect because it is unable to restore arterial and thus coronary perfusion pressure. Since dobutamine has only modest α activity, it was important to learn whether its positive ino-

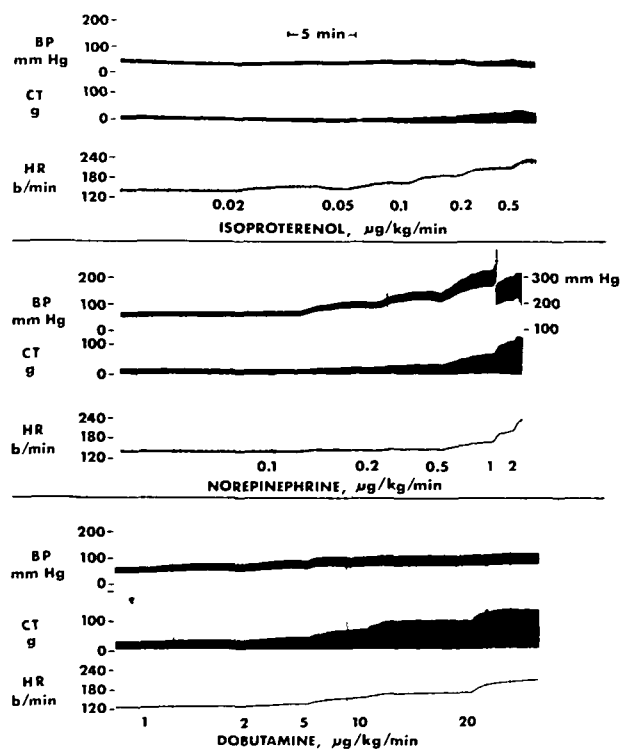


FIGURE 5

Oscillograph tracings comparing the effects of isoproterenol, norepinephrine, and dobutamine on blood pressure (BP), cardiac contractile tension (CT), and heart rate (HR) in dogs with coronary artery ligation and ganglionic blockade. The arrow above the blood pressure tracing for norepinephrine marks a change in recorder gain. Note the changed scale on the right of this tracing.

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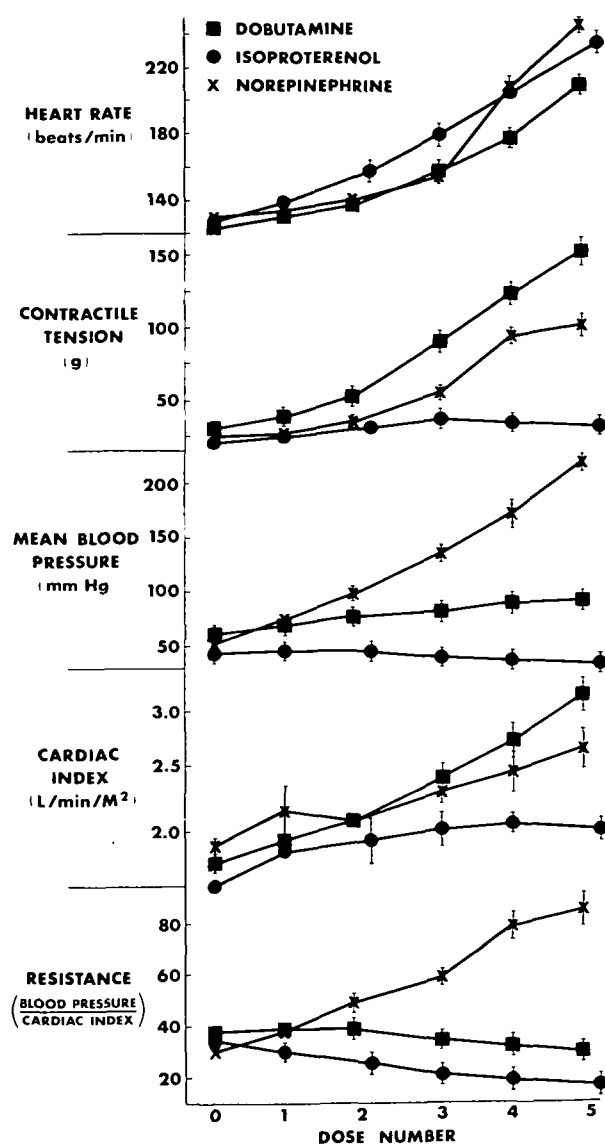


FIGURE 6

Mean results comparing dobutamine, isoproterenol, and norepinephrine after coronary artery ligation and ganglionic blockade. The doses of each agonist are the same as those shown in Figure 5. Dose numbers 0–5 represent (in $\mu\text{g/kg min}^{-1}$): dobutamine 0, 1.0, 2.0, 5.0, 10.0, and 20.0, isoproterenol 0, 0.02, 0.05, 0.1, 0.2, and 0.5, and norepinephrine 0, 0.1, 0.2, 0.5, 1.0, and 2.0.

tropic effect would also fail in the presence of hypotension.

We depressed blood pressure, cardiac contractility, and cardiac output by ligation of the left coronary artery just below the circumflex branch and ganglionic block (hexamethonium, 10 mg/kg, iv) in ten dogs. Pressure fell from 95 ± 3 to 59 ± 3 mm Hg ($P < 0.001$), contractility fell from 67 ± 6 to 28 ± 3 g ($P < 0.001$), and cardiac index decreased from 2.1 ± 0.1 to 1.8 ± 0.2 liters/min

m^{-2} ($P < 0.05$). Six of the dogs were tested with graded intravenous infusions of dobutamine ($1-20 \mu\text{g/kg min}^{-1}$). The other four were infused with isoproterenol ($0.02-0.2 \mu\text{g/kg min}^{-1}$) and norepinephrine ($0.1-2.0 \mu\text{g/kg min}^{-1}$).

The recordings shown in Figure 5 indicate the time course of the infusions and vividly illustrate the differences in the cardiac and blood pressure effects of the three agonists. Hypotension did not prevent the positive inotropic effect of dobutamine. Compared with the strong inotropic effect, the chronotropic effect was modest, and blood pressure returned to a physiological level. But isoproterenol did not improve the hypotension, and the inotropic response was meager. There was, however, a striking chronotropic response to isoproterenol. With norepinephrine, the pressor response dominated. Neither cardiac contractility nor rate increased substantially until the systolic blood pressure exceeded 200 mm Hg (Fig. 5). The data from all of the dogs are summarized in Figure 6; they show that, of the three agonists, dobutamine increased cardiac contractility and output the most but had the least effect on heart rate and total peripheral resistance.

D. The Arrhythmogenic Activity of Dobutamine, Dopamine, Isoproterenol, and Norepinephrine in Ischemic Dog Hearts.—The papillary muscle data showed that dobutamine had a more favorable contractility-automaticity ratio than did isoproterenol. At $1 \times 10^{-7}M$ isoproterenol and $1 \times 10^{-5}M$ dobutamine, there was an equal incidence of automaticity (50%). But dobutamine caused a significantly greater increase in contractility (6.5 ± 0.8 vs. 4.4 ± 0.6 mm, $P < 0.05$).

These papillary muscle data coupled with the data showing that dobutamine had only slight effects on blood pressure suggested that the relationship between inotropic and arrhythmogenic activity would be better for dobutamine than for the other agonists. Therefore, we tested these agonists in four dogs 2 hours after ligating the left descending coronary artery, leaving the vagus nerves intact. The order of testing was balanced among the dogs so that each agonist was tested first, second, third, or fourth in one experiment. The rhythm was sinus before the tests, and sufficient time was allowed between each agonist for the heart to return to sinus rhythm. Although the pentobarbital anesthesia had not yet worn off, the chests were closed and the dogs were breathing without artificial support.

Figure 7 illustrates the results. Dobutamine was the only agonist that caused no significant change

in rate or rhythm. Dopamine, given in the same doses as dobutamine, caused a significant decrease in sinus rate ($P < 0.05$) and a significant increase in ectopic rate ($P < 0.05$). When inotropic potency is taken into account, the contrasts in arrhythmogenic activity between dobutamine and dopamine sharpens. The highest doses given equal 43 times the CT_{50} for dobutamine and only 9 times dopamine's CT_{50} . Nevertheless, dopamine increased ectopic rate by 50 ± 14 beats/min ($P < 0.05$) although dobutamine increased it by only 4 ± 2 beats/min. The difference was statistically significant ($P < 0.05$).

Norepinephrine also caused a significant decrease in sinus rate ($P < 0.05$) and a significant increase in ectopic rate ($P < 0.005$). At the highest dose ($8 \mu\text{g/kg}$, 33 times CT_{50}), ectopic rate equaled

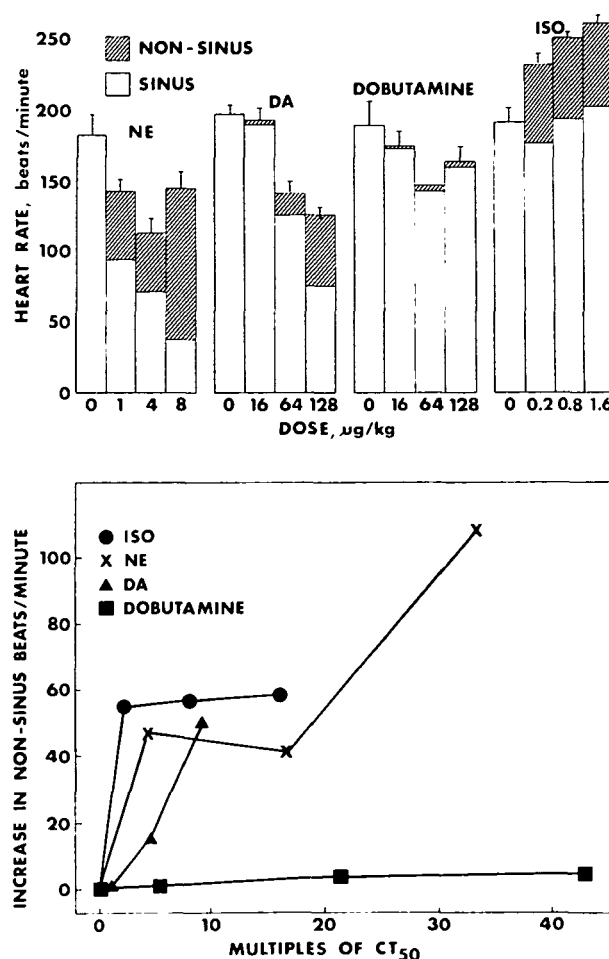


FIGURE 7

Effect of norepinephrine (NE), dopamine (DA), dobutamine, and isoproterenol (ISO) on the rate and rhythm of four dogs 2 hours after ligation of the left anterior descending coronary artery. CT_{50} = dose of each agonist required to increase cardiac contractile tension by 50%. (CT_{50} values are given in Table 2.)

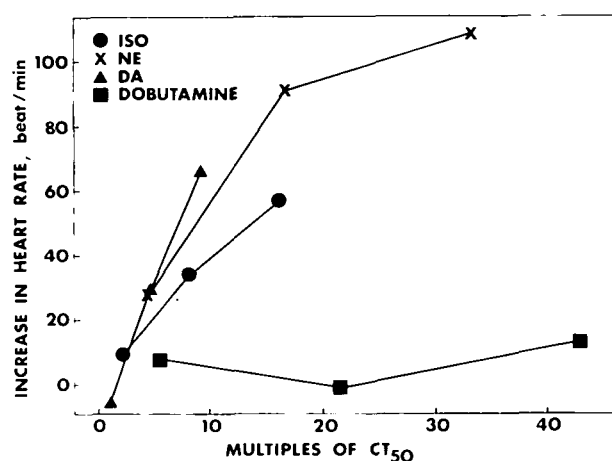
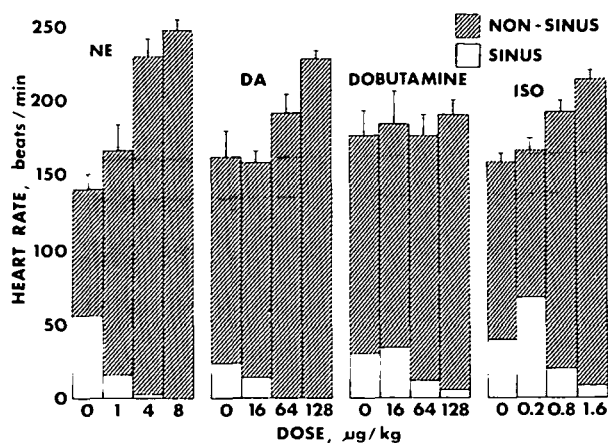


FIGURE 8

Same dogs considered in Figure 7 48 hours after coronary artery ligation.

108 ± 14 beats/min, which was significantly greater than the 4 ± 2 ectopic beats/min caused by dobutamine at 43 times its CT_{50} ($P < 0.005$).

Isoproterenol was the only agonist that increased overall rate (sinus plus ectopic). At eight times CT_{50} ($0.8 \mu\text{g/kg}$), the rate increase was significantly greater than that which occurred with even the highest dose of any of the other agonists ($P < 0.01$). In three of the four dogs, isoproterenol did not cause ectopic beats, but in the fourth dog even the lowest dose of isoproterenol ($0.2 \mu\text{g/kg}$, two times CT_{50}) produced an arrhythmia of 213 ectopic beats/min.

Forty-eight hours later, these dogs were tested again in the same manner. The dogs were conscious and ectopic beats dominated their electrocardiograms (Fig. 8). As before, dobutamine was the only agonist that caused no significant change in rate or rhythm. Norepinephrine significantly increased ectopic activity at each dose given ($P < 0.05$). Dopamine and isoproterenol also evoked

significant increases in ectopic activity at the highest doses ($P < 0.05$).

Discussion

Results from the papillary muscles showed that dobutamine caused less automaticity than did isoproterenol. But, one would not have predicted from the papillary muscle data alone the contrasts that occurred between dobutamine and the other three catecholamines in evoking or exacerbating ectopic activity in the dogs with coronary artery ligation (section II-D). The fact that dobutamine, even in very high doses, did not cause large fluctuations in arterial blood pressure was probably responsible. The high arrhythmogenic activity of dopamine in these experiments agreed with the work of others (12).

Release of endogenous norepinephrine could be a factor in the arrhythmogenic activity of dopamine, but that remains to be determined. However, our experiments with DMI (section IIA) showed that the adrenergic nerve fibers and the release of norepinephrine were of considerable importance in determining the relative inotropic-pressor and inotropic-chronotropic ratios of dopamine.

The norepinephrine content of cardiac tissue is greater than that of most other tissues (19). So, endogenous norepinephrine would contribute more to the inotropic effect of a releasing agonist than to its vascular effects. Therefore, prevention of release would reduce the inotropic response more than the pressor response; this situation accounts for the depression in dopamine's inotropic-pressor ratio that we observed after DMI administration.

Depression of dopamine's inotropic-chronotropic ratio by DMI can be accounted for by the differences in the density and in the norepinephrine content of the sympathetic nerve fibers within the heart. Sympathetic innervation is heaviest in the pacemaker region (sinoatrial node), but the norepinephrine content of these nerve fibers is less than that of the sympathetic fibers in ventricular muscle (20). Consequently, there is a considerable capacity of uptake of amines in the sinoatrial node, which attenuates the chronotropic more than the inotropic effect of exogenously administered norepinephrine (21). As others have pointed out (2), dopamine has a lower chronotropic effect than does norepinephrine; we think this fact is due to a high uptake-release ratio in the region of the sinoatrial node. That is, for a given amount of dopamine uptake, there is less endogenous norepinephrine available for release in the pacemaker region than in the ventricles. Consequently, prevention of nor-

epinephrine release by DMI has a greater impact on the inotropic effect than it does on the chronotropic effect of releasing agonists like dopamine and tyramine (22).

The DMI experiments showed that the low chronotropic effect of dobutamine was not due to a modulating influence of uptake by sympathetic nerve fibers. Whether it reflects a difference in the β_1 receptors of the sinoatrial node that control heart rate and those of ventricular muscle that control myocardial contractility cannot be decided from the data presented in this paper. However, these data do show that the relatively greater chronotropic response to isoproterenol cannot be explained merely by reflex stimulation resulting from isoproterenol's vasodepressor effect. As Table 3 shows, hydroxyphenylethyl- α -methyl-dopamine (XVIII, Table 1) at the CT_{50} dose caused a significantly greater fall in pressure (-40 ± 5 vs. -19 ± 6 mm Hg, $P < 0.05$) and a significantly smaller increase in heart rate (19 ± 3 vs. 33 ± 3 beats/min, $P < 0.05$) than did isoproterenol. Moreover, a recent preliminary report on in vitro experiments with cat hearts (23) has shown that, for an equivalent inotropic effect on the electrically paced papillary muscle, isoproterenol increases the rate of the spontaneously beating right atria more than does dobutamine; this report thus provides further evidence of a hemodynamically independent difference in the chronotropic effect.

The experiments comparing dobutamine and epinephrine before and after selective adrenergic blockade (section IIB) showed that dobutamine had the required strong inotropic activity but had little effect on blood pressure, because its activity on the α and β_2 adrenergic receptors that control arterial resistance was weak relative to its activity on the β_1 receptors that control myocardial contractility. In conscious dogs chronically instrumented to measure cardiac contractility, arterial blood pressure, and regional blood flows, Vatner et al. (6) compared dobutamine, dopamine, norepinephrine, and isoproterenol and came to a similar conclusion: "... dobutamine is a potent positive inotropic agent with relatively slight effects on preload, afterload, or heart rate, and thus may be a potentially useful clinical agent." The recent studies of Jewitt et al. (24) in man supported this conclusion. The work of Vatner et al. (6) showed that at $8.0 \mu\text{g/kg min}^{-1}$ β_2 activity appeared and an increase in skeletal muscle flow accompanied the increase in coronary flow. At this high dose, the increases in coronary and skeletal muscle flow were significantly greater than those which occurred in the mesenteric or renal beds.

Robie et al. (25) have confirmed our work on anesthetized dogs, showing that dobutamine has strong β_1 cardiac activity and relatively weak vascular α and β_2 activity. They have noted that to increase femoral artery flow by 50% 180 times the dose of dobutamine that increases cardiac contractility by 50% has to be given, whereas with isoproterenol the corresponding ratio is 43 times. This finding suggests that for an equivalent cardiac effect dobutamine has about a fourth the vascular effect of isoproterenol. Robie et al. (25) also have shown that dobutamine does not possess dopamine-like renal vasodilating activity as would be predicted from the early work of Goldberg et al. (26), who showed that substituents larger than methyl on the nitrogen destroy dopaminergic activity on the kidney.

Important to the potential clinical usefulness of dobutamine is the fact that its modulated effect on blood pressure reflects a balance of weak rather than strong α and β_2 actions. If there were strong effects on the peripheral vasculature, cancellation of the opposing vasodilating and vasoconstricting effects would probably not occur over such a wide dose range. Dobutamine's attenuated α -adrenergic vascular effect permits great inotropic activity without an undue rise in resistance or arterial blood pressure. On the other hand, with epinephrine and dopamine, the α -adrenergic activity is not attenuated and the dose range over which β_2 and dopaminergic vasodilating activity mitigates their vasoconstriction is narrow (3-5). As our results show (section IIA), dopamine's inotropic range over which there is no accompanying marked pressor activity is further restricted when release of endogenous norepinephrine cannot occur.

The experiments on dogs with experimentally induced hypotension and low cardiac output (section IIC) amply demonstrated the advantage of attenuated vascular activity by showing that hypotension did not prevent the positive inotropic effect of dobutamine although it did with isoproterenol. Yet dobutamine restored arterial blood pressure without the increase in vascular resistance that occurred with norepinephrine.

Extensive clinical studies are underway to determine the therapeutic value of dobutamine. Dobutamine should be useful in patients with inadequate circulation due to acutely depressed circulation after cardiac surgery, since in most patients who fail to survive death is due to depressed cardiac contractility (27). Progressive deterioration of contractility also causes the deaths of thousands of patients who are hospitalized for acute myocardial infarction (28). However, Maroko et al. (29)

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have shown in acute experiments on dogs that positive inotropic intervention with isoproterenol extends the infarction. A preliminary report comparing isoproterenol and dobutamine in chronic experiments on dogs with a severely constricted left coronary artery confirms that isoproterenol increases infarction size but shows that dobutamine contains the infarction (30).

We believe that dobutamine could fulfill a need in the treatment of acute heart failure of various etiologies, because it does not have the chronotropic or vasodepressor actions of isoproterenol, the vasopressor actions of norepinephrine or dopamine, or the arrhythmogenic potential of any of these three agents. Yet, like isoproterenol and norepinephrine, dobutamine acts directly on the cardiac β_1 receptors and so has inotropic efficacy substantially greater than that of the digitalis glycosides (31). Like other catecholamines, dobutamine has an immediate onset but a brief duration of action that makes possible titration of the desired amount of inotropic effect by controlling the rate of intravenous infusion.

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