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Research Article

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ABSTRACT The effects of dobutamine ([±]-4-[2-[[3-(*p*-hydroxyphenyl)-1-methyl propyl] amino] ethyl] pyrocatechol hydrochloride), a new synthetic cardioactive sympathomimetic amine, were examined on direct and continuous measurements of left ventricular (LV) diameter (D), pressures (P), velocity of shortening (V), dP/dt, dP/dt/P, arterial pressure, cardiac output, and regional blood flows in the left circumflex coronary, mesenteric, renal, and iliac beds in healthy, conscious dogs. At the highest dose of dobutamine examined, 40 μg/kg/min, the drug increased dP/dt/P from 65±3 to 128±4 s^{-1} and isolength velocity from 72±4 to 120±7 mm/s without affecting LV end diastolic D significantly. Mean arterial P rose from 92±2 to 104±3 mm Hg and heart rate from 78±3 to 111±7 beats/min, while LV end systolic D fell from 24.1±1.4 to 19.9±1.8 mm, reflecting a rise in stroke volume from 30±4 to 42±3 ml. Cardiac output rose from 2.41±0.23 to 4.35±0.28 liter/min, while calculated total peripheral resistance declined from 0.042±0.005 to 0.028±0.003 mm Hg/ml/min. The greatest increases in flow and decreases in calculated resistance occurred in the iliac and coronary beds, and the least occurred in the renal bed. Propranolol blocked the inotropic and beta$_2$ dilator responses while vasoconstricting effects mediated by alpha adrenergic stimulation remained in each of the beds studied. When dobutamine was infused after a combination of practolol and phentolamine, dilatation occurred in each of the beds studied. These observations indicate that 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 one property of this drug which is not ideal is its tendency to cause a redistribution of cardiac output favoring the muscular beds at the expense of the kidney and visceral beds.

INTRODUCTION

Cardioactive sympathomimetic amines are frequently administered in a variety of situations involving "myocardial pump failure," particularly in states of cardiogenic shock after acute myocardial infarction, and after cardiopulmonary bypass. However, opinions as to the efficacy of these agents differ considerably (1). Isoproterenol, a potent inotropic agent by virtue of its pure beta adrenergic stimulating properties, is frequently used in myocardial pump failure regardless of the etiology (2, 3); however, unfavorable effects, e.g., excessive tachycardia, arrhythmias, and reduced perfusion pressure, often occur as well (4, 5). Furthermore, isoproterenol has been shown experimentally to extend infarct size after coronary occlusion (6), to intensify myocardial ischemia after coronary narrowing resulting in acute cardiac failure (7), and to impair left ventricular (LV)[1] function when coronary blood flow is restricted (8). Norepinephrine, on the other hand, while stimulating myocardial contractility, also causes a marked increase in peripheral resistance and coronary vasoconstriction as a consequence of its potent alpha adrenergic properties (9); these actions can also be

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[1] *Abbreviations used in this paper:* AP, arterial pressure; CO, cardiac output; D, diameter; HR, heart rate; LV, left ventricular; P, Pressure; TPR, total peripheral resistance; V, velocity.

deleterious. Dopamine is now administered frequently because it increases myocardial contractility and cardiac output (CO) with less alpha adrenergic vasoconstriction than norepinephrine and less cardiac acceleration than isoproterenol (10, 11). Nevertheless, dopamine exerts considerable alpha adrenergic stimulation (12, 13) and this property in combination with its tendency to elicit arrhythmias may limit its usefulness (14, 15), Dobutamine ([±]-4-[2-[[3-(*p*-hydroxyphenyl)-1-methyl propyl] amino] ethyl] pyrocatechol hydrochloride) is a new sympathomimetic amine developed by Tuttle and Mills to provide a more useful clinical inotropic agent; one that augments contractility while producing relatively little change in peripheral vascular resistance, heart rate, (HR) or rhythm.[2]

Since this new inotropic agent, dobutamine, may be of clinical importance, the goal of this investigation was to evaluate it in healthy, conscious dogs instrumented for direct and continuous measurements of LV diameter (D) and pressure (P), myocardial contractility, and coronary, mesenteric, renal, and iliac blood flows. It was particularly important to evaluate this agent in the normal, conscious animal for two reasons. First, the drug will be administered to conscious patients, and discomforting side effects, which might not be noted in anesthetized animals, could be observed in the conscious state. Secondly, and more important, many pharmacological agents and in particular inotropic agents (16) and catecholamines (9, 13) have markedly different effects in the presence and absence of general anesthesia. The specific goals of this investigation were first to examine the effects of graded doses of dobutamine on LV performance, coronary dynamics, and regional blood flow distribution, and second, to analyze its mechanism of action by comparing the responses in the control state and after selective and combined adrenergic blockades.

METHODS

13 normal mongrel dogs (24–34 kg) were studied in the conscious state. All operations were performed after i.v. pentobarbital Na, 30 mg/kg. Through a thoracotomy in the fifth left intercostal space in seven dogs, miniature pressure gauges (Konigsberg P22, Konigsberg Instruments, Inc., Pasadena, Calif.) were implanted within the left ventricle through a stab wound in the apex, ultrasonic diameter transducers were implanted on opposing endocardial surfaces of the left ventricle, and Doppler ultrasonic flow transducers were placed around the left circumflex coronary artery and stimulator electrodes were sutured to the left atrium. Electromagnetic flow transducers (Statham Instruments, Inc., Oxnard, Calif.) were implanted around the ascending aorta in four dogs. Through a midline laparotomy, Doppler ultrasonic (six dogs) transducers were placed around the mesenteric, left renal, and left iliac arteries.

The miniature pressure gauges were calibrated in vivo against a calibrated Statham P23 Db strain gauge manometer. At autopsy the position of the ventricular gauges within the ventricular cavity was confirmed. Arterial pressure was sampled with the previously implanted heparin-filled Tygon catheter (Norton Company, Plastics and Synthetics Div., Akron, Ohio) and measured with a Statham P23 Db strain gauge manometer. Regional blood flow was measured with an ultrasonic Doppler flowmeter. This system, which has been described in detail previously, has a reliable zero reference (17, 18) and in these experiments electrical zero blood flow was determined repeatedly and was confirmed by calibration when the animal was sacrificed. The relationship between velocity (V), as measured by the Doppler flowmeter, and volume flow is linear as long as the cross-sectional area of the blood vessel within the transducer remains constant. This linear relationship between V and volume flow has been demonstrated repeatedly previously and confirmed by means of timed collections of blood flow (18). At autopsy it was observed that the vessels were firmly adherent to the flow transducers through a fibrous scar, which minimized changes in the cross-sectional area of the blood vessel within the flow transducers. In the experiments in which aortic flow was measured with a Statham electromagnetic flowmeter, zero flow was assumed to occur during mid and late diastole. While blood flow measurements in each animal may have varied slightly from one experimental day to another, the average control values for the entire group of animals varied insignificantly.

An improved ultrasonic transit time dimension gauge was used to measure LVD[3] (19). This device measures the transit time of acoustic impulses traveling at the sonic velocity of approximately 1.5×10^6 mm/s between the 5 or 3 MHz piezoelectric crystals implanted on the LV endocardium at the opposing sites. It was calibrated by substituting signals of known time duration from a calibrated pulse generator. A voltage proportional to transit time was recorded and calibrated in terms of crystal separation. In this manner, a measure of the internal D of the left ventricle was continuously recorded. At a constant temperature, the drift of the instrument is less than 0.15 mm/h, and its frequency response is flat to 60 Hz.

The experiments were conducted 3 wk to 2 mo postoperatively when the dogs had recovered from operation and were vigorous and healthy. Control records of CO, LVP, D, dP/dt, dD/dt, regional blood flows, arterial pressure (AP), and HR were obtained continuously while the unsedated dogs were resting quietly and during administration of dobutamine. Dobutamine was dissolved in saline at a slightly acid pH and administered intravenously as an infusion of 8, 20, and 40 μg/kg/min for periods of 2 min each until a plateau of response was reached and also as a bolus, in doses of 8, 20, and 40 μg/kg in 13 dogs. This sequence was repeated while maintaining HR constant by electrical stimulation of the atria in seven dogs, and after beta adrenergic blockade with propranolol, 1–2 mg/kg, in nine dogs. On separate days the control protocol was repeated and dobutamine was also administered first after practolol, 4 mg/kg, and then after phentolamine, 1 mg/kg, in nine dogs. In the experiments in which coronary blood flow was measured, dobutamine was administered after practolol, 4 mg/kg, alone in five dogs and in combination

[2] Tuttle, R. R., and J. Mills. 1974. Dobutamine; development of a new catecholamine to selectively increase cardiac contractility. Submitted for publication.

[3] Construction details available from the author.

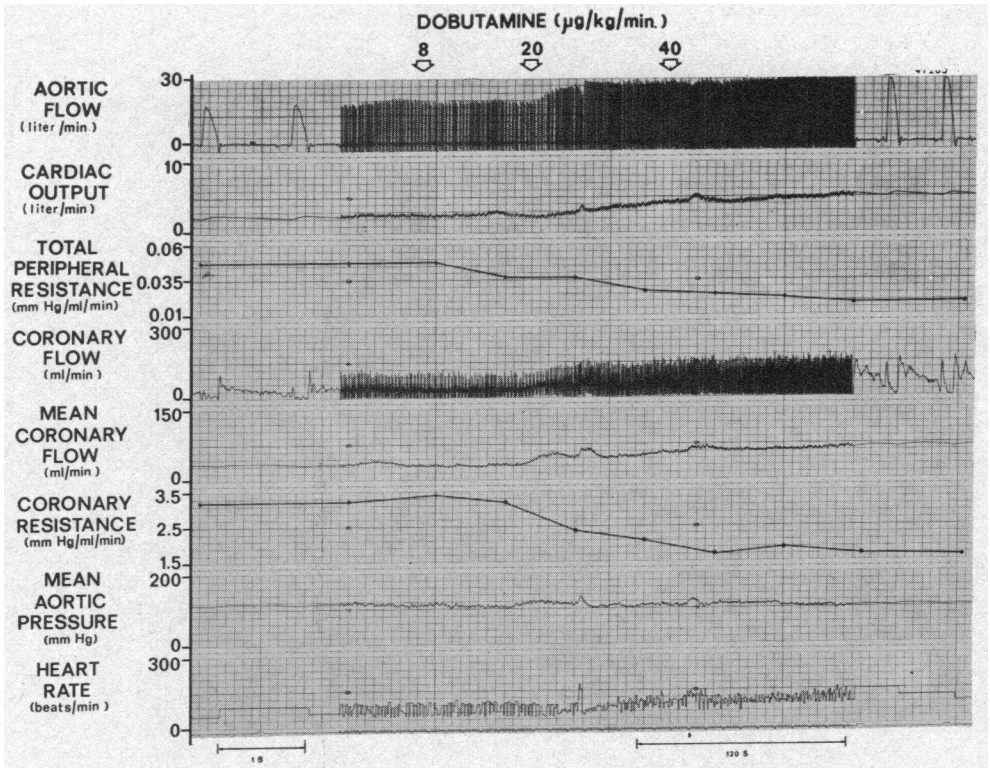

FIGURE 1 Response to dobutamine infusion for phasic aortic root flow, mean flow, (CO), calculated TPR, phasic and mean left circumflex coronary blood flow, calculated mean coronary resistance, mean AP, and HR. Phasic waveforms at rapid paper speed are compared at the left during the control period and at the right during the response to dobutamine. Note that dobutamine increases CO, stroke volume, and coronary flow without affecting mean AP or HR substantially.

with phentolamine, 1 mg/kg in six dogs. Beta$_1$ receptor blockade was tested with isoproterenol, 0.5 μg/kg i.v., and alpha receptor blockade was tested with norepinephrine, 0.5 μg/kg i.v. In six dogs, the effects on AP and HR were noted as infusion of isoproterenol, norepinephrine, dopamine, and epinephrine were administered to produce increases in contractility equivalent to those that had occurred with dobutamine.

The data were recorded on a multichannel tape recorder and played back on a direct-writing oscillograph. A cardiotachometer, triggered by the signal from the pressure pulse, provided instantaneous and continuous records of HR. Electronic resistance capacitance filters with 2-s time constants were used to derive mean arterial blood pressure and mean regional blood flow, while a resistance capacitance filter with an 8-s time constant was used to derive mean aortic flow (CO). Mean total and regional vascular resistances were calculated as the quotients of mean AP and aortic and regional blood flows, respectively. Mean and late diastolic coronary vascular resistances were calculated as the quotients of mean and late diastolic AP and coronary blood flows, respectively. Continuous records of dP/dt and dD/dt were derived from the LVP and D signals, with Philbrick operational amplifiers connected as differentiators with frequency responses of 60 and 30 Hz, respectively (Teledyne Philbrick, Dedham, Mass.). A triangular wave signal with known slope (rate-of-change) was substituted for P and D signals for direct calibration of the dP/dt and dD/dt channels.

The effects of dobutamine on myocardial force-velocity relations were assessed by determining their effects on the V of shortening, i.e. dD/dt, and intraventricular P at an identical ventricular D (isolength point), by the technique described in detail previously (9, 13, 17, 20). All isolength points were obtained during the first one-third of ejection. In addition, the effects on peak dP/dt and the quotient of dP/dt and developed P (LV minus end diastolic P, i.e., (dP/dt)/P, were examined. The same level of P which occurred during isovolumic contraction, before and after each intervention and ranged from 40 to 80 mmHg, was used for this calculation and dP/dt and P were determined at that level of pressure. This technique for evaluating the myocardial contractile state has also been described in detail previously (9, 13, 16, 21). Measurements after the drug were compared to control observations and changes from control in the different states were compared with the paired t test (22). Average ±SEM values are reported throughout.

RESULTS

While the effects of the bolus doses as well as infusions of dobutamine were examined, only the effects of the

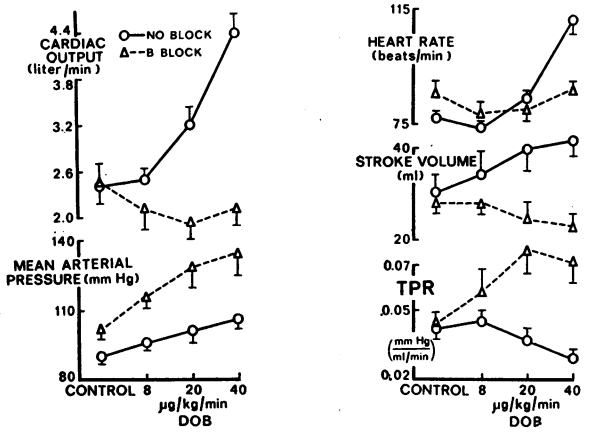

FIGURE 2 Average ±SEM responses to dobutamine infusions for CO, mean AP, HR, stroke volume, and TPR in the same dogs without adrenergic blockade (circles, solid lines) and after beta receptor blockade with propranolol, 1–2 mg/kg (triangles, broken lines). Without blockade, dobutamine increases CO and decreases TPR, but after beta receptor blockade only the alpha adrenergic effects of dobutamine remain and CO falls, while TPR rises.

infusion experiments will be presented. Bolus administration of dobutamine resulted in qualitatively similar results, except that alpha adrenergic vasoconstrictor effects predominated early in the response while beta adrenergic inotropic and peripheral vasodilator actions predominated later in the response.

Systemic hemodynamics: CO, AP, TPR, and HR

Control (unblocked) state. At the lowest dose, 8 μg/kg/min, dobutamine changed CO and TPR little, since it tended to increase stroke volume slightly while simultaneously tending to reduce HR, while AP remained constant. At the middle (20 μg/kg/min) and largest (40 μg/kg/min) doses, progressive and substantial increases ($P < 0.01$) in CO from 2.41±0.23 (control) to 3.23±0.25 and 4.35±0.27 liter/min, respectively, occurred, and these were accompanied by reductions in TPR from 0.042±0.005 to 0.037±0.0048, and 0.028±0.003 mm Hg/ml/min ($P < 0.01$) (Fig. 1). The increase in CO was due primarily to increases in stroke volume (+33±5%) at the mid dose, but was due to

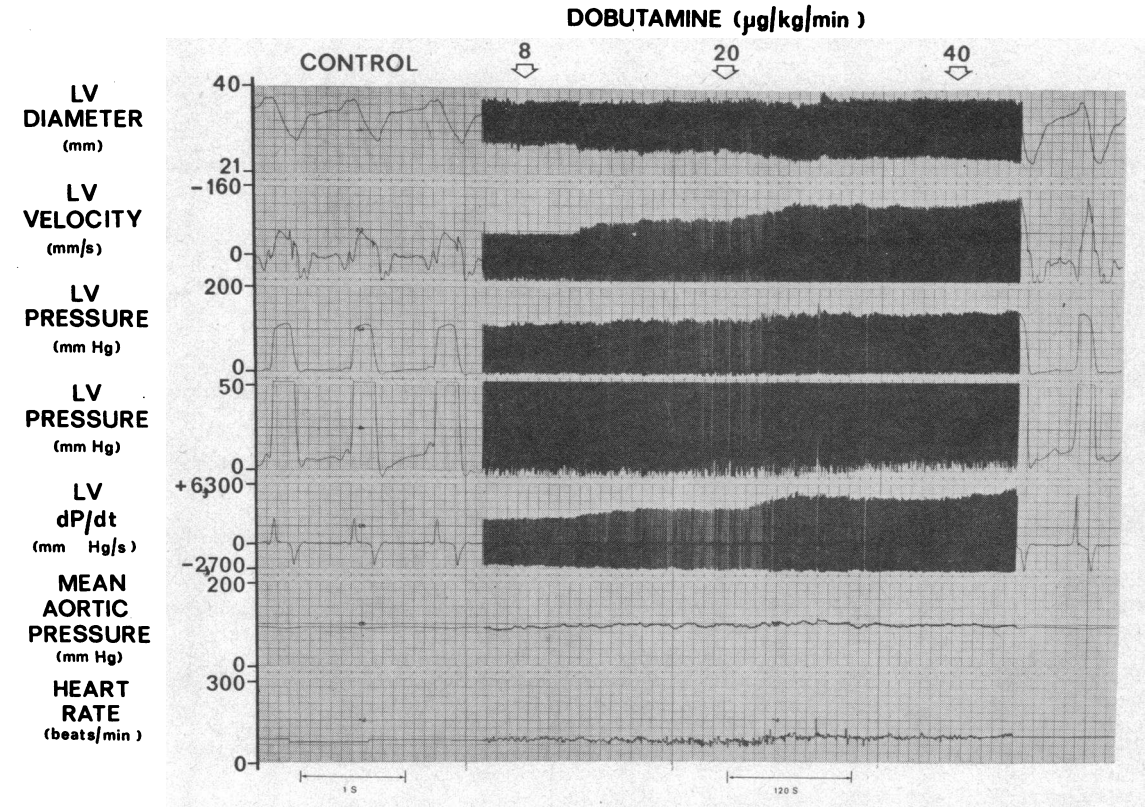

FIGURE 3 Response to dobutamine infusion in a conscious dog, illustrating the responses of phasic LV D, LV V, LV P, LV end diastolic P, dP/dt, mean AP, and HR. Waveforms at fast paper speed are compared during control (left) and after infusion of the drug (right). Note the large increases in V and dP/dt and stroke myocardial excursion and decrease in end systolic D, while LV end diastolic D, mean AP, and HR change little.

increases in both HR (+33±8 beats/min) and stroke volume (+42±9%) at the high dose (Fig. 2). Mean AP increased mimimally with increasing dosage.

Beta-blockade. Propranolol modified the response to dobutamine in the following manner: Substantially greater ($P < 0.02$) increases in mean AP occurred (Fig. 2), and the small HR increase that did occur in the unblocked state was prevented, presumably by the combination of baroreceptor reflex vagal activation and the blockade of the slight direct chronotropic effect. CO and stroke volume, instead of rising, fell at the highest dose from 2.45±0.32 to 2.15±0.26 liter/min, and from 28±3 to 23±3 ml. In the face of blockade of beta adrenergic receptors in the systemic vascular bed, the alpha adrenergic stimulating properties of the drug were unmasked and TPR rose rather than fell, as had occurred in the control, unblocked state (Fig. 2).

Beta$_1$ and alpha blockade. The combination of practolol and phentolamine modified the response to dobutamine by preventing the beta$_1$ adrenergic receptor-mediated increases in HR and contractility and the alpha adrenergic-mediated vasoconstriction, leaving beta$_2$ adrenergic receptor-mediated vasodilatation. Dobutamine caused a small, insignificant increase in cardiac output from 2.43±0.30 to 3.10±0.48 liter/min, and a reduction in stroke volume from 26±5 to 24±6 ml. Mean AP fell from 98±4 to 78±1 mm Hg, a change which differed significantly ($P < 0.01$) from that which occurred in the unblocked state or after propranolol, and which reflects the beta$_2$ adrenergic receptor-stimulating properties of the drug. TPR fell from 0.043±0.006 to 0.027±0.005 mm Hg/ml/min ($P < 0.001$).

P, D, and myocardial contractility

Spontaneous rhythm. Dobutamine elicited progressive increases in myocardial contractility (Fig. 3), as reflected by increases (with the largest dose), in peak dP/dt from a control level of 3,420±160 to 8,200±560 mm Hg/ml/min, dP/dt/P from 65±3 to 128±4 s^{-1}, isolength V from 72±4 to 120±7 mm/s, with a corresponding increase in isolength systolic LVP from 113±4 to 138±4 mm Hg (Fig. 4). These increases in contractility were not accompanied by significant changes in LV end diastolic P or D, while end systolic D fell progressively from 24.1±1.4 to 19.9±1.8 mm ($P < 0.001$) (Fig. 4), resulting in an increase in myocardial fiber shortening, corresponding to the increases in stroke volume.

HR constant. With the HR maintained constant in each experiment at rates that averaged 138±7 beats/min, dobutamine produced changes in LV function similar to those in spontaneous rhythm. LV end diastolic P and D remained essentially constant while end systolic D fell from 23.6±1.4 to 19.5±1.5 mm ($P < 0.001$) and

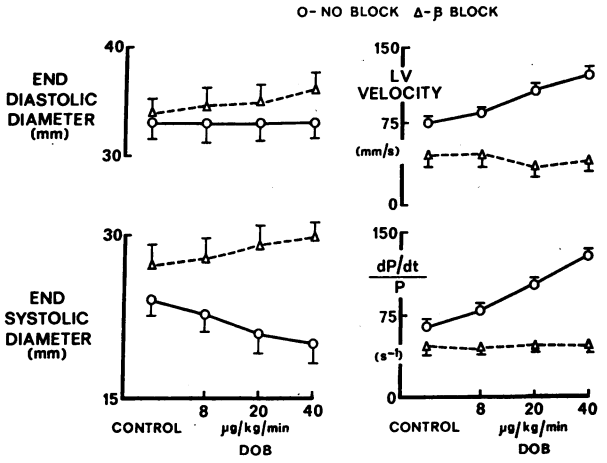

FIGURE 4 Comparison of the average ±SEM responses to dobutamine in the same dogs without blockade (circles, solid lines) and after beta receptor blockade (triangles, broken lines) for LV end diastolic D (open circles and triangles), end systolic D (closed circles and triangles), isolength V, and dP/dt/P. Note that beta receptor blockade with propranolol blocks the inotropic response to dobutamine and results in increases rather than decreases in end systolic D and increases end diastolic D.

progressive increases were observed in dP/dt (from 2,980±190 to 5,900±480 mm Hg/sec), dP/dt/P from 54±3 to 92±7 s^{-1} and isolength V from 61±2 to 114±6 mm/s.

Beta blockade. Propranolol prevented the inotropic increases induced by dobutamine (Fig. 4), and produced significantly different responses in LV Ds and Ps. After propranolol, dobutamine increased LV end diastolic P from 7±1 to 11±1 mm Hg and D from 34.0±

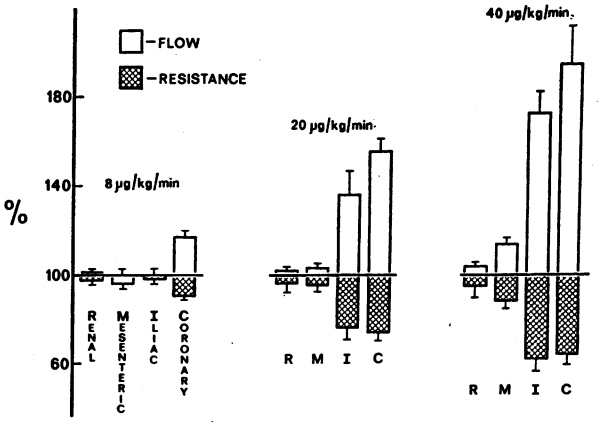

FIGURE 5 Distribution of regional blood flow and resistance for the renal (R), mesenteric (M), iliac (I), and coronary (C) beds are shown for the three dosage levels studied. The coronary and iliac beds showed the greatest increases in flow and decreases in resistance while the renal bed showed the least.

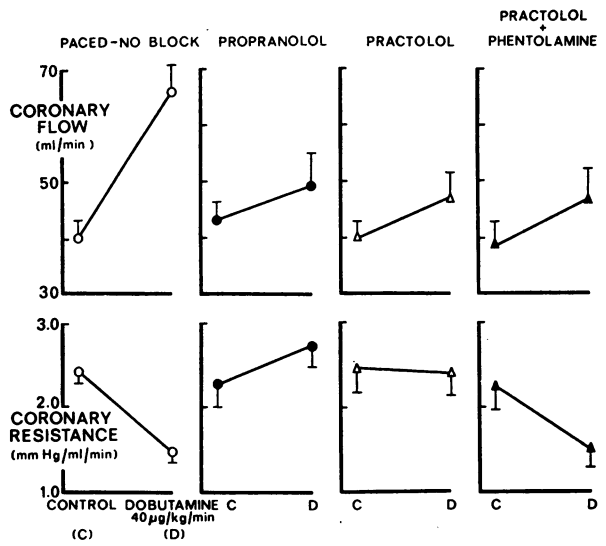

FIGURE 6 Average ±SEM responses to the 40 μg/kg/min dose of dobutamine infusion on mean left circumflex coronary flow and resistance in the control state and after adrenergic receptor blockades. In all these experiments the same animals were studied and HR was maintained constant by pacing.

1.1 to 35.9±1.6 mm, as well as end systolic D from 27.2± 1.5 to 29.7±1.1 mm and systolic LVP_{180} from 113±7 to 154±11 mm Hg.

Beta₁ and alpha blockade. Practolol, like propranolol, blocked dobutamine's positive inotropic responses but did not block the peripheral vasodilator effects. With the addition of phentolamine to block peripheral alpha adrenergic effects, dobutamine produced no change in LV end diastolic D but reductions in end systolic D (−1.4 mm) and LVP_{180} (−5 mm Hg) occurred.

Coronary bed

Spontaneous rhythm. Dobutamine caused progressive increases in mean left circumflex coronary flow from 37±3 to 68±6 ml/min at the highest dose and reduction in mean calculated coronary resistance from 2.58±0.15 to 1.48±0.20 mm Hg/ml/min (Fig. 1). Changes in late diastolic coronary flow and resistance paralleled the mean responses. At the low dose of dobutamine, 8 μg/kg/min, the coronary bed was the only one that showed a significant increase in flow and reduction in resistance (Fig. 5).

The unblocked state (HR constant). Maintaining HR constant did not affect the response of the coronary bed significantly. Mean coronary flow rose from 40±3 to 66±4 ml/min and resistance fell from 2.39±0.15 to 1.43±0.09 mm Hg/ml/min.

Beta blockade (HR constant). Propranolol reversed the coronary vasodilatation and only coronary vasoconstriction was observed (Fig. 6); mean coronary resistance rose from 2.26±0.23 to 2.71±0.25 mm Hg/ml/min, demonstrating the slight but significant ($P < 0.05$) vasoconstricting effects mediated by stimulating alpha adrenergic receptors in the coronary bed.

Beta₁ and alpha blockade (HR constant). Practolol prevented the beta₁ adrenergic receptor-mediated increases in contractility. Dobutamine then increased coronary flow only slightly, from 38±3 to 45±4 ml/min ($P < 0.05$) but did not affect coronary resistance significantly (Fig. 6) suggesting that the vasodilator action mediated by beta₂ adrenergic receptors was opposed by the alpha constrictor action of the drug. With the addition of phentolamine, the beta₂ properties were unmasked; coronary flow rose from 39±4 to 47±5 ml/min ($P < 0.02$) and coronary resistance fell from 2.34±0.22 to 1.59±0.18 mm Hg/ml/min ($P < 0.001$) (Fig. 6).

Distribution of blood flows and resistances

The unblocked state. As mentioned above, at 8 μg/kg/min only the coronary bed was affected significantly. At 20 μg/kg/min, only the coronary and iliac beds manifested increases in flow and decreases in resistance (Fig. 5). At the 40 μg/kg/min dose, all four beds studied exhibited increased flows and decreased resistances, but the relative changes from control in the coronary and iliac beds were significantly greater ($P < 0.001$) than those in the mesenteric bed, while the changes in the mesenteric bed were significantly greater ($P < 0.05$) than those in the renal bed. At the highest dose, iliac flow rose from 110±9 to 187±21 ml/min ($P <$

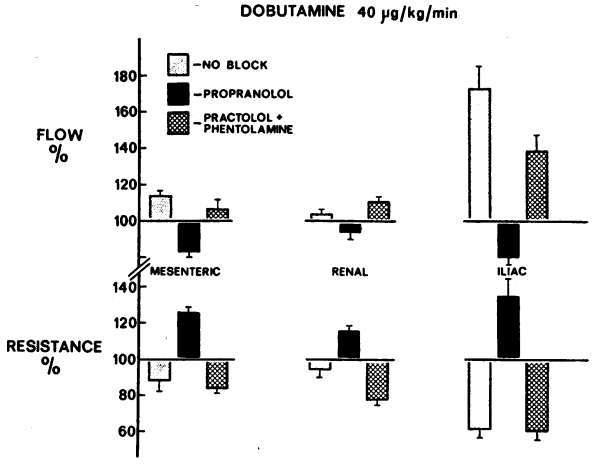

FIGURE 7 Effects of beta receptor blockade with propranolol 1–2 mg/kg and combined beta₁ receptor (practolol 4 mg/kg) and alpha receptor (phentolamine 1 mg/kg) blockades on changes from control in mesenteric, renal, and iliac flows (top) and resistances (bottom). After propranolol only vasoconstriction was noted, while after practolol and phentolamine only vasodilatation was observed.

0.01), while resistance in this bed declined from 0.99± 0.10 to 0.62±0.08 mm Hg/ml/min ($P < 0.01$); mesenteric flow rose from 467±42 to 530±49 ml/min ($P < 0.01$) and resistance fell from 0.23±0.017 to 0.20±0.014 mm Hg/ml/min ($P < 0.05$). The renal bed showed the least response: flow rose from 183±15 to 190±15 ml/min (NS) and resistance fell from 0.57±0.037 to 0.54± 0.021 mm Hg/ml/min (NS).

Beta-blockade. Propranolol unmasked the alpha adrenergic receptor properties of the drug and resulted in reduced flows and increased resistance in the mesenteric, renal, and iliac beds (Fig. 7).

Beta$_2$ and alpha blockades. Practolol and phentolamine unmasked the beta$_2$ adrenergic receptor properties of the drug. Dobutamine then produced substantial dilatation in each of the regional beds. The iliac bed showed relatively greater ($P < 0.01$) increases in flow (139±8%) and decreases in resistance (−61±5%) tthan occurred in the renal and mesenteric bed, suggesting a greater density and/or sensitivity of beta$_2$ adrenergic receptors in that bed.

Comparison of dobutamine with other sympathomimetic amines

Isoproterenol, norepinephrine, dopamine, and epinephrine were infused individually into the same dogs in concentrations which matched the increases in dP/dt (from 3,380±180 to 8,290±650 mm Hg/s) that occurred with the infusion of dobutamine (40 μg/kg/min) (Fig. 8). This dose of dobutamine raised mean AP by 7±6 mm Hg and HR by 43±11 beats/min.

Isoproterenol resulted in a decline in mean AP by 14± 1.0 mm Hg ($P = 0.05$) while HR rose to a far greater extent, by 126±6 beats/min ($P < 0.01$) than after dobutamine.

Norepinephrine caused a much greater ($P < 0.05$) increase in mean AP (+71±11 mm Hg) but a significantly smaller increase in HR (+14±10 beats/min) ($P < 0.05$).

Dopamine resulted in significantly greater ($P < 0.05$) increases in mean AP (45±14 mm Hg) at the peak inotropic response and a slightly greater increase in HR (50±7 beats/min). In addition, after attaining this point, emesis was uniformly observed. The other drugs did not produce this side effect.

Epinephrine, like dopamine and norepinephrine, caused greater increases in AP (+70±15 mm Hg) than did dobutamine, while the HR response was variable.

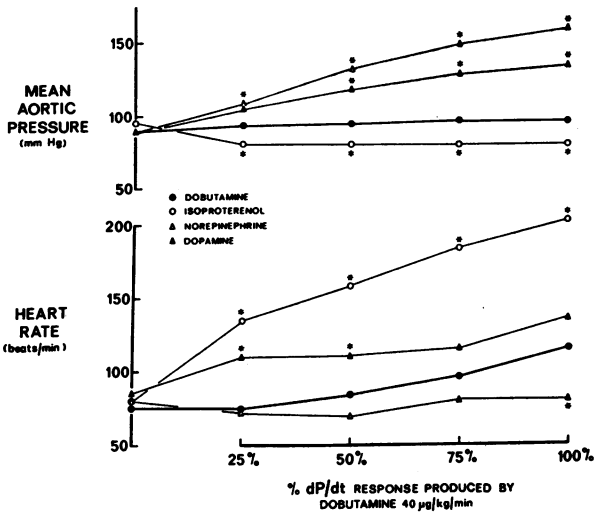

FIGURE 8 Comparison of equi-inotropic doses of dobutamine (closed circles) with isoproterenol (open circles), norepinephrine (open triangles) and dopamine (closed triangles) for mean AP (top) and HR (bottom). The abscissa represents the percent of the peak dP/dt responses produced with 40 μg/kg/min dobutamine. Each of the other drugs was infused in amounts sufficient to equal this inotropic response. Asterisks show changes that are significantly different from those occurring with dobutamine at each percentage level.

* $P < 0.05$ compared with dobutamine.

DISCUSSION

The treatment of shock of all etiologies, and in particular that due to myocardial pump failure, remains a therapeutic challenge. It is clear that isoproterenol can be deleterious in this situation because of its intense stimulation of myocardial metabolism, tachycardia, and hypotensive actions and tendency to produce arrhythmias (4–7, 23, 24). Norepinephrine has been advocated by some investigators (23), while others have suggested dopamine (10, 11). The intense stimulation of alpha adrenergic receptors by norepinephrine is undesirable for critically perfused beds, such as the coronary and renal circulations. Dopamine, on the other hand, also exerts considerable stimulation of alpha adrenergic receptors, though less so than norepinephrine (12, 13) and its tendency to produce arrhythmias limits its usefulness (14, 15).

The ideal inotropic agent would augment myocardial contractility and increase cardiac output without affecting other determinants of myocardial oxygen consumption, such as cardiac rate or rhythm, preload, or afterload, appreciably. In the normal, healthy conscious animal dobutamine appears to possess these attractive features to a large extent. While, under the conditions of these experiments, it increased CO, peak dP/dt, dP/dt/P, and V strikingly, HR and mean AP rose only slightly, and LV end diastolic D and P remained constant. This should not be interpreted to mean that dobutamine is devoid of a positive chronotropic effect, since a 33 beat/min rise in HR occurred at the largest dose studied. It is more likely that dobutamine's tendency to

increase HR and AP was tempered to some extent by reflex vagal cardiac slowing and withdrawal of peripheral symypathetic tone, stimulated by dobutamine's increases in systolic AP. It is clear that this agent elicits less undesirable effects on AP and HR than other cardioactive sympathomimetic amines commonly used clinically. Equi-inotropic dosage of isoproterenol caused mean AP to fall and HR to increase to a far greater extent (Fig. 8); both of these effects can be deleterious in the presence of pump failure due to myocardial ischemia (4, 7, 8). On the other hand, equi-inotropic doses of norepinephrine, epinephrine, and dopamine caused significantly greater pressor responses than dobutamine, suggesting that they produced more powerful alpha adrenergic stimulation. Moreover, dopamine increased HR to a greater extent than did dobutamine and in conscious dogs uniformly resulted in emesis at an inotropic level, which was consistently reached with dobutamine without evidence of adverse somatic or visceral effects. Thus, in comparison with isoproterenol, norepinephrine and dopamine, dobutamine exerts less undesirable effects on AP and HR in the normal dog.

While dobutamine appears to exert its main action on myocardial $beta_1$ adrenergic receptors, resulting in augmented contractility, it also has significant effects on $beta_2$ and alpha adrenergic receptors in the vascular bed. Simulation of these $beta_2$ adrenergic receptors, which was unmasked after the administration of the combination of practolol and phentolamine, was most intense in the coronary and iliac vascular beds, but less evident in the mesenteric and minimal in the renal bed. While, under certain circumstances, coronary $beta_2$ adrenergic receptor-mediated vasodilatation might be beneficial, under others a redistribution of CO favoring the muscle beds at the expense of the kidney and viscera might be deleterious.

Dobutamine possesses alpha adrenergic stimulating properties as well, which to some extent, offset the $beta_2$ adrenergic receptor vasodilating properties of the drug. The alpha adrenergic effects were shown clearly after beta adrenergic receptor blockade with propranolol. After propranolol, dobutamine's inotropic effects were abolished and vasoconstriction was observed in each of the regional beds studied. In that situation the LV as well as the peripheral vascular effects of dobutamine were radically different; stroke volume and CO fell instead of rising, end systolic D rose instead of falling, and end diastolic D rose substantially.

The response of the coronary bed to dobutamine involved a combination of actions, the sum of which was substantial vasodilatation. The difference between the responses before and after practolol represented the amount of coronary dilatation secondary to increased myocardial metabolic demand induced primarily by the powerful positive inotropic action of the drug. After practolol alone, dobutamine did not affect coronary resistance significantly, indicating that the remaining $beta_2$-vasodilating and alpha-vasoconstricting properties counteracted each other, resulting in no change in coronary resistance. This was substantiated by the findings of significant coronary vasoconstriction after propranolol alone and significant coronary vasodilatation after a combination of practolol and phentolamine.

In conclusion, dobutamine, a new cardioactive sympathomimetic amine,[2] shows considerable promise therapeutically. This agent may be useful in the presence of myocardial failure, where undesirable side effects of intense alpha vasoconstriction, hypotension, tachycardia, and other arrhythmias can be deleterious. However, extrapolation to clinical conditions such as myocardial failure or ischemia must be done cautiously, since dobutamine may well act differently in those situations than in healthy, conscious animals with normal hearts. For instance, although arrhythmias were not observed in the present study, the beta adrenergic stimulating properties of dobutamine might elicit arrhythmias in diseased hearts. The one property of this drug which does not appear to be ideal is its tendency to cause a redistribution of CO favoring the muscular beds at the expense of the kidney and visceral beds.

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