

Dobutamine for Inotropic Support during Emergence from Cardiopulmonary Bypass

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Dobutamine, a recently introduced derivative of dopamine, is reported to retain inotropic properties with less pronounced chronotropic and arrhythmogenic effects than isoproterenol. The drug was evaluated in two doses, 5 $\mu\text{g}/\text{kg}/\text{min}$ and 10 $\mu\text{g}/\text{kg}/\text{min}$, in two groups of ten patients each, during emergence from cardiopulmonary bypass. A third group of five patients was studied similarly with isoproterenol, 0.02 $\mu\text{g}/\text{kg}/\text{min}$. Cardiac index increased 16 and 28 per cent with the two doses of dobutamine, respectively, and 9 per cent with isoproterenol. Heart rate, in contrast, increased 6 and 15 per cent with dobutamine (not significant) and 44 per cent with isoproterenol (significant). Dobutamine seemed to be associated with fewer arrhythmias than isoproterenol. It is concluded that dobutamine, 5–10 $\mu\text{g}/\text{kg}/\text{min}$, is suitable for use during emergence from cardiopulmonary bypass and may possess advantages over isoproterenol. (Key words: Heart, dobutamine; Heart, isoproterenol; Surgery, cardiovascular.)

THERE IS CONSIDERABLE variation among different institutions in the use of inotropic drugs for support of the heart during emergence from cardiopulmonary bypass. Whether a patient needs such support appears to depend in part upon preoperative impairment, type of surgery, *i.e.*, hemodynamic improvement obtained by repair, and length of bypass.¹ At the present time isoproterenol and/or epinephrine are most commonly employed for this purpose.

Epinephrine stimulates α and β receptors,

with resultant splanchnic vasoconstriction, impaired renal and hepatic flow, and with diversion of cardiac output to dilated muscle vasculature.² Depending upon the dominant effect, arterial pressure may rise enough to significantly increase impedance to ventricular ejection.² While isoproterenol eliminates the vasoconstrictive objections, it still diverts cardiac output to skeletal musculature. This may be sufficient to lower diastolic pressure and reduce coronary perfusion pressure.^{2,3} Often, during emergence from bypass, the intrinsic rate is somewhat elevated. The chronotropic response to isoproterenol, therefore, becomes another major drawback.^{4,5} In some patients, doses of isoproterenol too small to obtain adequate increases in cardiac output may increase heart rate to unacceptable levels.

The tendency of epinephrine and isoproterenol to induce arrhythmias can be enhanced in the presence of halothane, and probably enflurane.^{3,4} During this unstable period, arrhythmias may further reduce cardiac output, and may be quite refractory to treatment, especially when electrolyte imbalance is present.

Dobutamine (fig. 1) is a derivative of dopamine. Tuttle and Mills² found that removal of the side-chain hydroxyl group from isoproterenol (desoxy-isoproterenol = isopropyl-dopamine) tended to reduce arrhythmogenicity while retaining inotropic properties. Dobutamine is one of several derivatives in this group.

Dobutamine has been extensively evaluated in animals and man and appears to retain inotropic effect while reducing chronotropic and arrhythmogenicity. We therefore evaluated the drug in 20 patients during emergence from cardiopulmonary bypass, and compared it with isoproterenol in five other patients similarly treated.

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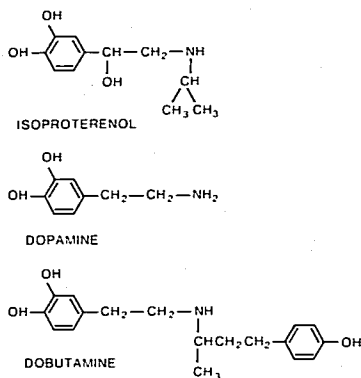


FIG. 1. Dobutamine: relationship to dopamine and isoproterenol.

Methods

Two groups of ten patients each were given dobutamine, 5 $\mu\text{g}/\text{kg}/\text{min}$ (Group I), or 10 $\mu\text{g}/\text{kg}/\text{min}$ (Group II). A third group of five patients was treated with isoproterenol, 0.02 $\mu\text{g}/\text{kg}/\text{min}$ (Group III). Patients ranged in age from 31 to 76 years. Twenty-three of the 25 had valvular disease; the remaining two had coronary-artery disease. The surgical procedures performed are listed in table 1. All patients were in New York Heart Association Class III or IV, and all had elevated left ventricular end diastolic pressures at preoperative catheterization. The protocol was reviewed and approved by the institutional Human Studies Committee. Each patient was visited preoperatively and informed written consent obtained.

Anesthesia was induced with thiopental and maintained with nitrous oxide and meperidine, with pancuronium for neuromuscular blockade. A catheter was placed in the abdominal aorta via the femoral artery for dye-dilution cardiac output determinations and to monitor arterial pressure.

In each case a left atrial pressure catheter was placed by the surgeon prior to cessation of bypass. Blood was then transfused slowly from the pump-oxygenator (venous line clamped) until either a satisfactory arterial pressure was obtained or a rapidly rising left atrial pressure (usually ≥ 30 mm Hg) occurred. If cardiac function improved gradually over the first five to ten minutes off bypass, as indicated by further acceptance of transfusion, or by maintenance of adequate arterial pressure (above 80 mm Hg) without further increase in left atrial pressure, no inotropic agent was given and that patient was not studied.

If arterial pressure above 80 mm Hg systolic could not be maintained with transfusion to mean left atrial pressures of 25 mm Hg during the first five minutes after the termination of bypass, administration of an inotropic agent was considered indicated and the study carried out. Because of the unique nature of the emergence period, only one study could be performed on each patient. Each patient, studied before and after ten minutes of dobutamine or isoproterenol administration, served as his own control. The patients who did not require inotropic support were not considered to constitute a comparable control group and were not studied.

At the start of the ten-minute study period, with the patient breathing 100 per cent oxygen, cardiac output was measured in duplicate by the indicator-dilution technique of Moore

TABLE 1. Patient Distribution and Procedures Performed

	Mitral Valve Replacement	Aortic Valve Replacement	Double Valve Replacement	Coronary-artery Bypass
Group I Dobutamine, 5 $\mu\text{g}/\text{kg}/\text{min}$ (10 patients)	4	3	3	
Group II Dobutamine, 10 $\mu\text{g}/\text{kg}/\text{min}$ (10 patients)	4		4	2
Group III Isoproterenol, 0.02 $\mu\text{g}/\text{kg}/\text{min}$ (5 patients)	4		1	

FIG. 2. Changes in cardiac output with dobutamine (Db) and isoproterenol (Iso). Vertical lines represent standard error of mean.

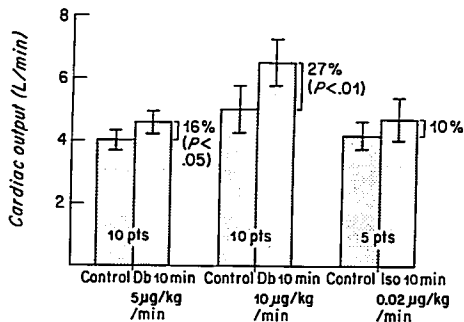
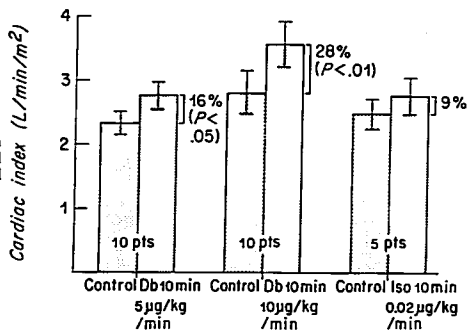


FIG. 3. Changes in cardiac index with dobutamine (Db) and isoproterenol (Iso). Vertical lines represent standard error of mean.



*et al.*⁶ Left atrial, left ventricular, and aortic pressures were also recorded. Dobutamine or isoproterenol was then administered with a calibrated drug-infusion pump via an external jugular cannula used only for drug administration. During the ten-minute test period, left atrial pressure was maintained as constant as possible by transfusion only. No other inotropic agent or other drug was given during the test period. The electrocardiogram was recorded and observed throughout the period for arrhythmias and heart rate. Drug dilutions were: dobutamine, 250 mg/250 ml 5 per cent dextrose in water; isoproterenol, 1 mg/250 ml 5 per cent dextrose in water. After the ten-minute test period, the above-mentioned measurements were again performed. Dobutamine was usually continued at the discretion

of the attending anesthesiologist. Data were analyzed using Student's *t* test for paired data.

Results

Cardiac output increased in nine of ten patients in Group I (given dobutamine, 5 µg/kg/min) and also in nine of the ten patients in Group II (dobutamine, 10 µg/kg/min). At the lower dose of dobutamine, cardiac outputs (see fig. 2) averaged 16 per cent higher than prior to drug administration ($P < .05$). At the higher dose of dobutamine, cardiac outputs increased an average of 27 per cent ($P < .01$). Cardiac indices in the two groups increased the same amount, with the same *P* value (see fig. 3). Both cardiac output and cardiac index are reported as an indication of patient group

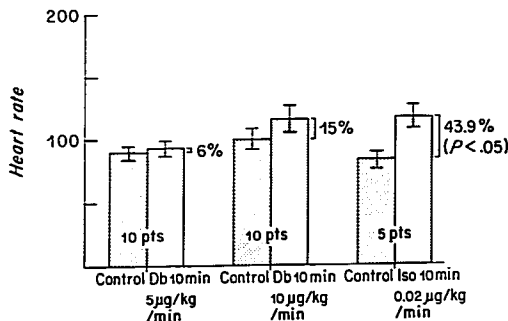


FIG. 4. Changes in heart rate with dobutamine (Db) and isoproterenol (Iso). Vertical lines represent standard error of mean.

uniformity. Group III (five patients) received $0.02 \mu\text{g}/\text{kg}/\text{min}$ isoproterenol, a dose selected to yield approximately a 20–25 per cent increase in cardiac output, as reported by Holloway and Frederickson.⁷ Our observed mean increase with this dose in this small group of patients was 10 per cent.

Mean heart rates increased 6 per cent in Group I and 15 per cent in Group II (fig. 4). Neither increase in heart rate was significant by paired (before vs. after) t test at the 0.05 level. In contrast, the larger 43.9 per cent increase with isoproterenol was significant ($P < 0.05$).

Mean arterial pressures (fig. 5) increased 18 per cent ($P < .01$) and 25 per cent ($P < .01$) in Groups I and II, respectively, during the test period. Systolic and diastolic pressures increased similarly. With isoproterenol, mean arterial pressure increased an average of 12 per cent in the small group. The changes in systemic vascular resistance (decreases of 6 per cent for Group I, 10 per cent for Group 4, and 15 per cent for Group III) were not significant at the .05 level.

One patient in each dobutamine group developed occasional premature ventricular beats during the test period. Each of the five patients given $0.02 \mu\text{g}/\text{kg}/\text{min}$ isoproterenol developed frequent premature ventricular beats and during the test period two of the five patients studied with isoproterenol had several premature ventricular beats in succession.

The administration of dobutamine seemed

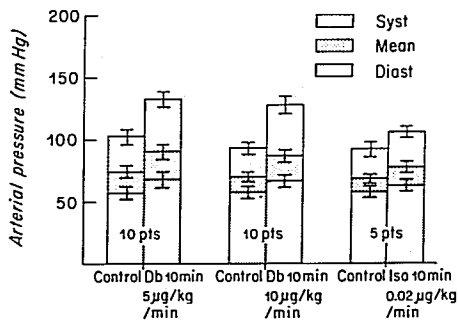
to permit maintenance of reasonable arterial pressure when blood loss transiently lowered left atrial pressure despite efforts to keep this pressure as constant as possible. Heart rates increased rapidly in three of the five patients studied with isoproterenol, in contrast to the gradual increase seen with dobutamine.

Discussion

The period of emergence from cardiopulmonary bypass may be accompanied by considerable hemodynamic instability, and studies performed during this time must be interpreted in the light of changing circulatory status. Periods of ischemia, hypothermia, direct trauma to the heart and electrolyte imbalance are some of the possible explanations for this instability.¹ Less obvious are the complex reflex vascular changes that may be occurring with resumption of pulsatile flow. No clear explanation for these changes is yet available. The sudden fall in arterial pressure upon institution of bypass and later the gradual rise, sometimes to troublesome levels, suggest that vascular reflexes may play a role. It is reasonable to postulate that such reflexes might play a part when pulsatile flow resumes at the termination of bypass, partly accounting for the hemodynamic instability.

Because the period of emergence from bypass is hemodynamically unique, comparison of two inotropic drugs in the same patient during this period is not possible, yet it is during this time that inotropic agents are

FIG. 5. Changes in arterial pressure with dobutamine (Db) and isoproterenol (Iso). Vertical lines represent standard error of mean.



perhaps most often indicated. Thus our comparison of two different agents in different patient groups is justified.

Since dobutamine is a derivative of dopamine, it is appropriate to discuss their relationship. Several studies⁸⁻¹⁰ indicate that dopamine exerts part of its inotropic effect by releasing endogenous norepinephrine. This may not be desirable because of the arrhythmogenicity of the natural catecholamines, and because of the relatively unreliable cardiac stores of norepinephrine in patients with previous failure.^{2,11} Dobutamine is believed by Tuttle and Mills² not to depend upon endogenous catecholamine release for its action, possibly accounting for its lesser arrhythmogenicity.

The cardiovascular effects of dobutamine in man have been examined in several clinical settings. Jewitt *et al.*⁴ studied phonocardiographically 17 patients who had aortic prostheses, coronary-artery disease, or congestive cardiomyopathy, and found that 2-10 µg/kg/min dobutamine produced increases in left ventricular ejection rate comparable to those produced by 0.02-0.08 µg/kg/min isoproterenol. They found considerably greater increases in heart rate with isoproterenol than with dobutamine, in agreement with the present study. Sutton¹² indicates that inotropically 5 µg/kg/min dobutamine would be comparable to 0.02 µg/kg/min isoproterenol, also compatible with our findings. Loeb *et al.*,⁵ comparing a similar dosage of dobutamine (6.1 µg/kg/min) with a smaller (0.012 µg/kg/min)

dosage of isoproterenol in 12 patients also found a lower sinus rate with dobutamine, with otherwise quite similar electrophysiologic effects.

Dobutamine has been found to exert positive inotropic effects with relatively minor chronotropic effects in patients who have coronary-artery disease^{1,13} or congestive heart failure,¹⁴ and after experimental coronary occlusion in animals.¹⁵⁻¹⁷ Holloway and Frederickson⁷ studied the drug in dogs under halothane anesthesia and suggested that it might be less arrhythmogenic with such volatile agents than epinephrine, isoproterenol or dopamine. The same investigators studied the agent in man during open-heart surgery. Studies with dobutamine during emergence from cardiopulmonary bypass, however, have not previously been reported.

We found dobutamine to increase cardiac index in the present groups of patients approximately 15-30 per cent in the 5-10 µg/kg/min dosage range. Dobutamine was associated with considerably less increase in heart rate than observed after isoproterenol, despite a greater increase in cardiac index associated with dobutamine than with isoproterenol. The large increases in cardiac rate observed in the five patients given isoproterenol may account for the relatively limited (9 per cent) increase in cardiac index seen in that group.

We conclude that dobutamine may be utilized for inotropic support during emergence from cardiopulmonary bypass. It is likely that the higher (10 µg/kg/min) dose will

be the more useful in this application. The agent appears to have significantly less chronotropic effect and less arrhythmogenicity than isoproterenol.

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