Efficacy of Dopamine, Dobutamine, and Epinephrine During Emergence from Cardiopulmonary Bypass in Man

Petter A. Steen, M.D., John H. Tinker, M.D., James R. Pluth, M.D., Donald A. Barnhorst, M.D., and Sait Tarhan, M.D.

SUMMARY  Hemodynamic effects of dobutamine and dopamine (both 5, 10, 15 μg/kg/min) and epinephrine (0.04 μg/kg/min) were studied immediately following cessation of cardiopulmonary bypass in 34 patients with preoperative evidence of left ventricular dysfunction. Significant increases in mean cardiac index were seen with dobutamine (15, 25, and 26% respectively), and dopamine (30%). The largest increases occurred with dopamine (44, 53, and 64 percent respectively). Responses varied from patient to patient, however. Seven patients developed marked output increases without concomitant increases in arterial pressure, whereas seven others showed "satisfying" increases in arterial pressure without appreciable output increases. Heart rate increases were small and few arrhythmias were noted. We conclude that dopamine, epinephrine, and dobutamine are effective inotropic agents during the immediate post-bypass period, with variations discussed in detail. None possess the disturbing chronotropic and arrhythmogenic effects of isoproterenol (previously studied). Efficacy of administration of inotropic drugs seems best assessed by serial output measurements during this period.

MANY STUDIES OF THE HEMODYNAMIC EFFECTS of various inotropic agents have been conducted in patients following open cardiac surgery.1-4 Most investigators have examined only one drug in each patient, and have studied patients several hours1-4 to days5 following termination of bypass, often in the intensive care unit. Undeniably, this timing and setting provide more stable and controlled conditions. However, a critical time for many of these patients is that period immediately following cessation of cardiopulmonary bypass, when workload is re-imposed on the myocardium. Adequacy of cardiac performance is usually monitored by observing arterial pressure in conjunction with left atrial pressure. Patients are given transfusions until certain arterial and/or left atrial pressures are reached; the target pressures are set rather arbitrarily. Inotropic agents are widely used during this period, often briefly, to permit “satisfactory” acceptance of this workload. Choice of inotropic drug is largely based on personal preference because there is little available information on what happens during this period. Efficacy of inotropic drug administration is also usually judged by arterial and atrial pressure responses. Cardiac output is seldom monitored immediately following bypass.

We previously reported6 that dobutamine was associated with moderate increases in cardiac index without significant heart rate increases, in sharp contrast to isoproterenol. Isoproterenol (0.02 μg/kg/min) caused a mean heart rate increase of 43.9%, with multiple premature ventricular contractions, and little change in output.

In this study, our objectives were twofold: first, to provide a comparison of the effects of three inotropic agents (dobutamine, dopamine, and epinephrine) during the period immediately following emergence from cardiopulmonary bypass; and second, to make recommendations regarding appropriate methods of monitoring the efficacy of inotropic drug administration in this specific situation.

Methods

Thirty-four patients were studied, usually with two of the three drugs in each patient. Dopamine and dobutamine were usually studied in two infusion rates, epinephrine in one infusion rate. This resulted in 56 patient-inotropic drug exposures, and a total of 81 inotropic drug dosages. Patients were studied who had documented evidence of left ventricular dysfunction preoperatively, based upon review of catheterization data and history/physical exam. Elevated left ventricular end diastolic pressure (> 15 torr), ventricular hypokinesia, and/or ejection fraction < 50% were present. All patients were New York Heart Association functional class III or IV. Twenty-three underwent valve replacement, seven had coronary artery bypass grafting, and four had both. Table 1 summarizes patient data.
The protocol was reviewed and approved by the institutional Human Studies Committee. Patients were visited preoperatively and informed written consent obtained.

Anesthesia was induced with thiopental 2-4 mg/kg and maintained prior to bypass with nitrous oxide 50%, diazepam (0.15-0.4 mg/kg) and incremental doses of meperidine (3-7 mg/kg). Pancuronium 0.15-0.3 mg/kg provided neuromuscular blockade. A catheter was placed in the thoracic aorta from the femoral artery for dye-dilution sampling and measurement of arterial pressure. Left and right atria were cannulated directly by the surgeon before cessation of bypass. The left atrial catheter was used for pressure measurements and dye-injections. Infusions of inotropic agents were given by calibrated drug pump via an external or internal jugular line used for no other purpose.

For emergence from bypass, the venous outflow line to the bypass pump was gradually occluded and the patient received transfusion until systolic arterial pressure reached 80-120 torr, unless left atrial pressure increased to greater than 25 torr. At either point, transfusion was stopped, arterial, left and right atrial pressures were recorded, and control cardiac outputs were measured in duplicate by dilution with Cardio-green. Patients whose systolic arterial pressures rose above 120 torr following the initial transfusion and whose left atrial pressures remained below 25 torr were not given inotropic drugs. Infusion with inotropic agents was begun in all other cases.

Control cardiac outputs were always obtained within four minutes of cessation of bypass and were computed by a Waters Cardiac Output Computer (checked daily by manual extrapolation and calculation from obtained curves). During inotropic drug infusion, cardiac outputs and pressures were measured at 5 and 10 min. After 10 min the first drug dosage was changed to the next higher increment of the same drug unless systolic arterial pressure was greater than 140 torr, in which case the initial dosage was halved. After an additional 5 min at this second dosage, outputs were again measured, and the first drug was then discontinued over a 5 min period. Between the first and second inotropic drug dose the appropriate dose of protamine for heparin reversal was administered. The second inotropic drug was then given in the same fashion after cardiac outputs had returned to ± 10% of the first control value. For dobutamine and dopamine 10 µg/kg/min was the starting infusion rate, going either to 15 or to 5 µg/kg/min. Only one dose of epinephrine, 0.04 µg/kg/min, was studied.

Left atrial (LAP), right atrial (RAP), and aortic pressures were continuously recorded. Left atrial pressure was maintained at control levels during the study period by appropriate additional transfusion if needed. The electrocardiogram was monitored throughout the period for arrhythmias and heart rate.

During the test period, patients were ventilated with oxygen only; no inotropic agents other than the drug studied were given. After the second drug was studied, nitrous oxide was started and the inotropic drug tapered or continued at the discretion of the attending anesthesiologist. Diazepam and meperidine were administered before termination of bypass and provided adequate hypnosis and analgesia. No patient had any recall of the procedure.

Drug dilutions were: dopamine and dobutamine 1 mg/ml and epinephrine 16 µg/ml, all in 5% dextrose in water. The following formulae and units were used for calculated values:

\[
(CI) = \frac{CO}{BSA} \\
SVR = \frac{(MAP - RAP) \cdot 79.98}{CO} \\
SVI = \frac{CI}{HR} \\
LVSWI = \frac{(MAP - LAP) \cdot SVI \cdot 14.4}{1000}
\]

where CI = cardiac index; BSA = body surface area; SVR = systemic vascular resistance in dynes \cdot sec \cdot cm^2; CO = cardiac output; SVI = stroke volume index in L/min \cdot M^2 \cdot beat; MAP = mean arterial pressure; RAP = right atrial pressure; LVSWI = left ventricular stroke work index in gram-meters/m^2 \cdot beat.

Data for each drug given before protamine were compared to that for the same drug given to other patients after protamine by Student's t-test for unpaired values. Data for each drug exposure were compared to the appropriate control value by Student's t-test for paired values.

**Results**

No significant differences in any measured parameters were noted to depend upon whether a drug was given first or second in the sequence, therefore all results for each drug are taken together. For the first drug dose (10 µg/kg/min for dopamine and dobutamine; 0.04 µg/kg/min for epinephrine) data reported were obtained after the 10-min test period. For the second dose of dopamine and dobutamine (5 and 15 µg/kg/min) data reported were obtained after 5 min.

Epinephrine 0.04 µg/kg/min was studied in ten patients; dobutamine 5 µg/kg/min in 11 patients, 10 µg/kg/min in 17 patients, 15 µg/kg/min in ten patients; dopamine 5 µg/kg/min in seven patients, 10 µg/kg/min in 20 patients, and 15 µg/kg/min in six patients.

**Cardiac Index (CI)**

Most but not all patients responded to the inotropic drugs with an increase in cardiac index (table 2, fig. 1). In three instances, during infusion of dobutamine 5 µg/kg/min, three instances during infusion of dopamine 10 µg/kg/min, and in one patient receiving dopamine 10 µg/kg/min, there was no increase or a slight decrease in cardiac index. In each instance of failure to respond to either dobutamine or dopamine, cardiac index did increase in response to the other drug. There were no instances in which epinephrine failed to elicit an increase in cardiac index.

<table>
<thead>
<tr>
<th>TABLE 1. Drug Administered by Type of Surgery</th>
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<tbody>
<tr>
<td>MV replacement</td>
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<td>AV replacement</td>
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<td>Double valve replacement</td>
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<td>TV replacement</td>
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<td>CABG + valve</td>
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**Abbreviations:** MV = mitral valve; AV = aortic valve; TV = tricuspid valve; CABG = coronary artery bypass graft.
Mean CI increased 15%, 25%, and 26% with dobutamine, at 5, 10 and 15 μg/kg/min, respectively. With dopamine the mean increases in cardiac index were 44%, 53%, and 64% at 5, 10 and 15 μg/kg/min, respectively. The mean increase in CI with epinephrine 0.04 μg/kg/min was 30%. All mean values were significantly different from mean control values (P < 0.01 for all except dobutamine 5 μg/kg/min, which was significant at P < 0.05).

Mean Arterial Pressure (MAP)

Average MAP increased 23%, 21%, and 19% with dobutamine, 5, 10, and 15 μg/kg/min, respectively (table 2, fig. 2). With dopamine, the mean increases with the same doses were respectively 33%, 21%, and 30%, and the increase with epinephrine 0.04 μg/kg/min was 27%. All mean values were significantly different from the appropriate control values (P < 0.01 except dobutamine 15 μg/kg/min with P < 0.05).

Pulse Pressure

Mean pulse pressures increased 25%, 39%, and 30% with dobutamine, 5, 10, and 15 μg/kg/min respectively (table 2). With dopamine, the mean increases were respectively 52%, 46%, and 42% and the increase with epinephrine was 75% (P < 0.05 for dobutamine 5 and 15 μg, P < 0.01 for the rest).

Heart Rate (HR)

Mean HR increased 10%, 7% and 7% for dobutamine 5, 10 and 15 μg/kg/min respectively (table 3, fig. 3). For dopamine the mean increases were respectively 9%, 12%, and 13%. With epinephrine 0.04 μg/kg/min, the mean increase in HR was 11%. The increase for dobutamine 5 and 10 and dopamine 10 μg/kg/min had a P value < 0.05, the other heart rate changes were not significant at the P < 0.05 level.

Systemic Vascular Resistance (SVR)

The only significant change in mean SVR seen with any of the three drugs in any dosage was a 15% decrease with dopamine 10 μg/kg/min (P < 0.01).

Stroke Volume Index (SVI)

Mean SVI increased 21% and 19% with dobutamine 10 and 15 μg/kg/min respectively (table 3). With dopamine the increases were 38%, 51% and 49% for 5, 10, and 15 μg/kg/min, respectively (P < 0.01 with dopamine 5 and 10 μg/kg/min, and with dobutamine 10 μg/kg/min; P < 0.05 with dopamine and dobutamine 15 μg/kg/min). Mean SVI was not changed significantly by dobutamine 5 μg/kg/min or epinephrine.

Left Ventricular Stroke Work Index (LVSWI)

LVSWI increased 36%, 58% and 49% for dobutamine 5, 10 and 15 μg/kg/min respectively (table 3, fig. 4). With dopamine the increases were respectively 82%, 74%, and 93%, and the increase for epinephrine was 52% (P < 0.05 for epinephrine, for the other values P < 0.01).
Arrhythmias

One patient developed a brief run of ventricular tachycardia during dopamine 10 μg/kg/min infusion. The dopamine dosage was reduced, lidocaine administered, and the arrhythmias did not recur. One patient had a short run of bigeminy during dobutamine infusion. Occasional PVCs were seen in most patients in all groups, most commonly with surgical manipulation. Qualitative differences between the three agents with regard to arrhythmogenicity were not apparent.

Blood Gas, Acid Base, and Electrolyte Balance

Mean values are listed in table 4. All patients had adequate blood gas, acid-base, and electrolyte values.

Discussion

Emergence from cardiopulmonary bypass is a unique situation with obvious potential for unstable hemodynamics. Results of any study conducted during this period must be interpreted with caution. This is, however, a period during which inotropic drugs are commonly, often uncritically, used. Changes in cardiac output are due to bleeding, changing ventricular function, and peripheral resistance, combined with anesthetics. Because bleeding can be considerable during this period, we chose to transfuse in order to maintain constant left atrial pressure; thus increases in output after inotropic drug infusion reflect increased inotropic state at constant preload. Return of output to ± 10% of control values after discontinuance of inotropic drugs in all cases is evidence that output changes reported were predominantly due to the inotropic agents themselves.

The dosages 5, 10 and 15 μg/kg/min for dopamine9, 7-10 and dobutamine2, 6, 4, 11 were chosen because similar dosages were used in previous reports in other situations, and to compare potencies. In open chest dogs, Tuttle and Mills12 found dobutamine to be four times more potent than dopamine with respect to increasing contractile tension, yet Loeb et al.9 reported that dopamine was twice as potent as dobutamine in increasing cardiac output in patients with chronic low output. The epinephrine dosage of 0.04 μg/kg/min was chosen because pilot studies indicated that it would cause cardiac output increases similar to those caused by 10 μg/kg/min dobutamine.

Cardiac index increases observed in this study with

![Figure 1. Changes in cardiac index with epinephrine (0.04 μg/kg/min), dopamine (10 μg/kg/min), and dobutamine (10 μg/kg/min) after 10 min. Vertical lines represent standard error of mean.](https://example.com/figure1.png)

![Figure 2. Changes in mean arterial pressure with epinephrine (0.04 μg/kg/min), dopamine (10 μg/kg/min), and dobutamine (10 μg/kg/min) after 10 min. Vertical lines represent standard error of mean.](https://example.com/figure2.png)
dobutamine are similar to those we previously reported during emergence from bypass but somewhat lower than those reported by others in other situations. Loeb et al. used dobutamine 10.3 μg/kg/min in 13 patients with chronic low cardiac output, and reported a 34% increase in CI. Jewitt et al. observed CI increases of 23 and 43% with 5 and 10 μg/kg/min dobutamine respectively in ten patients with coronary artery disease. Sakamoto et al. reported 22 and 38% CI increases with 4 and 8 μg/kg/min dobutamine respectively in 22 patients several hours after cardiac surgery. Kersting et al. found 47 and 91% CI increases with dobutamine 5 and 10 μg/kg/min respectively, in cardiac surgical patients. Our lower CI increases of 15 and 23% for 5 and 10 μg/kg/min dobutamine might in part be accounted for by higher control cardiac indices. Also, our measurements are not exactly comparable, being the only ones obtained during emergence from bypass.

With dopamine, our CI increases of 44, 53 and 64% with 5, 10, and 15 μg/kg/min are in approximate agreement with other reports. We conclude that dopamine is about twice as potent in this usage as dobutamine. This is in agreement with Loeb et al. who found equivalent increases in CI for 10.3 μg/kg/min dobutamine vs 5.4 μg/kg/min dopamine.

With epinephrine, Goldberg et al. reported a 78–98% increase in CI with 0.15–0.30 μg/kg/min. Barcroft and Starr found a 40% CI increase with 0.10–0.18 μg/kg/min, again in circumstances other than emergence from bypass. We interpret our results to be in general agreement.

The arterial pressure increases noted with all three drugs are in agreement with most studies although some investigations have not observed significant increases in MAP with dopamine or dobutamine. Despite the larger output increases seen with dopamine, the increase in MAP with this drug was not significantly higher than that for dobutamine or epinephrine. This is interpreted as indicating a greater tendency of dopamine to produce peripheral vasodilation, although a significant (P < 0.01) decrease in calculated systemic vascular resistance was found with the 10 μg/kg/min dose of dopamine only. The

| Table 3. Hemodynamic Changes with Intropic Drug Administration: Heart Rate, Systemic Resistance, Stroke Volume Index, Left Ventricular Stroke Work Index |
|---|---|---|---|---|---|---|---|
| Drug | Dosage (μg/kg/min) | Time (min) | N | Heart rate (beats/min) | Systemic vascular resistance (dyne/sec/cm²) |
| | | | | Control | With drug | % change | Control | With drug | % change |
| Dobutamine | 5 | 5 | 11 | 102 ± 5 | 112 ± 6 | +10%* | 1244 ± 135 | 1390 ± 121 | +11% |
| Dobutamine | 10 | 10 | 17 | 103 ± 3 | 110 ± 4 | +7%* | 1302 ± 78 | 1274 ± 103 | –2% |
| Dobutamine | 15 | 5 | 10 | 106 ± 4 | 113 ± 6 | +7% | 1353 ± 146 | 1232 ± 121 | –9% |
| Dopamine | 5 | 5 | 7 | 91 ± 6 | 99 ± 7 | +9% | 1117 ± 131 | 1054 ± 136 | –6% |
| Dopamine | 10 | 10 | 20 | 97 ± 4 | 109 ± 5 | +12%* | 1159 ± 76 | 982 ± 87 | –15% |
| Dopamine | 15 | 5 | 5 | 100 ± 9 | 113 ± 12 | +13% | 1464 ± 140 | 1214 ± 154 | –17% |
| Epinephrine | 0.04 | 10 | 10 | 103 ± 4 | 115 ± 4 | +11% | 1200 ± 80 | 1228 ± 112 | +2% |

Values are mean ± SEM.

*p < 0.05.

**p < 0.01.

N = number of studies; Time = time after start of administration of drug that indices were measured.

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**FIGURE 3. Changes in heart rate with epinephrine (0.04 μg/kg/min), dopamine (10 μg/kg/min), and dobutamine (10 μg/kg/min) after 10 min. Vertical lines represent standard error of mean.**
vasodilating effects of lower doses of dopamine, especially on the renal and mesenteric vascular beds, are well documented, and are thought to be overridden by a receptor-stimulated vasoconstriction at higher doses. In the present study, only four of 20 patients developed an increase in peripheral vascular resistance at 10 \( \mu g/kg/min \) dopamine, and only one of six did so at the 15 \( \mu g/kg/min \) dosage. The failure to note increased vascular resistance in most patients at higher dopamine doses may be due to recent cardipulmonary bypass, with the possibility that rewarming was not yet complete in all vascular beds, despite the fact that nasopharyngeal temperatures were in the normal range.

Epinephrine did not alter peripheral vascular resistance, possibly because the dose (0.04 \( \mu g/kg/min \)) was sufficient to have obtained roughly equal \( \alpha \) and \( \beta \) effects. Dobutamine has been reported to be more cardioselective than epinephrine or dopamine, and this quality may explain the lack of change in peripheral vascular resistance seen with it.

All three drugs induced significant increases in left ventricular stroke work index, roughly proportionate to the increases in cardiac index. Because the studies were carried out with left atrial pressures held as constant as possible by transfusion, we interpret the increases in cardiac index and left ventricular stroke work index as evidence of increased contractility.

Heart rate increases were approximately 10% for all three drugs. This is in sharp contrast to the 43.9% increase in mean heart rate we reported earlier with 0.02 \( \mu g/kg/min \) isoproterenol, again during emergence from bypass. Further, isoproterenol was associated with severe arrhythmias in that study. The three drugs studied herein were not associated with potentially dangerous arrhythmias, except in one instance with dopamine. The marked chronotropicity and arrhythmogenicity of isoproterenol are reasons why the positive inotropic effects of this drug are often not able to be fully utilized. The arrhythmogenicity of isoproterenol (and epinephrine) are, of course, well known to be enhanced in the presence of halogenated anesthetics, especially halothane. Evidence that isoproterenol may harmfully increase O\(_2\) demand is provided by Maroko et al. who have shown in dogs that acutely produced experimental myocardial infarctions can be extended by treatment with the drug.

Another property of isoproterenol which may set it apart from the three drugs studied herein is the fact that the skeletal muscular vasodilation caused by it may divert the increased output (wastefully) to that tissue. Isoproterenol has been reported to induce enough skeletal muscle vasodilation to actually decrease MAP (and coronary perfusion).

With respect to comparisons between dopamine, dobutamine, and epinephrine, dopamine resulted in the largest increases in cardiac index at the chosen dosages during emergence from bypass. However, it also resulted in systemic vascular dilation. This may not be desirable during this critical period because of the resultant increase in myocardial oxygen requirement. Renal vasodilation is of course a likely part of the dopamine effect, and is of potential longer-term benefit, but the cardioselectivity of dobutamine might be better during the immediate post-bypass period. In addition, there is evidence that dopamine may depend upon release of endogenous catecholamines for part of its action. These catecholamine stores have been reported to be depleted in some patients with longstanding myocardial failure. It is therefore possible that the relatively larger increases in output reported here for dopamine may not be well sustained. We have no evidence on this point.

Epinephrine resulted in the largest increases in pulse pres-
sure. This has negative implications, especially after aortic valve replacement, because of increased bleeding and possible compromise of aortic suture line integrity by inordinately high systolic pressure.

Monitoring arterial and atrial pressures only, as is common practice, proved to be unreliable in assessing efficacy of inotropic drug administration. There were seven instances in which little or no increase in mean arterial pressure was noted during the inotropic drug administration, yet cardiac index increased markedly. There were, by contrast, seven other instances in which the inotropic agent led to “satisfying” arterial pressure increases with little or no increase in cardiac index. We could not single out any of the three drugs as more likely to be associated with such a disparity.

Increasing cardiac output and arterial pressure with inotropic drug alone may not be wise if myocardial oxygen supply/demand ratio is unfavorably affected. Oxygen demand is increased with inotropic agent-induced increases in contractility, heart rate, and aortic pressure. In some patients it seems beneficial to reduce aortic pressure with vasodilators alone. In other circumstances, vasodilators must be combined with inotropic drug to maintain adequate perfusion pressure. No studies including vasodilators during emergence from bypass have yet been reported. We do not imply that inotropic drug administration, even if accompanied by satisfying increases in output and pressure, is necessarily beneficial. Inotropic drugs are probably needed when severe myocardial failure occurs during the emergence period.

We conclude the following: 1) dopamine, 5–15 \( \mu \text{g/kg/min} \); dobutamine, 5–15 \( \mu \text{g/kg/min} \); and epinephrine, 0.04 \( \mu \text{g/kg/min} \), are all suitable for inotropic support during emergence from cardiopulmonary bypass, to produce increases in cardiac index at constant left atrial pressures, small increases in heart rate, and no severe arrhythmias; 2) dopamine appears about twice as potent as dobutamine for this purpose, although dobutamine appears to be more cardioselective; 3) considerable variance in individual patient responses should be expected. It is recommended that cardiac performance during the period immediately following bypass is best assessed by serial measurements of cardiac output. Reliance upon left atrial and arterial pressures alone may be inadequate, especially for evaluation of the results of inotropic drug administration.

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