

The Cardiovascular Effects of the Continuous Infusion of Dobutamine in Patients with Severe Cardiac Failure

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SUMMARY Twenty-five patients with left ventricular failure and low cardiac output received a 72 hour infusion of dobutamine ($10\text{--}15\text{ }\mu\text{g/kg/min}$) in order to determine the cardiovascular properties of this new inotropic agent. Left ventricular contractile performance improved significantly during the infusion as measured by systolic time intervals and echocardiographic parameters. Mean PEP/LVET decreased from 0.76 ± 0.03 to 0.58 ± 0.03 ($P < 0.05$). The percent change in internal dimension of the left ventricle from diastole to systole increased from 9.5 ± 1 to 16.8 ± 1 ($P < 0.05$) and Vcf increased from 0.47 ± 0.05 to 0.80 ± 0.06 circ/sec ($P < 0.05$). Mean cardiac output (nine patients) rose from 1.97 ± 0.15 to $3.33 \pm$

0.50 L/min/m^2 while mean pulmonary capillary wedge pressure fell from 28 ± 3 to 18 ± 2 mm Hg during the infusion period (both $P < 0.05$). These changes in cardiac function occurred without significant changes in heart rate, ventricular irritability, or blood pressure. Urine flow and urine sodium concentration increased during the infusion period.

The improvement of cardiac function without the simultaneous development or exacerbation of undesirable effects (tachycardia, premature ventricular contractions, increased pulmonary or systemic resistance, tachyphylaxis, etc.) makes dobutamine a highly desirable inotropic agent.

DOBUTAMINE is a synthetic catecholamine systematically formulated and synthesized by Tuttle and Mills^{1, 2} in an attempt to develop the ideal inotropic drug. Animal experiments³⁻⁶ demonstrated that this compound did increase ventricular contractility and cardiac output with little to no effect on heart rate and systemic blood pressure. The total systemic resistance generally decreased. Because these favorable pharmacologic properties differed from the properties of the available inotropic agents, dobutamine was tested in man.⁶⁻⁸ The human data, based on brief infusion periods (10–30 min) in patients with and without congestive heart failure, are similar to the information obtained from the animal studies. At doses which significantly increased ventricular contractility and cardiac output, dobutamine did not significantly increase heart rate or systemic blood pressure. Additionally, the brief infusion resulted in some reduction in pre-load as measured by the pulmonary capillary wedge pressure or directly from the left ventricular end-diastolic pressure.

This study was designed to determine the cardiovascular effects and other properties of dobutamine during a long-term continuous infusion in patients with severe left heart failure.

Methods

Patients

Twenty-five patients with severe left ventricular failure were studied. The mean age was 53 years (range 16–72 years) with 18 males and seven females. Twenty-one patients had a form of cardiomyopathy (15 idiopathic, 2 viral, 2 hypertensive, 1 peripartum, 1 amyloid) and four patients had severe left ventricular dysfunction associated with valvular disease (3 aortic insufficiency, 1 had had aortic and mitral pros-

theses inserted for rheumatic valvular disease). Patients with arteriosclerotic heart disease or alcoholic cardiomyopathy were excluded from the study. The diagnoses were confirmed in 22 patients with cardiac catheterization and in one patient at autopsy. Two patients were evaluated with non-invasive data alone. All patients were categorized as functional class IV (NYHA). Mean duration of dyspnea on exertion was five years and of other signs and symptoms of congestive heart failure, four years. All patients had dyspnea at rest with a mean duration of nine months. Eighty-eight percent of the patients had peripheral edema for an average time of two years and 60% had generalized edema for a mean duration of ten months. All patients had gross cardiomegaly on chest X-ray with additional findings of pulmonary venous congestion in 72% and pleural effusion in 16%. All patients were on a digitalis preparation (daily oral digoxin dose of 0.375 mg in two patients, 0.25 mg in 13 patients, 0.125 mg in five patients and digitoxin 0.1 mg in five patients) and a diuretic (furosemide, daily oral dose range of 80 to 480 mg). The digitalis and diuretic were continued throughout the study period. Written informed consent was obtained prior to each study.

Infusion Period and Studies

The infusion period lasted 72 hours. Dobutamine was placed in solution with 5% dextrose in water and delivered intravenously with a calibrated Harvard pump. The initial infusion dose was $2.5\text{ }\mu\text{g/kg/min}$. The rate of administration was increased every 30 minutes to dose levels of 5.0, 10.0, and $15.0\text{ }\mu\text{g/kg/min}$. The maximal dose ($15\text{ }\mu\text{g/kg/min}$ in 20 patients; $10.0\text{ }\mu\text{g/kg/min}$ in five patients) was then continued for the remainder of the 72 hour period.

Determinations of urine flow, urine sodium concentration, BUN and serum creatinine, and measurements of daily weight and indirect blood pressures were obtained over 48 hours prior to the infusion period and continued during the 72 hour infusion. The ECG was monitored continuously over 48 hours pre-infusion and during the entire infusion period. The mean heart rate and frequency of PVCs/min were determined from one minute monitor recordings taken every five minutes during the increasing dose period and one out of

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every 10 minutes during the continuous, pre-, and post infusion periods. An echocardiogram and systolic time intervals were performed 30 minutes before the infusion period, 20 minutes after the beginning of each dose increment, every 12 hours during the maximal dose infusion and 30 minutes after the discontinuation of the infusion.

Echocardiograms were performed with a Unirad series C echoscope and an Electronics for Medicine VR6 recorder. The echocardiographic determinants of LV function were derived from formulas previously described⁹⁻¹¹ and included

$$\% \Delta D = \frac{EDD - ESD}{EDD} \times 100; Vcf = \frac{EDD - ESD}{EDD \times LVET}; \text{ and}$$

$$\text{ejection fraction (E.F.)} = \frac{(EDD)^3 - (ESD)^3}{(EDD)^3} \times 100. * \text{ The LVET of}$$

the Vcf determination was obtained from a simultaneous carotid pulse recording taken at 100 mm/sec. Systolic time intervals (STI) were obtained with the Electronics for Medicine VR6 unit utilizing the specifications previously outlined.¹² The STI were derived from the simultaneous recording of the scalar ECG, carotid pulse and a precordial phonocardiogram. Total systole (QS₂), left ventricular ejection time (LVET) and the pre-ejection period (PEP) were corrected for heart rate and then designated QS₂I, LVETI, and PEPI. The ratio of the PEP/LVET was used as a primary measure of left ventricular performance.

In nine patients a Swan-Ganz flow-directed thermodilution catheter was inserted into the right antecubital vein and placed in the pulmonary artery for the measurement of pulmonary artery pressures, pulmonary capillary wedge pressure (pulmonary arterial occlusive pressure), and cardiac outputs (thermodilution technique¹³). These measurements were made following the same schedule outlined above for the echocardiograms and systolic time intervals. Pulmonary capillary wedge positioning was verified by the development of a pulmonary capillary pressure waveform and a mean pressure lower than the mean pulmonary artery pressure upon inflation of the balloon. The pulmonary artery and pulmonary capillary wedge pressures were measured by Electronics for Medicine M2101 pressure amplifier units. The cardiac outputs were computed with an Instrumentation laboratory computer unit 601 and recorder unit 602. Each cardiac output value represents the mean of at least three measurements.

The noninvasive and hemodynamic data were analyzed with the analysis of variance of repeated measures. The changes in urine flow and sodium concentration, serum BUN and creatinine were analyzed with the paired *t*-test.

Results

Noninvasive Cardiovascular Data

The severe left ventricular dysfunction of the patient population is confirmed by the baseline mean PEP/LVET of 0.76 ± 0.03 (fig. 1A), $\% \Delta D$ of 9.5 ± 1 , Vcf of 0.47 ± 0.05 circ/sec, and an ejection fraction of 0.25 ± 0.02 (fig. 2). The

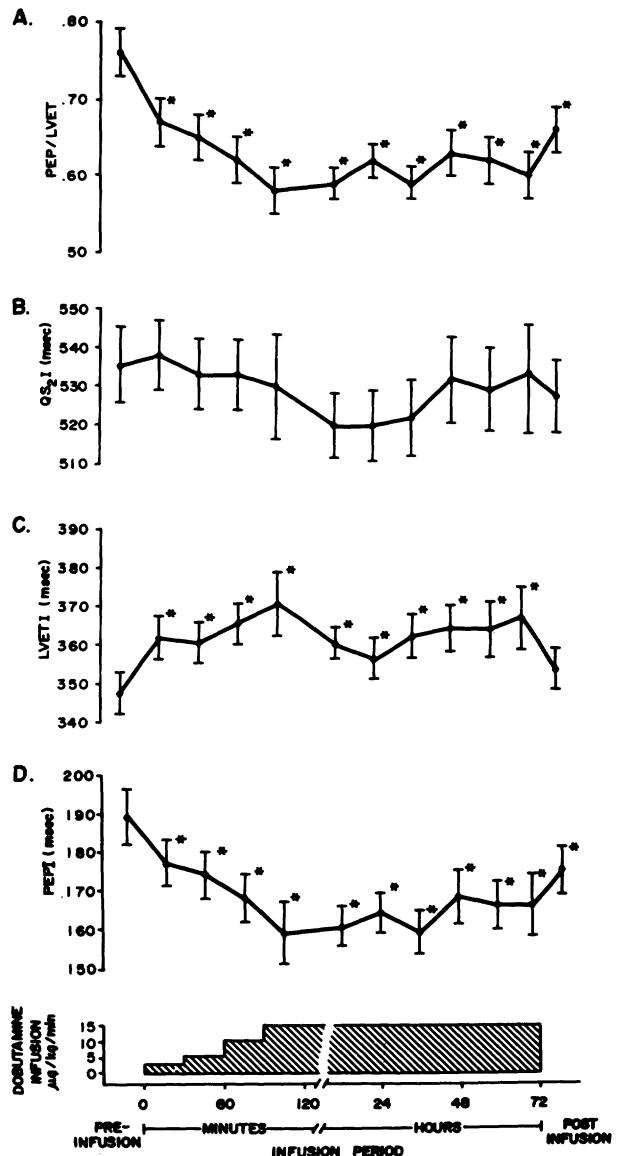


FIGURE 1. A graph of systolic time interval data obtained during the pre-, post-, and infusion periods in 25 patients. The PEP/LVET measurement of left ventricular function is presented in panel A. Panels B, C, and D respectively demonstrate the changes in total electromechanical systole (QS₂I), left ventricular ejection time (LVETI) and the pre-ejection period (PEPI) — all corrected for heart rate. **P* < 0.05.

upper limits of normal for the PEP/LVET in our laboratory is 0.42, while the lower limits of normal for $\% \Delta D$, Vcf, and EF are 24%, 1.10 circ/sec, and 0.59, respectively. The smallest infusion dose of dobutamine ($2.5 \mu\text{g/kg/min}$) significantly improved LV function as measured by these parameters (figs. 1A, 2). Further improvement occurred as the infusion rate increased. During the maximal dose infusion (pooled data of five patients at $10 \mu\text{g/kg/min}$ and 20 patients at $15 \mu\text{g/kg/min}$) the PEP/LVET decreased to values of 0.58 to 0.63 and the $\% \Delta D$, Vcf, and EF increased to values of 16 to 17%, 0.72 to 0.80 circ/sec and 0.35 to 0.42 respectively. The $\% \Delta D$, Vcf, and EF remained significantly above control values and similarly the PEP/LVET remained significantly below the control value during the entire infu-

* $\% \Delta D$ = percent change of the internal dimensions of the left ventricle from diastole to systole; Vcf = velocity of circumferential fiber shortening; EDD = left ventricular end diastolic dimension; ESD = left ventricular end systolic dimension; LVET = left ventricular ejection time.

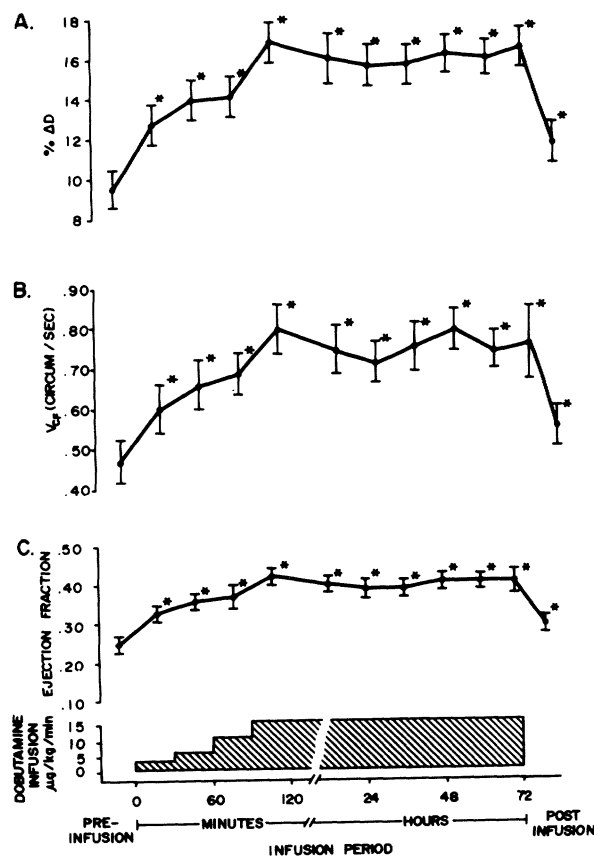


FIGURE 2. The echocardiographic evaluation of left ventricular function during the pre-, and post-, and infusion periods in 25 patients is shown and include A) the percent change in internal dimension of the left ventricle from diastole to systole (% ΔD); B) Vcf; and C) ejection fraction. * $P < 0.05$.

sion period. Thirty minutes after the discontinuation of dobutamine all values returned toward control, however, the % ΔD , Vcf, and EF remained significantly above and the PEP/LVET significantly below the pre-infusion values.

The reduction in the PEP/LVET during the infusion was secondary to both shortening of the PEP (fig. 1C) and lengthening of the LVET (fig. 1D). These reciprocal and hemodynamically complementary effects resulted in little to no change of the QS₂I during the infusion (fig. 1B).

Figure 3A illustrates the heart rate changes during the study. A significant increase in heart rate was noted only during the initial segment of the 15 $\mu\text{g/kg/min}$ dose and thereafter decreased to values similar to baseline. At no time during the infusion did the mean frequency of premature ventricular contractions significantly increase above baseline (fig. 3B). However, in one patient, the infusion was discontinued at 48 hours because of an increase in the frequency of his PVCs. The systolic and diastolic blood pressures did not change significantly during the infusion compared to baseline values (fig. 3C).

Hemodynamic Data

Figure 4 illustrates the hemodynamic data in nine patients. Values at 90–120 min and 60 and 72 hours are deleted because of insufficient data points. The control cardiac index

of 1.97 ± 0.15 L/min/m² increased significantly with increasing doses of dobutamine to the range of 2.8 to 3.4 L/min/m² during the 10–15 $\mu\text{g/kg/min}$ infusion dose (fig. 4A). The post infusion cardiac index decreased but remained above baseline ($P < 0.05$). The heart range changes were insignificant in this group, so the calculated stroke volume index increased during the infusion (fig. 4B). The pulmonary capillary wedge pressure decreased significantly during the entire infusion period (fig. 4C). There was no significant difference between the pulmonary capillary wedge pressures at the various infusion rates. The total systemic resistance decreased significantly during the infusion by virtue of an increasing cardiac output and an unaltered systemic blood pressure (fig. 4D). Similarly, the total pulmonary resistance decreased significantly during the infusion. Although the pulmonary arteriolar resistance decreased, the changes were not significant.

Additional Data

The mean percent changes in serum BUN and creatinine per day are illustrated in figure 5A, B. During the pre-infusion period the serum BUN and creatinine rose an average of 3.9%/day and 0.84%/day respectively. During the 72 hour infusion period the serum BUN dropped 9.1%/day and the creatinine fell 2.2%/day (both $P < 0.05$). Both the urine flow and urine sodium concentrations increased significantly during the infusion period compared to pre-infusion

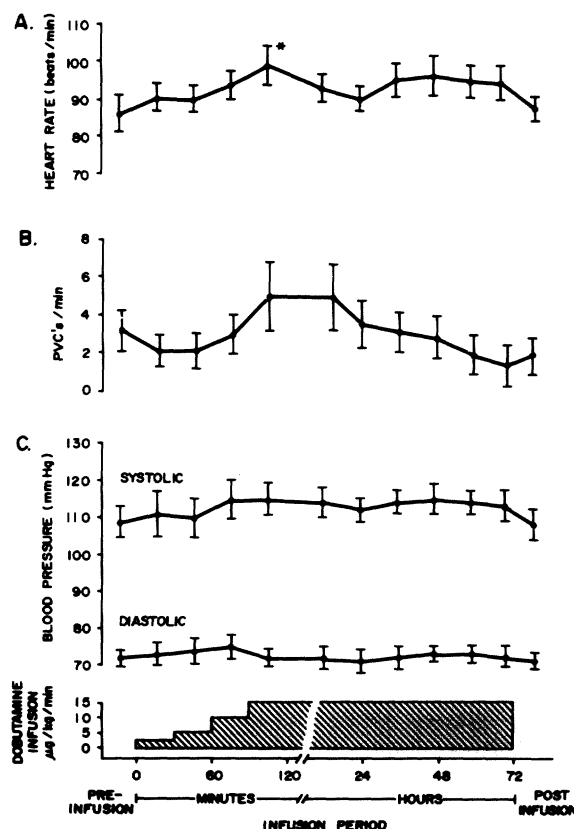


FIGURE 3. A graph depicting the effect of dobutamine in 25 patients on heart rate (A), premature ventricular contractions (B), and blood pressure (C) compared to the pre- and postinfusion values. * $P < 0.05$.

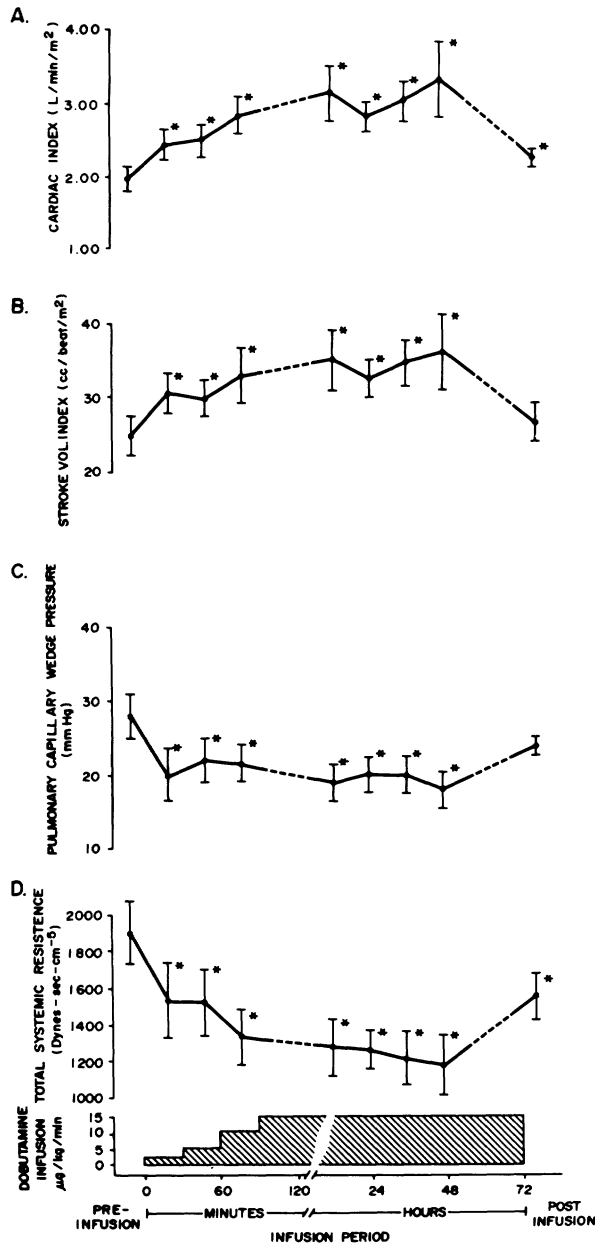


FIGURE 4. The hemodynamic data obtained in nine patients during the pre-, post-, and infusion periods is shown. * $P < 0.05$.

values (fig. 5 C,D). Although the daily weight loss went from a reduction of 0.9 ± 4 kg/day to a reduction of 2.6 ± 0.9 kg/day, this change did not achieve the significance of $P < 0.05$.

Clinical Information

Twenty of the 25 patients noted subjective improvement of symptoms (reduction of dyspnea, orthopnea, fatigue, etc.) during the infusion. The improvement of symptoms persisted to one week post-infusion in 17 patients. One patient developed nausea and vomiting during the 15 µg/kg/min dose with disappearance of these symptoms as the dose was decreased to 10 µg/kg/min. Two patients became nervous and restless during the first 30 min of the 15 µg/kg/min dose with abatement of these symptoms as the infusion con-

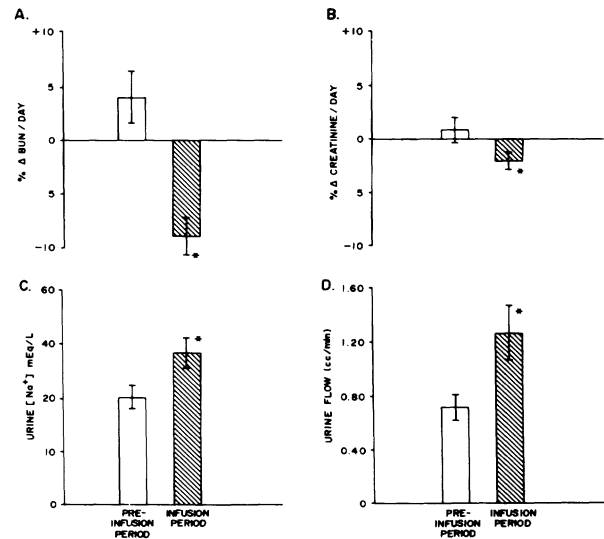


FIGURE 5. The changes in serum creatinine and BUN during the pre-infusion and infusion periods are illustrated in panels A and B respectively. The effects of dobutamine on urine sodium concentration and urine flow are presented in panels C and D respectively. * $P < 0.05$.

tinued. Inadvertent overadministration occurred in two patients. One patient received a two hour infusion of 30 µg/kg/min, which elicited mild nervousness and a mild increase in heart rate from 96 to 106 beats/min. The other patient received a five minute infusion of 80 µg/kg/min which increased the patient's heart rate from 88 to 132 beats/min and elicited fatigue, marked nervousness and a headache. No significant blood pressure changes or ventricular irritability occurred in either of these instances and the symptoms and tachycardia abated within 20 minutes after the dose was returned to protocol levels. A patient with aortic stenosis and severe LV dysfunction was excluded from the study after he experienced chest pain during the initial phase of the study (10 µg/kg/min). Dobutamine infiltrated into the subcutaneous tissue in four patients in amounts of 30–60 mg. One patient noted an aching pain over the infiltration site; however, none of the patients developed local signs of ischemia. None of the 25 patients developed signs of peripheral vasoconstriction; in fact, peripheral perfusion (clinical assessment) appeared to improve in most patients during the infusion. No other side effects or problems were noted with the dobutamine administration.

Discussion

The hemodynamic improvements demonstrated during the infusion rates of 2.5, 5.0, 10.0 µg/kg/min of this study are similar to the dose related curves of previous studies.⁶⁻⁸ This study added another 5 µg/kg/min dose increment and demonstrated further improvement of all hemodynamic parameters at the 15 µg/kg/min infusion rate. At this dose, however, the mean heart rate increased significantly above the control rate. The heart rate elevation appeared to be a transient event and in most instances decreased as the infusion continued. It is conceivable that the blunted chronotropic response in our patient population may have been related to concomitant digitalis administration; however,

both animal and human studies^{3, 4, 7, 8} have demonstrated a similar lack of chronotropic effect without digitalis administration. The improved cardiac performance with little change in cardiac work (heart rate, afterload, etc.) or irritability should theoretically make dobutamine an ideal inotropic agent in the setting of coronary artery disease. This study was performed in patients with severe LV dysfunction without coronary artery disease, so the data are primarily applicable to this patient population.

Unlike previous studies of dobutamine, this investigation provides data on the continuous infusion of this drug. Improvement of renal function parameters was demonstrated. These changes were probably secondary to improved cardiac output and renal perfusion during the infusion period. This study does not present data to suggest or refute the possibility of dobutamine acting directly on renal receptor sites in man. Tachyphylaxis was not demonstrated over the 72 hour infusion. The drug was well-tolerated and elicited few side effects. The side effects were rather mild and generally abated as the infusion continued or as the dosage was decreased. Relative to other available inotropic agents, dobutamine appears to have a wide margin of safety, as evidenced by the paucity of toxic manifestations in a population of patients with severe heart disease. In addition, the two patients who received 2 to 5 times the therapeutic dose developed symptoms and blood pressure and heart rate changes which were probably less dramatic than those which would have occurred with a similar overadministration of other catecholamine preparations, particularly isoproterenol and norepinephrine. The occurrence of nervousness and the onset of a mild tachycardia with the overadministration of dobutamine are relatively safe signals which would direct the physician to reduce the rate of administration of this drug.

The exact role of inotropic agents in the overall therapeutic schema of low cardiac output failure is less well defined than it was several years ago. The advent of vasodilator therapy has placed the inotropic group into a secondary role in many clinical settings. In clinical situations in which temporary inotropic support is necessary (e.g., post-operative states, vasodilator ineffectiveness, etc.) dobutamine appears to be the inotropic agent of choice. In this study, 17 of 25 patients (all functional class IV) maintained clinical improvement (5 functional class II, 12 functional class III) for at least one week after the infusion period was completed. The explanation for this sustained improvement is unclear, but it is of interest that at 30 minutes after the infusion was discontinued, the measurements of LV function were still significantly above control values. The left ventricular end diastolic volumes by echo did not change during the

infusion. The amount of bed rest in hours/day during the infusion period did not differ from the pre-infusion period. Whatever the underlying mechanism for the continued improvement, dobutamine infusion may potentially become a therapeutic modality in the overall treatment plan of the low cardiac output states. Studies of the effect of intermittent continuous infusions of dobutamine in patients with low cardiac output states and studies comparing vasodilator therapy with intermittent dobutamine infusion merit consideration as possible next steps in the clinical investigation of this drug.

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