Dobutamine Increases Cardiac Output of the Total Artificial Heart

Implications for Vascular Contribution of Inotropic Agents to Augmented Ventricular Function

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Background. The synthetic catecholamine dobutamine increases stroke volume in normal subjects and in patients with congestive heart failure. In addition to its direct influence on myocardial contractility, dobutamine may significantly modulate vascular tone because of its \( \alpha \)-and \( \beta \)-adrenergic agonist activity.

Methods and Results. To test the hypothesis that such vasoactive properties significantly contribute to the improved ventricular performance noted with this agent, hemodynamic parameters were measured during stepped ascension infusion of dobutamine in a model that is insensitive to positive inotropic stimulation. Administration of dobutamine in nine calves that underwent replacement of the native right and left ventricles with pneumatically driven total artificial hearts resulted in a significant \( (p=0.0001) \) increase in cardiac output from 7.0\( \pm \)1.8 to 8.2\( \pm \)1.8 l/min and a significant \( (p=0.0001) \) decrease in total peripheral vascular resistance from 1,224\( \pm \)559 to 745\( \pm \)317 dyne-sec/cm\( ^2 \). A less marked influence was noted on the pulmonary vasculature, with pulmonary vascular resistance exhibiting a significant \( (p<0.05) \) decrease from its baseline value only at the peak infusion. Consistent with an increase in venous return, both left and right atrial pressures increased significantly \( (p<0.005) \) with dobutamine administration.

Conclusions. These data demonstrate that the vasoactive properties of dobutamine significantly contribute to improved ventricular performance independent of direct myocardial stimulation. This effect appears to result in part from a direct modulation of arterial and venous tones rather than from a reflex response to primary changes in contractility. (Circulation 1991;84:1210–1215)

Dobutamine is a synthetic catecholamine that is known to increase cardiac output in normal subjects and in patients with congestive heart failure.\(^1\)\(^-\)\(^3\) Although this effect is attributed in large part to direct stimulation of the myocardium and consequent increases in ventricular contractility, dobutamine may influence the arterial and venous vasculature because of \( \alpha \)-and \( \beta \)-adrenergic agonist activity.\(^3\)\(^-\)\(^10\) Dobutamine exists as a racemic mixture of two stereoisomers in which the \( \alpha \)-adrenergic activity is found to reside in the levo isomer and \( \beta \)-adrenergic activity is expressed by the dextro isomer.\(^10\) Varying degrees of peripheral vasodilation have been reported that have been ascribed to either direct or reflex effects on the vasculature, but the mechanism of this vascular response remains incompletely described.\(^6\)\(^-\)\(^9\) The present investigation used a model that is insensitive to the positive inotropic influence of dobutamine to test the hypothesis that the vasoactive properties of this agent significantly contribute to improved ventricular performance. The results indicate that dobutamine is associated with a significant reduction of systemic vascular resistance coincident with a significant increase in cardiac output that appears to be independent of its effects on myocardial contractility and may be ascribed to its direct effects on the vasculature.

Methods

All investigations and procedures were reviewed and approved by the animal use committee of the...
Ohio State University. The model consisted of nine calves that underwent replacement of the native right and left ventricles with pneumatically driven total artificial right and left ventricles (Jarvik 7, Symbion, Inc., Salt Lake City, or Utah 100, University of Utah, Salt Lake City). The procedure for implantation of the artificial ventricles has been previously described. Briefly, general anesthesia was maintained with halothane after pentobarbital induction and endotracheal intubation. A right lateral thoracotomy was performed, and the animal was placed on cardiopulmonary bypass. The native right and left ventricles were excised along the atroventricular valve rings and above the semilunar valves. Atrial quick-connect cuffs were sewn into the right and left atria, and vascular grafts were anastomosed to the pulmonary artery and aorta. The artificial right and left ventricles were then positioned and secured using the respective atrial quick-connect cuffs and vascular grafts. The right and left ventricles were connected via drive line tubing to the respective pneumatic chambers of the heart driver. Control parameters for each ventricle consisted of heart rate, drive pressure, and percent time in systole. With activation of the artificial ventricles, the animal was weaned from total cardiopulmonary bypass. Device parameters were adjusted to maintain physiological pressures and ensure adequate cardiac output. The wound was closed with running sutures, and drainage tubes were inserted in the pleural space. The animal was transported to a specially constructed cage that optimized animal mobility while ensuring the integrity of the drive line connection to the heart driver. All animals were extubated and pleural drainage tubes were removed within 24 to 48 hours. A 4-day recovery period preceded the study protocol.

All drug infusions were performed with the animal in the sternal recumbent posture. Aortic, pulmonary arterial, and left and right atrial pressures and cardiac outputs were monitored for a total of 20 minutes to ensure hemodynamic equilibrium, which was defined as less than 10% variation in any of these parameters. Device parameters were adjusted so that the artificial ventricles were not completely filling at baseline. Specifically, heart rate for the nine animals ranged from 100 to 120 beats/min (mean ± SD, 109 ± 7 beats/min), and percent time in systole ranged from 44% to 50% (mean ± SD, 47 ± 3%). Right ventricular drive pressures ranged from 75 to 120 mm Hg (mean ± SD, 103 ± 17 mm Hg), and left ventricular drive pressures ranged from 235 to 285 mm Hg (mean ± SD, 262 ± 16 mm Hg). These initial device parameters were maintained constant throughout the subsequent dobutamine infusions. Cardiac outputs were measured using the cardiac output monitoring and diagnostic unit (COMDU, Symbion) of the heart driver. This device integrates diastolic exhaust air flow and applies a volume conversion factor to calculate stroke volume on a beat-by-beat basis. Validation of this technique has been performed by comparison with simultaneously measured cardiac outputs using turbine flowmeters.

After establishing hemodynamic equilibrium, dobutamine was administered for three consecutive 10-minute infusions at rates of 6, 12, and 24 μg/kg/min using a percutaneously inserted external jugular line. Minute averages of cardiac output were printed continuously by the COMDU, and atrial, pulmonary arterial, and aortic pressures were recorded at the peak of each infusion. After measurements were acquired at peak dosing, the infusion was discontinued, and the animal was allowed to return to baseline hemodynamic status.

**Derived Hemodynamic Parameters and Statistical Analysis**

Cardiac output was averaged during the last 5 minutes of the baseline period and of each infusion period and was used for assessment of dobutamine effects on stroke volume. Total peripheral vascular resistance (dyne·sec/cm²) was calculated as mean systemic pressure (mm Hg) multiplied by 80 and then divided by cardiac output (l/min). Similarly, total pulmonary vascular resistance was calculated according to the same formula using mean pulmonary artery pressure and cardiac output. Analysis of variance for repeated measures was used to test for significant changes in hemodynamic parameters associated with dobutamine administration. Posttest comparisons were performed to identify specific points that differed significantly from baseline. Statistical significance was defined as a probability of less than 0.05.

**Results**

**Systemic Vascular Response**

Cardiac output was noted to increase in each of the nine calves beginning with the first infusion rate. For the group as a whole, the mean cardiac output of 7.0±1.8 l/min significantly (p = 0.0001) increased over the range of dosages tested, attaining a peak value of 8.2±1.8 l/min at the 24-μg/kg/min infusion rate (Figure 1A). Posttest comparison of values indicated that all infusion rates were associated with cardiac outputs significantly greater than baseline. Coincident with the increase in cardiac output, total peripheral vascular resistance significantly (p = 0.0001) decreased from the baseline value of 1,224±559 dyne·sec/cm² with each of the three infusion rates, with the lowest value of 745±317 dyne·sec/cm² noted at the 24-μg/kg/min infusion rate (Figure 1B). This response was accompanied by a significant (p = 0.001) decrease in mean aortic pressure from 98±32 to 70±14 mm Hg at the peak infusion rate (Figure 1C).

**Pulmonary Vascular Response**

In contrast to the effect noted in the systemic vasculature, less marked decreases in pulmonary vascular resistance were observed (Figure 2). The baseline value of 367±313 dyne·sec/cm² significantly (p < 0.05) decreased to a value of 280±261 dyne·sec/cm² at the peak infusion rates.
Right and left atrial pressures increased with dobutamine infusion (Figure 3). A progressive and significant (p = 0.0004) increase in left atrial pressure was noted with the baseline value of 13±5 mm Hg increasing to 18±7 mm Hg with peak infusion and with left atrial pressure significantly greater than baseline with each infusion rate. Similarly, right atrial pressure exhibited a moderate but statistically significant (p = 0.004) increase from 9±4 to 13±3 mm Hg.

To test the specific role of the α- and β-agonist properties of dobutamine in mediating the observed circulatory response, selective pharmacological stimulation of the vasculature was performed in a subset of the experimental animals. The influence of α-adren-
nergic stimulation was established in one cow using a 1-mg i.v. bolus of phenylephrine, which resulted in an increase in cardiac output from 9.6 to 11.1 l/min despite increases in mean systemic pressure from 1.13 to 149 mm Hg and in total peripheral resistance from 9.42 to 1.074 dyne-sec/cm². Having characterized the influence of α-agonist stimulation on circulatory function in this model, the α-adrenergic properties of dobutamine were isolated by β-blockade using 20 mg propranolol administered intravenously in the same cow before infusion of dobutamine. Dobutamine infusion after this pretreatment with propranolol resulted in an increase in cardiac output from 8.7 to 10.1 l/min with an increase in mean blood pressure from 112 to 131 mm Hg. The specific influence of the α-adrenergic properties of dobutamine were further examined in two different cows by infusion of the levo isomer of dobutamine (Eli Lilly and Co., Indianapolis, Ind.) in which reside the α-agonist properties of racemic dobutamine. In these two cows, infusion of the levo stereoisomer of dobutamine resulted in increases in cardiac output from 7.9±1.0 to 10.0±1.1 l/min, in mean systemic pressure from 77±4 to 148±3 mm Hg, in total peripheral resistance from 788±138 to 1,186±122 dyne-sec/cm², in left atrial pressure from 14±7 to 28±1 mm Hg, and in right atrial pressure from 7±7 to 11±8 mm Hg.

The influence of β-adrenergic stimulation in this model was characterized in two cows in which isoproterenol was infused. Isoproterenol infusion resulted in an increase in cardiac output from 7.0±0.1 to 8.3±0.2 l/min, a decrease in systemic vascular resistance from 1,132±6 to 609±23 dyne-sec/cm², and an increase in right and left atrial pressures of 50%. The influence of the β-adrenergic stimulating properties of dobutamine was then tested in two different cows by infusion of the dextro isomer of dobutamine, which imparts the β-agonist properties of racemic dobutamine. Infusion of the dextro isomer resulted in an increase in cardiac output from 6.7±0.8 to 8.3±1.1 l/min, a decrease in systemic vascular resistance from 845±262 to 611±96 dyne-sec/cm², and an increase in atrial pressures equal to those seen with isoproterenol.

Discussion

The present investigation demonstrates that in addition to its positive inotropic properties, the vascular effects of dobutamine significantly contribute to the enhanced cardiac output that results from its administration. Dobutamine infusion resulted in significant increases in cardiac output despite the absence of any change in the drive parameters of the artificial heart, indicating that the changes in cardiac output must be solely ascribed to the influence of dobutamine on the vasculature. This vasoactive augmentation of cardiac output appears to consist of a reduction in ventricular afterload and potentially an increase in venous return mediated by a reduction of venous capacitance.

The model used in the present investigation is uniquely suited to the analysis of mechanisms of vascular control. Because the total artificial heart is devoid of any sensitivity to positive inotropic stimulus, the model may be viewed as one in which the vascular response to a given perturbation may be isolated from any coincident influence on myocardial contractility. Observed vascular responses must therefore be ascribed to the direct influence of an intervention on the vasculature rather than to reflex mechanisms arising from primary changes in myocardial contractility. Although the innate “contractility” of the artificial heart is fixed once the initial functional parameters of the device have been set, the performance of the artificial ventricle is sensitive to preload and afterload, and its function may be modified by alterations in loading conditions. This has been demonstrated in animal models at rest, during exercise, and in response to various pharmacological interventions. Thus, given the properties of this model, the vascular determinants of ventricular and overall circulatory performance may be segregated and analyzed. Finally, this is an otherwise physiological model in that the animals are not anesthetized and are alert and active in a manner resembling the preoperative state.

That dobutamine may directly or indirectly modulate systemic vascular resistance has been noted in prior investigations in human subjects and animal models. However, none of these has completely eliminated the direct positive inotropic effects of dobutamine on the myocardium and the possible attendant secondary vascular responses. Varying reductions in systemic vascular resistance have been described and attributed to either direct β-adrenergic stimulation of peripheral resistance vessels or to reflex mechanisms. Using a canine model, Li and Hood reported that lower-dose infusions of dobutamine resulted in reductions in peripheral vascular resistance that could be prevented by ganglionic blockade. However, at higher doses, reductions in vascular resistance could be prevented by β-adrenergic but not ganglionic blockade. It was concluded that lower-dose infusions of dobutamine indirectly mediated vasodilation because of baroreceptor activation resulting from enhanced ventricular contractility and consequent increase in pulse pressure.

In the present investigation, significant reductions in total peripheral vascular resistance were observed at low as well as high infusion rates. In this model, which is insensitive to positive inotropic stimulation, augmented contractility and subsequent increases in pulse pressure would not be primary events initiating reflex vasodilation. It would appear that in this context, even low-dose infusion of dobutamine would bring about vasodilation via direct β-adrenergic stimulation of peripheral resistance vessels.

In addition to its influence on the systemic arterial vasculature, dobutamine may also modulate venous capacitance and, consequently, venous return. Both α- and β-adrenergic stimulations have been shown to reduce venous capacitance in a variety of models. Because dobutamine possesses α- and β-adrenergic
agonist activities, it may augment venous return by stimulation of both of these receptor systems. Consistent with this hypothesis, Fuchs et al.\textsuperscript{23} demonstrated a decrease in venous capacitance accompanying dobutamine infusion as measured by splanchnic volume and found that this decrease could be prevented by \(\alpha\)-blockade. Thus, both afterload reduction (via \(\beta\)-agonist effects) and augmentation of venous return (resulting from \(\alpha\)– and \(\beta\)-agonist activities) may contribute to the increase in cardiac output mediated by dobutamine’s influence on the vasculature.

The subset of cows in which the responses to specific \(\alpha\)– and \(\beta\)-adrenergic stimulations were examined further substantiates these mechanisms. \(\alpha\)-Adrenergic stimulation with phenylephrine resulted in an increase in cardiac output similar in magnitude to that observed with dobutamine infusion. This occurred despite marked increases in systemic arterial pressure and systemic vascular resistance. Because the pneumatically driven artificial heart operates at a driving pressure greater than even the peak systemic pressure achieved with phenylephrine, it will continue to eject the volume of blood returned by the venous circulation despite such elevations in afterload. As such, the artificial ventricle resembles the normally functioning human heart in its capacity to maintain stroke volume despite elevations in afterload.\textsuperscript{24} Therefore, although the artificial ventricle has a demonstrated sensitivity to afterload,\textsuperscript{16–19} in the setting of augmented venous return, a net increase in stroke volume may result despite an increase in afterload, especially if the magnitude of increased venous return is relatively greater than the increase in afterload. Thus, the only mechanism by which \(\alpha\)-adrenergic stimulation could increase cardiac output in this model is through augmentation of venous return. Similarly, this would account for the observed response to dobutamine infusion after \(\beta\)-blockade with propranolol, in which the \(\alpha\)-adrenergic activity of dobutamine would be unmasked, and with infusion of the levo isomer of dobutamine, which possesses only \(\alpha\)-agonist activity. As with phenylephrine, an increase in cardiac output was observed with infusion of these agents despite substantial increases in systemic pressure. The increase in atrial pressures with the levo isomer infusion further supports this mechanism.

That the \(\beta\)-agonist properties of dobutamine contribute to the increase in cardiac output in this model is demonstrated by the responses to the dextro isomer of dobutamine, which possesses only \(\beta\)-adrenergic stimulating properties, and to the infusion of isoproterenol. Infusion of the dextro isomer in two of the cows resulted in an increase in cardiac output accompanied by a reduction of systemic vascular resistance. Both right and left atrial pressures increased with infusion of this isomer. Similarly, isoproterenol infusion resulted in an increase in cardiac output at all infusion rates and was accompanied by a decrease in systemic vascular resistance and an increase in atrial pressures. Whether the increase in cardiac output associated with these agents derives from the influence of \(\beta\)-adrenergic stim-

ulation on afterload, from \(\beta\)-adrenergic–mediated reduction of venous capacitance and augmented venous return, or from a combination of these mechanisms cannot be completely resolved based on the current data. However, an increase in atrial pressure similar to that seen after the levo isomer suggests that a primary influence on venous return is an important component of this response.

The influence of dobutamine on the pulmonary vasculature appears to be less marked than that noted for the systemic vasculature. Although a decrease in pulmonary vascular resistance was noted, this occurred only at the maximal infusion rate. This contrasts with the marked sensitivity of the systemic vasculature in which significant decreases in resistance were noted at even the lowest infusion rate. These differences may arise because of variations in pulmonary and systemic vascular \(\alpha\)–adrenergic receptor populations and affinities for dobutamine. Significant decreases in pulmonary vascular resistance accompanying dobutamine administration have been reported in humans with congestive heart failure.\textsuperscript{2,3,7} The present data suggest that such a decline in pulmonary vascular resistance may result from indirect influences such as reductions in ventricular filling pressures or reflex responses to increased cardiac output rather than from a direct effect on the pulmonary vasculature.

Unlike previous investigations in humans with congestive heart failure, dobutamine administration in this model is associated with significant increases in right and left atrial pressures.\textsuperscript{2,3,7} This is consistent with the increase in forward flow and venous return observed in this setting. Unlike the native ventricle, which can shift both to new pressure–volume relations and to different points within a given relation in response to positive inotropic influence, the artificial ventricle will operate along a relatively fixed pressure–volume curve; this will tend to increase filling pressures in the setting of augmented venous return.

These changes in atrial pressures and volumes may themselves contribute to the increase in cardiac output through potentiation of atrial contractility by an effect similar to the Starling mechanism of ventricular muscle contraction. Alternatively, dobutamine may directly influence contractility of the atria and in this manner augment ventricular filling. However, the importance of atrial systole is uncertain in this model in which atrioventricular synchrony is not preserved and, consequently, atrial filling occurs at random intervals relative to ventricular filling.

The observed increase in cardiac output in this model was noted to occur with the first infusion rate and increase less markedly with subsequent infusions (Figure 1). This phenomenon is most likely a result of the fact that the maximal filling volume of the artificial ventricle was approached with the increase in cardiac output resulting from the first infusion, leaving little margin for further increase with subsequent infusions. It is conceivable that if a greater margin for increased filling were allowed, the cardiac output would continue to increase with further infu-
sions rather than achieving the observed plateau. However, operating the artificial ventricle at filling volumes below those used in the present study would result in inappropriately low cardiac outputs that would not be tolerated by the animal.

The relevance of these observations to the clinically observed hemodynamic response to dobutamine infusion in patients with congestive heart failure provides a focus for future investigation. Although direct comparisons of the afterload sensitivity of the normal or failing ventricle with that of the artificial heart have not been made, extrapolation from prior studies in humans suggests that the artificial heart resembles the normal ventricle in terms of its sensitivity to afterload. In a report by Ross and Braunwald, decreases in stroke volume were not seen in ventricles with normal contractility until levels of afterload approaching the drive pressure of the artificial ventricle were achieved. The failing ventricle is known to have a much greater sensitivity to afterload; thus, it may be speculated that in the setting of ventricular failure, the vasoactive properties of dobutamine may have an even more profound effect on circulatory performance because of their modulation of loading conditions. This principle must be further tested in humans with congestive heart failure and in animal models of circulatory failure such as those that may be adapted from the present model.

Conclusions

The present data indicate that the vasoactive properties of dobutamine contribute significantly to the improved ventricular performance and augmentation of cardiac output associated with its administration. The model used in the present study effectively eliminates the inotropic influence of this agent and thus allows an analysis of the direct vascular effects of dobutamine distinct from its influence on myocardial contractility and attendant reflex vascular changes. Further elucidation of the mechanisms of vascular response to dobutamine and related positive inotropic agents may be provided through this model by comparing and contrasting the hemodynamic response to agents that vary in their adrenergic receptor affinity and activity.

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References


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