TITLE: VASCULAR RESPONSES TO DOPAMINE AND DOBUTAMINE IN CALVES IMPLANTED WITH A TOTAL ARTIFICIAL HEART

AUTHORS: A.S. Greiner, M.D., T.M. Skeehan, M.D., D.R. Larach, M.D.,PhD., H.G. Schuler, B.A., W.S. Pierce, M.D.

AFFILIATION: Departments of Anesthesia and Surgery, The Pennsylvania State University College of Medicine, P.O. Box 850, Hershey, Pennsylvania 17033

INTRODUCTION: Calves implanted with the Penn State total artificial heart (TAH) provide a unique opportunity to study purely vascular effects of drugs as isolated from their cardiac effects in an awake in vivo model. The control system of the artificial heart allows operation in either of two conditions: 1) **constant flow** (CF), in which the cardiac output is fixed and aortic blood pressure (BP) can vary as systemic vascular resistance (SVR) changes, and 2) **constant pressure** (CP), in which the cardiac output (CO) is varied to maintain a constant BP in the face of changing SVR[1]. In this study we infused clinically relevant doses of dopamine or dobutamine while maintaining either CP or CF conditions. Our aim was to extend prior pharmacological studies of dopamine and dobutamine in TAH animals, and to compare the resultant hemodynamic effects under the two types of controller modes.

METHOD: 22 studies of dopamine HCl and 12 of dobutamine HCl in four female Holstein or Holstein/Angus calves (85 to 142 kg) were performed 1 to 4 months post-op after implantation of the pneumatic TAH. The TAH is designed to deliver a fixed stroke volume when operating under documented full-to-empty conditions. CO is altered by varying the left heart rate. During CF studies CO was maintained constant by holding the left heart rate fixed and allowing the arterial BP to vary. During CP studies the arterial BP was maintained constant by changing the CO (through servo-control of the left heart rate). Arterial BP in this mode was maintained within ± 5mm Hg of baseline pressure. Arterial BP was measured either by a catheter in the carotid artery or by calculating mean arterial pressure from the calibrated left heart air pressure wave. Central venous pressure was measured from the external jugular vein. After baseline hemodynamic measurements, either dopamine or dobutamine was administered by iv infusion at increasing doses every 15 minutes. Statistical analysis included unpaired t test with α=0.05 and Bonferroni's correction. No more than one study per calf was performed in any twenty four hour period. Data are presented as mean ± sem.

RESULTS: (Refer to Figure and Table) As increasing doses of dopamine were administered at CF, BP and SVR initially showed a small decrease, followed by an increase in SVR and BP (maximum increase in BP of 53% at highest doses). During CP, similar SVR results were obtained, with a dose dependent reduction in CO (maximum reduction of 36%) needed in order to maintain the aortic BP. At no dose was the difference between CF and CP SVR responses significant (>.05).

Dobutamine caused a dose dependent decrease in BP and SVR under both CF and CP conditions at all drug concentrations, with no statistically significant difference between the two controller conditions. During CP measurements, as the dobutamine dose increased it was necessary to raise the CO as much as 27% to maintain the CP conditions. During CF studies the BP was lowered a maximum of 11%.

DISCUSSION: Previous studies of dopamine and dobutamine in TAH calves have not maintained constant infusions to allow steady state measurements[2], or did not adjust the output of the TAH to maintain the CF or CP conditions[3] that are possible with this TAH.

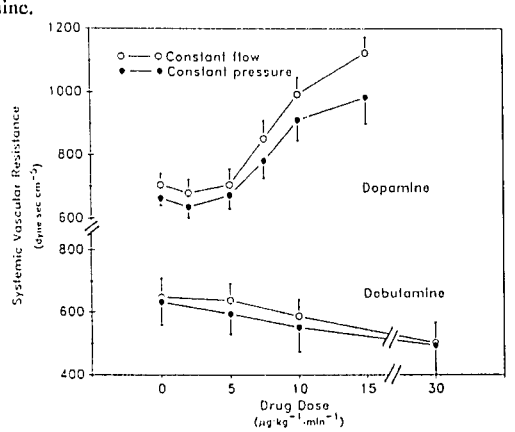
Dopamine has both direct and indirect effects on the vasculature in humans, having dopaminergic, beta adrenergic, and alpha adrenergic effects depending on the dosage infused. Our study was consistent with these observations in showing a slight decrease in SVR followed by an increased SVR at increasing doses. Dobutamine acts directly on vascular beta receptors in the vasculature to decrease SVR as we observed.

It was interesting to note the lack of statistical difference between CF and CP for both dopamine and dobutamine. We anticipated that CP SVR values might be higher than CF for 2 reasons. Indirect baroreceptor stimulation by dopamine-induced hypertension could be expected to cause vasodilator reflexes to be activated, attenuating the SVR changes in the CF trials. Directly, when BP increases, the passive transmural pressure gradient across the vessel wall increases, tending to distend the vessel and decrease SVR. In CP studies with dopamine, this transmural pressure should have been constant resulting in a higher SVR when compared to constant flow. We did not observe higher SVR with dopamine during CP indicating that either these effects do not play a significant role in the calf or they are overshadowed by other factors.

In the constant pressure trials at the highest dopamine doses the CO was decreased to such as extent that shock-like conditions were present. This could cause differences in drug metabolism between CP and CF states secondary to alterations in regional blood flow. The SVR was statistically equivalent in both instances despite large variations in CO. It is conceiveable that decreased regional blood flow with higher dose dopamine at CP inhibited drug elimination. Conversely, the increase in blood flow under CP dobutamine could enhance elimination. These pharmacokinetic hypotheses are being investigated.

The calf with the TAH is an important model for study of vascular effects of drugs and anesthetics because the vasculature is isolated functionally in vivo: CNS and hormonal control remain intact but the link between the heart and the blood vessels is not present.

Figure. Systemic vascular resistance vs increasing doses of dopamine or dobutamine.



DOSE (μg·kg⁻¹·min⁻¹)	CONSTANT FLOW MAP	CONSTANT FLOW CO	CONSTANT PRESSURE MAP	CONSTANT PRESSURE CO
DOPAMINE				
0	98±4	9.1±.2	94±3	9.3±.2
15	150±5	9.1±.2	94±2	6.1±.3
DOBUTAMINE				
0	96±5	9.7±.2	98±5	9.6±.4
30	85±6	9.7±.2	97±6	12.2±.4

REFERENCES: 1. Landis DL, Rosenberg G, Donachy JH, Pierce WS: Automatic control for the artificial heart. Proc Ann Conf Eng Med Biol 22:305-310,1980

2. Stanley TH, English JB, Lunn JK, Olsen D, Kolff W: Use of the bovine with an artificial heart as an experimental pharmacologic model. Artif Organs 2:310-313,1978

3. Horcher E, Deutsch M, Losert U, Stohr H, Wolner E: Peripheral Circulatory Effects of Nitroglycerin, and Beta 1 agonist and Beta 1 antagonist Drugs in Calves after Artificial Heart Implantation. Heart Transplantation, 1:318-324,1982