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Hemodynamic Effects of Epinephrine, Dopamine, Nitroglycerin, and Nitroprusside
in a Patient with a Total Artificial Heart (TAH)

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Many drugs with vascular effects also have a direct cardiac effect. The cardiac responses to these drugs are naturally absent in patients with a total artificial heart (TAH).

Vascular effects of cardiovascular drugs have been described in animals subjected to TAH implantation, but to our knowledge investigations in patients have not been reported. The purpose of this study was to evaluate the circulatory effects of epinephrine, dopamine, nitroglycerin, and nitroprusside in a hemodynamically stable patient after a TAH implantation.

CASE REPORT
A 55-yr-old man with a 5-yr history of angina symptoms and four previous myocardial infarctions was admitted for coronary artery bypass surgery. Preoperative angiography demonstrated obstruction of four large coronary artery branches and depressed left ventricular function. Four bypass grafts were implanted. Two months later the patient had an additional acute myocardial infarction complicated by cardiogenic shock, including hypotension and oliguria. Catheterization revealed a cardiac index of 1.3 l.min⁻¹.m⁻² and an arteriovenous oxygen difference (AVO₂ difference) of 90 ml.l⁻¹. Repeated angiography showed occlusion of three grafts and poor left ventricular function with an ejection fraction of less than 10%. As the patient deteriorated rapidly, a Jarvik-7/70 ml cardiac prosthesis was implanted. The surgical technique and TAH design has been reported elsewhere. The postoperative course was uncomplicated and the trachea was extubated on the second postoperative day. On the tenth postoperative day the patient underwent a biological orthotopic heart transplantation with an uncomplicated postoperative course.

METHODS
On the seventh postoperative day after the TAH implantation, having been hemodynamically stable for several days and without vasoactive drug therapy, the patient's response to cardiovascular drugs was evaluated. The study was approved by the Ethical Committee of the Karolinska Hospital and the patient's informed consent was obtained. The drugs were administered intravenously as a continuous infusion through a catheter positioned in the left internal jugular vein. The dosage for each drug was epinephrine (Adrenalin®, ACO): 25, 50, and 75 ng.kg⁻¹.min⁻¹; dopamine (Intropin®, American Critical Care): 2.5, 5, and 7.5 µg.kg⁻¹.min⁻¹; nitroglycerin (5 mg/ml clinical solution from the pharmacy of the Karolinska Hospital): 0.5, 1, and 2 µg.kg⁻¹.min⁻¹; nitroprusside (Nipride®, Roche): 0.5, 1, and 2 µg.kg⁻¹.min⁻¹. The infusion was increased in a stepwise fashion for 15 min periods, at each infusion rate. Each drug was tested with at least a 1-h interval between different drugs. The hemodynamic condition of the patient prior to each drug tested served as a control. The TAH driver (Utah drive® System II) was adjusted to the following drive settings: pump rate, 100 beats per min; systolic duration, 50%; left drive and right drive pressures, 170 mmHg and 35 mmHg, respectively. The following pressures, central venous pressure (CVP), mean pulmonary artery pressure (MPAP), left atrial pressure (LAP), and mean arterial pressure (MAP), were obtained by positioning catheters in the right internal jugular vein, pulmonary artery, left

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Received from the Departments of Thoracic Surgery and Clinical Physiology, Karolinska Hospital, Stockholm, Sweden. Accepted for publication December 4, 1989.

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Key words: Heart: artificial. Sympathetic nervous system, catecholamines: dopamine; epinephrine. Pharmacology, hemodynamics: nitroglycerin; nitroprusside.
atrium, and left radial artery, respectively. Pressures were measured with Hewlett Packard (HP® 1290A) liquid transducers and recorded on a Siemens® Elema Mingograf 81 recorder. Cardiac output (CO) was obtained by the Utah drive unit, previously calibrated by the Fick method. Systemic vascular resistance (SVR) was calculated from the formula:

\[ SVR = \frac{MAP - CVP}{CO} \text{ (units)} \]

The pulmonary vascular resistance (PVR) was calculated from the formula:

\[ PVR = \frac{MPAP - LAP}{CO} \text{ (units)} \]

The sinus node frequency (P wave) from the residual atria was recorded using a modified four-lead electrocardiogram and recorded with increased amplification on a Siemens® Elema Mingolog 7 recorder. Mixed venous and arterial blood samples were taken for determination of AVO₂ difference. The oxygen content was determined spectrophotometrically with a CO oximeter (182 Instrument Technical Laboratory). The PaO₂ in the radial artery was determined on a blood gas analyzer (ABL 2 Acid-Base Laboratory, Radiometer, Copenhagen).

RESULTS

Epinephrine (figure 1). The MAP decreased 25% at a dosage of 50 ng·kg⁻¹·min⁻¹ and then increased 11% at an infusion rate of 75 ng·kg⁻¹·min⁻¹. No changes were seen in MPAP, CVP, LAP, or PVR. An increase in CO of 9% was observed at a dose exceeding 50 ng·kg⁻¹·min⁻¹. The SVR followed the same pattern as MAP with a maximal reduction of 33% at an infusion rate of 50 ng·kg⁻¹·min⁻¹. Sinus node frequency increased 17% at the highest infusion rate. The AVO₂ difference showed a marked reduction of 23% at an infusion rate of 25 ng·kg⁻¹·min⁻¹ and then remained unchanged at higher dosages.

Dopamine (figure 2). At a dose of 2.5 µg·kg⁻¹·min⁻¹, MAP decreased 23%, a slight additional reduction was observed at higher dosages. MPAP, CVP, LAP, and PVR remained approximately constant. CO increased 10%. SVR followed a similar pattern as MAP with a pronounced

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**FIG. 1.** Hemodynamic effects following continuous infusion of epinephrine at infusion rates of 0, 25, 50, and 75 ng·kg⁻¹·min⁻¹, respectively.

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**FIG. 2.** Hemodynamic effects following continuous infusion of dopamine at infusion rates of 0, 2.5, 5, and 7.5 µg·kg⁻¹·min⁻¹, respectively.

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**FIG. 3.** Hemodynamic effects following continuous infusion of nitroglycerin at infusion rates of 0, 0.5, 1, and 2 µg·kg⁻¹·min⁻¹, respectively.
maximal reduction of 31%. The sinus node frequency increased 13% at the highest dose compared with the control value. The AVO₂ difference was not affected.

_Nitroglycerin_ (figure 3). MAP increased at an infusion rate of 0.5 μg·kg⁻¹·min⁻¹, it subsequently decreased, however, at an infusion rate of 2 μg·kg⁻¹·min⁻¹. The MPAP, CVP, LAC, PVR followed a similar pattern. The AVO₂ difference and sinus node frequency remained approximately unchanged. CO increased 10% at a dosage of 1 μg·kg⁻¹·min⁻¹ and returned to the control value at a dosage of 2 μg·kg⁻¹·min⁻¹. SVR increased 10% at an infusion rate of 0.5 μg·kg⁻¹·min⁻¹, followed by a slight decrease at higher dosages. The PAO₂ was approximately unchanged.

_Nitroprusside_ (figure 4). The MAP and the MAP decreased consistently with maximal reduction of 24% and 41%, respectively. A slight decrease in CVP and LAC was observed at an infusion rate of 2 μg·kg⁻¹·min⁻¹. The sinus node frequency remained unaffected. The SVR and PVR decreased 20% and 47%, respectively. CO remained approximately unchanged. The AVO₂ difference increased gradually to a maximum of 25%. PAO₂ decreased 35% at an infusion rate of 0.5–1.0 μg·kg⁻¹·min⁻¹ and then a slight increase of 11% was observed at a dosage of 2 μg·kg⁻¹·min⁻¹.

**DISCUSSION**

Evaluation of drugs with cardiovascular effects in a patient with an implanted TAH is a unique situation. The hemodynamic effects are predominantly vascular since all direct influence of the cardiac mechanism is lost with the replacement of the natural heart. In this study, epinephrine, dopamine, nitroglycerin, and nitroprusside were chosen to evaluate the vascular effects in a hemodynamically stable patient following TAH implantation.

Epinephrine has proved to be a very useful drug in patients with acute heart failure. When administered in low doses the effects are primarily those of β1 and β2 receptor stimulation of the heart and vascular bed, respectively. On increasing the dosages to a moderate level, the α-adrenergic stimulation effects becomes more evident and at high dosages the α stimulation dominates, leading to vasoconstriction. Because the effects of β1 receptor stimulation are absent in a patient with a TAH implanta, the dose-response relationship in the peripheral vascular bed can be demonstrated. At an infusion rate of 25–50 ng·kg⁻¹·min⁻¹, the β2 stimulating effect was dominant, leading to a substantial decrease in the systemic vascular resistance; however, at a dosage of 75 ng·kg⁻¹·min⁻¹ the α-stimulating effect was evident and led to a subsequent increase in SVR. Dose-response relationships were in accord with those from previous investigations. The decrease in AVO₂ difference has also been previously demonstrated but was interpreted as an effect of an increased CO. Our results showed a reduction of the AVO₂ difference comitant with only a slight increase in CO, suggesting increased arteriovenous shunting.

Dopamine is a naturally occurring neurotransmitter with both pre- and postsynaptic effects on specific receptors, mediating both the release, and some of the effects of norepinephrine. The vasodilator effect has mainly been demonstrated in the renal mesenteric and peripheral arteries at low dosages, α-adrenergic stimulation becomes evident at dosages above approximately 5 μg·kg⁻¹·min⁻¹. In our patient peripheral vasodilation was present at an infusion rate of 2.5–7.5 μg·kg⁻¹·min⁻¹. At the higher dosage the reduction of SVR was less, which is interpreted as an increasing influence of α-adrenergic stimulation. The dose-response relationship corresponded well with that from previous clinical observations in patients retaining their hearts, and as well as in studies of larger groups of animals with TAH using equivalent doses.

Nitroprusside causes both arterial and venous dilatation, whereas nitroglycerin is predominantly a venodilator. The dose-related effects of nitroprusside, which resulted in a substantial reduction of SVR and PVR in the TAH patient, were consistent with the findings of several other investigators. Nitroprusside caused a dose-related increase in the AVO₂ difference and a concurrent...

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decrease in the PAO₂, indicating increased pulmonary shunting.

Infusion of nitroglycerin resulted in no dramatic alterations in SVR, PVR, and CVP, which is in contrast to most investigations,¹⁶,¹⁸ which report a decrease in these parameters in the equivalent dose range. However, our results are supported by other studies,¹⁷,¹⁹ showing limited or no effect of nitroglycerin infusion in the SVR or PVR at equivalent doses. By the ventricular resection, cardiac receptors mediating venodilatation are lost, resulting in an increased venous tone;²⁰ this may explain the lack of effect at the relatively low doses of nitroglycerin used. The increase of MAP at the low dose is somewhat unclear and is considered to be isolated.

The effect of the different drugs on the remnant sinus node was demonstrated by recording the P wave. Epinephrine and dopamine caused an increase in frequency, whereas nitroglycerin did not affect the frequency, nor did nitroprusside despite the lowering of SVR. The slight changes in cardiac output were due to alterations in afterload and filling pressures.

In conclusion, our results suggest that a patient with an excised natural heart replaced by a TAH maintains the regulation of the pulmonary and the peripheral vascular bed after 1 week with regard to the influence of naturally occurring substances such as epinephrine and dopamine. The study also demonstrates that one of the main pharmacotherapeutic actions of epinephrine and dopamine, in the dose range of 25–75 ng·kg⁻¹·min⁻¹ and 2.5–7.5 µg·kg⁻¹·min⁻¹, respectively, is afterload reduction. The vascular effects of nitroprusside were in accord with previous clinical and experimental findings in subjects retaining their natural heart, while the effects of nitroglycerin were not in agreement with most previous investigations. It must be emphasized, that all of the above observations are based on only one patient and further studies in a series of patients are required to determine whether the findings are typical or unusual.

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