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Peripheral Vascular Effects of Thiopental and Propofol in Humans with Artificial Hearts

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The peripheral vascular effects of thiopental 5 mg/kg and propofol 2.5 mg/kg were compared in five patients whose lungs were being ventilated and in whom a Jarvik-7 artificial heart had been implanted. The patients were monitored, using catheters that had been surgically inserted into the radial artery, the right and left atria, and the pulmonary artery. The Jarvik-7 settings were modified to render the artificial heart "preload independent" and to maintain cardiac output constant. Each patient received both drugs, with the interval between each drug ranging from 16 to 28 h. Hemodynamic parameters and catecholamine and atrial natriuretic peptide plasma concentrations were measured before drug administration and 5, 10, 15, 30, and 45 min later. Both drugs significantly decreased arterial pressure, systemic vascular resistance index, pulmonary arterial pressure (PAP), and right and left atrial pressures (RAP and LAP, respectively). However, propofol 2.5 mg/kg induced a significantly greater and more prolonged decrease in arterial pressure, systemic vascular resistance index, and RAP than that after administration of thiopental 5 mg/kg ($P < 0.05$). Five minutes after drug injection, mean arterial pressure decreased by 21% after thiopental and by 39% after propofol ($P < 0.01$); systemic vascular resistance index decreased by 21% after thiopental and by 44% after propofol ($P < 0.05$); RAP decreased by 20% after thiopental and by 50% after propofol ($P < 0.05$); mean PAP decreased by 18% after thiopental and by 32% after propofol ($P < 0.09$); and LAP decreased by 40% after thiopental and by 46% after propofol ($P < 0.2$). With both drugs, atrial natriuretic peptide, norepinephrine, and epinephrine plasma concentrations remained stable throughout the study period. Because cardiac output was maintained constant throughout the study, these results suggest that propofol 2.5 mg/kg is a more potent vasodilator of venous and arterial beds than is thiopental 5 mg/kg. (Key words: Anesthetics, intravenous: propofol; thiopental. Heart: artificial.)

PROPOFOL ADMINISTRATION is associated with a significant decrease in arterial pressure.[1] Conflicting data exist in the literature concerning the mechanisms involved in this hypotensive effect: decreased,‡‡ unchanged,[2,3] or even increased total vascular resistance (TVR)[4] have been reported after propofol administration. Cardiac effects are also controversial. Although a decrease in cardiac index (CI) was found in most studies,[2,3,5,6] no agreement has been reached concerning the effects of propofol on the heart itself; some studies have suggested a negative inotropic effect,[7] others a good preservation of left ventricular function.[3,8] The presence of an artificial heart, implanted as a bridge between prelethal heart failure and cardiac transplantation, enables the measurement of drug effects on veins, systemic arteries, and pulmonary vessels, independent of the effects on the heart muscle.[9] In this study, we compared the hemodynamic effects of thiopental and propofol in five critically ill patients with a Jarvik-7 artificial heart (Symbion, Inc.) in whom a brief period of anesthesia was required in the early postoperative period.

Materials and Methods

PATIENTS

Five patients admitted between September 1987 and November 1988 to the Cardiac Intensive Care Unit of la Pitié Hospital, Paris, after implantation of a total artificial heart (Jarvik-7) were studied. Informed consent was obtained directly from patients 1, 3, and 5 and from next of kin in patients 2 and 4. The protocol was approved by the Ethical Comittee of la Pitié Hospital. All patients were studied during the first postoperative days, and their lungs were mechanically ventilated because of a high incidence of preoperative pulmonary edema. Persisting postoperative pulmonary edema was present in patients 1–4. All patients were conscious except patient 2, who was comatose, and hemodialysis was required in patients 2 and 4 because of acute renal failure.

The five patients had a Jarvik-7 implanted in the 3 days preceding the study because of the rapid onset of terminal heart failure. In three patients, acute cardiac failure followed a massive myocardial infarction. In one patient, in

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whom orthotopic cardiac transplantation had been performed, heart failure developed rapidly, secondary to graft rejection resistant to immunosuppressive therapy. The fifth patient had a severe form of cardiomyopathy, leading to massive deterioration of cardiac function in 2 weeks. All patients were in a low-cardiac-output state associated with pulmonary edema, despite the administration of massive doses of inotropic agents. Because no heart was available for cardiac transplantation, a mechanical prosthesis was used to replace the failing heart and bridge the gap between prelethal heart failure and cardiac transplantation. The five patients studied had not received any sedative drugs during the previous 12 h and were hemodynamically stable without vasoactive drugs. In the immediate postoperative period, surgical wounds were cleaned daily, and dressings were changed during a brief period of general anesthesia, for the patient's comfort and safety. Routinely, a combination of midazolam and fentanyl is used for these procedures. For this study, propofol and thiopental were alternatively used at random over a 2-day period in each patient. The clinical characteristics of each patient are summarized in table 1.

Jarvik-7 Total Artificial Heart

A 100-ml Jarvik-7 was inserted in three patients and a 70-ml Jarvik-7 in two patients. The functions of the artificial heart were monitored continuously by the cardiac diagnostic unit of the Utah heart drive console, which calculates right and left cardiac output by multiplying right and left end-diastolic volumes—obtained from the diastolic area of the exhaust airflow curve of each ventricle—by heart rate (fixed). End-diastolic volume was measured by a flow transducer attached to the exhaust port of each drive system. The precision and bias of the flowmeters of the artificial heart were measured an *in vitro* study using a 100-ml Jarvik-7 connected to a mock circulation filled with saline. Right and left cardiac outputs were measured with two calibrated electromagnetic flowmeters. Jarvik-7 settings and conditions within the mock circulation were changed to modify right and left cardiac outputs. Simultaneous measurements then were made with the use of electromagnetic flowmeters (reference method) and flowmeters of the artificial heart. Eighty-one simultaneous measurements were performed in a range of 3.5–10.4 l/min. Bias and precision of the Utah heart drive console for measuring cardiac output were 115 and 468 ml, 2 and 7% of the reference value, respectively.

Normally, heart rate, drive pressures of the ventricles, and percentage of systole and vacuum are adjusted to ensure that there is complete ejection of blood from each ventricular chamber and that the the artificial heart is preload-dependent. Right cardiac output depends on right atrial pressure (RAP), and, consequently, any drug increasing venous capacitance and reducing RAP tends to decrease cardiac output.

With a technique described previously,[10] Jarvik settings were modified to render the artificial heart preload-independent. Briefly, each ventricular chamber was filled entirely, before the end of the period allotted to diastolic filling, by decreasing heart rate and systolic duration, so that any decrease in RAP or left atrial pressure (LAP) was not associated with a reduction in cardiac output (as long as the ventricular chambers were still filled completely at the end of diastole). Consequently, right cardiac output is equal to left cardiac output, and both remain constant with time. During thiopental studies, the following Jarvik settings were used (mean ± SD): heart rate 71 ± 7 beats per min, left drive pressure 183 ± 17 mmHg, right drive pressure 54 ± 7 mmHg, systolic duration 41 ± 2%, vacuum = 0. During propofol studies, the following Jarvik settings were used (mean ± SD): heart rate 76 ± 6 beats per min, left drive pressure 188 ± 16 mmHg, right drive pressure 56 ± 7 mmHg, systolic duration 43 ± 4%, vacuum = 0. Because these Jarvik-7 settings were not those recommended by the manufacturer and because the existence of the anastomotic bronchial blood flow could have resulted in a progressive increase in central blood volume as long as right cardiac output was equal to left cardiac output,[11] we assessed the hemodynamic stability of the model in six additional control patients with artificial hearts. The Jarvik-7 was rendered preload- and afterload-independent, and atrial, pulmonary arterial, and arterial pressures were recorded on a Gould ES 1000® recorder for a 90-min period.

Table 1. Clinical Characteristics of the Five Patients Studied

Patient	Age (yr)	Sex	Outcome	Delay Between Implantation of Jarvik-7 and Study (Days)	Indication for the Jarvik-7	Time Between Propofol and Thiopental (hr)
1	40	M	S	1	Cardiomyopathy	19
2	41	M	D	2	Graft rejection	27
3	47	M	D	1	Massive infarction	24
4	46	M	D	3	Massive infarction	28
5	50	M	D	2	Massive infarction	16

S = survived; D = died.

Left and right cardiac outputs also were recorded for the same period. As shown in table 2, atrial pressures, pulmonary and systemic arterial pressures, and left and right cardiac outputs remained unchanged throughout the 90-min period. In fact, cyclic increases in all pressures were observed during mechanical ventilation, as predicted in a recent article.[12] In addition, some slight variations in right and left end-diastolic volumes were observed intermittently when a beat-to-beat analysis was performed.

Hemodynamic and Respiratory Measurements

The catheters previously inserted for cardiovascular monitoring were used for the study. When the artificial heart was implanted, central venous and radial artery catheters were inserted percutaneously by the anesthesiologist, whereas pulmonary arterial and left atrial catheters were inserted intraoperatively by the surgeons. These catheters were kept in place in the postoperative period and used for pressure measurements and blood sampling. Arterial and mixed venous blood samples were withdrawn simultaneously and analyzed within 2 min for Pa_{O_2}, mixed venous oxygen blood ($P\bar{v}_{O_2}$), and *p*H, with the use of a blood gas analyzer (model 1302, Instrumentation Laboratory). Arterial and mixed venous O_2 saturations were measured with the use of a Hemoximeter OSM$_3$®. Arterial and mixed venous O_2 contents, arteriovenous O_2 difference, O_2 consumption ($\dot{V}_{O_2}$), O_2 delivery ($\dot{D}_{O_2}$), and pulmonary shunt ($\dot{Q}_s/\dot{Q}_t$) were calculated with standard formulas.

Because in patients with artificial hearts vascular pressures are influenced by cyclic changes in intrathoracic pressures,[12] mechanical ventilation-induced changes in lung volume were recorded continuously with an indirect spirometry method previously described in detail[13] and used for measuring cardiogenic oscillations related to the Jarvik-7 artificial heart.[14] Throughout the study, RAP, LAP, pulmonary arterial pressure (PAP), and arterial pressure were recorded simultaneously with changes in the rib cage perimeter (an index of lung volume changes induced by mechanical ventilation) on a Gould ES 1000® recorder. Hemodynamic pressures always were taken at the end-expiratory phase.

Total vascular resistance (TVR) index and pulmonary vascular resistance (PVR) index were calculated as follows:

$$\text{TVR (Wood units} \cdot \text{m}^2) = \frac{\text{MAP} - \text{RAP}}{\text{left CI}}$$

$$\text{PVR (Wood units} \cdot \text{m}^2) = \frac{\text{PAP mean} - \text{LAP mean}}{\text{right CI}}$$

where MAP = mean arterial pressure; PAP mean = mean pulmonary arterial pressure; LAP mean = mean left atrial pressure; and CI = cardiac index.

Because a vascular waterfall phenomenon characterizes systemic circulation,[9] hemodynamic pressures also were recorded "in zero-flow conditions" during an 8-s interruption of the Jarvik-7 artificial heart to calculate true systemic vascular resistance (SVR) index as follows:

$$\text{SVR (Wood units} \cdot \text{m}^2) = \frac{\text{MAP} - \text{AP}_{ZF}}{\text{left CI}}$$

where AP_{ZF} is the arterial pressure measured in "zero-flow conditions."

This formula takes into account that the true downstream pressure of the arterial compartment can no longer be considered RAP, simply because systemic arteries are characterized by a zero-flow pressure far greater than the zero-flow pressure within the venous compartment (RAP_{ZF}).[9]

Although it applies to the systemic circulation, the vascular waterfall concept does not apply to normal pulmonary circulation because pulmonary arteries are characterized by a zero-flow pressure less than the zero-flow pressure within pulmonary veins.[9] Consequently, PVR can be appreciated adequately with the usual formula mentioned above. Figures 1 and 2 show an example of the effects of these brief interruptions of the Jarvik-7 artificial heart on vascular pressures. As shown in the figures, systemic arterial, pulmonary arterial, and RAP curves are very similar to those obtained in patients with their native

TABLE 2. Hemodynamic Results of Control Group

		Time (min)					
	Control	15	30	45	60	75	90
MAP (mmHg)	70 ± 8	70 ± 8	71 ± 7	70 ± 8	71 ± 7	69 ± 10	71 ± 8
RAP (mmHg)	12 ± 3	12 ± 2	12 ± 3	11 ± 3	12 ± 2	12 ± 2	12 ± 2
LAP (mmHg)	13 ± 4	13 ± 3	13 ± 3	13 ± 3	12 ± 4	13 ± 3	12 ± 3
MPAP (mmHg)	16 ± 7	15 ± 7	15 ± 7	16 ± 8	16 ± 7	15 ± 6	16 ± 6
Left CO (l/min)	5.4 ± 1.2	5.4 ± 1.2	5.4 ± 1.1	5.4 ± 1.3	5.4 ± 1.2	5.3 ± 1.3	5.4 ± 1.2
Right CO (l/min)	5.4 ± 1	5.5 ± 1.1	5.3 ± 1	5.3 ± 1.1	5.4 ± 1.3	5.2 ± 1.1	5.3 ± 1.1
Pa_{O_2} (mmHg)	128 ± 12	131 ± 14	140 ± 15	129 ± 13	132 ± 16	135 ± 14	130 ± 12
$\dot{Q}_s/\dot{Q}_t$ (mmHg)	19 ± 6	20 ± 5	20 ± 6	19 ± 6	20 ± 6	19 ± 5	19 ± 6

Values are mean ± SD. n = six patients.

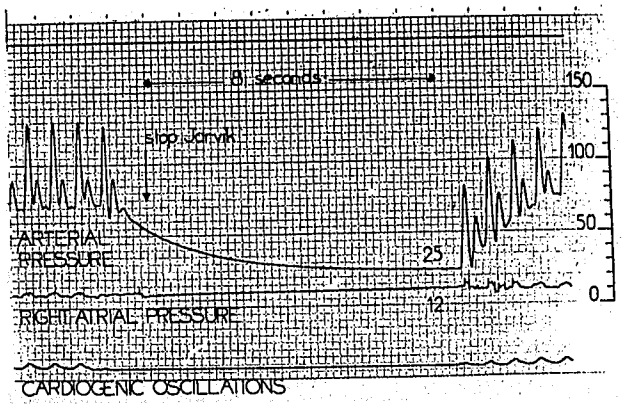

FIG. 1. Continuous recording in patient 2 of arterial pressure and right atrial pressure during an 8-s interruption of the Jarvik-7 artificial heart. After an initial curvilinear decrease in arterial pressure, a plateau pressure is observed at 25 mmHg, whereas right atrial pressure stabilizes at 12 mmHg. After a few seconds of zero-flow conditions, a 13-mmHg pressure gradient exists between arterial pressure and right atrial pressure, suggesting a vascular waterfall. Note that arterial and right atrial pressure curves are similar to those observed in patients with their native heart. On the bottom line, cardiogenic oscillations measured by indirect spirometry are absent during the Jarvik-7 interruption.

hearts. In contrast, the LAP curve is characterized by an abnormal v-wave. Similar aspects have been described by others.[12] To understand the reasons for this "abnormal" LAP curve, we performed transesophageal doppler echocardiography in two anesthetized patients with artificial hearts. The existence of atrioventricular valve regurgitation was ruled out, and a significant increase in left atrial volume was observed during ventricular ejection with right displacement of the interatrial septum. We concluded that, in the conditions of artificial heart in which both ventricular chambers eject simultaneously, right stroke volume enters the left atrium before the opening of the left atrioventricular valve, thus increasing the pressure within the left atrium during ventricular ejection.

THIOPENTAL AND PROPOFOL ADMINISTRATION

Thiopental 5 mg/kg and propofol 2.5 mg/kg were injected intravenously over a 10-s period. All patients received both drugs at intervals ranging from 16 to 28 h. Thiopental and propofol were the sole anesthetic agents, and no other sedative drugs were administered during a period ranging from 12 h before the first anesthetic procedure (propofol in three patients, thiopental in two patients) and the second anesthetic procedure. A fractional inspired O_2 concentration of 0.5 was used throughout each anesthesia. Hemodynamic parameters were recorded continuously over a period starting 5 min before and ending 45 min after drug injection. Blood samples were withdrawn before drug injection and 5, 10, 15, 30, and 45 min later. Hemodynamic parameters were measured simultaneously. Each set of measurements included—in the following order—recording of left and right cardiac outputs, withdrawal of pulmonary and arterial blood samples, and measurement of hemodynamic pressures and respiratory parameters. In addition, 20 ml arterial blood was withdrawn at the end of each set of measurements and was used to determine epinephrine and norepinephrine plasma concentrations with the use of a radioenzymatic assay. Atrial natriuretic peptide (ANP) also was measured by radioimmunoassay, according to a technique described recently.[15] Normal values were 25–80 pg/ml for epinephrine, 200–400 pg/ml for norepinephrine, and 18–26 pg/ml for ANP.

STATISTICAL ANALYSIS

Values of measured parameters during the 45-min experiments were analyzed with the use of an analysis of variance for two factors with repeated measures. Because one of the factors (time) was quantitative, we used orthogonal polynomials to characterize the profiles of time-dependent variations[16] and tests on linear and nonlinear trends. This analysis enabled us 1) to test the significance of variations of each parameter with time; 2) to characterize the profile by testing the significance of its linear

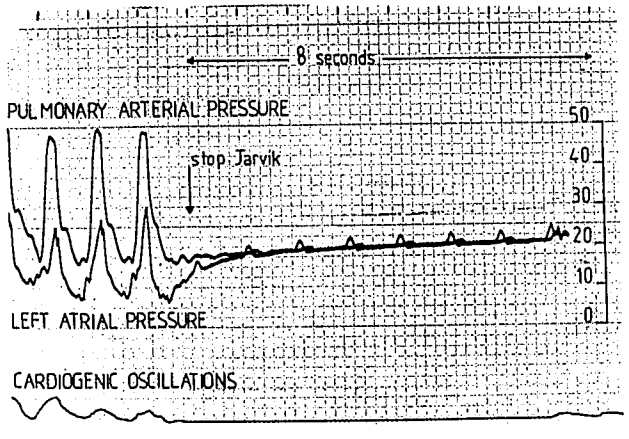

FIG. 2. Continuous recording in patient 2 of pulmonary arterial pressure and left atrial pressure during an 8-s interruption of the Jarvik-7 artificial heart. After a slight increase in pulmonary arterial pressure associated with a marked increase in left atrial pressure, both pressures rapidly stabilize at a level of 20 mmHg, indicating that left atrial pressure is largely greater than the critical opening pressure of the pulmonary arteries. The left atrium continues to beat in zero-flow conditions, and the pressure wave is transmitted backward to the pulmonary artery. The vascular waterfall concept does not apply to the pulmonary circulation. Note that the pulmonary arterial pressure curve is similar to that observed in patients with their native heart. In contrast, left atrial pressure curve is characterized by a marked systolic V-wave (see explanations in the text). On the bottom line, cardiogenic oscillations measured by indirect spirometry are absent during the Jarvik-7 interruption.

TABLE 3. Comparative Effects of Thiopental and Propofol on Systemic Circulation

	Control	Time (min) 5	10	15	30	45	Variation With Time (*P*)	Component of the Profile Affected
Thiopental 5 mg/kg								
SAP (mmHg)	129 ± 23	110 ± 18	112 ± 22	117 ± 24	122 ± 24	126 ± 22	<0.01	Nonlinear
DAP (mmHg)	57 ± 12	46 ± 5	48 ± 10	51 ± 13	49 ± 12	55 ± 12	<0.05	Linear and nonlinear
MAP(mmHg)	75 ± 15	59 ± 8	61 ± 12	64 ± 15	66 ± 17	73 ± 14	<0.05	Nonlinear
AP_{ZF} (mmHg)	26 ± 5	22 ± 4	22 ± 5	23 ± 5	23 ± 5	25 ± 5	<0.05	Nonlinear
TVR (units · m^2)	22 ± 4	17 ± 3	18 ± 4	18 ± 5	19 ± 4	21 ± 3	<0.05	Nonlinear
SVR (units · m^2)	18 ± 4	14 ± 3	14 ± 3	15 ± 4	15 ± 4	17 ± 4	<0.05	Nonlinear
RAP (mmHg)	15 ± 5	12 ± 5	12 ± 6	13 ± 5	13 ± 5	14 ± 5	<0.05	Nonlinear
RAP_{ZF} (mmHg)	18 ± 5	15 ± 66	14 ± 6	15 ± 5	16 ± 5	16 ± 6	<0.05	Nonlinear
Propofol 2.5 mg/kg								
SAP (mmHg)	126 ± 11	85 ± 16*	91 ± 18	97 ± 16	107 ± 18	117 ± 14	<0.01	Nonlinear
DAP (mmHg)	62 ± 9	33 ± 5*	35 ± 3	38 ± 4	42 ± 5	45 ± 4	<0.001	Linear and nonlinear
MAP(mmHg)	72 ± 9	44 ± 4†	49 ± 6	50 ± 7	55 ± 9	63 ± 10	<0.001	Nonlinear
AP_{ZF} (mmHg)	24 ± 3	18 ± 4*	19 ± 3	18 ± 3	21 ± 3	25 ± 1	<0.001	Nonlinear
TVR (units · m^2)	21 ± 6	12 ± 2	14 ± 4	16 ± 5	17 ± 5	19 ± 3	<0.01	Nonlinear
SVR (units · m^2)	17 ± 5	9 ± 1‡	12 ± 3	12 ± 3	12 ± 3	13 ± 3	<0.01	Nonlinear
RAP (mmHg)	12 ± 4	6 ± 4‡	7 ± 3	7 ± 3	9 ± 4	9 ± 3	<0.01	Nonlinear
RAP_{ZF} (mmHg)	15 ± 4	8 ± 13*	10 ± 3	11 ± 3	12 ± 5	13 ± 5	<0.01	Nonlinear

n = Five patients.

As mentioned in Materials and Methods, statistical analysis was performed using an analysis of variance, enabling testing of the significance of variation of each parameter with time and analysis of whether the drug affected the linear or the nonlinear component of the profile. In addition, the difference between the two drugs was tested at 5 min using covariance for repeated measures. Values are mean ± SD.

* $P < 0.01$ propofol *versus* thiopental.

† $P < 0.001$ propofol *versus* thiopental.

‡ $P < 0.05$ propofol *versus* thiopental.

and nonlinear components; 3) to test the difference between the profile of variations induced by the two drugs; and 4) to know whether the difference between the two drugs affected the linear or nonlinear component of the profiles. When the profiles of variations were significantly different between the two drugs, each profile was tested separately with the use of analysis of simple effect.[16] The degrees of significance were calculated using the criterion of Huyn and Feldt, which is more appropriate than the standard critical value of F for experimental designs with repeated measures (BMDP technical report). The differences between the two drugs 5 min after their administration were considered *a priori* as interesting to be tested. These differences were tested using a covariance analysis for repeated measures; the covariates were the corresponding control values of the studied parameters. All tests were performed with the use of BMDP software (UCLA University, Los Angeles, CA). Relationships between ANP plasma concentrations and RAP and LAP were analyzed with linear regressions by the least-squares method.

Results

The anesthetic effects of propofol and thiopental could be assessed adequately in four patients, with patient 2 being unresponsive before anesthetic induction. All patients fell asleep (loss of eyelash reflex) after a few seconds. No excitatory phenomenon was observed. During dressing change, which took approximately 10 min, all patients appeared quiet and remained immobile. All patients could open their eyes on command 15 min after induction of anesthesia. Three patients spontaneously opened their eyes at the end of the dressing procedure: two had received thiopental and one propofol. In all patients, the quality of anesthesia was considered satisfactory by the nurse when compared with the combination of midazolam and fentanyl used routinely in the unit.

As shown in table 3, thiopental and propofol induced a significant decrease in arterial pressure, TVR index, and RAP. This decrease was maximum at 5 min. After 45 min, a return to control values was observed only for thiopental, whereas arterial pressure and RAP remained slightly decreased in the case of propofol. Propofol induced a significantly greater decrease in arterial pressure and RAP at 5 min than that induced by thiopental. As shown in figures 3 and 4, both intravenous anesthetics significantly reduced SVR index and RAP measured in zero-flow conditions, but propofol did so to a greater extent than thiopental.

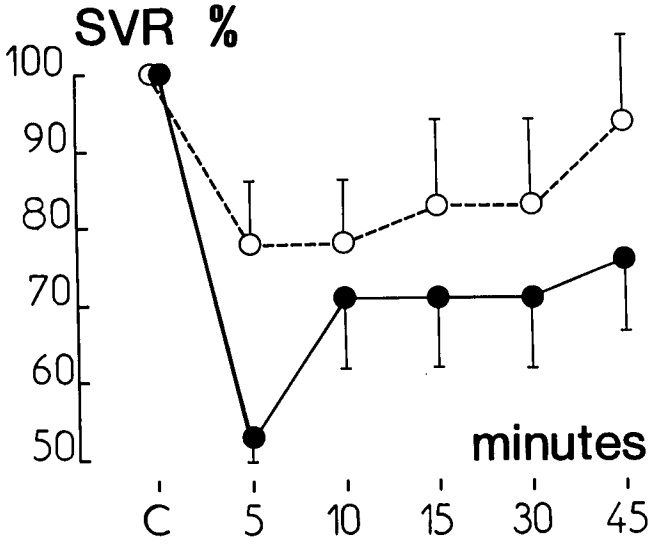

FIG. 3. Comparative changes (expressed in percent changes from control values) in "true" SVR induced by thiopental 5 mg/kg (open circles) and propofol 2.5 mg/kg (closed circles) in five patients (mean ± SD). SVR, calculated as mean arterial pressure minus arterial pressure in zero-flow conditions divided by left cardiac index, was measured before drug administration (control) and 5, 10, 15, 30, and 45 min later. Both anesthetic agents induced a significant decrease in SVR ($P < 0.01$). Differences in response patterns between the two drugs were statistically significant using a two-way analysis of variance of repeated-measures design. At 5 min, propofol induced a significantly greater decrease in SVR than did thiopental ($P < 0.05$).

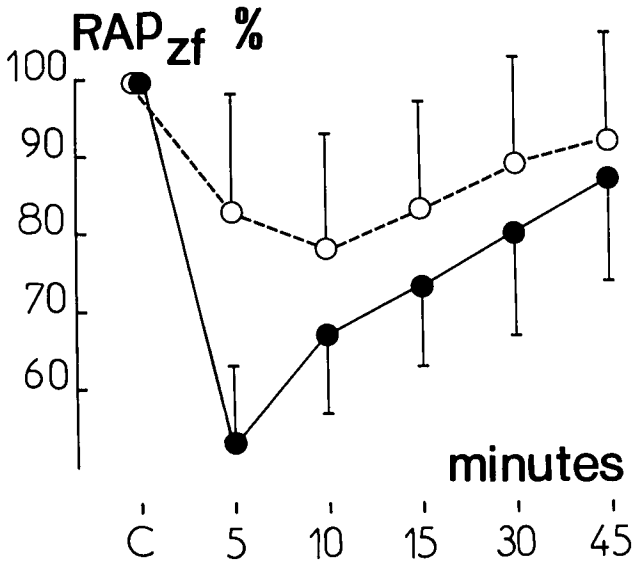

FIG. 4. Comparative changes (expressed in percent changes from control values) in right atrial pressure measured in zero-flow conditions (RAP_{ZF}) induced by thiopental 5 mg/kg (open circles) and propofol 2.5 mg/kg (closed circles) in five patients (mean ± SD). RAP_{ZF}, an excellent index of venous tone, was measured before drug administration (control) and 5, 10, 15, 30, and 45 min later. Both anesthetic agents induced a significant decrease in RAP_{ZF} ($P < 0.01$). Differences in response pattern between the two drugs were statistically significant using a two-way analysis of variance of repeated-measures design. At 5 min, propofol induced a significantly greater decrease in RAP_{ZF} than did thiopental ($P < 0.05$).

TABLE 4. Comparative Effects of Thiopental and Propofol on Pulmonary Circulation

	Control	Time (min) 5	10	15	30	45	Variation with Time (*P*)	Component of the Profile Affected
Thiopental 5 mg/kg								
PAP (systolic (mmHg)	42 ± 7	34 ± 9	35 ± 11	37 ± 11	39 ± 9	38 ± 10	<0.001	Nonlinear
PAP diastolic (mmHg)	16 ± 4	13 ± 5	14 ± 5	15 ± 5	13 ± 5	15 ± 6	<0.001	Nonlinear
PAP mean (mmHg)	22 ± 4	18 ± 6	20 ± 6	21 ± 6	20 ± 6	21 ± 7	<0.001	Nonlinear
LAP systolic (mmHg)	28 ± 4	19 ± 4	20 ± 5	20 ± 4	21 ± 5	23 ± 7	<0.01	Nonlinear
LAP mean (mmHg)	15 ± 3	9 ± 4	10 ± 4	11 ± 4	11 ± 5	11 ± 5	<0.001	Nonlinear
LAP diastolic (mmHg)	8 ± 4	5 ± 4	6 ± 4	6 ± 4	6 ± 4	7 ± 5	<0.01	Linear and nonlinear
PVR (units · m^2)	2.7 ± 1.3	3.4 ± 1.2	4.0 ± 1.4	3.9 ± 0.3	3.7 ± 0.7	4.3 ± 0.6	NS	—
$\dot{Q}_s/\dot{Q}_t$ (%)	26 ± 7	28 ± 8	26 ± 8	25 ± 8	28 ± 7	28 ± 7	NS	—
$P\bar{v}_{O_2}$ (mmHg)	36 ± 5	35 ± 5	35 ± 3	33 ± 3	35 ± 3	37 ± 4	NS	—
Propofol 2.5 mg/kg								
PAP (systolic (mmHg)	41 ± 10	30 ± 9	31 ± 8	33 ± 8	34 ± 10	36 ± 10	<0.001	Nonlinear
PAP diastolic (mmHg)	14 ± 10	10 ± 3	10 ± 2	11 ± 3	12 ± 4	13 ± 4	<0.001	Nonlinear
PAP mean (mmHg)	22 ± 6	15 ± 4	16 ± 3	17 ± 3	18 ± 5	19 ± 6	<0.001	Nonlinear
LAP systolic (mmHg)	29 ± 11	16 ± 6	16 ± 6	15 ± 7	19 ± 2	20 ± 13	<0.01	Nonlinear
LAP mean (mmHg)	13 ± 6	7 ± 4	7 ± 3	7 ± 4	8 ± 6	9 ± 7	<0.001	Nonlinear
LAP diastolic (mmHg)	8 ± 6	4 ± 3	4 ± 3	4 ± 3	4 ± 4	5 ± 5	<0.01	Linear and nonlinear
PVR (units · m^2)	3.3 ± 1.3	3.0 ± 1.4	3.4 ± 0.8	3.7 ± 1.3	3.5 ± 1.3	3.8 ± 1.5	NS	—
$\dot{Q}_s/\dot{Q}_t$ (%)	24 ± 7	27 ± 9	24 ± 8	23 ± 9	24 ± 9	23 ± 7	NS	—
$P\bar{v}_{O_2}$ (mmHg)	36 ± 4	35 ± 3	32 ± 2	33 ± 3	33 ± 3	34 ± 2	NS	—

As mentioned in Materials and Methods, statistical analysis was performed using an analysis of variance, enabling testing of the significance of variation of each parameter with time and analysis of whether each drug affected the linear or the nonlinear component of the profile. In addition, the difference between the two drugs was tested at 5 min using covariance analysis for repeated measures. Values are mean ± SD.

As shown in table 4, thiopental and propofol induced a comparable and significant decrease in PAP and LAP, suggesting that, assuming constant pulmonary blood volume, both drugs are pulmonary vasodilators, increasing compliance without changing resistance. Simultaneously, $P\bar{v}O_2$ and $\dot{Q}_s/\dot{Q}_t$ remained unchanged, suggesting that the regional ventilation–perfusion ratio ($\dot{V}/\dot{Q}$) distribution was unaffected by both anesthetic agents.

As shown in table 5, left CI, right CI, $\dot{V}_{O_2}$, $\dot{D}_{O_2}$ and arterial blood gases remained remarkably stable throughout the study. Although catecholamine plasma concentrations were increased slightly, as is frequently observed in postoperative critically ill patients, they remained stable throughout the study period. As a consequence, the observed hemodynamic changes cannot be explained by variations in catecholamine plasma concentration. As previously reported,[15] increased plasma concentrations of ANP were found in the five patients studied. Surprisingly, although thiopental and propofol significantly decreased RAP and LAP, no significant relationship was found between ANP plasma concentrations and RAP or LAP: ANP = 1.2 RAP + 39 (r = 0.29, n = 48) and ANP = −09 mean LAP + 60 (r = 0.20, n = 48).

Discussion

The main result of this study is that the peripheral vascular effects of propofol 2.5 mg/kg are more pronounced than those of thiopental 5 mg/kg. Propofol induced a greater decrease in SVR index and more profound venodilatation than thiopental, although both drugs induced comparable vasodilatation of pulmonary vessels.

Critique of Methods

These results were obtained in critically ill patients with artificial hearts who were anesthetized in the first postoperative days for dressing renewal. The presence of an artificial heart offers unique conditions for studying the peripheral vascular effects of anesthetic drugs. Heart rate remained constant. By using appropriate settings for the Jarvik-7, left and right cardiac outputs could be maintained constant, despite drug-induced changes in preload and afterload.[9,10]

The main reason for using constant cardiac output conditions is the following: if the blood volume of systemic and pulmonary vascular compartments remains constant, then the peripheral vascular effects of propofol and thiopental can be assessed and compared with observed changes in pressures characterizing each compartment. However, there is a theoretic reason why systemic and pulmonary volumes may not remain constant. Because of the anastomotic bronchial blood flow, when right cardiac output is equal to left cardiac output, a shift in blood volume from the systemic circulation to the pulmonary circulation should be observed with time, resulting in progressive systemic hypovolemia, pulmonary congestion, and pulmonary edema. Consequently, observed changes in pressures could depend not only on the dilating prop-

TABLE 5. Metabolic and Respiratory Effects of Thiopental and Propofol

	Control	Time (min) 5	10	15	30	45
Thiopental 5 mg/kg						
Left CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.8 ± 0.3	2.7 ± 0.2	2.7 ± 0.3	2.8 ± 0.3	2.8 ± 0.4	2.8 ± 0.4
Right CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.7 ± 0.3	2.6 ± 0.3	2.5 ± 0.3	2.6 ± 0.3	2.7 ± 0.3	2.7 ± 0.3
$\dot{V}_{O_2}$ ($ml \cdot min^{-1} \cdot m^{-2}$)	98 ± 8	90 ± 20	100 ± 14	115 ± 27	89 ± 9	90 ± 15
$\dot{D}_{O_2}$ ($ml \cdot min^{-1} \cdot m^{-2}$)	319 ± 95	294 ± 69	298 ± 80	307 ± 93	298 ± 83	308 ± 89
Pa_{O_2} (mmHg)	143 ± 50	141 ± 50	131 ± 53	132 ± 61	137 ± 53	144 ± 53
Pa_{CO_2} (mmHg)	37 ± 6	36 ± 6	37 ± 7	38 ± 7	36 ± 7	36 ± 7
Norepinephrine (pg/ml)	477 ± 277	394 ± 253	425 ± 259	350 ± 279	436 ± 426	476 ± 336
Epinephrine (pg/ml)	174 ± 55	139 ± 47	158 ± 47	237 ± 96	238 ± 122	267 ± 170
ANP (pg/ml)	47 ± 32	46 ± 28	44 ± 31	45 ± 29	52 ± 39	47 ± 30
Propofol 2.5 mg/kg						
Left CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.9 ± 0.5	2.8 ± 0.2	2.6 ± 0.3	2.8 ± 0.2	3.0 ± 0.4	2.9 ± 0.2
Right CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.8 ± 0.4	2.8 ± 0.2	2.7 ± 0.3	2.8 ± 0.3	2.9 ± 0.3	2.7 ± 0.3
$\dot{V}_{O_2}$ ($ml \cdot min^{-1} \cdot m^{-2}$)	98 ± 21	85 ± 13	94 ± 17	105 ± 17	103 ± 17	102 ± 12
$\dot{D}_{O_2}$ ($ml \cdot min^{-1} \cdot m^{-2}$)	284 ± 38	262 ± 35	249 ± 58	263 ± 30	278 ± 39	281 ± 43
Pa_{O_2} (mmHg)	180 ± 58	158 ± 69	159 ± 69	169 ± 70	163 ± 64	161 ± 55
Pa_{CO_2} (mmHg)	33 ± 3	33 ± 3	33 ± 4	34 ± 4	35 ± 4	34 ± 3
Norepinephrine (pg/ml)	499 ± 401	335 ± 264	337 ± 290	467 ± 433	389 ± 395	449 ± 389
Epinephrine (pg/ml)	249 ± 150	192 ± 86	165 ± 72	199 ± 92	220 ± 92	263 ± 95
ANP (pg/ml)	39 ± 23	34 ± 13	35 ± 8	45 ± 25	43 ± 24	46 ± 30

Values are mean ± SD.

erties of propofol and thiopental, but also on volemic changes.

Because blood volume measurement was not performed in this study, the volemic stability of each vascular compartment cannot be established firmly. However, the remarkable hemodynamic stability observed in the control group clearly suggests the absence of significant variations in central and peripheral blood volumes and tends to support the hypothesis that anastomotic bronchial blood flow was not quantitatively important in our patients with artificial hearts. One explanation may be found in the respective morphologic characteristics of LAP and RAP curves of patients with artificial hearts. Experimentally, it is well known that an increase in LAP can result in decreased anastomotic bronchial blood flow, or even in an inversion of the direction of the anastomotic flow.[17-20] As shown in figure 2, a large systolic v-wave characterizes the LAP curve of patients with Jarvik-7 artificial hearts. As a consequence, during systole, LAP is largely higher than RAP, and during diastole, RAP is higher than LAP. This could result in opposing changes in the direction of the flow within the anastomotic bronchial vessels during systole and diastole, with the net result over several cardiac cycles being an unchanged central blood volume.

Another advantage of the existence of a cardiac prosthesis is that changes in systemic circulation do not affect pulmonary circulation, as observed in the presence of the native heart. Therefore, the specific effects of thiopental and propofol on pulmonary circulation can be evaluated accurately, independent of their systemic effects. We previously demonstrated that the presence of an artificial heart enables accurate measurement of SVR and venous tone.[9] Because a vascular waterfall phenomenon characterizes the systemic circulation,[21] the true SVR index should be calculated as MAP minus arterial pressure, measured in zero-flow conditions, divided by left CI, instead of MAP minus RAP divided by CI. In the presence of an artificial heart, arterial pressure and RAP in zero-flow conditions can be measured during brief interruptions of the artificial heart, thus providing the possibility of an accurate evaluation of the respective effects of thiopental and propofol on arterial and venous vessels.

Finally, when the artificial heart is rendered preload and afterload independent, and if central and systemic blood volumes do not change significantly, any variation in RAP is related to a change in venous tone; any change in MAP is related to a change in arteriolar tone; and any change in PAP or in LAP is related to a change in pulmonary vessel tone. Because right cardiac output was maintained fairly constant throughout the study, PVR was influenced only by the difference between mean PAP and LAP. In the absence of pulmonary hypertension, no waterfall phenomenon characterizes pulmonary circulation because LAP is higher than the critical opening pressure of the pulmonary arteries (fig. 2). In conditions of constant flow, the pulmonary pressure flow relationship cannot be analyzed; therefore, the site of action of propofol and thiopental—compliant or resistive vessels—cannot be determined precisely. According to Bshouty and Younes,[22] when LAP is greater than the critical opening pressure of the pulmonary vessels, PAP increases or decreases in a one-to-one relationship with LAP. This condition was present in all of our patients. As a consequence, our data only show that thiopental and propofol dilate pulmonary vessels, without indicating which vessels are involved.

Although it is not known to what extent the presence of an artificial heart affects the cardiovascular system, we have no reason to believe that the Jarvik-7 artificial heart could have significantly modified thiopental- and propofol-induced peripheral vascular effects. As described previously,[9,10] patients with artificial hearts appear to be much closer to physiologic conditions than do patients undergoing cardiopulmonary bypass, another situation in which the peripheral vascular effects of anesthetics can be evaluated. The patients included in this study were still critically ill, with slightly increased plasma catecholamine concentrations that remained in the range that is observed in patients in the intensive care unit. Of the five patients studied, patients 1 and 2 had histories of chronic cardiac failure that could have profoundly altered the vascular reactivity of peripheral circulation. The other three had artificial hearts implanted because of massive inaugural myocardial infarction and were free of previous chronic cardiac disease. When the observed hemodynamic effects of thiopental and propofol were studied, no difference could be found between patients with or without a history of chronic cardiac insufficiency.

Vascular Effects of Thiopental and Propofol

Although most authors agree that the cardiovascular effects of propofol are profound and probably more pronounced that those of intravenous barbiturates, there is still controversy as to the circumstances in which vascular resistance and cardiac output are affected by both drugs.[23-25] If the potent negative inotropic effect of thiopental now has been recognized universally, its peripheral vascular effects still are being debated. Although barbiturates have been shown to dilate arteries *in vitro*[26] and to increase venous distensibility of the human hand,[27] most hemodynamic studies in intact animals and humans have reported increased TVR and an increase in RAP after thiopental administration.[28]

Our results clearly demonstrate that thiopental vasodilates systemic arteries, pulmonary vessels, and veins. In intact humans, observed changes in blood pressure and CI depend on the balance between myocardial depression,

decrease in venous return, reduction in afterload, and compensatory mechanisms. Very often, myocardial depression and reduction in preload are predominant over a decrease in SVR, and a significant decrease in CI is observed, associated with an increase in RAP and systemic resistance. In other words, the thiopental-induced decrease in vascular tone that tends to decrease RAP is offset by the thiopental-induced myocardial depression.

The hemodynamic effects of propofol appear quite different. Although contradictory results have been published concerning the effects of propofol on ventricular function,[3,7,8] recent experimental *in vitro* studies tend to show a lack of significant negative inotropic effect.[29,30] As demonstrated by our results, propofol is a potent vasodilator of systemic arteries, pulmonary vessels, and veins. A recent study, performed in dogs in which all neurogenic cardiovascular reflexes were abolished, clearly has shown that cardiac output and arterial pressure can be conserved after propofol administration by maintaining preload with the use of fluid administration.[8] This result suggests that propofol decreases cardiac output by reducing preload through a direct venodilator effect. Finally, observed changes in cardiac output after propofol administration in intact animals or humans depend on the balance between decrease in venous return, reduction in afterload, and compensatory mechanisms. The potent arterial vasodilator effect of propofol explains why its hypotensive effect is greater than that of thiopental. In contrast, both anesthetics similarly affect pulmonary circulation. Our study also shows that thiopental and propofol did not alter $\dot{V}/\dot{Q}$ distribution significantly, despite their significant pulmonary vasodilator effect.

Although both anesthetics significantly reduced RAP and LAP, no reduction in ANP plasma concentration was observed. The reasons for this surprising result are not clear. Like others,[15] we found an increased plasma concentration of ANP associated with increased atrial pressure in patients with artificial hearts. Because it has been shown that plasma ANP concentration follows short-term changes in RAP in humans with artificial hearts in whom 95% of the native atrial tissue remains *in situ*,[31] our results suggest that thiopental and propofol significantly interfere with the regulation of ANP. Additional studies must be done to verify this hypothesis.

Finally, when administered as a single dose over a 10-s period, propofol 2.5 mg/kg was found to be a more potent arterial and venous vasodilator than thiopental 5 mg/kg in patients with a Jarvik-7 artificial heart. This result was obtained in patients who had a slightly increased sympathetic tone to begin with; thus, the magnitude of the vasodilating effect could be different in patients with normal sympathetic tone. However, the observed vasodilatation was not mediated through changes in humoral mediators of vascular tone because epinephrine and norepinephrine plasma concentrations remained unchanged throughout the study period.

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