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Peripheral Vascular Effects of Halothane and Isoflurane in Humans with an Artificial Heart

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The peripheral vascular effects of isoflurane and halothane were compared in five critically ill patients in whom a Jarvik-7 artificial heart had been implanted. The lungs of all patients were mechanically ventilated in the postoperative period and the patients were monitored with an arterial catheter and with catheters that had been surgically inserted into the right and left atria and into the pulmonary artery. Noreperinephrine and epinephrine plasma concentrations were measured using a radioenzymatic assay. The Jarvik-7 settings were modified to render the artificial heart "preload independent" and to maintain cardiac output constant. Each patient was anesthetized twice using halothane and isoflurane at two different MAC levels, 1 and 1.5 (Datex vapour analyzer), with the interval between each anesthetic ranging from 12 to 26 h. Both anesthetics significantly decreased mean arterial pressure (from 100 ± 11 mmHg to 66 ± 13 mmHg for halothane and from 102 ± 17 mmHg to 48 ± 11 mmHg for isoflurane; mean ± SD) and systemic vascular resistance index (from 27 ± 11 Wood units/m² to 18 ± 6 Wood units/m² for halothane and from 30 ± 6 Wood units/m² to 13 ± 3 Wood units/m² for isoflurane; mean ± SD), but with isoflurane to a significantly greater extent than with halothane ($P < 0.01$). Both anesthetics induced significant and comparable decreases in right atrial pressure (from 15 ± 2 mmHg to 13 ± 4 mmHg for halothane and from 16 ± 3 mmHg to 11 ± 2 mmHg for isoflurane; mean ± SD), mean pulmonary arterial pressure (from 22 ± 10 mmHg to 17 ± 11 mmHg for halothane and from 19 ± 9 mmHg to 14 ± 8 mmHg for isoflurane; mean ± SD), and left atrial pressure (from 14 ± 6 mmHg to 11 ± 7 mmHg for halothane and from 11 ± 5 mmHg to 6 ± 5 mmHg for isoflurane, mean ± SD) without changing catecholamine plasma concentrations (from 474 ± 586 pg/ml to 206 ± 390 pg/ml for norepinephrine concentrations and from 100 ± 172 pg/ml to 96 ± 71 pg/ml for epinephrine concentrations during halothane, from 356 ± 92 pg/ml to 512 ± 269 pg/ml for norepinephrine concentrations and from 121 ± 118 pg/ml to 129 ± 95 pg/ml for epinephrine concentrations during isoflurane; mean ± SD). Because cardiac output was maintained constant throughout the anesthetic, these results suggest that halothane and isoflurane reduced vascular tone of veins, pulmonary vessels, and systemic arteries. (Key words: Anesthetics, volatile: halothane; isoflurane. Heart: artificial. Transplantation.)

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INITIALLY DESCRIBED as a means of prolonging life in patients with terminal cardiac failure and not qualifying for heart transplantation, the Jarvik-7 artificial heart is now one of the methods proposed to bridge the gap between premortem heart failure and cardiac transplantation.[1] Anesthesiologists are faced with patients with artificial hearts in two different situations: either during the artificial heart period when invasive procedures or surgical complications require general anesthesia[2] or during the heart transplantation itself. The hemodynamic effect of a volatile anesthetic is the result of the complex interaction between its effects on the heart and on the peripheral vascular system. Because heart and vessels are interconnected, it is difficult in intact humans (or animals) to know the specific effects of isoflurane and halothane on the different vascular beds. Moreover, in the presence of a cardiac prosthesis, hemodynamic effects of volatile anesthetics are only dependent on their peripheral vascular effects. Consequently, the cardiovascular stability provided by isoflurane and halothane could be different in patients with their natural heart and in patients with an artificial heart. In this study we compared the hemodynamic effects of isoflurane and halothane in five critically ill patients with a Jarvik-7 artificial heart in whom general anesthesia was required for invasive procedures in the early postoperative period.

Methods

PATIENTS

In La Pitié Hospital, Paris, from April 1986 to April 1989, 42 total artificial hearts were implanted in 42 patients with irreversible cardiac failure in whom an orthotopic heart transplantation could not be achieved within the short period preceding death. Seventeen patients subsequently underwent heart transplantation and eight ultimately survived. Due to the terminal stage of their heart-related illness, all patients were critically ill in the immediate postoperative period following the Jarvik implantation and were admitted to the cardiac intensive care unit (CICU). Because of a high incidence of preoperative pulmonary edema, mechanical ventilation was required in all patients. Invasive procedures, such as intravenous (iv) catheter insertion, creation of vascular access for he-

modialysis, tracheal intubation, and fiberoptic bronchoscopy for bacterial diagnosis of lung infection, were performed in the immediate postoperative period. In the intensive care unit, these invasive procedures are ordinarily performed under general anesthesia using a combination of benzodiazepines, opioids, and muscle relaxants. In five patients requiring two of these procedures, isoflurane and halothane were alternatively used at random for the purpose of this study. Informed consent was obtained from each patient and the protocol was approved by the Ethical Comittee of la Pitié Hospital. The five patients studied had not received any sedative, vasoactive, or antiarrhythmic drug during the 12 preceding h, were in a stable hemodynamic condition, and were free of any neurologic disorder. None of the five patients had a past history of chronic cardiac disease. Four had a massive myocardial infarction, which was the first manifestation of their coronary disease, leading to terminal cardiac failure over a 2- to 3-day period. The fifth was suffering from cardiomyopathy, leading in 2 weeks to refractory cardiac failure. Patients 1, 2, 3, and 4 had postoperative pulmonary edema and patients 2, 3, and 4 had acute renal failure requiring hemodialysis. Other clinical characteristics of the patients are summarized in table 1.

Jarvik-7 Total Artificial Heart

A Utah total artificial heart model Jarvik-7[3] had been implanted in each patient within the preceding 3 days. The 100-ml Jarvik-7 was used in two patients and the 70-ml Jarvik-7 was used in three patients. The function of the artificial ventricles was continuously monitored by the cardiac diagnostic unit of the Utah heart drive console (COMDU), which measures right and left end-diastolic ventricular volumes from the diastolic portion of the exhaust airflow curves of each ventricle.[4] Cardiac output is computed as the product of end-diastolic volume by heart rate. Before the study the drive functions of the Jarvik-7, including heart rate, drive pressure of the right and left chambers, and percentage of systole and vacuum, were adjusted to ensure complete ejection of blood from the ventricles and to obtain physiologic ranges of cardiac output, cardiac filling pressures, and arterial pressure.

In this study the initial Jarvik settings were modified to render the artificial heart partially preload-independent. By decreasing heart rate and systolic duration, the diastolic time was markedly increased, and the ventricular chamber was completely filled before the end of the period allotted to diastolic filling. When compared with previous settings, cardiac output was maintained because the decrease in heart rate was counteracted by an increase in end-diastolic ventricular volume. In addition, it was possible to maintain cardiac output constant despite a decrease in right or left atrial pressures, as long as the ventricular chambers were still completely filled at the end of time allotted to diastolic filling. Because such Jarvik settings were temporarily used during halothane and isoflurane administration, cardiac output was maintained constant throughout the study period. In these conditions any decrease in the measured pressures could be considered related to a decrease in vascular tone within the corresponding vascular bed. Jarvik-7 artificial heart settings used throughout the study are summarized in table 2.

Hemodynamic and Respiratory Measurements

In each patient a central venous catheter and a radial artery catheter were percutaneously inserted before the anesthetic induction performed for the implantation of the Jarvik-7 artificial heart. Intraoperatively, pulmonary and left atrial catheters were surgically implanted for cardiovascular monitoring. These catheters were maintained in place in the postoperative period after correct positioning had been radiologically confirmed. Blood samples were simultaneously withdrawn from the pulmonary and arterial catheters. Arterial and mixed venous blood samples were analyzed within 2 min for arterial O_2 tension (Pa_{O_2}), mixed venous O_2 tension ($P\bar{v}_{O_2}$), and pH (Instrumentation laboratory model 1302 blood gas analyzer). Arterial O_2 saturation (Sa_{O_2}) and mixed venous O_2 saturation ($S\bar{v}_{O_2}$) were measured using a Hemoximeter OSM_3. Arterial and mixed venous O_2 contents (Ca_{O_2} and $C\bar{v}_{O_2}$), arteriovenous O_2 difference ($C(a\text{-}\bar{v})_{O_2}$), O_2 consumption ($\dot{V}_{O_2}$), O_2 delivery ($\dot{D}_{O_2}$), and pulmonary shunt were calculated using standard formulas.

Because vascular pressures are greatly influenced by

Table 1. Clinical Characteristics of the 5 Patients Studied

Patient No.	Age (yr)	Outcome	Days with Implant	Delay between Implantation of Jarvik-7 and Study (days)	First Invasive Procedure	Second Invasive Procedure	Hours Between Halothane and Isoflurane
1	48	Died	37	13	Gastroscopy	Central catheter	19
2	32	Died	7	2	Bronchoscopy	Arteriovenous shunt	6
3	48	Died	136	3	Bronchoscopy	Arteriovenous shunt	20
4	52	Died	15	2	Bronchoscopy	Arteriovenous shunt	24
5	41	Died	21	2	Drive line abscess	Central catheter	16

TABLE 2. Jarvik-7 Settings Used during the Halothane and Isoflurane Studies

Patient No.	Heart Rate (beats/min)		Left Drive Pressure (mmHg)		Right Drive Pressure (mmHg)		Systolic Duration (%)	
	Halothane	Isoflurane	Halothane	Isoflurane	Halothane	Isoflurane	Halothane	Isoflurane
1	95	95	180	180	40	40	45	45
2	65	60	180	200	50	50	45	42
3	90	100	210	195	70	70	55	48
4	75	75	205	205	55	55	45	45
5	75	60	180	200	60	60	45	40

cyclic changes in intrathoracic pressure, mechanical ventilation-induced changes in lung volume were continuously recorded using an indirect spirometric method previously used for measuring cardiogenic oscillations related to the Jarvik-7 artificial heart.[5] Because it has been extensively described elsewhere,[6] only a brief summary of the methodology is given. Changes in rib cage perimeter were measured by a differential linear transformer mounted on a belt placed at the nipple level. The displacement of a ferromagnetic core inside the differential linear transformer, synchronized with the respiratory movements and the cardiogenic oscillations, creates a magnetic flux variation, which is directly proportional to changes in rib cage perimeter. In anesthetized patients the respiratory system is characterized by one degree of freedom and the variations in pulmonary volumes can be inferred from changes in rib cage perimeters after a calibration procedure.[7] In this study changes in rib cage perimeter were simultaneously recorded with hemodynamic pressures on a gould ES 1000 recorder. Hemodynamic pressures were always taken at the end-expiratory phase.

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

$$\text{TVR (Wood units/m}^2) = \frac{\text{MAP} - \text{RAP}}{\text{CI}} \quad \text{and}$$

$$\text{PVR (Wood units/m}^2) = \frac{\text{MPAP} - \text{LAP}}{\text{CI}}$$

where MAP = mean arterial pressure, RAP = right atrial pressure, MPAP = mean pulmonary arterial pressure, LAP = left atrial pressure, and CI = cardiac index.

Hemodynamic pressures were also recorded in "zero flow conditions" during brief interruptions of the Jarvik-7 artificial heart. The drive lines were disconnected for 8 s from the Utah pneumatic heart driver while pressure within each vascular compartment was continuously recorded. In concious patients this maneuver was psychologically unpleasant but well tolerated and felt as a prolonged ectopic cardiac beat. An example of arterial pressure and right atrial pressure recordings is shown in figure 1: in zero flow conditions there is a 7 mmHg pressure gradient between the venous and the arterial compartments. This phenomenon, recently described in patients without artificial heart,[8] was suspected some time ago and called the vascular waterfall.[9] Because systemic arteries are characterized by a zero flow pressure (AP_{zf}) far greater than the zero flow pressure within the venous compartment (RAP_{zf}), the true downstream pressure of the arterial compartment can no longer be considered as right atrial pressure. Applying Poiseuille's law, true systemic vascular resistance index (SVR) was calculated as follows:

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

In contrast to the systemic circulation, no pressure gradient was observed between the pulmonary arteries and the pulmonary veins, and, consequently, the vascular waterfall concept does not apply to the normal pulmonary circulation (fig. 2).

HALOTHANE AND ISOFLURANE ADMINISTRATION

Isoflurane and halothane were used as sole anesthetic agents in all patients. Each patient was anesthetized twice

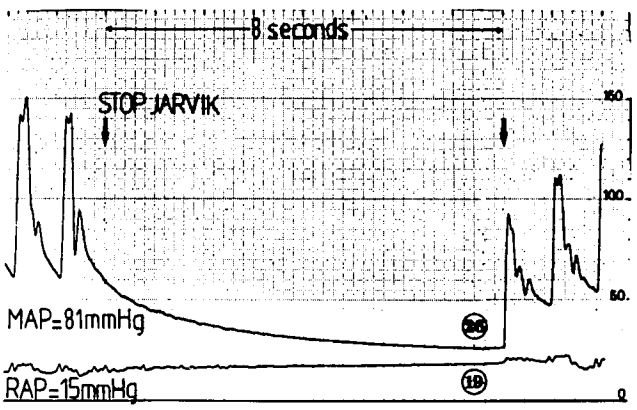

FIG. 1. Continuous recording of arterial pressure and right atrial pressure during an 8-s interruption of the Jarvik-7 artificial heart in patient 3. After an initial curvilinear decrease in arterial pressure, a plateau pressure is observed at 26 mmHg, whereas right atrial pressure stabilizes at 19 mmHg. After a few seconds of zero flow conditions, a 7 mmHg pressure gradient exists between arterial pressure and right atrial pressure, suggesting functional discontinuity between arterial and venous vascular beds due to a vascular waterfall.

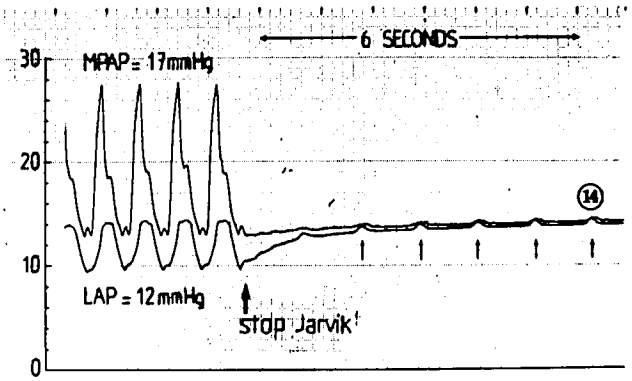

FIG. 2. Continuous recording of arterial pressure and left atrial pressure during a 6-s interruption of the Jarvik-7 artificial heart in patient 1. Both pressures rapidly stabilize at a level of 14 mmHg. The left atrium continues to beat in zero flow condition (arrows) and the pressure wave is transmitted backward to the pulmonary artery. The vascular waterfall concept does not apply to the normal pulmonary circulation.

at intervals ranging from 6 to 24 h. Isoflurane was used first in three patients and halothane was used first in the other two patients. End-tidal isoflurane and halothane concentrations were continuously measured by a Datex gas analyzer calibrated for halothane and isoflurane. Two different concentrations of gas were administered to every patient in random order, 1 MAC, and 1.5 MAC. Three series of hemodynamic and respiratory measurements were performed: 1) before administration of the volatile anesthetic agent (control); 2) after a steady state was reached at 1 MAC (end-tidal values of 0.75% for halothane and 1.25% for isoflurane); and 3) after a steady state was reached at 1.5 MAC (end-tidal values of 1.125% for halothane and 1.875% for isoflurane).

Each set of measurements were included in the following order: recording of CI and Jarvik settings, withdrawal of pulmonary and arterial blood samples, recording of hemodynamic and respiratory parameters in dynamic conditions, and recording of hemodynamic and respiratory parameters in zero flow conditions. In addition, an arterial blood sample was withdrawn at the end of each set of measurements to determine norepinephrine and epinephrine concentrations using a radioenzymatic assay. Normal values for epinephrine were 25–80 pg/ml and 200–400 pg/ml for norepinephrine. $FI_{O_2}1$ was used throughout the study period.

STATISTICAL ANALYSIS

All data are expressed as mean ± SD. All the studied parameters were analyzed using an analysis of variance (ANOVA) for two factors with repeated measures.[10] This analysis enabled us to 1) test the overall difference between the control and the two concentrations of drugs and 2) test the difference between the effects of the two drugs on each studied parameter. Analysis by contrasts was used to test the significance of the difference between the two concentrations of drugs and when the difference was significant to establish if the amplitude of the difference between the two concentrations was the same for the two drugs. The degrees of significance were calculated using the criterion of Huyn and Feldt, which is more appropriate for experimental designs with repeated measures (BMDP technical report) than the standard critical value of F. Each test was performed using BMDP software (UCLA University).

Results

As shown in table 3, CI, $C(a\text{-}\bar{v})_{O_2}$, $\dot{V}_{O_2}$, $\dot{D}_{O_2}$, Pa_{O_2}, Pa_{CO_2}, and catecholamine plasma concentrations remained unchanged throughout the study.

Both volatile anesthetics induced a significant decrease in systolic, diastolic, and mean arterial blood pressure (table 4). Isoflurane induced a significantly greater decrease in total vascular resistance index and in mean arterial pressure than that induced by halothane ($P < 0.001$). As shown in figure 3, systemic vascular resistance index, which is only dependent on the vascular tone of the arterial vessels, decreased significantly more with isoflurane than with halothane ($P < 0.001$).

Both volatile anesthetics decreased right atrial pressure,

TABLE 3. Metabolic and Respiratory Effects of Halothane and Isoflurane

	Halothane			Isoflurane		
	Control	1 MAC	1.5 MAC	Control	1 MAC	1.5 MAC
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.9 ± 0.4	2.8 ± 0.4	2.8 ± 0.1	2.8 ± 0.4	2.6 ± 0.6	2.8 ± 0.5
$C(a\text{-}\bar{v})_{O_2}$ (vol %)	3.8 ± 1.1	3.6 ± 1.2	4 ± 1.2	3.6 ± 0.5	3.2 ± 0.4	3 ± 0.6
$\dot{V}_{O_2}$ ($ml \cdot min^{-1} \cdot m^{-2}$)	98 ± 18	99 ± 21	109 ± 21	100 ± 4	87 ± 14	82 ± 16
$\dot{D}_{O_2}$ ($ml \cdot min^{-1} \cdot m^{-2}$)	349 ± 38	331 ± 70	323 ± 65	352 ± 77	326 ± 114	335 ± 110
Pa_{O_2} (mmHg)	296 ± 101	259 ± 120	221 ± 91	337 ± 108	349 ± 72	344 ± 82
Pa_{CO_2} (mmHg)	30 ± 6	31 ± 4	32 ± 5	30 ± 3	29 ± 2	30 ± 3
Norepinephrine (pg/ml)	474 ± 586	386 ± 317	206 ± 390	356 ± 92	433 ± 179	512 ± 269
Epinephrine (pg/ml)	100 ± 172	191 ± 135	96 ± 71	121 ± 118	103 ± 96	129 ± 95

Values are mean ± SD.

TABLE 4. Comparative Effects of Halothane and Isoflurane on Systemic and Venous Circulations

	Halothane			Isoflurane		
	Control	1 MAC	1.5 MAC	Control	1 MAC	1.5 MAC
SAP (mmHg)	159 ± 15	130 ± 17*	115 ± 15*	163 ± 8	111 ± 29*	90 ± 22*
DAP (mmHg)	79 ± 13	61 ± 16*	52 ± 12*	79 ± 8	49 ± 16*	38 ± 11*
MAP (mmHg)	100 ± 11	77 ± 18†	66 ± 13†‡	102 ± 17	65 ± 20†§	48 ± 11†‡§
TVR (units/m^2)	27 ± 11	22 ± 8†	18 ± 6†‡	30 ± 6	20 ± 6†§	13 ± 3†‡§
RAP (mmHg)	15 ± 2	14 ± 4	13 ± 4	16 ± 3	12 ± 2	11 ± 2
RAP_{zf} (mmHg)	21 ± 3	17 ± 4†	15 ± 4†	21 ± 4	15 ± 3†	13 ± 2†

Values are mean ± SD.
* $P < 0.05$, *versus* control value.
† $P < 0.01$, *versus* control value.
‡ $P < 0.05$, *versus* 1 MAC.
§ $P < 0.01$, *versus* halothane.

but the variation did not reach statistical significance ($P = 0.09$). In contrast, right atrial pressure measured in zero flow conditions (RAP_{zf}), which is dependent only on venous tone, was significantly reduced by halothane and isoflurane ($P < 0.01$).

Halothane and isoflurane induced a comparable and significant decrease in left atrial, systolic, diastolic, and mean pulmonary arterial pressures (table 5). A decrease in pulmonary vascular resistance was also observed with both drugs at 1.5 MAC, but the variation did not reach statistical significance ($P = 0.07$). Simultaneously, $P\bar{v}_{O_2}$ and pulmonary shunt remained unchanged, suggesting that hypoxic pulmonary vasoconstriction was not affected by both anesthetic agents.

Discussion

The presence of an artificial heart represents a unique opportunity to study the human peripheral vascular circulation, independent of changes affecting the cardiac function. Up until the present time, the peripheral vascular effects of anesthetic drugs have been studied through *in vitro* experiments using preparations of isolated vessels. Although useful, these experiments have two major disadvantages. First, hypothermia is often required to adequately maintain the preparation. Second, it is difficult to know whether the anesthetic concentration within the perfusion bath is close to physiologic concentrations obtained at the receptor level after parenteral administration of the anesthetic drug. It is also possible to study the peripheral vascular effects of anesthetic drugs during cardiopulmonary bypass.[11] However, cardiopulmonary bypass is, in many aspects, far from normal physiologic conditions[12]: pulsatile cardiac output is replaced by continuous flow; acute hemodilution is present, resulting in marked pharmacokinetic changes; various degrees of hypothermia (20–32° C) are used; and pulmonary circulation is excluded from the circulation. All these methodologic limitations are not encountered in patients with total artificial heart. Because right and left ventricular chambers eject a stroke volume at a preselected frequency, a normal pulsatile cardiac output is provided. By adequately setting drive pressures and systolic duration, cardiac output can be rendered preload- and afterload-independent. Therefore, if cardiac output and heart rate do not change, any change in arterial pressure, pulmonary arterial pressure, right atrial pressure, or left atrial pressure reflect a change in the vascular tone within the corresponding vascular bed. The term "cardiac filling pressure" does not apply any more to these pressures, which are no longer influenced by the mechanical properties of the ventricles.

Although patients with an artificial heart appear much closer to physiologic conditions than patients undergoing cardiopulmonary bypass, it is certain that the implantation of a cardiac prothesis affects the entire circulatory system; yet, the manner and extent are unknown. However, several points should be outlined. The arterial and pulmonary arterial pressure waveforms are similar to normal

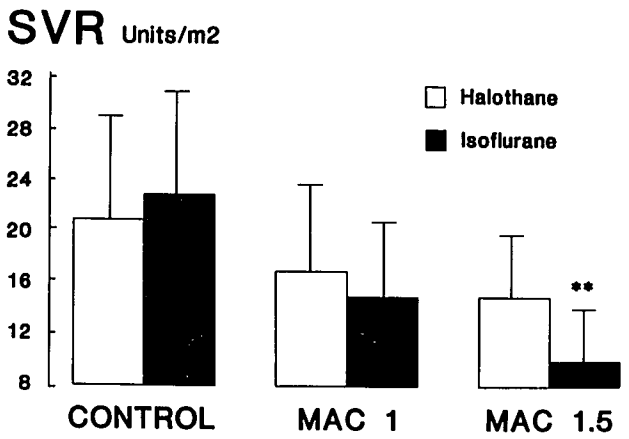

FIG. 3. Comparative changes in "true" SVR induced by two concentrations of halothane and isoflurane (1 MAC and 1.5 MAC) in five patients (mean ± SD). SVR is calculated as mean arterial pressure minus arterial pressure in zero flow conditions divided by cardiac index. Both anesthetic agents induce a significant decrease in SVR proportional to the MAC ($P < 0.01$). At 1.5 MAC isoflurane induces a significantly greater decrease in SVR than halothane (**$P < 0.01$).

TABLE 5. Comparative Effects of Halothane and Isoflurane on Pulmonary Circulation

	Halothane			Isoflurane		
	Control	1 MAC	1.5 MAC	Control	1 MAC	1.5 MAC
PAP systolic (mmHg)	39 ± 14	32 ± 19*	31 ± 16*	34 ± 12	30 ± 14*	28 ± 13*
PAP diastolic (mmHg)	15 ± 8	13 ± 8*	12 ± 9*	13 ± 7	11 ± 7*	9 ± 6*
MPAP (mmHg)	22 ± 10	19 ± 11†	17 ± 11†	19 ± 9	14 ± 9*	14 ± 8†
LAP (mmHg)	14 ± 6	10 ± 6*	11 ± 7*	11 ± 5	6 ± 5*	6 ± 5*
PVR (units/m^2)	3.6 ± 2.5	3.6 ± 2.7	2.6 ± 2.3	3.2 ± 2.2	3.5 ± 2.8	2.9 ± 2
$\dot{Q}_s/\dot{Q}_t$ (%)	28 ± 10	29 ± 7	28 ± 5	24 ± 5	25 ± 6	27 ± 9
$P\bar{v}_{O_2}$ (mmHg)	38 ± 4	38 ± 4	36 ± 2	38 ± 5	40 ± 3	41 ± 9

Values are mean ± SD.
* $P < 0.05$, *versus* control value.
† $P < 0.01$, *versus* control value.

physiologic waveforms. Following tracheal extubation these patients exhibit normal social behavior, have normal basic physiologic functions, can exercise, and do not complain of discomfort. The patients we studied were in the immediate postoperative period and still critically ill. Their blood catecholamine concentrations were slightly elevated but remained in the range of what is observed with postoperative critically ill patients. Two of them had normal catecholamine blood concentrations. Finally, we have no reason to think that the presence of a Jarvik-7 artificial heart could have markedly modified anesthetic-induced peripheral vascular effects.

The calculation of resistance characterizing the systemic circulation is derived from Poiseuille's law. Total vascular resistance is equal to the pressure decline within the arterial compartment divided by the flow. The pressure decline is assumed to be equal to the difference between mean arterial pressure and right atrial pressure. However, because of the existence of a permanent vascular tone, small arteries could close when the intravascular pressure declines below a critical closing pressure;[13] therefore, the true downstream pressure of the systemic circulation would be this critical closing pressure rather than right atrial pressure. According to a theory developed by Permutt,[9] if the arterial pressure at zero flow is higher than right atrial pressure, a vascular waterfall exists and the pressure flow relationship characterizing the systemic circulation is no longer influenced by the pressure within the venous bed and vice versa. Although the existence of critical closing pressure has been recently questioned,[13] our findings support the existence of a vascular waterfall within the systemic circulation. As shown in figure 1, the existence of a persistent gradient between pressures within the arterial and the venous beds after an 8-s period of zero flow suggests the existence of a functional discontinuity between the arterial and venous compartments. Similar results have been reported in patients undergoing placement of an automatic implantable converter defibrillator.[8] Such a gradient is not observed in the pulmonary circulation (fig. 2). These findings have the following important methodologic implications.

First, true systemic vascular resistance index should be calculated as mean arterial pressure minus arterial pressure measured in zero flow conditions divided by cardiac index. The standard calculation (mean arterial pressure minus right atrial pressure divided by cardiac index) tends to overestimate systemic resistance index. Because the existence of a Jarvik artificial heart made it possible to measure arterial pressure during zero flow conditions, true systemic vascular resistance index could be calculated in this study, thus enabling an accurate evaluation of the respective effects of halothane and isoflurane on arterial vessels. Second, the effects of halothane and isoflurane on the venous bed could also be accurately assessed. Because of the functional discontinuity existing between arterial and venous compartments, a decrease in arterial pressure does not automatically induce a decrease in right atrial pressure. Therefore, any decrease in right atrial pressure (which no longer depends on the right ventricle) is related to a decrease in the venous tone if cardiac index remains constant. Third, the presence of the Jarvik artificial heart gave the unique opportunity of studying the effects of isoflurane and halothane on pulmonary circulation. Pulmonary arterial pressure and left atrial pressure no longer depend on the right and left ventricles if artificial heart settings and right cardiac output remain unchanged. Therefore, any variation in these pressures reflects a change in vascular tone within the pulmonary circulation. Because of the absence of vascular waterfall in the pulmonary circulation, there is a functional continuity between pulmonary arteries and pulmonary veins, and any decrease in venous vascular tone will reduce not only left atrial pressure but also pulmonary arterial pressure and vice versa. Fourth, in the five patients included in the study right cardiac output, $P\bar{v}_{O_2}$, and alveolar oxygen tension remained unchanged throughout the study. Because these parameters are the main determinants of hypoxic pulmonary vasoconstriction, the specific effects of

halothane and isoflurane on hypoxic pulmonary vasoconstriction could be approached through changes in pulmonary shunt, a volatile anesthetic-induced increase in pulmonary shunt reflecting an inhibition in hypoxic pulmonary vasoconstriction.

We found that both halothane and isoflurane induced a decrease in mean arterial pressure, mean pulmonary arterial pressure, left atrial pressure, and right pressure measured in zero flow conditions. In accordance with the preceding discussion, these results clearly suggest that halothane and isoflurane decreased the vascular tone of each vascular compartment analyzed.

Both volatile agents decrease systemic arterial pressure in humans and produce arterial vasodilation.[14,15] However, it has been proposed that isoflurane decreases arterial pressure by reducing total peripheral resistance,[14] whereas halothane primarily reduces cardiac output.[16] Our study clearly demonstrates that both agents decrease systemic vascular resistance in a dose-dependent manner and that isoflurane is a more potent arterial vasodilator than halothane (fig. 3). Although some studies have shown that halothane could induce a venous dilatation,[17,18] isoflurane and halothane tend to increase right atrial pressure in humans.[14] Our results show that both volatile agents induce a comparable reduction in venous tone. Therefore, the increase in right atrial pressure observed in humans could be related to the anesthetic-induced myocardial depression.

The effects of halothane and isoflurane on pulmonary circulation are poorly documented and remain controversial,[14] mainly because of the difficulty in studying their pulmonary vascular effects independent of their systemic effects. Our results indicate that both anesthetics induce comparable pulmonary vasodilation, as suggested by a recent study.[19] Our study also shows that halothane and isoflurane do not markedly interfere with hypoxic pulmonary vasoconstriction, as recently suggested.[20]

Finally, administered to patients with an artificial heart, isoflurane and halothane appear to be potent vasodilators of all vascular compartments. What are the mechanisms involved? Although a previous study had suggested that a part of isoflurane-induced decrease in systemic vascular resistance index was related to a decrease in plasma norepinephrine concentration,[21] our results do not show any significant variation in plasma cathecholamine concentration following the administration of isoflurane or halothane. It has also been recently demonstrated that the vasodilation induced by clinical concentrations of isoflurane is not mediated by a mechanism of calcium entry blockade.[22] Most general anesthetics appear to inhibit sympathetic ganglionic transmission when used at clinical concentrations.[23] Isoflurane and halothane significantly depress postganglionic sympathetic efferent activity[24,25] and ganglionic transmission.[26] Therefore, it is not surprising to have found that they vasodilate systemic arteries, pulmonary vessels, and veins. However, isoflurane was found a more potent arterial vasodilator than halothane and, consequently, if volatile anesthetic agents are to be used in patients with an artificial heart, halothane could provide better cardiovascular stability than that provided by an equianesthetic concentration of isoflurane.

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