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The Cardiovascular Effects of Isoflurane in Lambs

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The effects of 1.0 and 1.5 minimum alveolar concentrations (MAC) of isoflurane on mean systemic arterial pressure, heart rate, stroke volume, cardiac output, total body oxygen consumption, myocardial oxygen consumption, and regional distribution of blood flow were studied in newborn lambs. Fractional extraction of oxygen for the total body and for the myocardium were calculated. MAC for isoflurane was first determined in eight lambs less than 10 days old. The mean value obtained was 1.51%. Six different lambs were used for cardiovascular study. Heart rate, stroke volume, cardiac output, and mean systemic arterial pressure decreased significantly during isoflurane anesthesia. Mean systemic arterial pressure and cardiac output decreased in a dose-dependent manner. Heart rate decreased significantly at 1.0 MAC isoflurane, but no further at 1.5 MAC. Stroke volume decreased only at 1.5 MAC. Cardiac output and total body oxygen consumption decreased by similar amounts at 1.0 MAC. Although cardiac output fell further at 1.5 MAC, oxygen consumption did not. Fractional extraction of oxygen increased only at 1.5 MAC. Myocardial blood flow and oxygen consumption decreased in parallel at 1.0 MAC, with no significant change during 1.5 MAC. Myocardial fractional oxygen extraction did not change. Although blood flow to all six body regions decreased significantly from control at both concentrations of isoflurane, blood flow to all organs except the adrenal did not differ significantly during 1.0 and 1.5 MAC. The authors conclude that a decrease in oxygen requirement during isoflurane anesthesia results in an appropriate decrease in oxygen delivery, with no apparent diversion of cardiac output from non-vital to vital organs. However, the increase in total body oxygen extraction at the higher concentration of isoflurane implies that the ability of the newborn to adapt to a decrease in oxygen supply may be limited during deeper levels of isoflurane anesthesia. (Key words: Anesthesia: pediatric. Anesthetics, volatile: isoflurane.)

ALTHOUGH MANY INVESTIGATORS have reported profound cardiovascular responses to inhalation anesthetics in adult animals and humans,[1–17] few have examined the cardiovascular responses of the newborn to these agents.[18–24,¶,**,††] Unfortunately, the information obtained from adults cannot be extrapolated to the younger organisms, because resting cardiovascular status and responses to stress in the newborn are different.[25–29]

At rest, cardiac output[25] and oxygen consumption[26] in the newborn lamb are high, limiting the reserve to increase oxygen delivery during periods of stress. Although cardiac output and oxygen consumption decrease rapidly during the first 4 weeks of life,[26] they do not reach adult levels for several months. All the major determinants of cardiac output demonstrate the lamb's limited reserve. Volume loading at birth is associated with an increase in cardiac output of only 35%, but by 4–6 weeks of life, the same load results in an increase in cardiac output of 58%.[25] Contractility at birth is near maximal, but, at 3–4 weeks, the lamb has a large reserve.[28] Heart rate at birth is high (approximately 220–240 bpm), limiting the lamb's potential to increase cardiac output in response to an increase in heart rate.[30,31] In addition, the newborn's reserve for increasing cardiac output also may be limited by immature neural control of the cardiovascular system.[32–35]

These characteristics raise important questions about the newborn's myocardial performance during anesthesia. Although several investigators have attempted to describe the effects of different inhalation agents in young animals and humans,[18–24] none have studied the effects of isoflurane. Thus, we examined the effects of 1.0 and 1.5 MAC isoflurane on the cardiovascular performance and distribution of cardiac output in normoxic lambs. We measured cardiac performance and myocardial and total body oxygen consumption simultaneously in order to correlate changes in performance (supply) with changes in oxygen consumption (demand).

Methods

MAC Studies

With approval from our Committee on Animal Research, we determined MAC for isoflurane in eight lambs less than 10 days old. We induced general anesthesia with isoflurane, measuring end-tidal concentra-

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tion after it had been constant for 15 min. We then briefly applied a clamp to one of the lamb's ears. If the lamb moved purposefully, we increased the concentration of isoflurane by 15–20%, maintaining it constant for 15 min prior to re-stimulation; if the lamb did not respond, we decreased the concentration by the same amount. We continued these adjustments until we had bracketed the concentration below and above which the lamb did and did not respond. End-tidal isoflurane concentrations were measured with a Beckman® LB-2 infared analyzer (Beckman Instruments, Inc., Fullerton, CA). MAC was calculated as the mean of the responses of these eight animals and was used in the subsequent studies.

Surgical Procedures

A thoracotomy was performed on six different lambs within 5 days of birth. General anesthesia was induced with halothane or isoflurane in oxygen. The trachea of each lamb was then intubated, and the lungs ventilated with a Harvard® pump. Catheters were inserted into the hind limb artery and vein. Through the fifth intercostal space, polyvinyl catheters were inserted through the left internal thoracic artery into the ascending aorta, through the internal thoracic vein into the superior vena cava, and directly into the left atrium, pulmonary artery, and coronary sinus. Because the hemiazygos vein in sheep drains into the coronary sinus, this vein was ligated distally and a catheter was inserted so that its tip was at the origin of the coronary sinus (the confluence of the hemiazygos and great cardiac veins). A precalibrated electromagnetic flow transducer (C&C Instruments, Culver City, CA) was placed around the main pulmonary artery. An 8F polyvinyl catheter was placed in the pleural space. The chest was closed in layers, and all catheters and transducer cables were tunneled through the skin and placed in a bag sutured to the lamb's flank. Catheters were flushed with 0.9% NaCl and filled with heparin daily. Intramuscular penicillin (200,000 units) and streptomycin (250 mg) were administered for 5 days following surgery. At least 3 days of recovery preceded any studies.

Experimental Protocol

All lambs were between 6 and 10 days old when cardiovascular studies began. Each remained with its mother and was allowed to feed at will until approximately 1 h before the study. Temperature was monitored by a rectal probe and was maintained normal (39° C) by placing a heating pad under the lamb and an infared lamp above.

Control measurements were taken while the lamb rested quietly. Aortic and pulmonary arterial mean and phasic pressures were measured with Statham P23Db® transducers, pulmonary arterial blood flow with a Statham SP2202® flowmeter, and heart rate with a Beckman® cardiotachometer triggered by the aortic pressure signal. Data were recorded on a direct writing Beckman® recorder. When the aortic, pulmonary, and left atrial pressures had been stable for 20 min, blood was drawn simultaneously from the aorta, pulmonary artery, and coronary sinus to measure hemoglobin concentration and oxygen saturation (Radiometer® hemoximeter) and blood gases (Corning® *p*H blood gas analyzer, model 158). Thereafter, 15-μ diameter radionuclide-labeled microspheres (57Co, 51Cr, 85Sr, 95Nb, 65Zn, 113Sn, 153Gd, 114In, 54Mn) were injected into the left atrium as blood was withdrawn from the ascending and descending aorta for 1.25 min at a rate of 4 $ml^{-1} \cdot min^{-1}$. Blood loss secondary to sampling was replaced with maternal blood after the microsphere injection.

General anesthesia was induced with isoflurane in oxygen, using a calibrated isoflurane vaporizer (Ohmeda,® Madison, WI) and fresh gas flows of 3–5 l/min delivered through an adult circle system. The trachea of each lamb was intubated and the lungs ventilated with a Ventimeter® ventilator (Narco Medical Co., Warminster, PA). No intravenous sedatives or muscle relaxants were administered. The inspired concentration of oxygen was adjusted to maintain aortic saturation equal to or greater than the control value, which was in the normal range for all animals. Ventilation was adjusted to maintain P_{CO_2} between 35 and 45 torr. Cardiovascular measurements and microsphere injections were repeated during 1.0 MAC and 1.5 MAC isoflurane. In three animals, the study of isoflurane at 1.5 MAC preceded the study at 1.0 MAC.

Data Analysis

Blood oxygen content was calculated as the sum of the oxygen bound to hemoglobin (the product of hemoglobin concentration, oxygen saturation, and binding capacity [1.36 ml O_2 per g Hgb]) and dissolved oxygen (the product of P_{O_2} and 0.003). Oxygen consumption was calculated by multiplying the difference between aortic and pulmonary arterial oxygen contents times cardiac output. Blood flow distribution and cardiac output were measured using the radionuclide-labeled microsphere technique with the least squares method.[36] Tissues were weighed, carbonized, and counted along with all drawn blood samples in a scintillation counter (Searle Analytic, Inc.) connected to a 512-channel pulse height analyzer. Samples were divided into six organ and body groups: adrenal, brain, carcass (muscle, bone, skin), heart, kidney, and splanchnic bed (spleen, gut,

TABLE 1. General Hemodynamics (n = 6)

	Awake	MAC 1.0	MAC 1.5
Mean systemic arterial pressure (mmHg)	76 ± 5	44 ± 11*	27 ± 6†
Heart rate (beats/min)	233 ± 33	148 ± 30*	140 ± 37*
Stroke volume (ml/kg)	1.4 ± 0.3	1.2 ± 0.5	0.9 ± .6*
SVR $\left(\frac{\text{mmHg}}{\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}}\right)$	248 ± 44	258 ± 42	307 ± 142
Cardiac output ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	316 ± 68	172 ± 37*	107 ± 60†
$\dot{V}O_2$ ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	16.9 ± 3.6	10.0 ± 2.0*	7.5 ± 2.0*
Systemic % oxygen extraction	50 ± 13	57 ± 9.8	68 ± 4.1*

* $P < 0.05$ Awake *vs.* MAC 1.0 or MAC 1.5.
† $P < 0.05$ MAC 1.0 *vs.* MAC 1.5.

and liver). Blood flow determined for the liver signified only hepatic arterial flow because microspheres are injected only into the left atrium. The left ventricular free wall was divided evenly into the inner and outer layers to determine the flow to each area. The ratio of the flow to each layer is the inner-to-outer ratio.

Eighty-eight percent of blood flow to the left ventricular free wall drains into the coronary sinus[37] (smaller percentages of flow from the left atrium, septum, and right ventricle also drain into the coronary sinus). By multiplying the difference between aortic and coronary sinus oxygen contents times the blood flow to the left ventricular free wall, we were able to calculate myocardial oxygen consumption. Fractional extraction of oxygen of the body and myocardium were calculated as the ratio of arteriovenous difference in blood oxygen content to arterial blood oxygen content.

Microsphere data are presented in two ways. First, total blood flow to each organ group is presented as milliliters per 100 grams of tissue weight per minute to measure any absolute change in blood flow from control. Second, flow to each organ group is calculated as a percent of the total cardiac output to evaluate for redistribution of blood flow toward or away from any organ group.

Data were analyzed by analysis of variance using repeated measures and the Student-Newman-Keuls test. A P value of less than 0.05 was considered significant.

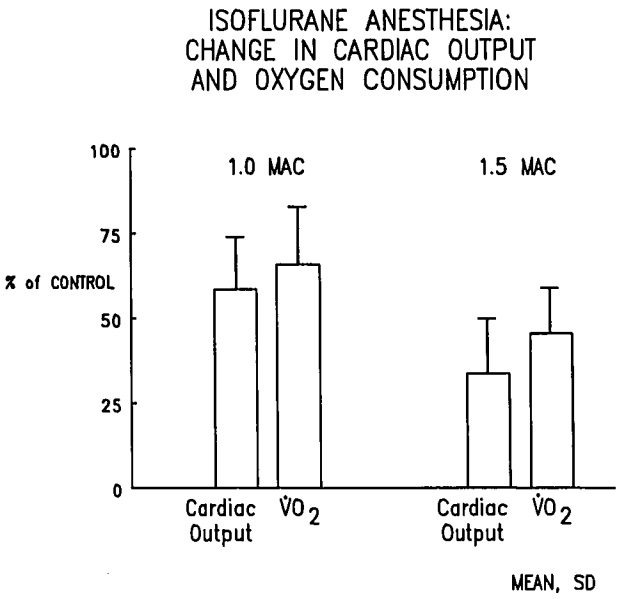

FIG. 1. Cardiac output (CO) and total body oxygen consumption ($\dot{V}O_2$) (as a % of control) decreased in parallel at both concentrations of isoflurane. The values represented are 58.7 ± 15 (CO) and 66.0 ± 16 ($\dot{V}O_2$) for 1.0 MAC and 33.9 ± 16 (CO) and 45.7 ± 13 ($\dot{V}O_2$) for 1.5 MAC.

Results

1.0 MAC for isoflurane in the newborn lamb ranged from 1.3–1.6% (end-tidal concentration). The mean for the eight values was 1.51%. To ensure immobility in all animals, 1.0 MAC for these studies was considered to be 1.60%.

General Hemodynamics

Heart rate, stroke volume, cardiac output, and mean systemic arterial pressure decreased significantly during anesthesia (table 1). Mean systemic arterial pressure and cardiac output decreased in a dose-dependent manner. Neither heart rate nor stroke volume followed this pattern: heart rate decreased significantly during 1.0 MAC isoflurane, but no further at 1.5 MAC; stroke volume decreased significantly only at 1.5 MAC. Systemic vascular resistance (SVR) did not change significantly.

Cardiac output and total body oxygen consumption decreased in parallel at both 1.0 and 1.5 MAC isoflurane (fig. 1). Both decreased significantly from control at 1.0 MAC, but only cardiac output fell significantly further at 1.5 MAC (table 1). Fractional extraction of oxygen of the total body increased significantly at 1.5 MAC (table 1).

The Myocardium

Myocardial blood flow and oxygen consumption decreased dramatically during 1.0 MAC isoflurane, but not significantly further during 1.5 MAC (table 2). They decreased in parallel at both concentrations (fig. 2). The inner-to-outer ratio of flow to the left ventricular free wall also decreased at both concentrations, but not significantly (table 2). Myocardial fractional oxygen extraction did not change.

TABLE 2. Myocardial Blood Flow, Myocardial Oxygen Consumption (n = 5), Inner/outer Ratio (Flow to Left Ventricular Free Wall) (n = 6)

	Awake	MAC 1.0	MAC 1.5
Myocardial blood flow (ml · 100g^{-1} · min^{-1})	250 ± 128	88 ± 32*	50 ± 19*
$M\dot{V}O_2$ (ml · 100g^{-1} · min^{-1})	18.7 ± 9.1	7.1 ± 2.7*	4.5 ± 1.6*
Inner/outer ratio	1.81 ± 0.50	1.50 ± 0.49	1.49 ± 0.46
Myocardial % oxygen extraction	70 ± 7.3	77 ± 7.4	76 ± 14

* $P < 0.05$ Awake *vs.* MAC 1.0 or MAC 1.5.
† $P < 0.05$ MAC 1.0 *vs.* MAC 1.5.

REGIONAL BLOOD FLOW

Blood flow to all six organ and body groups decreased (table 3). Regional blood flow in all six groups was significantly lower during 1.0 and 1.5 MAC isoflurane than during the control period. However, blood flows at 1.0 and 1.5 MAC did not differ significantly, except in the adrenal, where blood flow during 1.5 MAC was significantly lower than that during 1.0 MAC.

A redistribution of blood flow also occurred at both anesthetic concentrations (table 4). The percent of cardiac output to the kidney decreased significantly during 1.0 MAC isoflurane, and fell further during 1.5 MAC. The percent of cardiac output to the myocardium decreased significantly during 1.0 MAC. At 1.5 MAC, the percent of cardiac output to the adrenal decreased significantly, and cardiac output to the brain increased significantly. Cardiac output to the carcass and splanchnic bed remained unchanged at both 1.0 and 1.5 MAC.

Discussion

Isoflurane has widespread effects on the cardiovascular system of the newborn lamb, some of which are different from those described for adult animals and humans. Isoflurane decreases blood pressure in the adult human primarily by decreasing systemic vascular resistance,[2] and, in the newborn lamb, by decreasing cardiac output. The difference in response in the lamb may be due to characteristics specific to the newborn's cardiovascular system. Mean systemic arterial pressure in the newborn is lower than that in the older animal, while cardiac output is higher (300–425 ml · kg^{-1} · min^{-1}). Thus, the effects of isoflurane on SVR in the newborn may be much less noticeable than its effects on cardiac output. In infants younger than 6 months, Friesen[38] noted that mean systemic arterial pressure and heart rate decreased during induction of anesthesia with isoflurane by amounts similar to those reported during induction with halothane.[39] Because these effects were studied during induction, steady-state and end-tidal concentrations of the inhaled agents were not reported. However, isoflurane decreased heart rate in both the newborn lamb and human, suggesting that this agent causes a uniform, age-related difference in response. Unfortunately, the effects of isoflurane on cardiac output, oxygen consumption, myocardial blood flow, and myocardial oxygen consumption are unknown in the newborn human.

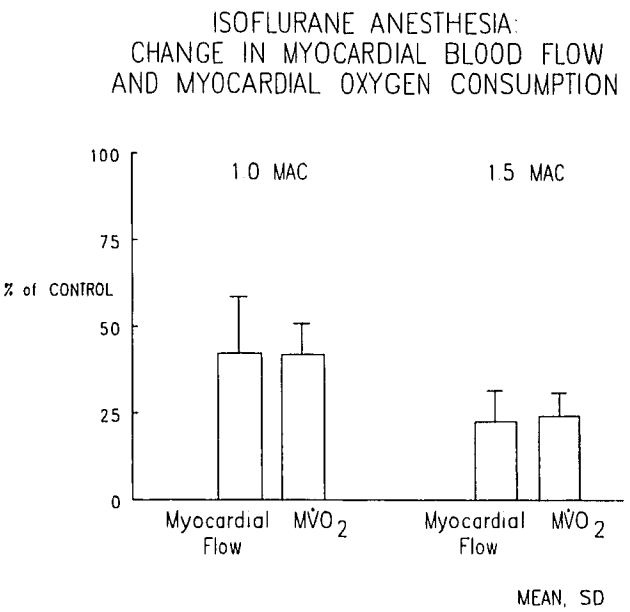

FIG. 2. Myocardial blood flow and myocardial oxygen consumption ($M\dot{V}O_2$) (as a % of control) decreased similarly at both 1.0 and 1.5 MAC isoflurane. Values for myocardial blood flow and $M\dot{V}O_2$ at 1.0 MAC were 42.4 ± 16 and 42.1 ± 8.9, respectively. Values at 1.5 MAC were 22.8 ± 8.9 (myocardial blood flow) and 24.4 ± 6.7 ($M\dot{V}O_2$).

During both 1.0 and 1.5 MAC isoflurane, total body and myocardial oxygen consumption in the newborn lamb decreased. Oxygen delivery and cardiac output also decreased. The decrease in cardiac output and in oxygen consumption was similar (fig. 1), suggesting that the decrease in oxygen delivery resulted from a decrease in demand. At 1.5 MAC isoflurane, total body extraction of oxygen increased significantly. However,

TABLE 3. Regional Blood Flow (ml · 100g^{-1} · min^{-1}) (n = 6)

	Awake	MAC 1.0	MAC 1.5
Adrenal	252 ± 73	112 ± 39*	46 ± 37†
Brain	111 ± 26	73 ± 27*	63 ± 37*
Carcass	24 ± 8	12 ± 3*	6.7 ± 3.5*
Myocardium	179 ± 81	65 ± 26*	38 ± 17*
Kidney	348 ± 102	112 ± 16*	38 ± 17*
Splanchnic	76 ± 25	49 ± 6*	30 ± 14*

* $P < 0.05$ Awake *vs.* MAC 1.0 or MAC 1.5.
† $P < 0.05$ MAC 1.0 *vs.* MAC 1.5.

TABLE 4. Regional Flow: % Cardiac Output (n = 6)

	Awake	MAC 1.0	MAC 1.5
Adrenal	0.198 ± .08	0.157 ± .06	0.098 ± .04*
Carcass	51.8 ± 8.1	49.0 ± 4.6	45.27 ± 2.6
Splanchnic	26.5 ± 7.6	29.1 ± 3.6	29.5 ± 3.4
Kidney	10.1 ± 2.8	5.83 ± 1.0*	3.46 ± .97†
Myocardium	6.38 ± 1.9	4.43 ± 1.0*	5.20 ± 1.7*
Brain	4.07 ± 1.3	4.88 ± 1.1	6.03 ± 1.5*

* $P < 0.05$ Awake *vs.* MAC 1.0 or MAC 1.5.
† $P < 0.05$ MAC 1.0 *vs.* MAC 1.5.

total extraction in the awake lamb had been only 50%. The anesthetized newborn was, therefore, able to adapt to low-flow state during 1.5 MAC by increasing oxygen extraction in various organs. Although acidosis did not develop, this increase in extraction at the higher concentration implied that the balance between oxygen supply and oxygen demand was approaching a limit. While we did not conduct our studies at deeper planes of anesthesia, it is probably safe to predict that higher concentrations of isoflurane would produce a decrease in oxygen supply that would result in metabolic decompensation when and if further adaptation (decrease in demand) were no longer possible. At that point, acidosis and redistribution of cardiac output would occur, with eventual permanent injury.

At both anesthetic concentrations, there was an absolute decrease in cardiac output, but no acidosis or significant redistribution of cardiac output to vital organs. Cardiac output was not diverted from the carcass and the splanchnic bed to the vital organs. In fact, the percent of cardiac output to the kidney, adrenal, and myocardium was significantly reduced. Oxygen delivery appeared to match oxygen demand. Myocardial blood flow decreased in exact proportion to the decrease in myocardial oxygen consumption (fig. 2). The inner:outer flow ratio was normal. The percent of myocardial oxygen extraction remained unchanged. These data indicate that the decrease in myocardial oxygen delivery did not exceed the decrease in myocardial oxygen demand during isoflurane anesthesia.

In studies of the cardiovascular responses to halothane and enflurane anesthesia in newborn, weanling and adult sheep, Robinson and Gregory‡‡§§ noted changes in mean systemic arterial pressure, heart rate, systemic vascular resistance, and total body oxygen consumption similar to those we observed during isoflurane. However, their methods of measurement differed from ours. They reported their results as "fraction of awake" values and, although they too measured regional distribution of cardiac output using microspheres, the organ groups studied were different. Similarly, they reported distribution of cardiac output in terms of flow/100 grams/minute, but did not report flow in terms of percent of cardiac output distributed to each organ. Finally, they did not measure myocardial oxygen consumption or calculate total body or myocardial oxygen extraction. In spite of these methodological differences, their results provide a useful comparison to our own.

In the newborn lamb, Robinson and Gregory found that heart rate decreased significantly during 1.0 MAC halothane (83% of control) and 1.0 MAC enflurane (59% of control), but no further at 1.5 MAC of either agent. Heart rate also decreased in weanling (65% of control) and adult sheep (84% of control) during 1.0 MAC enflurane, but remained at near-control level during 1.0 MAC halothane. When we compare our results to theirs, heart rate in the newborn lamb can be seen to decrease dramatically during inhalational anesthesia with all three agents, enflurane, halothane, and isoflurane. The decreases in cardiac output they report in the newborn lamb were similar during 1.0 MAC halothane (61% of control) and 1.0 MAC enflurane (59% of control), and only slightly smaller than the decrease we observed during isoflurane. In older sheep, the decrease in cardiac output was similar to that in newborns during enflurane, but significantly smaller than that (approximately 80% of control) during halothane. Consequently, there appears to be no clear-cut age-related difference in the response of cardiac output to the three inhaled agents. In addition, no one of these three agents appears to provide a clear advantage in maintaining newborn heart rate and cardiac output during anesthesia. As in our study, oxygen consumption and cardiac output decreased in parallel at both doses of anesthetic.

Robinson and Gregory also reported that total blood flow to brain, kidney, and heart in the newborn decreased, similar to our findings during isoflurane. Although they did not report the exact percent of cardiac output distributed to each organ, they found that total cardiac output and total flow/100 g/min to each organ group decreased to similar percents of control. This outcome suggests that there was no redistribution of flow away from nonvital organs toward vital organs, and is similar to the outcome we observed during isoflurane.

In summary, the cardiovascular system of the newborn lamb responds dramatically to isoflurane, but follows a pattern different from that reported for the adult animal and human. When oxygen requirements in the newborn decrease, a proportional decrease in oxygen delivery results. At anesthetic concentrations of 1.0 and

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§§ Robinson S, Gregory GA, Fisher D, Hoffman JIE, Rudolph AM: Circulatory effects of anesthesia in the developing sheep. II. Enflurane (abstract). ANESTHESIOLOGY 53:S331, 1980

1.5 MAC isoflurane and in the absence of coronary-artery disease, the newborn cardiovascular system was able to regulate oxygen delivery to accommodate changes in oxygen demand.

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