

Cardiovascular and Metabolic Response to Acute Normovolemic Anemia

Effects of Anesthesia

Brigitte E. Ickx, M.D.,* Michel Rigolet, M.D.,† Philippe J. Van der Linden, M.D., Ph.D.‡

Background: The maintenance of adequate tissue oxygenation during acute anemia depends on an increase in both cardiac output and tissue oxygen extraction. This study tested the hypothesis that anesthesia blunts the cardiac output response associated with acute normovolemic hemodilution.

Methods: Forty patients undergoing major abdominal surgery were prospectively randomized to undergo acute normovolemic hemodilution (ANH) either awake (awake group, n = 20) or with fentanyl–nitrous oxide–isoflurane anesthesia (anesthetized group, n = 20). Radial and pulmonary artery catheters were placed in all patients. After hemodynamic measurements were taken, patients in the two groups underwent hemodilution to decrease their hemoglobin concentration from 13 to 8 g/dl. A total of $1,875 \pm 222$ ml (mean \pm SD) of blood was collected and simultaneously replaced by the same volume of medium molecular weight hydroxyethylstarch in both groups.

Results: In the awake group, ANH resulted in a significant increase in cardiac index (from 3.1 ± 0.5 to 4.8 ± 1.0 $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) related to both an increase in heart rate and stroke index. Oxygen delivery remained unchanged, but oxygen consumption increased significantly, resulting in an increase in oxygen extraction ratio. In the anesthetized group, ANH resulted in a significantly smaller increase in cardiac index (from 2.3 ± 0.5 to 3.1 ± 0.7 $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) related solely to an increase in stroke index. Oxygen delivery decreased but oxygen consumption was maintained as oxygen extraction increased.

Conclusions: Anesthesia significantly reduces the cardiac output response associated with ANH. This could be related to the effects of the anesthetic drugs on the autonomic and the cardiovascular systems. (Key words: Anesthetic agents; cardiovascular system; oxygen consumption; oxygen transport.)

THE maintenance of adequate tissue oxygenation during normovolemic hemodilution depends on both an increase in cardiac output and an increase in blood oxygen extraction.¹ The increase in cardiac output is achieved by an increase in stroke volume and, to some extent, increase in heart rate.¹⁻³ As demonstrated in experimental studies, a decrease in blood viscosity plays a fundamental role by decreasing myocardial afterload and increasing venous return.⁴⁻⁶ Other studies have shown an increase in myocardial contractility,^{7,8} which could be

caused by an increase in sympathetic tone related to the activation of aortic chemoreceptors.⁹ Increase in blood oxygen extraction has been related to blood flow redistribution according to regional metabolic demand¹⁰ and to a better spatial and temporal redistribution of erythrocytes into the capillary network.¹¹ In conscious humans, Weiskopf *et al.*¹² recently demonstrated that an increase in cardiac output and oxygen extraction ratio allows the maintenance of adequate tissue oxygenation up to a hemoglobin concentration of 5.0 g/dl.

The influence of anesthesia on these compensatory mechanisms remains poorly studied in humans. Because most anesthetic agents decrease myocardial contractility and venous return,^{13,14} they may blunt the compensatory increase in cardiac output observed during acute normovolemic hemodilution. The use of opioids, such as fentanyl, by the bradycardia they are able to induce¹ could aggravate this effect. We tested this hypothesis in patients undergoing major abdominal surgery in whom intentional acute preoperative normovolemic hemodilution was part of the blood conservation program.

Materials and Methods

The Committee on Human Research of our institution approved this prospective, randomized, single-blinded study. Forty patients (American Society of Anesthesiologists physical status II or III) scheduled for major cancer surgery were enrolled after giving written informed consent. Criteria for inclusion in the study were a screening hemoglobin concentration more than 12 g/dl and the absence of contraindications to normovolemic hemodilution, including the presence of disabling or unstable angina, congestive heart failure (New York Heart Association III/IV), valvular disease, electrocardiographic rhythm other than regular sinus, uncontrolled hypertension, significant respiratory disease (arterial oxygen partial pressure less than 60 mmHg at room air), uncontrolled diabetes mellitus, acute infection, and coagulopathy. Exclusion criteria included significant hepatic (total bilirubin concentration more than 1.5 or aspartate transaminase or alanine transaminase concentrations more than 2 times the upper normal range) and renal (serum creatinin concentration more than 1.3 mg/dl) diseases and known allergy to hydroxyethylstarches.

Usual medication, except for platelet antiaggregates (discontinued at least 1 week before surgery) was administered on the morning of the procedure. Patients

* Assistant Professor, † Resident, Department of Anesthesiology, Erasme University Hospital; ‡ Professor, Department of Anesthesiology, University Hospital of Charleroi, Jumet, Belgium.

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Address reprint requests to Dr. Van der Linden: Department of Anesthesiology, CHU Charleroi, Site de Jumet, 73, route de Gosselies, 6040 Jumet, Belgium. Address electronic mail to: pvanderlinden@skynet.be. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

were premedicated with alprazolam 0.5 mg orally 1 h before the arrival in the operating room. They were equipped with an electrocardiogram lead V₅, a pulse oximeter, and a noninvasive blood pressure monitoring. Forty percent oxygen was provided through a facial mask. A 16-gauge catheter was inserted in a peripheral vein for fluids and drug infusion. After intravenous administration of 2 mg midazolam, a 20-gauge catheter was inserted in a radial artery for arterial pressure monitoring and blood sampling. A modified pulmonary artery catheter (Swan Ganz model 93A-43IH-7,5F; Baxter-Edwards, Irvine, CA) was inserted percutaneously through the internal jugular vein during local anesthesia. This catheter, allowing right ventricular ejection fraction measurement and determination of right ventricular end-diastolic volume, was positioned with its proximal port located 2 cm proximal to the tricuspid valve.

Acute Normovolemic Hemodilution Protocol

Acute normovolemic hemodilution (ANH) was performed either before or after induction of anesthesia. Blood was withdrawn from a peripheral vein to reach a target hemoglobin level of 8 g/dl and was simultaneously replaced by the same volume of 6% medium-weight hydroxyethylstarch (130/0.4/11, 10 patients in each group; or 200/0.5/5.1, 10 patients in each group; Fresenius AG, Bad Homburg, Germany). Blood collected in standard citrate-phosphate-dextrose storage bags was stored at room temperature and reinfused to the patient whenever necessary during surgery. Hemoglobin was measured using a cooximeter (Instrumentation Laboratory, Milan, Italy). Mean arterial pressure was carefully monitored during the ANH procedure. When mean arterial pressure decreased by more than 30% from baseline values, 5-mg ephedrine bolus doses were administered.

Anesthetic Technique

Anesthesia was induced with fentanyl (3 μ g/kg) and thiopental (3 mg/kg). The trachea was intubated after administration of cisatracurium (0.15 μ g/kg), and the patient underwent ventilation with a mixture of oxygen-nitrous oxide 40-60%. Respiratory rate was set at 12 min^{-1} , and tidal volume was adjusted to obtain an arterial carbon dioxide partial pressure of 40 mmHg. Anesthesia was maintained with isoflurane 0.4-1% end tidal and fentanyl bolus doses (50-100 μ g, according to patient's body weight). No fentanyl bolus doses were allowed during the hemodilution procedure.

Hemodynamic Measurements

Mean arterial pressure, mean pulmonary artery pressure, pulmonary artery occluded pressure, and right atrial pressure were measured through pressure transducers (model T321571A, Baxter) with the zero refer-

ence set at the midchest level. Electrocardiogram was used for determination of heart rate. Cardiac output was determined at least in triplicate by the thermodilution technique, using 10 ml of cold saline ($< 10^{\circ}\text{C}$) and a closed system (CO-set, Baxter). The injection was started at the end of inspiration.¹⁶ Right ventricular ejection fraction was simultaneously determined with each cardiac output measurement, using an algorithm based on an exponential analysis of the thermodilution curve and a computer (REF-1, Baxter). With this technique, the normal value of right ventricular ejection fraction is approximately 45%.^{17,18} Immediately after cardiac output determination, arterial and venous blood gases were analyzed with an automated system (Instrumentation Laboratory), and oxygen saturation and hemoglobin were measured with the cooximeter. Cardiac index, stroke index, systemic vascular resistance, left ventricular stroke work index, oxygen delivery (Do_2), oxygen consumption ($\dot{V}\text{O}_2$), and oxygen extraction were calculated using standard formulas. Right ventricular end-diastolic volume index was calculated by dividing stroke index by right ventricular ejection fraction. Body temperature was continuously monitored by the thermistor of the flow-directed thermodilution catheter.

Measurements and Data Analysis

Patients were randomized to undergo ANH either before (awake group, $n = 20$) or after induction of anesthesia (anesthetized group, $n = 20$). In the awake group, hemodynamic measurements were performed within 10 min after the insertion of the catheters (baseline) and 10 min after the end of the hemodilution procedure (after ANH). In the anesthetized group, hemodynamic measurements were performed within 10 min after the insertion of the catheters (baseline), within 10 min after induction of anesthesia (before ANH), and 10 min after the end of hemodilution (after ANH). Accordingly, the time point "baseline" was also the time point "before ANH" in the awake group. Ephedrine bolus doses were not allowed within the 10 min preceding the hemodynamic measurements.

Statistical Analysis

Demographic data were compared in the two groups using a Student *t* test. Differences for gender were assessed using a Fisher exact probability test. Hemodynamic data at baseline were compared in the two groups using one-way analysis of variance. Hemodynamic data obtained before and after ANH in the two groups were compared using a two-way analysis of variance, followed by pairwise comparisons using Bonferroni adjustments. A *P* value < 0.05 was considered significant. Results are presented as mean values \pm SD.

Table 1. Demographic Data

	Awake Group (N = 20)	Anesthetized Group (N = 20)
Age (yr)	62 ± 6	61 ± 7
BSA (m ²)	1.92 ± 0.11	1.92 ± 0.17
Gender (M/F)	20/0	19/1
ASA classification (II/III)	9/11	13/7
Medications		
β-blockers (%)	25	30
Ca ⁺⁺ blockers (%)	15	5

ASA = American Society of Anesthesiologists; BSA = body surface area; Ca = calcium.

Results

Demographic data were similar in the two groups (table 1). To reach the target hemoglobin level, the exchanged volume was 1,875 ± 222 ml in both groups. Time to perform hemodilution was 49 ± 13 min in the awake group and 41 ± 10 min in the anesthetized group. In the latter group, no fentanyl was administered throughout the hemodilution procedure, while isoflurane concentration was maintained constant in each patient (mean end-tidal concentration, 0.44 ± 0.19%). Two patients in this group required ephedrine (patient no. 6, 5 mg; patient no. 16, 20 mg) to sustain mean arterial pressure. The last dose of ephedrine was administered, respectively, 25 and 40 min before the hemodynamic measurements after ANH was performed.

In the awake group, ANH was associated with an increase in cardiac index, related to both an increase in heart rate and stroke index (table 2). Systemic vascular resistance decreased, and left ventricular stroke work index increased. Mean pulmonary artery pressure, right ventricular end-diastolic volume index, and right ventricular stroke work index also increased. Despite the decrease in arterial oxygen content, $\dot{V}O_2$ remained stable, but $\dot{V}O_2$ increased, resulting in an increase in oxygen extraction (table 2).

In the anesthetized group, ANH was associated with an increase in cardiac index, related solely to an increase in stroke index (table 2). Mean arterial pressure and systemic vascular resistance decreased. Right ventricular end-diastolic volume index increased. The decrease in arterial oxygen content was associated with a slight decrease in $\dot{V}O_2$, but $\dot{V}O_2$ was maintained as oxygen extraction increased. Between the two groups, there was a significant different response to ANH for body temperature, heart rate, cardiac index, and $\dot{V}O_2$.

For a similar increase in right ventricular end-diastolic volume index and pulmonary artery occluded pressure, right and left ventricular stroke work index increased more in the awake than in the anesthetized group (fig. 1).

Discussion

During acute normovolemic hemodilution, the maintenance of an adequate oxygen supply to the tissues depends on an increase in cardiac output and tissue oxygen extraction. In the conditions of the present study, anesthesia reduced significantly the increase in cardiac output associated with the reduction in the oxygen-carrying capacity of the blood. In the anesthetized patients, the increase in cardiac output was only related to an increase in stroke volume, whereas in the awake patients, the cardiac output increase resulted from both an increase in stroke volume and heart rate. Comparing data obtained in conscious^{12,19,20} and anesthetized humans^{17,19,21,22} undergoing acute isovolemic hemodilution resulted in similar observations. The absence of heart rate increase observed during ANH in anesthetized subjects is probably related to a depression of the autonomic nervous system by the anesthetic agents. In animals deprived of their autonomic system, heart rate did not increase during isovolemic anemia, and the increase in cardiac output was significantly lower than in intact animals.²³ A parasympathetic stimulation related to the central vagal stimulation induced by the fentanyl could also contribute to the absence of heart rate increase observed in the anesthetized subjects.¹⁵

The increase in stroke volume during hemodilution has been attributed to the decreased blood viscosity resulting in both an increased venous return and a reduced myocardial afterload, and possibly to an increased myocardial contractility caused by activation of the cardiac sympathetic nerves.⁶⁻⁹ Anesthetic agents may inter-

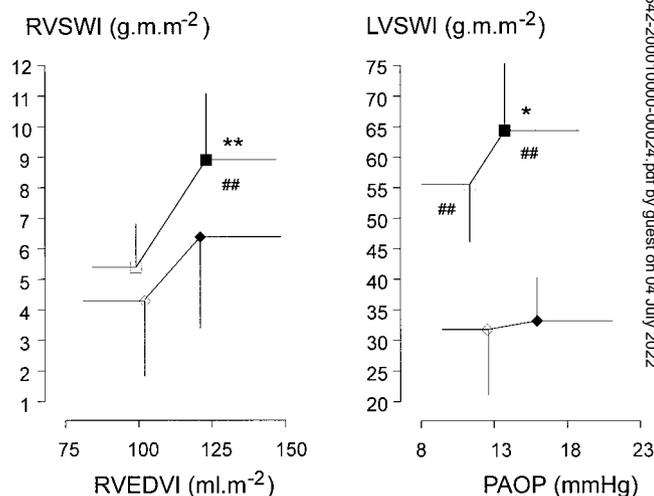


Fig. 1. (Left) Evolution of right ventricular stroke work index (RVSWI) as a function of right ventricular end-diastolic volume index (RVEDVI) during acute normovolemic hemodilution. **(Right)** Evolution of left ventricular stroke work index (LVSWI) as a function of pulmonary artery occluded pressure (PAOP) during acute normovolemic hemodilution. Squares = awake patients; diamonds = anesthetized patients; open symbols = before ANH; closed symbols = after ANH. * $P < 0.05$; ** $P < 0.01$ after versus before acute normovolemic hemodilution. ## $P < 0.01$ in awake versus anesthetized groups.

Table 2. Effects of Hemodilution in the Awake and the Anesthetized Groups

		Baseline	Before ANH	After ANH
Temperature (°C)	Awake		36.3 ± 0.3	36.2 ± 0.3
	Anesthetized		36.1 ± 0.3	35.7 ± 0.4†§
Heart rate (beats/min)	Awake	36.4 ± 0.3	69 ± 10	80 ± 10†
	Anesthetized		66 ± 12	66 ± 10§
MAP (mmHg)	Awake	77 ± 15	102 ± 14	93 ± 15
	Anesthetized		78 ± 14§	67 ± 10*§
MPAP (mmHg)	Awake	110 ± 15	15.4 ± 3.4	19.2 ± 5.3*
	Anesthetized		18.1 ± 3.7	21.2 ± 4.7
PAOP (mmHg)	Awake	16.7 ± 3.3	11.3 ± 3.3	13.7 ± 5.1
	Anesthetized		12.5 ± 3.1	15.9 ± 5.1
RAP (mmHg)	Awake	10.5 ± 3.2	6.6 ± 3.0	8.3 ± 4.2
	Anesthetized		9.4 ± 3.2	11.7 ± 4.2‡
CI (l · min ⁻¹ · m ⁻²)	Awake	6.6 ± 3.5	3.1 ± 0.5	4.8 ± 1.0†
	Anesthetized		2.3 ± 0.5§	3.1 ± 0.7†§
RVEF (%)	Awake	3.2 ± 0.6	45.4 ± 6.3	49.6 ± 5.8
	Anesthetized		34.8 ± 6.5§	40.4 ± 8.1§
SI (ml/m ⁻²)	Awake	42.0 ± 5.9	45.1 ± 7.0	60.5 ± 9.9†
	Anesthetized		34.9 ± 7.6§	47.4 ± 7.5†§
RVEDVI (ml/m ⁻²)	Awake	42.6 ± 6.2	99 ± 15	123 ± 24†
	Anesthetized		102 ± 21	121 ± 28*
SVR (d · s · cm ⁻⁵)	Awake	103 ± 21	1331 ± 290	760 ± 194†
	Anesthetized		1322 ± 365	779 ± 198†
LVSWI (g · m · m ⁻²)	Awake	1365 ± 287	55.4 ± 10.2	64.3 ± 11.6*
	Anesthetized		31.7 ± 11.6§	33.0 ± 7.2§
RVSWI (g · m · m ⁻²)	Awake	57.6 ± 13.6	5.4 ± 1.5	8.9 ± 2.3†
	Anesthetized		4.3 ± 2.6	6.4 ± 3.2§
Hb (g/dl ⁻¹)	Awake	5.9 ± 2.6	13.7 ± 0.9	8.6 ± 1.1†
	Anesthetized		13.4 ± 1.0	7.9 ± 0.9†
Arterial pH (U)	Awake	13.8 ± 1.0	7.41 ± 0.02	7.38 ± 0.03†
	Anesthetized		7.40 ± 0.04	7.39 ± 0.04
Paco ₂ (mmHg)	Awake	7.40 ± 0.02	41.5 ± 3.1	41.8 ± 3.5
	Anesthetized		40.8 ± 5.8	38.0 ± 4.7‡
PaO ₂ (mmHg)	Awake	41.5 ± 4.0	154 ± 33	171 ± 28
	Anesthetized		196 ± 59‡	178 ± 43
SaO ₂ (%)	Awake	143 ± 23	96.3 ± 1.8	97.0 ± 1.1
	Anesthetized		96.6 ± 1.5	97.0 ± 1.2
CaO ₂ (ml/dl ⁻¹)	Awake	96.5 ± 1.8	18.8 ± 1.2	12.1 ± 1.6†
	Anesthetized		18.7 ± 1.4	11.2 ± 1.1†
PvO ₂ (mmHg)	Awake	18.9 ± 1.4	43.8 ± 2.8	42.1 ± 2.4
	Anesthetized		47.2 ± 7.9	42.5 ± 6.5*
SvO ₂ (%)	Awake	45.2 ± 3.8	76.9 ± 3.7	74.6 ± 4.4
	Anesthetized		77.5 ± 5.7	72.2 ± 6.0†
CvO ₂ (ml/dl ⁻¹)	Awake	78.5 ± 3.6	14.7 ± 1.2	9.0 ± 1.4†
	Anesthetized		14.7 ± 1.8	8.1 ± 1.2†
Do ₂ (ml · min ⁻¹ · m ⁻²)	Awake	15.2 ± 1.4	575 ± 90	577 ± 112
	Anesthetized		424 ± 116§	349 ± 93§
Vo ₂ (ml · min ⁻¹ · m ⁻²)	Awake	616 ± 146	121 ± 17	145 ± 29†
	Anesthetized		88 ± 14§	94 ± 11§
O ₂ ER (%)	Awake	120 ± 27	21.4 ± 3.3	25.4 ± 4.0*
	Anesthetized		21.7 ± 5.1	28.1 ± 6.0†

In the awake group, the time point *Before ANH* corresponds to the time point *Baseline*.

* $P < 0.05$, † $P < 0.01$ versus before hemodilution, ‡ $P < 0.05$, § $P < 0.01$ anesthetized versus awake patients.

|| Significantly different response to ANH between groups.

ANH = acute normovolemic hemodilution; CaO₂ = arterial oxygen content; CvO₂ = mixed venous oxygen content; Hb = hemoglobin; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; Paco₂ = arterial carbon dioxide tension; PaO₂ = arterial oxygen tension; PAOP = pulmonary artery occlusion pressure; PvO₂ = mixed venous oxygen tension; SaO₂ = arterial oxygen saturation; SvO₂ = mixed venous oxygen saturation; SVR = systemic vascular resistance; RAP = right atrial pressure; CI = cardiac index; RVEF = right ventricular ejection fraction; SI = stroke index; RVEDVI = right ventricular end-diastolic volume index; LVSWI = left ventricular stroke work index; RVSWI = right ventricular stroke work index; Do₂ = oxygen delivery; Vo₂ = oxygen consumption; O₂ER = oxygen extraction ratio.

fere with these mechanisms both directly by their vasodilating and negative inotropic properties^{13,14} and indirectly by their effects on the sympathetic nervous system.²⁴ The anesthetic technique used in the present study did not seem to have altered cardiac preload and afterload. Indeed, cardiac filling pressures, right ventricular end-diastolic volume, and systemic vascular resistance in anesthetized patients were similar to those observed in awake patients. However, the anesthetic technique seemed to have decreased myocardial contractility as a comparable increase in cardiac filling pressures resulted in a lower augmentation in right and left ventricular stroke work index. These results contradict those of Habler *et al.*,⁸ who showed an increase in myocardial contractility in anesthetized dogs undergoing acute normovolemic hemodilution. This could be related to different factors such as the level of anesthesia and the fact that Habler *et al.* did not use nitrous oxide, which is known to have negative inotropic properties.²⁵ Increased myocardial contractility during hemodilution in anesthetized humans remains to be demonstrated. As in other experimental studies, Habler *et al.*⁸ observed that the increase in cardiac index during hemodilution was essentially related to an increase in stroke index with no change in heart rate in anesthetized animals. This might indicate that the effects of anesthesia on the autonomic nervous system are probably more important than the direct effects of the anesthetic agents on the myocardium in explaining the depressed cardiac output response observed during acute normovolemic hemodilution. Moreover, the effects of anesthesia on the cardiac output response during normovolemic hemodilution will depend not only on the anesthetic agents used but also on the depth of anesthesia, as demonstrated by Schou *et al.*²⁶ In both groups, ANH was associated with an increase in right ventricular end-diastolic volume and a trend toward higher filling pressures. This probably reflects the increased venous return resulting from the decreased blood viscosity. Increased flow increases venous return and therefore the filling pressures of the heart.²⁷

In both groups, ANH was associated not only with an increase in cardiac output, but also with an increase in oxygen extraction ratio. However, this increase in oxygen extraction ratio appeared to be triggered by different mechanisms in the two groups. In the awake patients, it increased because $\dot{V}O_2$ increased, whereas DO_2 remained constant. This increase in $\dot{V}O_2$ is probably related to an increased myocardial oxygen demand, related to the increase in heart rate.^{12,28} In the anesthetized patients, oxygen extraction ratio increased to maintain $\dot{V}O_2$ as DO_2 decreased. DO_2 decreased because the increase in cardiac output was not sufficient to compensate for the decreased arterial oxygen content. Although estimation of $\dot{V}O_2$ from thermodilution cardiac output measurements has been criticized because of the poten-

tial problem of "mathematical coupling,"²⁹ this effect is probably small in the present study, as cardiac index increased during ANH in the range of 55% in the awake group and 35% in the anesthetized group.

The results observed in this study may have been influenced by several factors. First, preoperative medications may have interfered with the cardiovascular response associated with ANH. This is especially the case with β blockers. Lieberman *et al.*²⁰ recently showed that acute administration of esmolol is associated in conscious humans with a marked decrease in cardiac output response to ANH. However, chronic β blockade did not blunt the cardiac output response associated with ANH in anesthetized patients.²² Calcium channel blockers may also play a role, in particular during isoflurane anesthesia. In the present study, only one patient in the anesthetized group took calcium channel blockers in the preoperative period.

Second, the use of benzodiazepines for premedication and catheter insertion might also have had an impact on the results. When administered alone, benzodiazepines have limited hemodynamic effects,³⁰ whereas when associated with other agents, such as opioids, they can result in more pronounced cardiovascular depression.³ Therefore, their use might have contributed to the depressed cardiac output response observed during ANH in the anesthetized patients.

Third, the use of positive pressure ventilation in the anesthetized patients may have also influenced our results. Increased intrathoracic pressure is usually associated with a decreased venous return responsible for decreased cardiac output.³² This may have contributed to the lower cardiac output observed in the anesthetized patients before hemodilution. However, ventilatory conditions were not modified during the hemodilution procedure, and the increase in cardiac index was significantly less in the anesthetized than in the awake patients, whereas the exchange volume was similar in the two groups.

In conclusion, when compared with the awake state, fentanyl-nitrous oxide-isoflurane anesthesia significantly reduces the cardiac output response associated with moderate ANH, mainly by blunting the heart rate response in these conditions. In the awake patients, the increase in heart rate resulted in an increased myocardial oxygen demand, which might be responsible for an increased $\dot{V}O_2$. In both awake and anesthetized conditions, tissue oxygen extraction must increase to meet metabolic oxygen requirements.

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