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The Influence of Hyperoxic Ventilation during Sodium Nitroprusside–induced Hypotension on Skeletal Muscle Tissue Oxygen Tension

Stefan W. Suttner, M.D., Katrin Lang, M.D.,* Joachim Boldt, M.D.,† Bernhard Kumle, M.D.,* Wolfgang H. Maleck, M.D.,* Swen N. Piper, M.D.**

Background: **Increasing inspired oxygen concentrations might provide a simple and effective intervention to increase oxygen tension in tissues during controlled hypotension. To test this hypothesis, the influence of hyperoxic ventilation (100% O_2) on skeletal muscle oxygen partial pressure (P_{TIO_2}) in patients receiving sodium nitroprusside–induced controlled hypotension was studied.**

Methods: **Forty-two patients undergoing radical prostatectomy were prospectively studied and randomly divided into three groups as follows: (1) Controlled hypotension induced by sodium nitroprusside (mean arterial blood pressure, 50 mmHg) and hyperoxic ventilation (CH-100%; n = 14); (2) controlled hypotension and ventilation with 50% O_2 in nitrous oxide (CH-50%; n = 14); and (3) standard normotensive anesthesia with 50% O_2 in nitrous oxide (control; n = 14). P_{TIO_2} values were measured continuously in all patients using implantable polarographic microprobes. Arterial blood gases and lactate concentrations were analyzed in 30-min intervals.**

Results: **Surgical blood loss and transfusion requirements were significantly reduced in both groups receiving hypotensive anesthesia. During surgery, arterial partial pressure of oxygen and arterial oxygen content were significantly higher in patients of the CH-100% group. Baseline values of P_{TIO_2} were comparable between the groups (CH-50%: 25.0 ± 0.7 mmHg; CH-100%: 25.2 ± 0.2 mmHg; control: 24.5 ± 0.2 mmHg). After a transient increase in P_{TIO_2} in the CH-100% group during normotension, P_{TIO_2} values returned to baseline and remained unchanged in the control group. P_{TIO_2} decreased significantly during the hypotensive period in the CH-50% group. The lowest mean P_{TIO_2} values were 15.0 ± 4.1 mmHg in the CH-50% group, 24.2 ± 4.9 mmHg in the CH-100% group, and 23.5 ± 3.8 mmHg in the control group. There were no significant changes in lactate plasma concentrations in any group throughout the study period.**

Conclusions: **Hyperoxic ventilation improved skeletal muscle tissue oxygenation during sodium nitroprusside–induced hypotension. This improved local tissue oxygenation seems to be most likely due to an increase in convective oxygen transport and the attenuation of hyperoxemia-induced arteriolar vasoconstriction by sodium nitroprusside.**

CONTROLLED hypotension is an anesthetic technique that is used in a variety of surgical procedures to improve operating conditions, decrease intraoperative blood loss, and hence decrease the need for allogeneic blood transfusions.[1–4] Sodium nitroprusside (SNP) is a direct-acting, peripheral vasodilator that is widely used for this purpose.[5] Nitric oxide (NO) has been found to be the active mediator that is responsible for the vasodilating effects of SNP.[5] Physiology and limits of blood flow and organ function during controlled hypotension have been investigated in a variety of clinical and experimental settings.[6–9] However, there is no widespread use of this technique because of the fear that a reduced perfusion pressure might lead to impaired oxygen availability to tissues and ischemic injury to vital organs.

Ventilation with pure oxygen may have beneficial effects during the perioperative period, including improved oxygen delivery to tissues and decreased incidence of surgical wound infections.[10] Because there is a linear relation between arterial partial pressure of oxygen (Pa_{O_2}) and arterial oxygen content in plasma, hyperoxic ventilation can be used to increase the amount of physically dissolved oxygen in the plasma compartment, thereby increasing oxygen delivery to tissues.[11] Therefore, it might be assumed that hyperoxic ventilation would provide a simple method to compensate for impaired tissue oxygenation during controlled hypotension. However, it should be noted that findings of experimental studies suggest impaired tissue oxygenation in association with hyperoxic ventilation and in patients with a normal packed red cell volume due to arteriolar vasoconstriction.[12–14]

Unfortunately, assessment of tissue oxygenation in the clinical setting is difficult and largely based on measuring global hemodynamics, whole body oxygen transport and uptake, or indirect biochemical markers.[15] Moreover, these parameters are considered to be poor surrogates for the oxygen availability at tissue levels because tissue oxygenation is determined by the net balance between cellular oxygen supply and oxygen demand.[15,16] Polarographic oxygen sensors enable us to measure oxygen partial pressure in tissues (P_{TIO_2}), organs, and body fluids directly and continuously. P_{TIO_2} values correspond to oxygen availability on a cellular level and provide information about oxygen supply and utilization in specific tissue beds.[16]

The influence of hyperoxic ventilation on tissue oxygenation is still controversial, and data from human studies are scarce. Therefore, the current study was designed to assess the effects of pure oxygen ventilation during SNP-induced hypotension on skele-

* Staff Anesthesiologist, † Professor of Anesthesiology.

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Address correspondence to Dr. Suttner: Department of Anesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen, Bremserstrasse 79, D-67063 Ludwigshafen, Germany. Address electronic mail to: suttner@gmx.de.

tal muscle oxygen partial pressure in patients undergoing radical prostatectomy.

Materials and Methods

After approval by the local ethics committee (University of Mainz, Mainz, Germany), a total of 42 male patients with American Society of Anesthesiologists physical status II or III who were scheduled to undergo elective radical prostatectomy with bilateral pelvic lymphadenectomy gave written informed consent to participate in the study. Exclusion criteria were American Society of Anesthesiologists physical status class greater than III, compensated or decompensated myocardial insufficiency, history of angina pectoris, documented coronary artery disease, history of myocardial infarction, carotid artery stenosis, liver dysfunction (alanine aminotransferase/aspartate aminotransferase > 40 U/l), renal insufficiency (creatinine > 1.5 mg/dl), insulin-dependent diabetes mellitus, hemoglobin concentration less than 12 g/dl, or severe uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mmHg while receiving medication). The patients were allocated randomly to one of three groups by using a closed-envelope system. After induction of anesthesia with thiopental, fentanyl, and rocuronium, patients in group 1 (CH-50%, n = 14) underwent mechanical ventilation with 50% oxygen in nitrous oxide and received controlled hypotension induced by SNP. Group 2 (CH-100%, n = 14) received 100% oxygen and controlled hypotension. Group 3 (control, n = 14) receiving normotensive general anesthesia while breathing 50% oxygen in nitrous oxide, served as the control group. Anesthesia was maintained with fentanyl, rocuronium, and desflurane. Doses for anesthetics were adjusted to provide optimal anesthetic and surgical conditions while maintaining hemodynamic stability. An end-expiratory maximum of 1 minimum alveolar concentration (MAC) of desflurane was used intraoperatively. Small increments of fentanyl (0.05–0.1 mg) were administered when signs of an inadequate depth of anesthesia occurred. Intraoperative muscle relaxation was maintained by additional doses of rocuronium aiming for two twitches of the train-of-four assessment. The intraoperative administration of gas at the assigned concentrations continued until immediately before extubation, when oxygen was increased to 100%. Ventilation was controlled with a tidal volume of 8 to 10 ml/kg, and the ventilatory rate was adjusted to maintain a partial pressure of carbon dioxide (P_{CO_2}) of 30 to 40 mmHg and pH between 7.35 and 7.45. Routine intraoperative monitoring included continuous invasive measurement of mean arterial blood pressure (MAP) and central venous pressure. Controlled hypotension was initiated in groups 1 and 2 at the beginning of bilateral pelvic lymphadenectomy and was completed with wound closure. The SNP doses applied were adjusted to reduce MAP to 50 mmHg. Maximal SNP infusion rate was limited to 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The lower limit of hypotension was defined as a MAP of less than 50 mmHg in groups 1 and 2, and 70 mmHg in the control group. Hypotensive episodes were treated by increasing the rate of fluid administration and reducing the concentration of desflurane, SNP, or both when necessary. Crystalloids and gelatin were administered to maintain central venous pressure at 12–14 mmHg. A hemoglobin concentration less than 8.0 g/dl was defined as a transfusion trigger and mandated the transfusion of 1 unit allogeneic packed erythrocytes. Blood loss was estimated from the blood and irrigation fluid in the suction containers. A rewarming cover blanket system and fluid warmers were used to maintain normothermia during surgery. Although anesthesia was provided by anesthetists who were not involved in data analysis, anesthetists were not blinded to the group assignment of the patient. After surgery, all patients were observed in the postanesthesia care unit. Supplemental oxygen was administered to all patients as necessary to maintain a pulse oximeter saturation of at least 95%. A Licox CMP system (GMS, Mielkendorf, Germany) and flexible, minimally invasive microprobes (Revoxode; GMS) were used for continuous assessment of tissue oxygenation and tissue temperature. The Revoxode is a closed polarographic cell that allows measurement of P_{TIO_2} in almost all organs and tissue types. These microcatheter P_{TIO_2} probes are precalibrated at the time of manufacture and are supplied with their individual calibration data (partial pressure of oxygen [P_{O_2}] sensitivity, temperature coefficient of sensitivity, zero current, response time, run-in drift) electronically stored on a smart card. P_{TIO_2} is determined at the tip of the P_{TIO_2} probe in a cylindric tissue layer located concentrically along the axis of the microcatheter. The P_{O_2}-sensitive area of the precalibrated catheter was inserted into the deltoid muscle *via* a 20-gauge guiding cannula (Vasofix; B.Braun, Melsungen, Germany). To avoid tissue damage or compression of capillaries, which might influence the P_{TIO_2} measurement, the guiding cannula was retracted by approximately 10 mm. After placement of the oxygen probes, P_{TIO_2} attained stable baseline values within 15 min. Thereafter, P_{TIO_2} probes were fixed with sterile bandages to the skin to stabilize the intramuscular position of the catheter tip. Then P_{TIO_2} values were measured continuously in all patients until 2 h after arrival in the postanesthesia care unit. For correction of the P_{TIO_2} data, the temperature within the deltoid muscle was measured simultaneously. In addition, arterial blood samples were analyzed immediately after sampling in an automatic blood gas tension analyzer in 30-min intervals for hemoglobin concentration, Pa_{O_2}, Pa_{CO_2}, *p*Ha, and lactate concentrations. Arterial oxygen content (Ca_{O_2}) was calculated using the formula (hemoglobin × 1.39 ×

Sao_2) + (0.0031 × Pao_2), where hemoglobin represents the hemoglobin concentration, and Sao_2 represents the arterial oxygen saturation.[15] $Ptio_2$ values and blood gas variables are reported after induction of anesthesia (baseline), 30, 60, 120, and 180 min after skin incision, and 1 h after arrival in the postanesthesia care unit. Time points 60 and 120 min denote the hypotensive period in the treatment groups.

Statistics

The Kolmogorov-Smirnov test was used to check the normality assumption. The normality assumption was fulfilled in all main measurements, except for blood loss and transfusion requirements. Analysis of variance for repeated measures was performed to analyze differences in means between and within groups for systemic hemodynamics, blood gas variables, lactate concentrations, and $Ptio_2$ values. In the case of significant differences, further comparisons were made with paired and unpaired Student *t* tests within groups to baseline and between groups at individual time points. The Bonferroni procedure was used to correct multiple comparisons. Blood loss and transfusion requirements were compared by using the Wilcoxon test, chi-square analysis, or Fisher exact test where appropriate. Data in text, tables, and figures are presented as mean ± SD, unless otherwise stated. The power of this study was calculated prospectively as follows: in an earlier animal study on the microcirculatory effects of SNP-induced hypotension, it has been shown that controlled hypotension could reduce skeletal muscle Po_2 by 45%.[17] We assumed that a reversal of these effects by hyperoxic ventilation would be of clinical importance. Using the SD of skeletal muscle Po_2, 14 patients per group were required to detect this difference with a power of 0.8. To account for the six time points, a Bonferroni-corrected value of $P < 0.0083$ (obtained by dividing 0.05 by 6) was used as the criterion for statistical significance.

Results

Of the 45 patients initially screened for the study, three could not be enrolled because they were in violation of one or more of the inclusion and exclusion criteria. Among these were patients with abnormal preoperative laboratory test results (hemoglobin concentration < 12 g/dl) and patients with severe hypertension (diastolic blood pressure > 100 mmHg). The patients in the three groups were comparable with respect to biometric data, American Society of Anesthesiologists physical status, preexisting disease, and duration of anesthesia and surgery (table 1). Duration of controlled hypotension and total dose of SNP administered did not differ between the two groups receiving hypotensive anesthesia (table 1). Blood loss in the CH-50% and CH-100% groups was significantly lower than in the control group (table 2).

Table 1. Patient Demographics and Data from the Perioperative Period

	CH-50% (n = 14)	CH-100% (n = 14)	Control (n = 14)
Age (yr)	63.9 (5.0) [57–72]	66.1 (5.8) [55–75]	65.0 (6.3) [54–74]
ASA physical status (n)			
Class I	2	3	1
Class II	9	8	11
Class III	3	3	2
Height (cm)	176.6 (7.6)	176.1 (9.4)	174.1 (5.3)
Weight (kg)	78.0 (8.4)	76.7 (8.5)	78.7 (5.8)
Duration of surgery (min)	158 (16) [125–180]	158 (22) [115–185]	150 (13) [125–180]
Duration of anesthesia (min)	206 (13) [175–230]	211 (20) [179–245]	209 (16) [185–236]
Duration of hypotension	97 (10)	95 (9)	—
Dosage of SNP per patient (mg)	16.5 (5.0)	19.8 (4.3)	—
Consumption of anesthetics (mg)			
Thiopental	410 (35)	389 (50)	404 (45)
Fentanyl	0.9 (0.2)	1.3 (0.1)*	1.0 (0.2)
Rocuronium	85 (22)	82 (20)	86 (19)

Values are expressed as mean (SD), number of patients, or [range].

* $P < 0.05$ compared with other groups.

CH-50% = controlled hypotension and ventilation with 50% oxygen in nitrous oxide, CH-100% = controlled hypotension and ventilation with pure oxygen; ASA = American Society of Anesthesiologists; SNP = sodium nitroprusside.

Significantly fewer units of allogeneic packed erythrocytes were transfused in the patients receiving hypotensive anesthesia. At the end of surgery, hemoglobin concentration was significantly lower in the control group than in the two other groups (table 3). During surgery, mean end-tidal desflurane concentrations and the use of additional fentanyl were significantly higher in the CH-100% group than in the other groups (tables 2 and 3). Except for MAP during the hypotensive period, hemodynamic data did not differ among patients. Intraoperatively, Pao_2, Cao_2, hemoglobin-bound oxygen content, and plasma oxygen content were significantly higher in patients who underwent ventilation with pure oxygen; all other arterial blood gas variables and tissue temperature were without a difference between the groups (table 3). Baseline values of $Ptio_2$ were comparable between the groups (table 3). Increasing inspired oxygen fraction to 1.0 during normotension in the CH-100% group increased $Ptio_2$ values transiently. During controlled hypotension, a significant decrease in skeletal muscle Po_2 compared with baseline was observed only in the CH-50% group. No changes in $Ptio_2$ levels were found in patients of the CH-100% group and in normotensive control patients. A return to baseline $Ptio_2$ values was observed in the CH-50% group at the end of surgery. There were no significant changes in lactate plasma concentrations in any group throughout the whole study period. Peak values were 1.7 ± 0.5 mM in the CH-50% group, 1.6 ± 0.6 mM in the CH-100% group, and 1.7 ± 0.7 mM in the control group.

Table 2. Blood Loss and Perioperative Fluid Management

	CH-50% (n = 14)	CH-100% (n = 14)	Control (n = 14)
Intraoperative blood loss (ml)	800 [600–1,250]	850 [700–1,100]	1,260* [650–1,850]
Number of patients receiving PE	2	1	5*
Cumulative PE intraoperative/PACU (units)	4	3	13*
Intraoperative volume infusion			
Crystalloids (ml)	2,892 (645)	2,679 (468)	2,914 (939)
Colloids (ml)	1,239 (2733)	1,254 (451)	1,285 (297)

Values are expressed as median [range], mean (SD), or total.

* $P < 0.05$ compared with other groups.

CH-50% = controlled hypotension and ventilation with 50% oxygen in nitrous oxide; CH-100% = controlled hypotension and ventilation with pure oxygen; PE = packed erythrocytes; PACU = postanesthesia care unit.

Discussion

Although blood flow to vital organs, such as the brain and the myocardium, is characterized by well-functioning autoregulatory mechanisms, concerns have been raised that controlled hypotension may impair oxygen availability to tissues.[17] Therefore, maintenance of an oxygen supply sufficient for the metabolic needs of the tissues seems to be of primary importance during controlled hypotension.

It is one of the main findings of the current study that skeletal muscle Po_2 decreased significantly in patients receiving a combination of hypotensive anesthesia and ventilation with 50% oxygen in nitrous oxide. One possible explanation for the development of impaired tissue oxygenation during hypotensive anesthesia with SNP would be cyanide intoxication. Free cyanide diffuses rapidly into tissues, where it binds and inactivates tissue cytochrome oxidase. Such binding prevents oxidative phosphorylation and may produce anaerobic metabolism and tissue dysoxia, a state at which adenosine triphosphate is no longer produced.[5,16] In healthy adults, cyanide is metabolized in the liver by rhodanese at a rate equivalent to cyanide production during SNP infusion, depending on the rate of administration and

Table 3. Changes of Skeletal Muscle Partial Pressure of Oxygen, Blood Gas Variables, and Desflurane Concentrations

Time Group	$ptio_2$ (mmHg)	Hgb (g/dl)	Pao_2 (mmHg)	$Paco_2$ (mmHg)	BE	Cao_2 (ml/dl)	Hgb-O_2 (ml/dl)	Plasma-O_2 (ml/dl)	ET Des (%)
Baseline									
CH-50%	25.0 (6.7)	13.7 (1.3)	155 (22)	35.1 (2.2)	1.0 (0.4)	19.2 (1.5)	18.6 (0.6)	0.5 (0.01)	2.9 (0.3)
CH-100%	25.2 (6.2)	14.0 (0.9)	420 (37)*	35.7 (1.7)	0.4 (0.9)	21.0 (0.9)*	19.4 (0.6)*	1.6 (0.02)*	5.2 (0.4)*
Control	24.5 (5.2)	13.9 (1.1)	139 (28)	35.4 (1.6)	1.1 (0.2)	19.3 (0.8)	18.8 (0.5)	0.5 (0.01)	3.1 (0.3)
30 min									
CH-50%	26.5 (5.0)	12.9 (2.0)	137 (28)	34.7 (1.2)	1.1 (0.8)	18.0 (1.0)†	17.4 (0.6)†	0.5 (0.01)	3.2 (0.4)
CH-100%	31.5 (5.2)†	13.1 (1.4)	455 (41)*	35.2 (1.5)	0.4 (0.8)	21.0 (1.3)*†	19.3 (0.5)*	1.7 (0.02)*	5.3 (0.6)*
Control	25.5 (6.5)	13.0 (2.0)	141 (27)	35.3 (1.7)	1.0 (0.7)	18.0 (0.9)†	17.5 (0.5)†	0.5 (0.009)	3.3 (0.4)
60 min									
CH-50%	22.0 (5.0)	11.9 (2.5)	142 (30)	34.2 (2.1)	0.7 (0.5)	16.5 (1.3)†	16.0 (0.4)†	0.5 (0.01)	2.9 (0.5)
CH-100%	30.0 (4.2)*	12.2 (2.1)†	471 (52)*	34.3 (2.3)	0.3 (0.7)	18.6 (1.1)*†	16.9 (0.5)*†	1.7 (0.02)*	5.3 (0.5)*
Control	25.0 (7.0)	11.5 (1.2)†	132 (19)	35.1 (2.4)	1.2 (0.5)	15.9 (1.6)†	15.4 (0.6)†	0.4 (0.009)	3.1 (0.3)
120 min									
CH-50%	15.0 (4.1)*†	11.0 (2.1)†	137 (31)	34.9 (2.5)	1.4 (0.5)	15.2 (0.9)†	14.7 (0.5)†	0.5 (0.01)	3.3 (0.3)
CH-100%	24.2 (4.9)	11.3 (1.9)†	451 (39)*	34.6 (2.9)	0.2 (0.7)	17.4 (1.2)*†	15.7 (0.4)*†	1.6 (0.03)*	5.1 (0.5)*
Control	23.5 (3.8)	9.5 (2.2)†	148 (28)	34.5 (2.8)	1.4 (0.5)	13.2 (1.0)†	12.7 (0.4)†	0.5 (0.01)	2.9 (0.3)
180 min									
CH-50%	18.7 (5.0)*†	10.2 (3.1)†	141 (29)	35.3 (2.3)	1.0 (0.5)	14.1 (1.1)†	13.6 (0.3)†	0.5 (0.009)	3.1 (0.3)
CH-100%	25.5 (5.0)	10.8 (2.8)†	411 (41)*	35.0 (2.2)	0.5 (0.8)	16.5 (1.4)*†	15.0 (0.4)*†	1.5 (0.02)*	4.9 (0.4)*
Control	27.1 (5.1)	8.7 (2.1)†	130 (22)	34.6 (2.1)	1.2 (0.5)	12.1 (0.9)†	11.6 (0.5)†	0.4 (0.01)	3.1 (0.3)
1 h PACU									
CH-50%	21.3 (4.9)	10.2 (2.2)†	100 (17)	36.0 (2.1)	1.3 (0.5)	13.3 (0.9)†	12.9 (0.3)†	0.4 (0.01)	—
CH-100%	24.2 (4.7)	10.3 (2.8)†	91 (11)†	35.7 (1.4)	1.1 (0.5)	13.7 (1.0)†	13.3 (0.3)*†	0.3 (0.01)†	—
Control	23.5 (5.1)	8.9 (2.7)†	97 (10)	36.3 (2.3)	0.6 (0.5)	11.9 (1.1)*†	11.5 (0.4)†	0.4 (0.01)	—

Skeletal muscle partial pressure of oxygen ($ptio_2$), hemoglobin (Hgb) concentration, partial pressure of oxygen (Pao_2) and carbon dioxide ($Paco_2$), base excess (BE), arterial oxygen content (Cao_2), hemoglobin-bound oxygen content (Hgb-O_2), plasma oxygen content (Plasma-O_2), and end-tidal desflurane concentration (ET Des) in the three groups. Values are reported after induction of anesthesia (baseline); 30, 60, 120, 180 min after skin incision; and 1 h after arrival in the postanesthesia care unit (PACU). Time points 60 and 120 min denote the hypotensive period in the treatment groups.

* $P < 0.05/6$ (Bonferroni-corrected) compared with other groups. † $P < 0.05/6$ (Bonferroni-corrected): significantly different from baseline.

CH-50% = controlled hypotension and ventilation with 50% oxygen in nitrous oxide; CH-100% = controlled hypotension and ventilation with pure oxygen.

total dose administered.[5] Clinical evidence of cyanide toxicity may occur when body sulfur stores are exhausted or when SNP infusions exceed a total dosage of 1.5 mg/kg SNP or an infusion rate of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[5,18] SNP infusion in the patients in this study was only of short duration (less than 100 min on average) and never exceeded 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. By measuring systemic plasma lactate concentrations and several blood gas variables in short intervals throughout the perioperative course, we did not detect any signs of anaerobic metabolism or systemic metabolic acidosis. However, normal systemic *p*H and lactate values do not guarantee that local acidosis does not exist.[19,20] Therefore, cyanide toxicity cannot be totally ruled out, but seems to be unlikely to explain the results of our study.

Other more reasonable explanations for our findings are in accordance with the results of an earlier study by Endrich *et al.*[17] comparing the effects of SNP *versus* nitroglycerine-induced hypotension on striated hamster muscle. These authors examined nutritional capillary blood flow by using intravital microscopy and tissue oxygenation with platinum multiwire electrodes for local P_{O_2} measurements. When MAP was reduced to 40 mmHg by SNP, functional capillary density and the arteriolar–venular pressure gradient, which determines capillary perfusion, decreased significantly, and skeletal muscle tissue hypoxia was present.[17] Although extrapolating these experimental findings to clinical studies might be premature, similar mechanisms probably explain why skeletal muscle tissue oxygenation decreased in the patients of the CH-50% group.

In experimental and clinical studies, ventilation with high inspiratory fractions of oxygen has emerged as a simple and effective intervention to increase oxygen tension in tissues.[10,11] It was the main finding of the current study that skeletal muscle P_{O_2} was well-preserved during SNP-induced hypotension supplemented with pure oxygen ventilation. The beneficial effects of hyperoxic ventilation on tissue oxygenation have been described in an experimental study by Habler *et al.*[11] They evaluated systemic oxygenation status and organ tissue oxygenation in anesthetized dogs undergoing progressive acute normovolemic hemodilution while breathing room air or pure oxygen. As a result of hyperoxic ventilation, local tissue oxygenation, measured on the surface of liver and skeletal muscle, improved significantly. The authors suggested that this improvement was due to an increased contribution of physically dissolved oxygen in plasma to systemic oxygen transport. At a hemoglobin concentration of 7.0 g/dl, almost 15% of oxygen transport and 47% of oxygen uptake was due to physically dissolved oxygen.[11] The improved local tissue oxygenation that was observed in the current patients receiving hypotensive anesthesia and pure oxygen ventilation might be attributed to a similar mechanism. This assumption is supported by the fact that Pa_{O_2}, plasma oxygen content, and total Ca_{O_2} were significantly higher in patients receiving hyperoxic ventilation. Because plasma dissolved oxygen is highly diffusible and is used for tissue oxygenation before hemoglobin-bound oxygen, it seems reasonable to assume that an increase in convective oxygen transport by hyperoxic ventilation seemed to preserve tissue oxygenation in the patients of the CH-100% group. However, it has also been shown in clinical and experimental studies that hyperoxia in the presence of physiologic hemoglobin concentrations may impair tissue oxygenation because of hyperoxic arteriolar vasoconstriction.[12–14] This hyperoxemia-induced microcirculatory dysregulation is mediated by oxygen metabolites and oxyhemoglobin, which are known to inactivate endothelial-derived NO.[21–24] When infused intravenously, interaction of SNP with oxyhemoglobin results in the immediate dissociation of the SNP molecule to cyanide and NO. Therefore, SNP can be considered to be a prodrug for the generation of NO and might attenuate the vasoconstrictive effects of hyperoxemia.[5] The latter mechanism might further explain the unchanged skeletal muscle tissue oxygen tension observed during hyperoxia and SNP-induced hypotension in our study. Supporting evidence for this assumption is provided by an experimental study of Rooney *et al.*[25] These authors administered SNP as an exogenous NO donor to anesthetized dogs ventilated with 100% oxygen during isovolemic hemodilution with a hemoglobin–colloid. Systemic hemodynamics, as well as distribution of cardiac output and regional blood flows, were measured with a microsphere technique. The vasoconstrictive effects of oxyhemoglobin and hyperoxic ventilation were completely reversed by SNP infusion. The results of this experimental study indicate that the microcirculatory dysregulation due to hyperoxia might be counteracted by infusion of SNP. Therefore, the total amount of oxygen transported to capillaries and tissues might be maintained during SNP-induced hypotension supplemented with hyperoxic ventilation.

There are several limitations to the current study. First, a major flaw is the lack of a fourth study group not receiving SNP, but being ventilated with 100% O_2. This would have been particularly important to show hyperoxia-associated vasoconstriction. Second, large concentrations of inhalation anesthetic agents, including desflurane or isoflurane, may increase tissue oxygen tension. This has been shown for brain tissue in experimental and clinical settings.[26,27] In our study, P_{TIO_2} increased before hypotension in those patients receiving 100% oxygen. Similar results are reported by Greif *et al.*,[10] who found a significant difference in muscle tissue oxygen tension between patients receiving 80% and 30% oxygen in nitrogen. Unfortunately, one can only speculate as to whether vasoconstriction was present because cardiac output or systemic vascular resistance was not measured. However, in both studies, volatile anesthetics were used, which are known to decrease systemic

vascular resistance in a dose-dependent manner. Moreover, end-tidal desflurane concentrations in the current study were higher in the CH-100% group than in the other groups because of the omission of nitrous oxide. Therefore, the effects of desflurane have to be taken into account in the interpretation of our data. Third, a major problem with using monitoring tissue gas tensions in clinical practice might be that normal and critically abnormal values have not been established. In previous clinical studies, "normal" values for skeletal muscle P_{O_2} have been reported to be 14–25 mmHg in patients undergoing coronary artery bypass grafting with extracorporal circulation,[28] 28 mmHg in intensive care unit patients with limited infection, 48 mmHg in critically ill patients with severe sepsis, and 22 mmHg in patients with cardiogenic shock.[28] However, heterogeneity in microvascular blood flow and oxygenation exists between organs as well as at the level of each organ. This heterogeneity increases further during shock, sepsis, or other states of critical illness. Consequently, a common dysoxic threshold in skeletal muscle or any given tissue remains unclear. Further studies with much larger patient populations are required to establish such values.

We conclude that skeletal muscle P_{O_2} during SNP-induced hypotension improved by using hyperoxic ventilation. This improved local tissue oxygenation seems to be most likely due to an increase in convective oxygen transport by hyperoxic ventilation. In addition, the microcirculatory changes caused by hyperoxemia might be attenuated because SNP counteracts the hyperoxemia-induced arteriolar vasoconstriction. Therefore, hyperoxic ventilation might be a useful adjunct for the maintenance of adequate tissue oxygenation during SNP-induced hypotension.

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