

Hypercapnia Improves Tissue Oxygenation

Ozan Akça, M.D.,* Anthony G. Doufas, M.D., Ph.D.,† Nobutada Morioka, M.D.,‡ Steve Iscoe, Ph.D.,§ Joseph Fisher, M.D.,|| Daniel I. Sessler, M.D.#

Background: Wound infections are common, serious, surgical complications. Oxidative killing by neutrophils is the primary defense against surgical pathogens and increasing intraoperative tissue oxygen tension markedly reduces the risk of such infections. Since hypercapnia improves cardiac output and peripheral tissue perfusion, we tested the hypothesis that peripheral tissue oxygenation increases as a function of arterial carbon dioxide tension (P_{aCO_2}) in anesthetized humans.

Methods: General anesthesia was induced with propofol and maintained with sevoflurane in 30% oxygen in 10 healthy volunteers. Subcutaneous tissue oxygen tension (P_{sqO_2}) was recorded from a subcutaneous tonometer. An oximeter probe on the upper arm measured muscle oxygen saturation. Cardiac output was monitored noninvasively. P_{aCO_2} was adjusted to 20, 30, 40, 50, or 60 mmHg in random order with each concentration being maintained for 45 min.

Results: Increasing P_{aCO_2} linearly increased cardiac index and P_{sqO_2} : $P_{sqO_2} = 35.42 + 0.77 (P_{aCO_2})$, $P < 0.001$.

Conclusions: The observed difference in P_{sqO_2} is clinically important because previous work suggests that comparable increases in tissue oxygenation reduced the risk of surgical infection from -8% to 2 to 3%. We conclude that mild intraoperative hypercapnia increased peripheral tissue oxygenation in healthy human subjects, which may improve resistance to surgical wound infections.

Wound infections are common and serious complications of surgery with anesthesia.^{1,2} During surgery, the first few hours after bacterial contamination constitute a *decisive period* during which wound infections are established.³ This critical period explains why perioperative factors influence the incidence of infection—even though infections are typically not detected until many days after surgery. Major factors influencing the inci-

dence of surgical wound infection and tissue oxygenation include the site and complexity of surgery,⁴ underlying illness,⁴ timely administration of prophylactic antibiotics,⁵⁻⁷ intraoperative patient temperature,¹ and hypovolemia.^{8,9}

The primary defense against surgical pathogens is oxidative killing by neutrophils.¹⁰ Oxygen is a substrate for this process, and the reaction critically depends on tissue oxygen tension throughout the observed physiologic range. It is therefore unsurprising that subcutaneous tissue oxygen tension (P_{sqO_2}) is inversely correlated with the risk of surgical wound infection.^{2,11}

The primary determinants of tissue oxygen availability are arterial oxygen tension,² hemoglobin concentration,¹² cardiac output,¹³ and local perfusion.^{14,15} Hypercapnia increases the cardiac index: for example, augmenting arterial carbon dioxide tension (P_{aCO_2}) by 10–12 mmHg increases cardiac index by about 15%.¹⁶ As might be expected, hypocapnia decreases the cardiac index.¹⁷ We therefore tested the hypothesis that peripheral tissue oxygenation increases as a function of P_{aCO_2} in anesthetized humans. We simultaneously evaluated the relationship between P_{aCO_2} and cardiac index, subcutaneous tissue oxygen tension, and muscle oxygen saturation.

Methods

With the approval of the Human Studies Committee of the University of Louisville, and written informed consent, 10 healthy American Society of Anesthesiologists Status I volunteers (7 men, 3 women) were enrolled in the study. Exclusion criteria included use of vasoactive or α_2 -agonist drugs, obesity, and smoking. Participants were screened for systemic illness or conditions that might confound study results or increase their anesthetic risk. Applicants having any known illness were excluded.

Protocol

Anesthesia was induced with propofol (2.5 mg/kg) and vecuronium bromide (0.1 mg/kg) and the volunteers' tracheas were intubated. A vecuronium infusion was subsequently adjusted to maintain 1 to 2 mechanical twitches in response to supermaximal train-of-four stimulation of the ulnar nerve at the wrist. Anesthesia was maintained with sevoflurane in 30% oxygen at an end-tidal concentration between 1.5–2.0%. Volunteers were hydrated (3–4 ml · kg⁻¹ · h⁻¹ crystalloid)^{3,8,18} and kept normothermic.¹⁹

A catheter was inserted into the radial artery after confirming ulnar collateral flow with an Allen test.²⁰ A

* Assistant Director, Outcomes Research® Institute; Assistant Professor, Department of Anesthesiology, University of Louisville. † Assistant Professor, ‡ Research Fellow, Outcomes Research® Institute and Department of Anesthesiology, University of Louisville. § Associate Professor, Department of Physiology, Queens University, Kingston, Ontario, Canada. || Associate Professor, Department of Anaesthesia, University of Toronto, Toronto, Ontario, Canada. # Associate Dean for Research, Director Outcomes Research® Institute, Weakley Distinguished University Professor of Anesthesiology, University of Louisville; Professor and Vice-Chair, Ludwig Boltzmann Institute, University of Vienna, Vienna, Austria.

Received from the Outcomes Research® Institute and Department of Anesthesiology, University of Louisville, Louisville, Kentucky; the Department of Physiology, Queen's University, Kingston, Ontario, Canada; and the Department of Anesthesia, the Toronto General Hospital, Ontario, Canada. Submitted for publication October 1, 2001. Accepted for publication April 15, 2002. Supported by grant No. GM49670 from the National Institutes of Health, Bethesda, MD, the Joseph Drown Foundation, Los Angeles, CA, the Jewish Hospital Foundation, Louisville, KY, and the Commonwealth of Kentucky Research Challenge Trust Fund, Louisville, KY. Somanetics, Inc., Troy, MI, donated the cerebral oximeter probes. Novamatrix Medical System, Inc., Wallingford, CT, donated the "NICO" (noninvasive cardiac output monitoring system) probes; Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO, donated the tympanic membrane thermocouples; and Augustine Medical, Inc., Eden Prairie, MN, donated the forced-air warmer and disposable covers. The authors do not consult for, accept honoraria from, or own stock or stock options in any company related to this research.

Address correspondence to Dr. Akça: Outcomes Research® Institute, Med-Center One, 501 East Broadway, Suite 210, Louisville, KY 40202. Address electronic mail to: ozan.akca@louisville.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

15-cm-long Silastic tonometer (Silastic, Dow-Corning, Midland, MI; 1.0-mm OD, 0.8-mm ID) was inserted subcutaneously 5 to 6 cm on the lateral aspect of the upper arm to measure PsqO_2 .^{8,21-24} Subcutaneous tissue oxygen tension was measured with a polarographic electrode system (Licor Medical Systems, Corp., Greenvale, NY), as previously described.²¹⁻²³ The oxygen electrode was calibrated with room air (154 mmHg) and then positioned within the Silastic tonometer. A thermocouple was inserted into the opposite lumen of the tonometer, and positioned approximately 1 cm from the oxygen electrode. The system was flushed with hypoxic saline to remove air from the catheter. Calibration and stabilization of the system requires approximately 1 h. *In vitro* accuracy of the optodes (in a water bath at 37°C) is ± 3 mmHg for the range from 0–100 mmHg, and $\pm 5\%$ for the range 100–360 mmHg. Temperature sensitivity is 0.25% /°C, but thermistors are incorporated into the probes and temperature-compensation is included in the PsqO_2 calculations. Optode calibration remains stable (within 8% of baseline value for room air) *in vivo* for at least 8 h. Consequently, optodes measure oxygen tension accurately and reliably over a broad range of subcutaneous temperatures and Po_2 values.²³ At the end of each study day, the oxygen sensor was removed from the tonometer and allowed to equilibrate in room air. If the value differed from the calibrated room air value (154 mmHg) by more than 10%, the measurement was repeated as defined by Hopf *et al.*¹¹

An oximeter probe (INVOS 3100 Somanetics, Troy, MI) was positioned on the upper arm to measure regional (mostly muscular) oxygen saturation.²⁴ A noninvasive cardiac output monitor was activated for continuous measurements of cardiac output.²⁵

End-tidal Pco_2 in the volunteers was adjusted, in a randomly assigned order, to 20, 30, 40, 50, or 60 mmHg. Target Pco_2 was obtained by eliminating soda-lime from the anesthesia circuit and selecting a respiratory rate between 11 and 14 breaths/min at a constant tidal volume of 10 ml/kg. Each target end-tidal Pco_2 was maintained for 45 min. After the final set of measurements, anesthesia was discontinued and the trachea extubated.

Measurements

PsqO_2 was measured with a polarographic Clark-type electrode system (Licor Medical Systems, Corp., Greenvale, NY), as described previously.²¹⁻²³ These electrodes measure oxygen tension accurately and reliably over a broad range of subcutaneous temperatures and Po_2 values.²³ Skin blood flow velocity was measured from the lateral side of upper arm with a laser Doppler perfusion monitor (Periflux PF3, Medex Inc, Hilliard, OH).

Cardiac output and index were measured by a noninvasive system which measures cardiac output from end-tidal carbon dioxide with a specific probe connected to the breathing circuit Y-piece (NICO, Novamatrix Medi-

cal System Inc, Wallingford, CT). NICO measures cardiac output from partial carbon dioxide rebreathing by a differential Fick method.²⁵ The NICO monitor is specified to work under carbon dioxide levels between 0 and 150 mmHg. The capnogram specific accuracy is as follows: 2 mmHg for 0–40 mmHg, 5% of reading for 41–70 mmHg and 8% of reading for 71–100 mmHg. In addition, Maxwell *et al.* showed that no more than 5% of the total number of paired continuous cardiac output (measured by thermodilution technique) and NICO measurements deviated by more than 1.4 l/min as a function of increased pulmonary shunt, venous desaturation, anemia, hypercapnia, increased dead-space ventilation, or hyperlactacidemia.²⁶ Recently, it was validated in cardiac surgery patients²⁷ and bluntly traumatized swine.²⁶

Potential confounding factors including mean arterial pressure and heart rate were recorded at each assigned carbon dioxide level. Core temperature was measured from tympanic membrane thermocouples with a Mon-a-Therm 6510 thermometer that is accurate to 0.1°C (Mallinckrodt Anesthesiology Products, St. Louis, MO). At the end of each period of steady-state end-tidal carbon dioxide, we recorded pulse-oximeter oxygen saturation, cardiac index, arterial pH, Paco_2 , Pao_2 , PsqO_2 , peripheral tissue perfusion, and muscle oxygen saturation.

Statistical Analysis

Potential confounding variables were assessed by repeated-measures ANOVA across the five levels of Paco_2 . Major outcome variables (cardiac index, PsqO_2 , muscle oxygen saturation, and skin blood flow velocity) were also analyzed by repeated measures ANOVA except when the data were not normally distributed, in which case the Friedman test was used. Data are presented as mean \pm SD. Linear regression was used to further explore the relationship between the major outcome variables and Paco_2 . The means of each major outcome variable at each level of Paco_2 were regressed against the levels Paco_2 to characterize this relationship and to better understand how this information could be applied clinically.

Results

The volunteers were 29 ± 4 yr old with a body mass index of 23 ± 2 kg/m². Initial (preinduction) blood pressure averaged 75 ± 8 mmHg; heart rate was 77 ± 9 beats/min; and oxygen saturation (Spo_2) was $99 \pm 1\%$. Mean arterial pressure, heart rate, core temperature, and Pao_2 did not differ significantly among the randomly assigned target Pco_2 levels. Per protocol, Paco_2 and pH differed significantly at each target end-tidal Pco_2 . At a Paco_2 of near 20 mmHg, there was a distinct respiratory alkalosis (7.57 ± 0.04). Conversely, a Paco_2 near 60 mmHg caused mild respiratory acidosis (7.31 ± 0.02 , table 1).

Table 1. Blood Gas Results and Potential Confounding Factors as a Function of Target End-Tidal Pco₂

Target Pco ₂ (mmHg)	20	30	40	50	60
Measured Pco ₂ (mmHg)	24 ± 2	33 ± 1	42 ± 2	51 ± 1	60 ± 2
pH	7.57 ± 0.04	7.50 ± 0.02	7.43 ± 0.04	7.37 ± 0.03	7.31 ± 0.02
RR (breaths/min)	14 ± 1	13 ± 1	13 ± 2	11 ± 1	11 ± 1
MAP (mmHg)	71 ± 4	69 ± 4	70 ± 5	70 ± 4	70 ± 6
Heart rate (beats/min)	79 ± 11	77 ± 9	79 ± 10	82 ± 8	82 ± 10
Core temperature (°C)	36.4 ± 0.3	36.4 ± 0.3	36.5 ± 0.2	36.5 ± 0.4	36.4 ± 0.2
SpO ₂ (%)	98.9 ± 1.3	98.9 ± 1.2	98.8 ± 1.0	98.9 ± 1.2	98.7 ± 1.1
Pao ₂ (mmHg)	178 ± 21	179 ± 19	175 ± 21	183 ± 21	179 ± 21
Subcutaneous tissue temperature (°C)	34.2 ± 1.2	34.1 ± 1.1	34.4 ± 1.3	34.7 ± 1.4	34.7 ± 1.4

None of the values below the middle space differed significantly between CO₂ concentrations. Data presented as mean ± SD.

MAP = mean arterial pressure; RR = respiratory rate; SpO₂ = oxygen saturation as determined by pulse oximeter; Pao₂ and Pco₂ = arterial oxygen and carbon dioxide partial pressures.

Cardiac index and subcutaneous tissue oxygen tension at each level of Pco₂ were analyzed by repeated measures ANOVA; there were statistically significant differences in each parameter (table 2). Because they were not normally distributed, muscle tissue oxygen saturation and skin blood flow velocity at each level of Pco₂ were analyzed with the Friedman test. Muscle tissue oxygen saturation measurements were statistically significant different from one another, but skin blood flow velocities were not (table 2). Linear regression was then used to explore the relationships between the means of each major outcome variable at each level of Pco₂.

Cardiac index (CI) was normal (2.7–2.9 l · min⁻¹ · m⁻²) at the lower Pco₂ values, but increased linearly to 3.9 l · min⁻¹ · m⁻² at the highest Pco₂; CI = 1.93 + 0.03 (Pco₂), *P* < 0.001. Thus, we would expect that, on average, a 10-mmHg increase in Pco₂ would result in a 0.3 increase in cardiac index. Across the full range of Pco₂ from 20 to 60 mmHg, cardiac index increased 44%.

Subcutaneous tissue oxygen tension (Psqo₂) was also linearly related to Pco₂ (fig. 1). Increasing Pco₂ linearly increased Psqo₂; Psqo₂ = 35.37 + 0.77 (Pco₂), *P* < 0.001. Hence, we would expect on average that Psqo₂ would increase by 0.77 mmHg for each 10-mmHg increase in Pco₂. Psqo₂ increased 59% from a Pco₂ of 20 to 60 mmHg.

Muscle oxygen saturation and skin blood flow velocity measured by laser Doppler also increased linearly. However, their slopes were small compared with the increase in Psqo₂; Muscle Saturation = 82.34 + 0.11

(Pco₂), *P* = 0.002; skin blood flow velocity = 11.20 + 0.11 (Pco₂), *P* = 0.026 (table 2 and fig. 2).

In addition, for subcutaneous tissue oxygen tension (Psqo₂), a separate regression was done for each volunteer in the study to see if the positive linear association between Psqo₂ and Pco₂ was consistent within individuals (fig. 2). Even with the extra variability associated with individual data, the pattern of positive linear association was consistent, with the exception of one volunteer. Hence the regression with averaged Psqo₂ values appears to adequately summarize the individual data.

Discussion

Surgical wound infections prolong hospitalization by 5–20 days per infection,¹ and substantially increase cost.^{4,28} Oxidative killing by neutrophils is the primary immune defense against surgical pathogens.¹⁰ Oxidative killing depends on the production of bactericidal superoxide radical from molecular oxygen. The rate of this reaction, catalyzed by the NADPH-linked oxygenase, is Po₂-dependent. Neutrophil superoxide production has a Michaelis-Menten rate constant (K_m) for oxygen of the NADPH-linked oxygenase of at least 60 mmHg.²⁹ Consistent with this observation, oxidative killing is oxygen-dependent in the range from 0 to greater than 150 mmHg.²⁹ It is thus unsurprising that Psqo₂ correlates highly with the risk of infection.¹¹

The partial pressure of oxygen in subcutaneous tissues varies widely, even in patients whose arterial hemoglo-

Table 2. Global Hemodynamics and Tissue Oxygenation as a Function of Target End-Tidal Pco₂

Target Pco ₂ (mmHg)	20	30	40	50	60	p
Cardiac index (l · min ⁻¹ · m ⁻²)	2.7 ± 0.4	2.9 ± 0.4	3.2 ± 0.5	3.6 ± 0.7	3.9 ± 0.2	0.0001
Muscle tissue oxygen saturation (%)*	84.4 ± 7.4	85.8 ± 9.6	86.6 ± 8.1	87.2 ± 8.9	89.0 ± 8.6	0.0004
Laser Doppler flow velocity (U)*	13.6 ± 6.3	13.7 ± 7.7	16.7 ± 6.8	16.2 ± 9.3	17.8 ± 8.5	0.2169
Subcutaneous tissue oxygen tension (mmHg)	51.9 ± 9.9	57.8 ± 11.2	65.2 ± 14.5	74.0 ± 12.3	82.4 ± 18.6	<0.0001

Data presented as mean ± SD. See Fig. 1 for regression analysis. Repeated measure ANOVA was used to analyze normally distributed data. Asterisks (*) indicate non-normally distributed data sets analyzed by Friedman test.

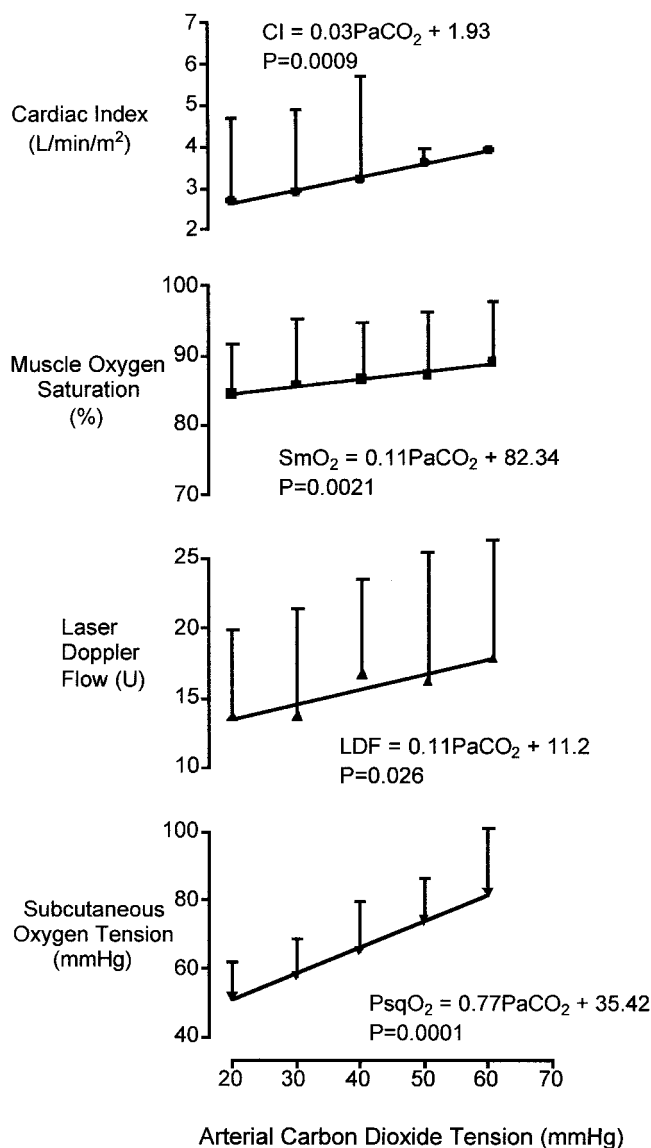


Fig. 1. Cardiac index (CI), muscle tissue oxygen saturation (SmO_2), skin blood flow (Laser Doppler Flow velocity [LDF]), and subcutaneous tissue oxygen tension ($PsqO_2$) all increased as a linear function of $Paco_2$. P values were obtained from linear regression formula.

bin is fully saturated. As might be expected, increasing the fraction of inspired oxygen augments tissue oxygen tension,^{2,21} and reduces the risk for anastomotic leak³⁰ and surgical wound infection.² Other factors known to influence tissue oxygen tension include systemic¹⁹ and local temperature,^{15,31} smoking,³² anemia,¹² perioperative fluid management,^{8,12,18} and uncontrolled surgical pain.³³

Cardiac output is one of the major determinants of peripheral oxygen delivery.³⁴ Although the mechanisms are not clear, it is well established that increasing $Paco_2$ markedly augments cardiac output.¹⁶ The range of clinically accepted $Paco_2$ varies widely during anesthesia, ranging from near 30 mmHg in mechanically ventilated

patients to near 50 mmHg in those breathing spontaneously. Increasing carbon dioxide can initiate a sympathetically mediated release of catecholamines to increase cardiac output. On the other hand, elevation of carbon dioxide increases flow by local vasodilation, and this might well increase cardiac output, as well. Regardless of the mechanism, our results are consistent with a strong relationship between carbon dioxide and cardiac output. We found that cardiac index increased by an average of $1.2 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ when $Paco_2$ was increased from 20 to 60 mmHg.

This hypercapnia-induced increase in cardiac output results in higher tissue oxygen pressure. In the current study $PsqO_2$ went from 58 to 74 mmHg with only a 20-mmHg increase in $Paco_2$. This increase in $PsqO_2$ is likely to be clinically important because it is associated with a substantial reduction in the risk of surgical wound infection.¹¹ These results suggest that maintaining slight hypercapnia is likely to reduce the risk of surgical wound infection. Carbon dioxide management thus joins the growing list of anesthetic factors that do or are likely to influence the risk of wound infection.

Hypercapnia appears to provide other benefits as well.³⁵ For example, hypercapnia and hypercapnic acidosis decrease ischemia-reperfusion injury by inhibiting xanthine oxidase in an *in vitro* model of acute lung injury.³⁶ Hypercapnia similarly improves functional recovery and coronary blood flow during hypercapnic acidosis in an isolated blood-perfused heart model.³⁷ Furthermore, small tidal volume ventilation (associated with mild hypercapnia) and permissive hypercapnia have been shown to improve the outcome of patients with acute respiratory distress syndrome as a result of decreased mechanical stretch of the diseased pulmonary tissues.^{38,39}

Hypercapnia also increases cerebral blood flow and decreases cerebrovascular resistance through dilation of arterioles whereas hypocapnia does the opposite.^{40,41} In a recent study, hyper- and hypocapnia were shown to influence brain oxygen tension in swine during hemorrhagic shock⁴²; hyperventilation and the resulting hypocapnia (15–20 mmHg) decreased cerebral oxygen pressure a further 56%. Hypercapnia has been utilized clinically to improve cerebral perfusion during carotid endarterectomy^{43,44} and for emergency treatment of retinal artery occlusion.⁴⁵

This study was conducted in young, healthy, volunteers under highly controlled circumstances. As a result, variability was low and it was easy to identify the effects of $Paco_2$ on $PsqO_2$, skin blood flow, cardiac index, and muscle oximeter saturation. The effects may well differ in patients with underlying illness and other confounding factors.⁴⁶ Furthermore, we evaluated each $Paco_2$ level for 45 min; it is possible that physiologic adaptation would diminish the effects of carbon dioxide if the

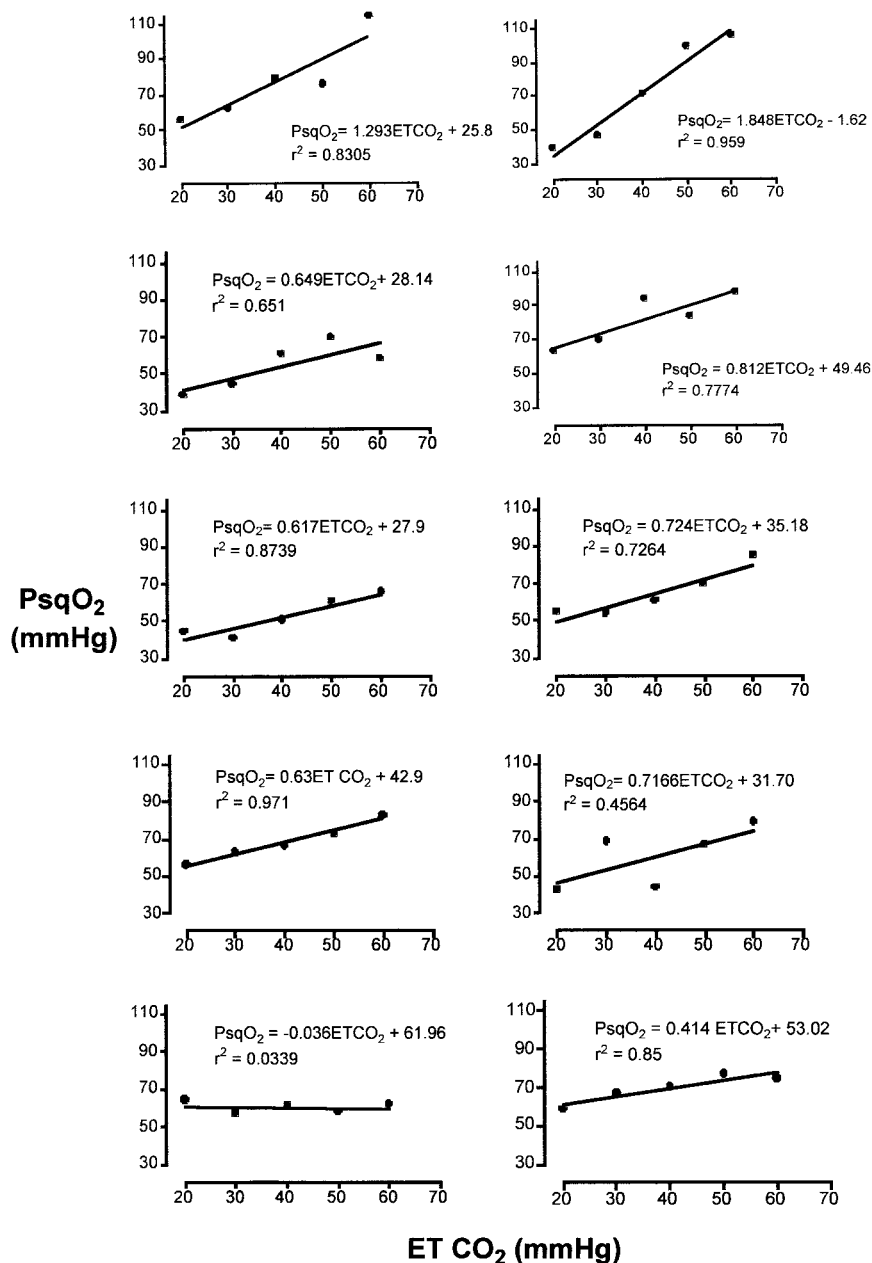


Fig. 2. Linear regression between measured subcutaneous tissue oxygen tension ($PsqO_2$) and end-tidal carbon dioxide levels ($ETCO_2$) in each individual volunteer.

designated concentrations were maintained for prolonged periods.

We measured the tissue oxygenation from only one single electrode located on the upper arm. Although it is not likely, it might be that the rest of the tissue gets oxygenated differently than where we measured. It should also be noted that, although neither the noninvasive cardiac output or muscle tissue saturation measurements was the major outcome of the study, these systems are not validated specifically to operate under the circumstances mentioned in our methodology. In addition, a patient's general health status and existing illnesses should always be considered before application of any hypercapnia. For example, hypercapnia increases cerebral blood flow, which also causes an increase in

intracranial pressure. Therefore, hypercapnia should be avoided in neurosurgical cases with high intracranial pressure in which cerebral perfusion is not threatened.

In summary, tissue oxygen partial pressure ($PsqO_2$), skin blood flow velocity, cardiac index, and muscle oximeter saturation all increased as a linear function of $Paco_2$. The observed difference in $PsqO_2$ is clinically important since previous work indicates that comparable increases in tissue oxygenation reduce the risk of infection from 7 to 8% to 2 to 3%. We thus conclude that permitting mild intraoperative hypercapnia is likely to improve resistance to surgical wound infections.

The authors would like to thank Nancy Alsip, Ph.D., (Outcomes Research@Institute, University of Louisville, Louisville, Kentucky) for editorial assistance.

References

- Kurz A, Sessler DI, Lenhardt RA: Study of wound infections and temperature group: Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *N Engl J Med* 1996; 334:1209-15
- Greif R, Akça O, Horn E-P, Kurz A, Sessler DI, Outcomes Research® Group: Supplemental perioperative oxygen to reduce the incidence of surgical wound infection. *N Engl J Med* 2000; 342:161-7
- Miles AA, Miles EM, Burke J: The value and duration of defense reactions of the skin to the primary lodgement of bacteria. *Br J Exp Pathol* 1957; 38:79-97
- Haley RW, Culver DH, Morgan WM, White JW, Emori TG, Hooton TM: Identifying patients at high risk of surgical wound infection: A simple multivariate index of patient susceptibility and wound contamination. *Am J Epidemiol* 1985; 121:206-15
- Classen DC, Evans RS, Pestotnik R, Horn SD, Menlove RL, Burke JP: The timing of prophylactic administration of antibiotics and the risk of surgical wound infection. *N Engl J Med* 1992; 326:281-6
- Burke JF: The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery* 1961; 50:161-8
- Van Oss CJ, Absolam DR, Moore LL, Park BH, Humbert JR: Effect of temperature on the chemotaxis, phagocytic engulfment, digestion and O₂ consumption of human polymorphonuclear leukocytes. *J Reticuloendothel Soc* 1980; 27:561-5
- Jonsson K, Jensen JA, Goodson WH, West JM, Hunt TK: Assessment of perfusion in postoperative patients using tissue oxygen measurements. *Br J Surg* 1987; 74:263-7
- Hartmann M, Jonsson K, Zederfeldt B: Effect of tissue perfusion and oxygenation on accumulation of collagen in healing wounds. Randomized study in patients after major abdominal operations. *Eur J Surg* 1992; 158:521-6
- Babior BM: Oxygen-dependent microbial killing by phagocytes. *N Engl J Med* 1978; 298:659-68
- Hopf HW, Hunt TK, West JM: Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch Surg* 1997; 132:997-1005
- Gosain A, Rabin J, Reymond JP, Jensen JA, Hunt TK, Upton RA: Tissue oxygen tension and other indicators of blood loss or organ perfusion during graded hemorrhage. *Surgery* 1991; 523-32
- Shoemaker W, Appel P, Kram H: Oxygen transport measurements to evaluate tissue perfusion and titrate therapy: dobutamine and dopamine effects. *Crit Care Med* 1991; 19:672-88
- Plattner O, Akça O, Herbst F, Arkiliç CF, Függer R, Barlan M, Kurz A, Hopf H, Werba A, Sessler DI: The influence of two surgical bandage systems on wound tissue oxygen tension. *Arch Surg* 2000; 135:818-22
- Ikeda T, Tayefeh F, Sessler DI, Kurz A, Plattner O, Petschnigg B, Hopf HW, West J: Local radiant heating increases subcutaneous oxygen tension. *Am J Surg* 1998; 175:33-7
- Mas A, Saura P, Joseph D, Blanch L, Baigorri F, Artigas A, Fernandez R: Effects of acute moderate changes in PaCO₂ on global hemodynamics and gastric perfusion. *Crit Care Med* 2000; 28:360-5
- Guzman J, Kruse J: Splanchnic hemodynamics and gut-mucosal-arterial PCO₂ gradient during systemic hypocapnia. *J Appl Physiol* 1999; 87:1102-6
- Arkiliç C, Tagushi A, Ahluwalia A, Sessler D, Kurz A: The effect of supplemental fluid administration on tissue perfusion and tissue oxygen pressure. *ANESTHESIOLOGY* 2000; 93:A207
- Sheffield CW, Sessler DI, Hopf HW, Schroeder M, Moayeri A, Hunt TK, West JM: Centrally and locally mediated thermoregulatory responses alter subcutaneous oxygen tension. *Wound Rep Reg* 1997; 4:339-45
- Levinsohn DG, Gordon L, Sessler DI: The Allen's test: Analysis of four methods. *J Hand Surg [Am]* 1991; 16A:279-82
- Gotttrup F, Firmin R, Rabkin J, Halliday B, Hunt TK: Directly measured tissue oxygen tension and arterial oxygen tension assess tissue perfusion. *Crit Care Med* 1987; 15:1030-6
- Chang N, Goodson WH, Gotttrup F, Hunt TK: Direct measurement of wound and tissue oxygen tension in postoperative patients. *Ann Surg* 1983; 197:470-8
- Gotttrup F, Firmin R, Chang N, Goodson III WH, Hunt TK: Continuous direct tissue oxygen tension measurement by a new method using an implantable silastic tonometer and oxygen polarography. *Am J Surg* 1983; 146:399-403
- Singer I, Edmonds H: Tissue oximetry for the diagnosis of neurally mediated syncope. *Pacing Clin Electrophysiol* 2000; 23:2006-9
- Jaffe M: Partial CO₂ rebreathing cardiac output-operating principles of the NICO system. *J Clin Monit* 1999; 15:387-401
- Maxwell R, Gibson J, Slade J, Fabian T, Proctor K: Noninvasive cardiac output by partial CO₂ rebreathing after severe chest trauma. *J Trauma* 2001; 51:849-53
- van Heerden P, Baker S, Lim S, Weidman C, Bulsara M: Clinical evaluation of the non-invasive cardiac output (NICO) monitor in the intensive care unit. *Anaesth Intensive Care* 2000; 28:427-30
- Bremmelgaard A, Raahave D, Beir-Holgersen R, Pedersen JV, Andersen S, Sorensen AI: Computer-aided surveillance of surgical infections and identification of risk factors. *J Hosp Infect* 1989; 13:1-18
- Allen DB, Maguire JJ, Mahdavian M, Wicke C, Marcocci L, Scheuenstuhl H, Chang M, Le AX, Hopf HW, Hunt TK: Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. *Arch Surg* 1997; 132:991-6
- Sheridan WG, Lowndes RH, Young HL: Tissue oxygen tension as a predictor of colonic anastomotic healing. *Dis Colon Rectum* 1987; 30:867-71
- Plattner O, Semsroth M, Sessler DI, Papousek A, Klasen C, Wagner O: Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol. *ANESTHESIOLOGY* 1997; 86:772-7
- Jensen JA, Goodson WH, Hopf HW, Hunt TK: Cigarette smoking decreases tissue oxygen. *Arch Surg* 1991; 126:1131-4
- Akça O, Melischek M, Scheck T, Hellwagner K, Arkiliç C, Kurz A, Kapral S, Heinz T, Lackner FX, Sessler DI: Postoperative pain and subcutaneous oxygen tension. *Lancet* 1999; 354:41-2
- Boyd O, Grounds RM, Bennett ED: A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* 1993; 270:2699-707
- Laffey J, Kavanagh B: Biological effects of hypercapnia. *Intensive Care Med* 2000; 26:133-38
- Shibata K, Cregg N, Engelberts D, Takeuchi A, Fedorko L, Kavanagh B: Hypercapnic acidosis may attenuate acute lung injury by inhibition of endogenous xanthine oxidase. *Am J Respir Crit Care Med* 1998; 158:1578-84
- Nomura F, Aoki M, Forbess J, Mayer J: Effects of hypercarbic acidotic reperfusion on recovery of myocardial function after cardioplegic ischemia in neonatal lambs. *Circulation* 1994; 90:321-7
- Amato M, Barbas C, Medeiros D, Magaldi R, Schettino G, Lorenzi-Filho G, Kairalla R, Deheinzelin D, Munoz C, Oliveira R, Takagaki T, Carvalho C: Effect of a protective ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347-54
- Hickling K, Walsh J, Henderson S, Jackson R: Low mortality rate in adult respiratory distress syndrome using low volume, pressure limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med* 1994; 22:1568-78
- Grubb R, Jr, Raichle M, Eichling J, Ter-pogossian M: The effects of changes in PaCO₂ on cerebral blood volume, blood flow, and vascular mean transit time. *Stroke* 1974; 5:630-9
- Kontos H: Regulation of cerebral circulation. *Annu Rev Physiol* 1981; 43:397-407
- Manley G, Hemphill J, Morabito D, Derugin N, Erickson V, Pitts L, Knudson M: Cerebral oxygenation during hemorrhagic shock: perils of hyperventilation and therapeutic potential of hypoventilation. *J Trauma* 2000; 48:1025-33
- Cho H, Nemoto E, Yonas H, Balzer J, Sciallasi R: Cerebral monitoring by means of oximetry and somatosensory evoked potentials during carotid endarterectomy. *J Neurosurg* 1998; 89:533-8
- Samra S, Dy E, Welch K, Dorje P, Zelenock G, JC S: Evaluation of a cerebral oximeter as a monitor of cerebral ischemia during carotid endarterectomy. *ANESTHESIOLOGY* 2000; 93:964-70
- Atebara N, Brown G, Cater J: Efficacy of anterior chamber paracentesis and carbogen intreating acute nonarteritic central retinal artery occlusion. *Ophthalmology* 1995; 102:2029-34
- Schulte am Esch J, Bause HW, Kochs E: Influences of various respiratory and circulatory conditions on muscle tissue oxygenation in critically ill patients, Yearbook of Intensive Care and Emergency Medicine. Edited by Vincent JL. Basel, Springer-Verlag, 1992, pp 303-9