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Hypercapnia Improves Tissue Oxygenation

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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 ($Paco_2$) 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 ($Psqo_2$) was recorded from a subcutaneous tonometer. An oximeter probe on the upper arm measured muscle oxygen saturation. Cardiac output was monitored noninvasively. $Paco_2$ was adjusted to 20, 30, 40, 50, or 60 mmHg in random order with each concentration being maintained for 45 min.**

Results: **Increasing $Paco_2$ linearly increased cardiac index and $Psqo_2$: $Psqo_2 = 35.42 + 0.77\ (Paco_2)$, $P < 0.001$.**

Conclusions: **The observed difference in $PsqO_2$ 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 incidence 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 ($Psqo_2$) 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 ($Paco_2$) 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 $Paco_2$ in anesthetized humans. We simultaneously evaluated the relationship between $Paco_2$ 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 $ml \cdot kg^{-1} \cdot h^{-1}$ 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

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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 polographic electrode system (Licox 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 ± 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 (Licox 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, Novametrix Medical 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 patients[27] 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 ± 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/m^2. Initial (preinduction) blood pressure averaged 75 ± 8 mmHg; heart rate was 77 ± 9 beats/min; and oxygen saturation (Spo_2) was 99 ± 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 P_{CO_2}

Target Pa_{CO_2} (mmHg)	20	30	40	50	60
Measured Pa_{CO_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
Pa_{O_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 CO_2 concentrations. Data presented as mean ± SD.

MAP = mean arterial pressure; RR = respiratory rate; Spo_2 = oxygen saturation as determined by pulse oximeter; Pa_{O_2} and Pa_{CO_2} = arterial oxygen and carbon dioxide partial pressures.

Cardiac index and subcutaneous tissue oxygen tension at each level of Pa_{CO_2} 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 Pa_{CO_2} 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 Pa_{CO_2}.

Cardiac index (CI) was normal (2.7–2.9 $l \cdot min^{-1} \cdot m^{-2}$) at the lower Pa_{CO_2} values, but increased linearly to 3.9 $l \cdot min^{-1} \cdot m^{-2}$ at the highest Pa_{CO_2}: CI = 1.93 + 0.03 (Pa_{CO_2}), $P < 0.001$. Thus, we would expect that, on average, a 10-mmHg increase in Pa_{CO_2} would result in a 0.3 increase in cardiac index. Across the full range of Pa_{CO_2} from 20 to 60 mmHg, cardiac index increased 44%.

Subcutaneous tissue oxygen tension ($Psqo_2$) was also linearly related to Pa_{CO_2} (fig. 1). Increasing Pa_{CO_2} linearly increased $Psqo_2$: $Psqo_2$ = 35.37 + 0.77 (Pa_{CO_2}), $P < 0.001$. Hence, we would expect on average that $Psqo_2$ would increase by 0.77 mmHg for each 10-mmHg increase in Pa_{CO_2}. $Psqo_2$ increased 59% from a Pa_{CO_2} 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 $Psqo_2$: Muscle Saturation = 82.34 + 0.11 (Pa_{CO_2}), $P = 0.002$; skin blood flow velocity = 11.20 + 0.11 (Pa_{CO_2}), $P = 0.026$ (table 2 and fig. 2).

In addition, for subcutaneous tissue oxygen tension ($Psqo_2$), a separate regression was done for each volunteer in the study to see if the positive linear association between $Psqo_2$ and Pa_{CO_2} 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 $Psqo_2$ 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 Po_2-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 $Psqo_2$ 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 P_{CO_2}

Target Pa_{CO_2} (mmHg)	20	30	40	50	60	p
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	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.

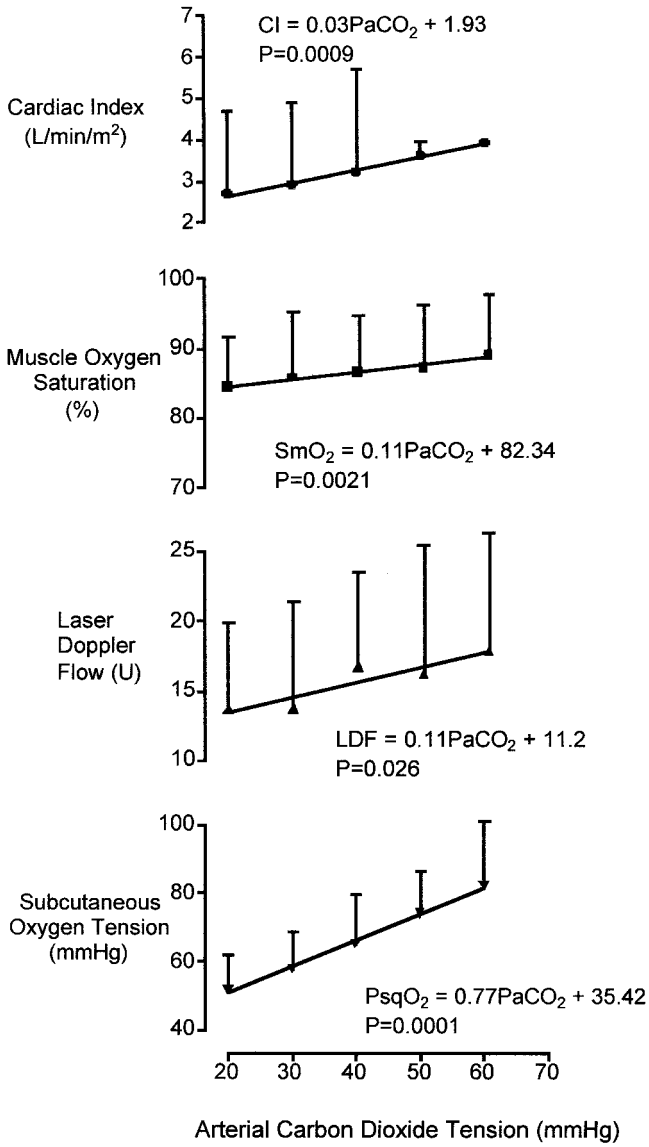

Fig. 1. Cardiac index (CI), muscle tissue oxygen saturation (Smo_2), skin blood flow (Laser Doppler Flow velocity [LDF]), and subcutaneous tissue oxygen tension ($Psqo_2$) all increased as a linear function of $Paco_2$. *P* values were obtained from linear regression formula.

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 leak[30] and surgical wound infection.[2] Other factors known to influence tissue oxygen tension include systemic[19] 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 l · min^{-1} · 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 shock[42]; 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 Pco_2 level for 45 min; it is possible that physiologic adaptation would diminish the effects of carbon dioxide if the

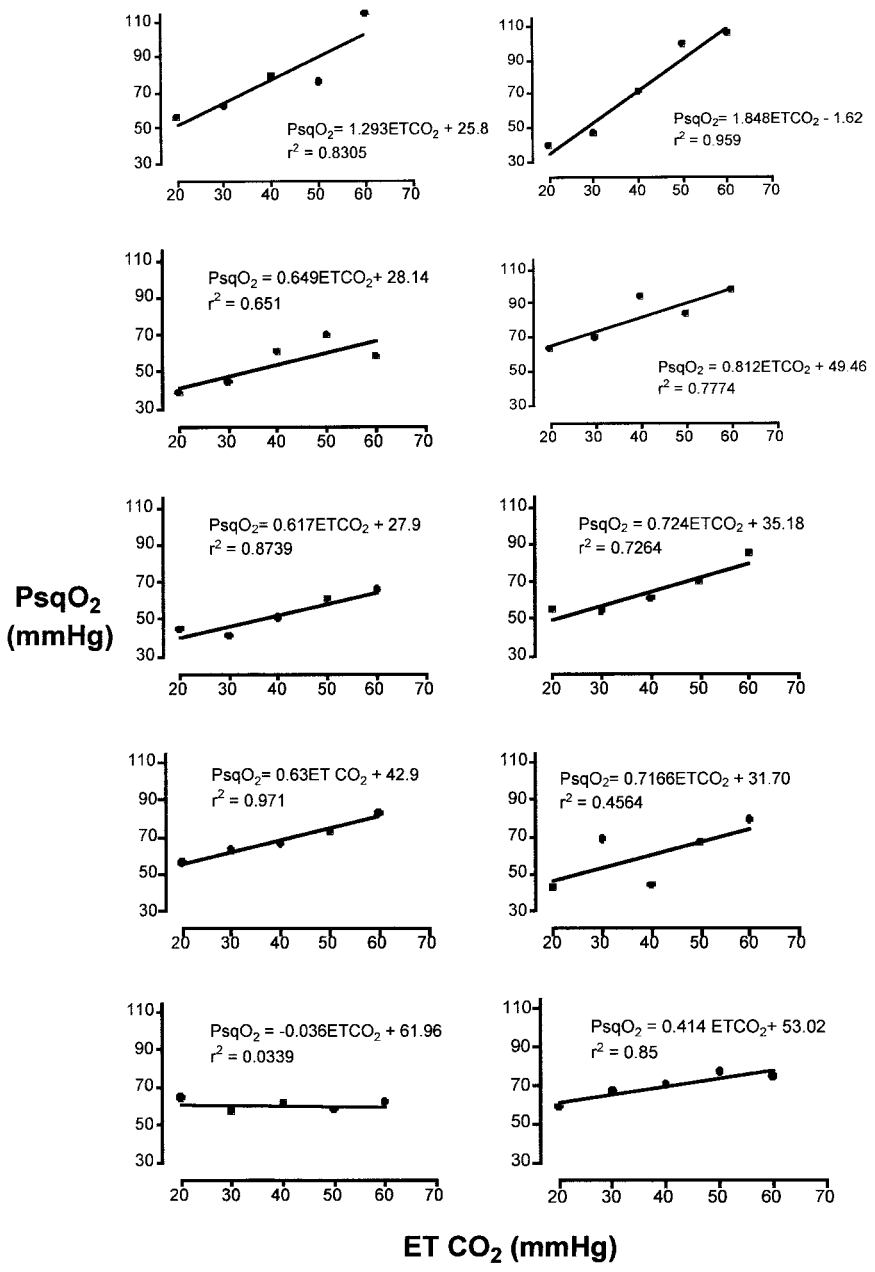

Fig. 2. Linear regression between measured subcutaneous tissue oxygen tension ($Psqo_2$) and end-tidal carbon dioxide levels ($ETco_2$) in each individual volunteer.

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.

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