Thermoregulatory Vasodilation Increases the Venous Partial Pressure of Oxygen

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Thermoregulatory arteriovenous shunt vasoconstriction may facilitate deep-vein thrombosis by producing relative venous stasis and hypoxia. Accordingly, we evaluated the effect of vasomotion on leg blood flow and venous oxygen tension. We studied five male volunteers, each of whom was warmed enough to trigger vasoconstriction and then cooled sufficiently to provoke thermoregulatory vasoconstriction. The process was then repeated during N₂O/O₃ desflurane anesthesia. Venous oxygen tension and saturation (with a fraction of inspired oxygen of 1.0) were evaluated in blood samples taken from a catheter that was inserted into a saphenous vein at the ankle and advanced until the tip was proximal to the knee. Thermoregulatory vasodilation with or without general anesthesia significantly increased arteriovenous shunt flow by approximately 10-fold, and increased total leg flow approximately sixfold. However, vasodilated flows were similar with and without general anesthesia, as were vasoconstricted flows. Before induction of anesthesia, thermoregulatory vasodilation increased venous oxygen tension from 46 ± 6 to 107 ± 99 mm Hg and venous saturation from 79% ± 6% to 99% ± 2%. After induction of anesthesia, thermoregulatory vasodilation increased venous oxygen tension from 35 ± 11 to 356 ± 103 mm Hg and venous saturation from 84% ± 8% to 100% ± 0%. Our data thus indicate that thermoregulatory vasodilation markedly increases both leg flow and venous oxygenation, and that both factors may help prevent perioperative venous thrombosis. Implications: Thermoregulatory arteriovenous shunt vasoconstriction may facilitate deep-vein thrombosis by producing related venous stasis and hypoxia. In male volunteers, the authors found that when vasodilation induced by warming was produced, both blood flow and venous oxygenation increased, both of which may help prevent perioperative venous thrombosis.


Despite the use of prophylactic techniques, venous thromboembolism continues to be a major cause of morbidity and mortality, especially in association with limb immobilization and trauma or orthopedic surgery (1). In the 1850s, Virchow (2) linked venous thrombosis to hypercoagulability, vascular damage, and stasis. More recently, nonpulsatile stasis has been associated with rapid intravascular hypoxemia, white blood cell margination, and thrombus formation in veins of the lower extremities in animal models of limb immobilization (3,4). Additionally, hypoxia directly modulates endothelial cell antiocoagulant properties in cell culture (5) and causes fibrin deposition in intact animals (6).

These data suggest that intravascular oxygen deprivation may contribute to pathologic venous thrombosis, particularly during the perioperative period, when factors such as immobilization, venous stasis, and venous hypoxemia combine to increase risk. Lower extremity venous thrombosis leads to venous insufficiency and is the precursor of pulmonary embolism, which results in 50,000–100,000 deaths annually (7). Surgical patients have a high risk of developing deep-vein thrombosis, which in some cases progresses to pulmonary embolism. The rate of deep-vein thrombosis...
in general surgical patients is 27% without prophylactic measures (8). Even with prophylaxis, the rate remains approximately 6%. Patients undergoing orthopedic procedures are at especially high risk of deep-vein thrombosis, perhaps because of compounded stasis or vascular damage from tourniquet use or surgical positioning. In total hip arthroplasty, the incidence of deep-vein thrombosis ranges from 45% to 70%, with pulmonary embolism occurring in 5%-20% (9).

Hands and feet are equipped with thermoregulatory arteriovenous shunts (10). These 100-μm diameter vessels convey 10,000 times more blood than a comparable length of 10-μm diameter capillary (11). The purpose of arteriovenous shunts is apparently to augment limb blood flow, thus warming peripheral tissues and dissipating heat to the environment. A consequence of shunt flow is that limb perfusion normally far exceeds tissue nutritional needs.

Thermoregulatory vasoconstriction, however, virtually obligates shunt flow (12), thus markedly reducing total limb perfusion (13). Intraoperative vasoconstriction usually occurs at core temperatures between 34 and 35°C, depending on type and dose of general anesthesia (14,15). However, vasoconstriction is universal in hypothermic postoperative patients and persists for several hours (16). Consequently, many surgical patients are vasoconstricted for a good fraction of the perioperative period.

Vasoconstriction is likely to facilitate deep-vein thrombosis via two mechanisms. First, relative hypoperfusion may promote stasis that reduces washout of activated clotting factors from areas of venous pooling. Second, vasoconstriction prevents mixing of shunted arterial blood with oxygen-depleted capillary (nutritional) flow, producing relative venous hypoxia. Vasodilation, on the other hand, should have the opposite effects. Accordingly, we tested the hypothesis that thermoregulatory vasodilation markedly increases leg blood flow and venous oxygen tension. To better characterize the perioperative period, we evaluated the effects of thermoregulatory vasodilation on leg blood flow and venous oxygen tension before and during general anesthesia.

**Methods**

With approval of the Committee on Human Research at the University of California, San Francisco, we studied five healthy male volunteers. Morphometric characteristics included: age 30 ± 6 yr, height 168 ± 8 cm, and weight 66 ± 10 kg. The percentage of body fat was 16 ± 3, as determined by infrared interactance (Futrex Inc., Hagerstown, MD). None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud’s syndrome.

Studies started at approximately 9:30 AM, and the volunteers fasted during the 8 preceding h. They were minimally clothed and rested supine in a 22-23°C room during the protocol. A 16-gauge, 60-cm long catheter was inserted into the saphenous vein at the ankle and advanced until the tip was just proximal to the knee. During the first portion of the study, arteriovenous shunt vasodilation (see below) was induced by cutaneous warming using circulating water (Cincinnati Sub-Zero, Cincinnati, OH) and forced air (Augustine Medical, Inc.). Warming and cooling were restricted to the upper body. Vasodilation was maintained for 1 h, but the volunteers were not heated enough to trigger sweating. The same devices then cooled the volunteers sufficiently to induce foot arteriovenous shunt vasoconstriction, which was maintained for 1 h.

General anesthesia was then induced by the administration of 200 mg propofol, nitrous oxide 70%, vecuronium bromide 0.1 mg/kg, and incremental concentrations of desflurane to approximately 10%. Nitrous oxide was discontinued, and the volunteers’ tracheas were intubated. Anesthesia was maintained with desflurane 0.6 minimum alveolar anesthetic concentration in oxygen. The patients’ lungs were mechanically ventilated to maintain an end-tidal carbon dioxide partial pressure value near 35 mm Hg. Additional vecuronium was administered, as necessary, to maintain one to two mechanical twitches in response to supramaximal train-of-four stimulation of the ulnar nerve at the wrist. Anesthetic-induced arteriovenous shunt vasodilation (14) was maintained for 1 h, but again, the volunteers were not heated enough to trigger sweating. The volunteers were then cooled sufficiently to induce vasoconstriction, which was maintained for 1 h.

Core temperature was recorded from the tympanic membrane using Mon-a-Therm® thermocouples (Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO). The auricular probe was inserted by volunteers until they felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when volunteers easily detected a gentle rubbing of the attached wire. The aural canal was occluded with cotton, the probe was securely taped in place, and a gauze bandage was positioned over the external ear. Mean skin-surface temperature and cutaneous heat transfer were calculated from measurements at 15 area-weighted sites (17). Temperatures were recorded at 1-min intervals from thermocouples connected to calibrated Iso-Thermex® (Columbus Instruments Corp., Columbus, OH) thermometers having an accuracy of 0.1°C and a precision of 0.01°C.

Arteriovenous shunt tone was evaluated on the second toe by using the perfusion index, which is derived from absorption of icant thermoregula fied by a sustained determined by an core temperature. Ver the studies were used extensometer evaluate leg blood function to the fab uses impedance ins rately measure sma flow was determine shunts with a distal distal tourniquet wa leg flow.

Heart rate and were measured con and blood pressure at 5-min intervals at measured using a Datex Medical Ins land). Temperature were recorded at 5- Venous oxygen te were measured in 1 nous catheter. Oxyg University of Calif ratory; saturation calibrate co-oxim difficult during inte low-pressure tourni tly aspirating each times: after 1 h of after 1 h of vasocar 1 h of vasodilation vasoconstriction du Oxygen was adn to minimize differe ences resulting fr ical ventilation. Oxy a sealed face mask blood samples were breathed only oxyge neal anesthesia.

**Results**

Arteriovenous shun perfusion index, inc warming before ind tor of 11 ± 7 duri
from absorption of two infrared wave lengths. Significant thermoregulatory vasoconstriction was identified by a sustained decrease in the perfusion index, as determined by an observer blinded to treatment and core temperature. Vasoconstriction was evaluated after the studies were complete from coded graphs. We used extensometer strain-gauge plethysmography to evaluate leg blood flow (18). This device is similar in function to the familiar Whitney strain gauge, but it uses impedance instead of mercury in rubber to accurately measure small changes in length. Calf blood flow was determined by excluding foot arteriovenous shunts with a distal arterial tourniquet. In contrast, a distal tourniquet was avoided when determining total leg flow.

Heart rate and oxyhemoglobin saturation (SpO₂) were measured continuously using pulse oximetry, and blood pressure was determined oscillometrically at 5-min intervals at the left ankle. End-tidal Pco₂ was measured using a respiratory monitor (Capnomac®; Datex Medical Instrumentation, Inc. Helsinki, Finland). Temperatures, flows, and anesthetic safety data were recorded at 5-min intervals.

Venous oxygen tension (PvO₂) and saturation (SvO₂) were measured in blood withdrawn from the saphenous catheter. Oxygen tension was determined by the University of California, San Francisco Clinical Laboratory; saturation was similarly determined with a calibrated co-oximeter. Because blood sampling can be difficult during intense vasoconstriction, we applied a low-pressure tourniquet around the thigh before gently aspirating each sample. Blood was sampled four times: after 1 h of vasodilation without anesthesia, after 1 h of vasoconstriction without anesthesia, after 1 h of vasodilation during anesthesia, and after 1 h of vasoconstriction during anesthesia.

Oxygen was administered during blood sampling to minimize differences in alveolar-to-arterial differences resulting from general anesthesia and mechanical ventilation. Oxygen (100%) was thus delivered via a sealed face mask for 15 min before the first two blood samples were aspirated. Similarly, the volunteer breathed only oxygen and desflurane throughout general anesthesia.

Toe and leg blood flows, PvO₂, SvO₂, and core temperature during dilation and constriction were compared using two-tailed, paired t-tests. Data are presented as mean ± sp. P < 0.05 was considered statistically significant.

Results

Arteriovenous shunt flow, as determined by using the perfusion index, increased by a factor of 10 ± 6 during warming before induction of anesthesia and by a factor of 11 ± 7 during anesthesia. Thermoregulatory vasodilation increased total leg blood flow 5.4 ± 1.1-fold before the induction of general anesthesia; flows were similarly increased (7.3 ± 3.4-fold) during anesthesia. Both increases were statistically significant. Individual values (circles) are connected by lines; squares and error bars indicate means and so.

Figure 1. Thermoregulatory vasodilation increased total leg blood flow 5.4 ± 1.1-fold before the induction of general anesthesia; flows were similarly increased (7.3 ± 3.4-fold) during anesthesia (Fig. 1). Vasodilation increased calf blood flow 3.9 ± 2.0-fold before induction of general anesthesia and 4.6 ± 2.4-fold during anesthesia. All vasodilation-induced flow increases were statistically significant. However, vasodilated flows were similar without and with general anesthesia, as were vasoconstricted flows.

Before the induction of anesthesia, thermoregulatory vasodilation significantly increased PvO₂ from 46 ± 6 to 187 ± 99 mm Hg, and it increased SvO₂ from 79% ± 6% to 99% ± 2%. After induction of anesthesia, thermoregulatory vasodilation significantly increased PvO₂ from 55 ± 11 to 356 ± 103 mm Hg, and it increased SvO₂ from 84% ± 8% to 100% ± 0% (Fig. 2). Core temperatures remained nearly constant before the induction of anesthesia. During anesthesia, core temperature decreased slightly between the vasodilation and vasoconstriction portions of the study (Table 1).

Discussion

During the perioperative period, a combination of events may overwhelm patients’ anticoagulant defenses and result in pathologic coagulation that can present as venous thrombosis and, consequently, pulmonary embolism. Genetically susceptible individuals, such as those with activated protein C resistance (19) and patients with cancer (20), have an inherent tendency to form venous thrombi and are thus at special risk of perioperative thrombosis. Surgery per se also causes a period of "fibrinolytic shutdown" (21), which may be a manifestation of the stress response (22). Finally, advanced age is a risk factor for venous thromboembolism (1), as is the lower limb venous
stasis and pooling that results from bedrest or spinal cord injury (1).

General anesthesia decreases the threshold for arteriovenous shunt vasoconstriction approximately 2-4°C (14) and reduces the gain of vasoconstriction threefold (23). However, the maximal intensity of shunt vasoconstriction remains normal during anesthesia (24). It is therefore not surprising that vasoconstriction-induced decreases in leg blood flow, PVO₂, and SVO₂ were similar with and without anesthesia. In both cases, thermoregulatory vasoconstriction reduced arteriovenous shunt flow approximately 10-fold and reduced total leg flow approximately six-fold. Vasoconstriction produced relative leg stasis compared with the normal situation, in which the thermoregulatory resistance vessels are dilated to dissipate heat and leg blood flow far exceeds nutritional needs. This reduction alone would not normally cause deep-vein thrombosis; however, stasis is a long and well-established etiology of deep-vein thrombosis (2). Thermoregulatory vasoconstriction may well exacerbate venous thrombosis when combined with other factors, such as perioperative immobilization or activation of the coagulation system from surgical tissue damage.

Although stasis is a known etiology of venous thrombosis (2), the extent to which stasis reduces PVO₂ has only recently been appreciated. When venous flow is restricted by immobilization during anesthesia, for example, PO₂ in the vessel lumen decreases to approximately 37 mm Hg; however, PO₂ in venous valve pockets decreases to approximately 2 mm Hg. Pulsations produced by manual compression of the lower extremity muscles replenishes blood in the valve pockets and returns PO₂ to luminal values (4). Thermoregulatory vasoconstriction also significantly decreased venous PO₂ and hemoglobin saturation in our volunteers. Relative venous hypoxia presumably resulted from two processes: decreased shunting of oxygenated arterial blood to the venous circulation and ongoing cellular metabolism in static venous blood.

Oxygen deprivation (PO₂, 14 mm Hg) modulates the normal anticoagulant properties of vascular endothelium by suppressing thrombomodulin production, increasing factor X activation, and interfering with barrier function in cell culture (25). Hypoxic mice (PVO₂, 35 mm Hg) exhibit pulmonary fibrin and platelet deposition and have impaired fibrinolysis. The venous PO₂ partial pressures in our study (approximately 45-55 mm Hg) were somewhat greater than those found in previous limb studies experiments (2-38 mm Hg) (4), cell culture preparations (14 mm Hg) (25), and murine studies (35 mm Hg) (13,14). However, our volunteers were given 100% oxygen during blood sampling to minimize alveolar-to-arterial differences during the transit from spontaneous ventilation to mechanical ventilation during general anesthesia. Vasoconstriction may decrease venous oxygen tension less than sixfold in patients given less oxygen. Nonetheless, absolute venous partial pressure is likely to be considerably less than the approximately 50 mm Hg observed in our volunteers. Similarly, PVO₂ is surely lower in patients having poor pulmonary function or extremity flow that is compromised by preexisting arterial occlusive disease or surgical positioning.

Our observation that thermoregulatory vasoconstriction decreases lower extremity blood flow and venous oxygen partial pressure may contribute to the beneficial effect of regional anesthesia on venous thrombosis. Epidural anesthesia decreases the incidence of deep-vein thrombosis in patients undergoing knee and hip replacement surgery (26,27). Purported mechanisms include modulation of the stress response (28) and improved leg blood flow (29).

Arteriovenous shunt vasoconstriction in response to core and skin cooling is an active process mediated by efferent sympathetic nerves that terminate on α-adrenergic receptors (11). Leg blood flow in unanesthetized, vasodilated subjects is similar to that during epidural anesthesia. The reported 160%-100% increase in leg blood flow during epidural anesthesia results because many patients are initially vasocostricted in the cold operating room environment (30). However, the sympathetic block associated with epidural anesthesia prevents the thermoregulatory vasoconstriction that is so often triggered by mild perioperative hypothermia (16). The primary vasomotor effect of epidural anesthesia is thus to prevent thermoregulatory vasoconstriction (31). Our data suggest that maintaining perioperative normothermia also prevents stasis and may similarly reduce the risk of deep-vein thrombosis.

The vasomotor response to heat is also an active process mediated via postganglionic, cholinergic, sympathetic fibers. Sweat glands, in their state that triggers vasoconstriction can increase 2 and 7.5 L/min by regional anesthesia blood flow may be heated beyond the p anesthesia.

The hypercoagulable state is presumably pends on blood flow and characteristics therefore unlikely to be a consequence tests, such as tilted boltasim times, which can alter garlics and hip replacement without anesthesia. It was large, and varis were highly statistic ally selected only five volunteer.

In summary, it has been that venous hypoxia and to venous thromboembolism monary emboli. Our operative hypothermia triggers the Active warming increases total leg flow proportionately sixfold.

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We appreciate the good a Severinghaus, MD. Mallin Louis, MOI donated the Zero, Inc. (Cincinnati, OH and cover. Augustine Me prototype forced-air cool
Table 1. Leg and Calf Blood Flows, Venous Oxygen Tension and Saturation, and Core Temperature

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<th>Unanesthetized</th>
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<td></td>
<td>Dilated</td>
<td>Constricted</td>
<td>Dilated</td>
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<tr>
<td>Perfusion index (U)</td>
<td>2.0 ± 0.5</td>
<td>0.2 ± 0.1</td>
<td>3.1 ± 0.7</td>
<td>0.3 ± 0.1</td>
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<td>Leg flow (mL·min⁻¹·100 g⁻¹)</td>
<td>2.7 ± 1.1</td>
<td>0.5 ± 0.2</td>
<td>2.8 ± 1.2</td>
<td>0.4 ± 0.2</td>
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<tr>
<td>Calf flow (mL·min⁻¹·100 g⁻¹)</td>
<td>3.3 ± 1.5</td>
<td>0.9 ± 0.5</td>
<td>2.6 ± 0.6</td>
<td>0.7 ± 0.4</td>
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<tr>
<td>Pvo₂ (mm Hg)</td>
<td>187 ± 99</td>
<td>46 ± 6</td>
<td>356 ± 103</td>
<td>55 ± 11</td>
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<tr>
<td>SvO₂ (%)</td>
<td>99 ± 2</td>
<td>79 ± 6</td>
<td>100 ± 0</td>
<td>84 ± 8</td>
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<td>Core temperature (°C)</td>
<td>37 ± 0.2</td>
<td>36.8 ± 0.3</td>
<td>36.4 ± 0.3</td>
<td>35.9 ± 0.3</td>
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Pvo₂ = venous partial pressure of oxygen, SvO₂ = venous oxygen saturation.

All constricted and dilated values differed significantly, except core temperature without anaesthesia.

sympathetic fibers that terminate on sweat glands. Sweat glands, in turn, release an unidentified substance that triggers precapillary vasodilation. Active vasodilation can increase total skin blood flow to between 2 and 7.5 L/min, but this increase is prevented by regional anaesthesia. The greatest perioperative leg blood flow may thus be obtained when patients are heated beyond the point of sweating without regional anaesthesia.

The hypercoagulability leading to deep-vein thrombosis is presumably a localized phenomenon that depends on blood flow, regional oxygen partial pressure, and characteristics of the adjacent vessel wall. It is therefore unlikely that traditional systemic coagulation tests, such as the prothrombin or partial thromboplastin times, would identify clinically important alterations in deep-venous clotting potential. Accordingly, we do not report measures of coagulation. We used a cross-over design, in which each volunteer was evaluated vasodilated and vasoconstricted, with and without anaesthesia. Because the effect of vasomotion was large, and variability relatively small, the results were highly statistically significant although we studied only five volunteers.

In summary, it has previously been established that venous hypoxia and lower extremity stasis contribute to venous thromboembolism and, consequently, pulmonary emboli. Our data indicate that sufficient perioperative hypothermia with or without general anaesthesia triggers thermoregulatory vasoconstriction. Active warming maintains vasodilation, which increases total leg flow and venous oxygen tension approximately sixfold. We postulate that maintenance of perioperative normothermia, which prevents thermoregulatory vasoconstriction, may decrease the risk of venous thromboembolism.

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References


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Department of Anesthesia

The priming paralyzing drug to block tracheal intubation serve the effect of rocuronium on weakness in (65–73 yr of age) patients of various groups. (TOF) ratio were percent dose (ED50) of new tests. All tests were performed hourly. All rocuronium and muscular tension showed groups. The TOF ratio of rocuronium at 0.89 and 0.90 in

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