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ORIGINAL ARTICLE

# Lowered microvascular vessel wall oxygen consumption augments tissue $pO_2$ during PgE1-induced vasodilation

**Barbara Friesenecker · A. G. Tsai · M. W. Dünser · J. Martini · W. Hasibeder · M. Intaglietta**

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**Abstract** Continuous infusion of intravenous prostaglandin E1 (PgE1, 2.5 μg/kg/min) was used to determine how vasodilation affects oxygen consumption of the microvascular wall and tissue $pO_2$ in the hamster window chamber model. While systemic measurements (mean arterial pressure and heart rate) and central blood gas measurements were not affected, PgE1 treatment caused arteriolar (64.6 ± 25.1 μm) and venular diameter (71.9 ± 29.5 μm) to rise to 1.15 ± 0.21 and 1.06 ± 0.19, respectively, relative to baseline. Arteriolar ($3.2 \times 10^{-2} \pm 4.3 \times 10^{-2}$ nl/s) and venular flow ($7.8 \times 10^{-3} \pm 1.1 \times 10^{-2}$/s) increased to 1.65 ± 0.93 and 1.32 ± 0.72 relative to baseline. Interstitial tissue $pO_2$ was increased significantly from baseline (21 ± 8 to 28 ± 7 mmHg; $P < 0.001$). The arteriolar vessel wall gradient, a measure of oxygen consumption by the microvascular wall decreased from 20 ± 6 to 16 ± 3 mmHg ($P < 0.001$). The arteriolar vessel wall gradient, a measure of oxygen consumption by the vascular wall, decreased from 20 ± 6 to 16 ± 3 mmHg ($P < 0.001$). This reduction reflects a 20% decrease in oxygen consumption by the vessel wall and up to 50% when cylindrical geometry is considered. The venular vessel wall gradient decreased from 12 ± 4 to 9 ± 4 mmHg ($P < 0.001$). Thus PgE1-mediated vasodilation has a positive microvascular effect: enhancement of tissue perfusion by increasing flow and then augmentation of tissue oxygenation by reducing oxygen consumption by the microvascular wall.

**Keywords** Vascular wall metabolism · Oxygen gradient · Tissue oxygenation · Microcirculation · Prostaglandins · Transmural vessel wall gradient · Hamster skinfold

B. Friesenecker (✉) · J. Martini
Division of General and Surgical Intensive Care Medicine,
Department of Anesthesia and Critical Care Medicine,
The Leopold-Franzens-University of Innsbruck,
Anichstr. 35, Innsbruck 6020, Austria
e-mail: barbara.friesenecker@uibk.ac.at

A. G. Tsai · M. Intaglietta
Department of Bioengineering, University of California,
San Diego, La Jolla, CA 92093-0412, USA

A. G. Tsai · M. Intaglietta
La Jolla Bioengineering Institute, La Jolla, CA 92037, USA

M. W. Dünser
Department of Intensive Care Medicine,
University Hospital of Bern, Bern, Switzerland

W. Hasibeder
Krankenhaus der Barmherzigen Schwestern,
Ried im Innkreis 4910, Austria

## Introduction

Prostaglandins are effective vasodilators that are physiologically produced in the vascular endothelium (Messina et al. 1974). Prostaglandin E1 (PgE1) directly relaxes vascular smooth muscle via stimulation of the adenylate cyclase system (Moncada and Vane 1978a, b), an effect that does not necessarily involve the vascular endothelium since its removal does not influence PgE1-induced vasodilation (Bevan et al. 1988). Prostanoids have been described to induce both vasoconstriction and vasorelaxation in arteriolar smooth muscle (Hedlund and Andersson 1985), thus PgE1 is a mediator of the regulation of vascular tone as shown by the dose- and vessel size-dependent increase and de-

crease of vascular tone described in pig coronary arteries after PgE1 treatment (Fukuda et al. 1992). Aside from prostanoids, NO has been described as a regulator of vascular wall oxygen consumption and a modulator of tissue oxygenation by Shibata et al. (2005b). Shear stress at the surface of endothelial cells is the stimulus for the liberation of prostaglandins (and NO) from the endothelium due to increased blood flow velocity in the rat cremaster. This mechanism of flow-sensitive, prostaglandin-mediated dilation counteracts pressure-sensitive myogenic vasoconstriction and plays an important role in the regulation of microvascular tone (Koller and Kaley 1990a, b, c). Due to their vasodilative properties, prostaglandins have been used in clinical practice to improve tissue oxygenation in hypoxic areas for many years (Carlson and Eriksson 1973; Creutzig et al. 2004). Anti-inflammatory effects of prostaglandins add up to the positive effects observed in the treatment of limb ischemia (Gladis-Villanueva and Schror 1996). Vasoconstriction, however, is associated with ischemic skin lesions as a common complication from arginine–vasopressin (Dünser et al. 2003), epinephrine (Joynt et al. 1996) and norepinephrine therapy (Hayes et al. 1992). In a recent study we could demonstrate that a cause for evolving tissue hypoxia under conditions of vasopressin-induced vasoconstriction is a significantly increased vessel wall oxygen consumption in the microcirculation of the hamster window model, while on the other hand, vasomotion, a rhythmic combination of arteriolar vasoconstriction and relaxation, was found to be an energetically neutral process which did not consume oxygen beyond the level of steady vasoconstriction (Friesenecker et al. 2004). Hangai-Hoger et al. (2005) showed that verapamil-induced vasodilatation increased oxygen supply to the tissue and could improve tissue oxygenation by lowering oxygen consumption of the microvascular wall.

The aim of the present study was to determine if PgE1-mediated vasodilation improves tissue $pO_2$ solely due to improved microvascular flow conditions or if PgE1-mediated improvement of tissue oxygenation may also be a consequence of lowered microvessel wall oxygen consumption.

## Materials and methods

### Animal model and preparation

The animal experiments carried out in this study were approved by the Austrian Ministry of Science and Research. Investigations were performed in 50–85 g golden Syrian hamsters (Charles River Laboratories, Sulzfeld, Germany). The basic surgical technique has been previously described in detail (Colantuoni et al. 1984; Endrich et al. 1980). Briefly, a double layer of the hamster dorsal skinfold consisting of two layers of skin and corresponding muscle tissue was placed between two titanium frames under pentobarbital anesthesia (50 mg/kg body weight). A 15 mm circular part of the skin including two skin muscles were carefully removed so that only one thin monolayer of skin muscle with the underlying skin remained in place. The tissue was covered with a thin cover glass. The preparation is stable for repeated microscopic observations over a period of several days.

Two days after chamber implantation, polyethylene microcatheters (PE-50 with PE-10 tips), filled with a heparinized saline solution (30 IU/ml), were inserted into the internal carotid artery and external jugular vein under pentobarbital anesthesia in order to allow evaluation of systemic measurements and application of drugs during the experiment. Catheters are guided subcutaneously to the base of the chamber and then exteriorized through the skin and tied to the chamber frame.

### Inclusion criteria

Animals were suitable for the experiments if (1) systemic measurements were within normal range, namely heart rate (HR) >340 beats per minute, mean arterial pressure (MAP) >80 mmHg, systemic hematocrit (Hct) >45%, arterial $pO_2$ >50 mmHg and, (2) microscopic examination of the tissue in the chamber observed under ×650 magnification did not reveal signs of edema or bleeding. Experiments were carried out at least 1 day after catheter implantation in an awake animal in order to avoid side effects of anesthesia on the microcirculation.

### Systemic measurements and blood chemistry

Mean arterial pressure was recorded continuously during the experiments via the arterial catheter and HR was determined periodically from the pressure tracing (Recom pressure transducer system, Model 13-6615-50, Gould Instrument Systems Inc., OH, USA). Arteriolar blood was sampled from the carotid artery catheter into a heparinized capillary tube and immediately analyzed for pH, $pO_2$ and $pCO_2$ at 37°C (Ciba Corning pH/Blood gas analyzer, Model 248, Essex, England). Blood and plasma hemoglobin (Hb) content was determined with a hand-held photometer from a drop of blood. (B-Hemoglobin Photometer, HemoCue

AB, Ängelholm, Sweden), Hct was determined from centrifuged blood sampled in heparinized capillary tubes (Hettich Hct 24 Centrifuge, Tuttlingen, Germany).

### Functional capillary density

Detailed mappings were made of the chamber vasculature so that the same vessels were studied throughout the experiment. Capillary segments were considered functional if red blood cells (RBCs) were observed to transit through the capillary segments during a 45-s period. FCD is tabulated from the capillary lengths with RBC flow in an area comprised of ten successive microscopic fields (~ 510 × 400 μm). FCD ($cm^{-1}$) is the total length of RBC-perfused capillaries divided by the area of the microscopic field of view.

### Microhemodynamic measurements

Vessel diameter ($D$) and RBC velocity ($V$) were measured with a digital video image shearing monitor (Model 908; Vista Electronics, Vista, CA, USA) and a video dual-window, velocity-tracking photodiode cross-correlator (Fibre Optic Photo Diode Pickup and Velocity Tracker model 102 B-C; Vista Electronics), respectively (Lipowsky and Zweifach 1978). The measured centerline velocity was corrected according to vessel size to obtain the mean RBC velocity (Koller and Kaley 1990a). Blood flow was calculated from measurements as $Q = \pi\ V\ (D/2)^2$. The change in overall microvascular flow through the network was estimated by averaging microvascular flow for all microvessels because their response is heterogeneous within the network. The averaged flow has been shown to closely represent the change in cardiac index (Tsai and Intaglietta 2001; Martini et al. 2006).

### Microvascular $pO_2$ distribution

High-resolution microvascular $pO_2$ measurements were made using Phosphorescence Quenching Microscopy (Torres Filho and Intaglietta 1993). This noninvasive method of measuring oxygen levels is based on the oxygen-dependent quenching of phosphorescence emitted by albumin-bound metalloporphyrine complex after pulsed light excitation. With the use of this technique $pO_2$ measurements are obtained by determining the rate of decay of the excited phosphorescence, which is inversely proportional to the amount of oxygen that surrounds the dye and independent of the amount dye present or the intensity of light excitation provided that the signal-to-noise ratio is adequate. The phosphorescence decay curves were converted to $pO_2$ values with the use of a fluorescence decay curve fitter (Model 802, Vista Electronics) (Kerger et al. 2003). This technique has been used in this animal preparation and others for both intra- and extravascular (=perivascular + interstitial/tissue) $pO_2$ measurements because albumin exchange between plasma and tissue allows for sufficient concentrations of albumin-bound dye within the interstitium to achieve an adequate signal-to-noise ratio. Interstitial $pO_2$ measurements made with this system have been compared with simultaneous measurements with recessed oxygen electrodes and their differences were found not to be statistically significant (Buerk et al. 1998). Animals received a slow intravenous injection of 15 mg/kg body weight at a concentration of 10.1 mg/ml of a palladium-meso-tetra(4-carboxylphenyl) porphyrin (Porphyrin Products; Logan, UT, USA). The dye is allowed to circulate for 20 min before $pO_2$ measurements to allow enough dye to diffuse into the interstitial space from the more permeable vessels in the network.

In our system, intra- and perivascular measurements are made by placing an optical rectangular window of ~5 × 40 μm longitudinally within the vessel of interest (intravascular) or just outside the vessel wall (perivascular) where the longest side of the rectangle is positioned parallel to the vessel wall. Interstitial tissue $pO_2$ was measured in regions void of large vessels within intercapillary spaces with an optical window size of 10 × 10 μm. This method allows for exact localization of the $pO_2$ measurement (intraarteriolar/intravenular (=intravascular), periarteriolar/perivenular (=perivascular) or in the interstitial tissue. Such precise localization is not possible with needle or surface array electrode techniques. Results from this type of measurement allow for detailed understanding of oxygen consumption of the vascular wall (transmural $pO_2$ gradient = intravascular $pO_2$ – perivascular $pO_2$), microvascular oxygen delivery and most importantly to assess oxygen uptake by the tissue. The phosphorescence decay due to quenching at a specific $pO_2$ yields a single decay constant and in vitro calibration has been demonstrated to be valid for in vivo measurements. The use of this technique with the window chamber model assures a high-resolution optical noninvasive method of assessing microvascular oxygen distribution in an intact tissue.

Intra- and perivascular $pO_2$ measurements were made immediately downstream from branching bifurcation points (Friesenecker et al. 2004). Interstitial tissue $pO_2$ was measured within the interstitium far away from visible underlying and adjacent vessels.

### Global oxygen transport measurements

Oxygen release by blood was determined in the microcirculation by the difference between the oxygen content at the arterial (A) and venular (V) segments of the microvascular network times the average flow through the tissue according to the equation:

$$O_2 \text{ release by blood} = (RBC_{Hb} \times \gamma \times S_{A-V}\%) \times Q_M$$

where $RBC_{Hb}$ is the Hb concentration in RBCs (g/dl blood), $\gamma$ is the oxygen-carrying capacity of Hb at 100% saturation or 1.34 ml $O_2$/g Hb, $S_{A\text{-}V}$% is the arteriolar–venous difference in RBC $O_2$ saturation and $Q_M$ is the volumetric blood flow calculated as the averaged microvascular flow (Lipowsky and Zweifach 1978). Hb saturation is determined from the measured blood $pO_2$ using the oxygen dissociation curve for hamster blood.

### Experimental setup

The unanesthetized animal was placed in a restraining tube from which the window chamber protrudes, which is affixed to a Plexiglas plate. The animal had free access to wet feed during the entire experimental period. The Plexiglas stage that holds the animal was then placed on an intravital microscope (Mikron Instruments, Inc., San Diego, CA, USA) equipped with a halogen lamp source (F0-150 halogen fiberoptic illuminator; CHIU Technical Corporation, Kings Park, NY, USA) and an infinity corrected objective (Zeiss Achroplan X20/0.50 W). The tissue image was projected onto a charge-coupled device camera (COHU, Model FK 6990 IQ-S, Pieper GmbH, Düsseldorf, Germany), viewed on a monitor (Model PVM–1454 QM; Sony) and recorded on a video recording system (Model AG 7355-E; Panasonic). The animal was allowed a 30-min adjustment period to the tube environment before the baseline systemic measurements (MAP, HR, arteriolar blood gases, Hb and Hct) were measured. Microvascular fields of study were chosen by their visual acuity within the window chamber tissue. A 420-nm blue filter was used for contrast enhancement of the transilluminated image.

### Experimental design and drug dosage

Twelve animals were included into the study protocol (control group, $N = 7$; arterioles $n = 52$; venules $n = 41$; treated group, $N = 5$; arterioles $n = 52$; venules $n = 41$). Preliminary dose response experiments showed that moderate but constant arteriolar dilation (~15%) without significant changes in macrocirculatory measurements (MAP, HR) was obtained during a continuous infusion of PgE1 at dosage of 2.5 μg/kg/min, which is a clinically relevant dosage. The infusion volume in the treated group was calculated for each animal not to exceed a 10% increase in the total blood volume, estimated as 7% of the body weight, which has been reported not to influence microvascular hemodynamics (Nolte et al. 1994). Similarly, Tsai et al. (2006) confirmed in a just recently accepted paper that a 10% topload infusion of saline did not affect MAP and the slight decrease in HR was not statistically significant. Also, arteriolar and venular diameters and flows before and after saline infusion were not statistically different from baseline (Tsai et al. 2006). The animals were subjected to a continuous intravenous infusion of PgE1 (prostavasin = alprostadil, Schwarz Pharma AG, Monheim, BRD) for the time of the experiment. Microhemodynamic and $pO_2$ distribution attained a steady state after 30 min; at the end of this period measurements were started.

$pO_2$ measurements were obtained in two different groups of animals, a control group and another group of animals during PgE1 infusion (treated group) as repeated $pO_2$ measurements within the same vessel may lead to incorrect $pO_2$ readings. Baseline hemodynamic measurements were not significantly different between control and treated group.

### Statistical analysis

Study endpoint was to determine the PgE1-mediated effects on vessel wall oxygen consumption. All measurements were compared to baseline levels obtained before start of the experimental procedure. Identical vessels' segments and functional capillary fields were followed so that direct comparisons to their own baseline levels could be performed. For repeated measurements, changes before and after treatment were statistically tested using nonparametric repeated measurements. Microvascular oxygen tension measurements can only be performed once in each animal, therefore these measurements were compared to a control group of animals. Results are presented as mean ± SD. Data are presented as absolute values and ratio relative to baseline. A ratio of 1.0 signifies no change from baseline, while higher or lower ratios are indicative of changes proportional higher or lower than baseline (i.e., 1.5 would indicate a 50% increase from baseline level). All statistics were calculated with computer software (Prism 4.0, Graph Pad, San Diego, CA, USA). Changes were considered statistically significant if the $P$ value was less than 0.05.

## Results

Twelve animals which complied with all inclusion criteria were entered into the study. All animals completed the protocol without any visible signs of discomfort. Animals were observed resting and periodically eating moist feed throughout the experimental period. Baseline systemic and microvascular data in the treated group ($N = 5$) and the control group ($N = 7$) were found not to be different.

### Systemic measurements

Systemic measurements were not affected by the PgE1 treatment. The change in MAP and HR was not statistically significant, 1.07 ± 0.13 (108 ± 10 to 116 ± 14 mmHg) and 1.09 ± 0.27 (387 ± 63 to 406 ± 41 beats/min) of baseline, respectively. Systemic Hb and Hct at baseline were 15.1 ± 0.9 g/dl and 48 ± 2%, respectively. These parameters were not assessed again as we assumed that the total volume of fluid infused during the experimental period of 1.5 h did not constitute enough to statistically change these parameters. Blood gases were not affected by the PgE1 infusion (pH 0.99 ± 0.3, $pO_2$ 1.07 ± 0.07, $pCO_2$ 0.99 ± 0.05; values relative to baseline). Baseline blood gas measurements (pH 7.30 ± 0.02; $pO_2$ 60 ± 9 mmHg; $pCO_2$ 60 ± 5 mmHg), which were within the range reported by others (Kreienbuhl et al. 1976; Tsai et al. 2004), were taken at the beginning of the experiments; there was no difference between groups.

### Microvascular hemodynamics

#### *Arterioles*

A1 and A2 arterioles were chosen and studied within the chamber network for the evaluation of microvascular hemodynamics and oxygen measurements. Baseline diameter measurements in control animals (57.0 ± 20.8 μm; $n = 52$ vessels) were not significantly different from baseline diameters in the treated group. PgE1 infusion caused significant arteriolar dilation to 1.15 ± 0.21 ($P < 0.001$, $n = 52$ vessels) of baseline (64.6 ± 25.1 μm). Velocity (4.0 ± 1.5 mm/s) increased to 1.23 ± 0.56 ($P < 0.01$) of baseline. Baseline arteriolar blood flow was $3.2 \times 10^{-2} \pm 4.3 \times 10^{-2}$ nl/s. Both vasodilation and increase in velocity lead to a significantly increased flow of 1.65 ± 0.93 ($P < 0.001$) during PgE1 infusion as shown in Fig. 1.

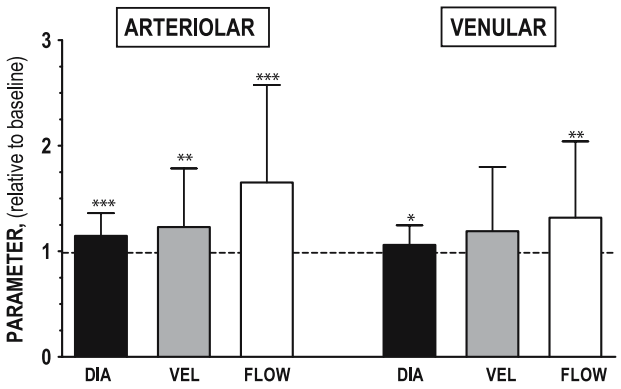


**Fig. 1** Arteriolar and venular microvascular measurements relative to baseline. Arteriolar diameter and velocity at baseline were 64.6 ± 25.1 μm and 3.95 ± 1.5 mm/s, respectively. Venular diameter and velocity at baseline were 71.9 ± 29.5 μm and 1.5 ± 0.6 mm/s, respectively. Data are presented as mean ± SD. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$

#### *Venules*

Large and collecting venules were chosen and studied within the chamber network for the evaluation of microvascular hemodynamics and oxygen measurements. Baseline diameter measurements in control animals (69.9 ± 35.3 μm; $n = 41$ vessels) were not significantly different from baseline diameters in the treated group. PgE1 infusion caused significant venular dilation to 1.06 ± 0.19 ($P < 0.05$, $n = 41$ vessels) of baseline (71.9 ± 29.5 μm); a rise in venular velocity to 1.19 ± 0. 61 was not statistically significant when compared to baseline (1.5 ± 0.6 mm/s). Baseline venular blood flow was $7.8 \times 10^{-}3 \pm 1.1 \times 10^{-2}$ nl/s. Venular flow increased to 1.32 ± 0.72 of baseline ($P < 0.01$) during PgE1 infusion as shown in Fig. 1.

#### *Functional capillary density*

Functional capillary density was 29.1 ± 10.8/10 fields of view during baseline and 28.5 ± 13.8/10 fields of view during PgE1 infusion which was statistically not different (0.95 ± 0.11).

### Oxygen distribution in the microvascular network

The systemic and blood gas analyses for the control and treated group were not statistically different and were within normal levels (Tsai et al. 2004). Systemic Hb and Hct at baseline were 15.1 ± 0.9 g/dl and 48 ± 2%, respectively. These parameters were not assessed again in the treatment group as we assumed that the total volume of fluid infused during the experimental period of 1.5 h did not constitute enough to

statistically change these parameters. Figure 2 shows the intravascular $pO_2$, transmural vessel wall $pO_2$ gradients and tissue $pO_2$ in the microvascular network in untreated and PgE1-treated animals.

*Arteriolar and venular oxygen distribution*

Infusion of PgE1 caused average arteriolar intravascular $pO_2$ to be 48 ± 8 mmHg which was statistically, significantly different from control levels (54 ± 9 mmHg; $P < 0.001$). Average venular intravascular $pO_2$ (28 ± 6 mmHg) at baseline was significantly elevated during PgE1 infusion (33 ± 7 mmHg; $P < 0.01$).

*Transmural microvascular wall oxygen gradients/ microvessel oxygen consumption*

Arteriolar transmural vessel wall $pO_2$ gradient decreased from 20 ± 6 to 16 ± 3 mmHg, while venular transmural vessel wall $pO_2$ gradient decreased from 12 ± 4 to 9 ± 4 mmHg during PgE1 treatment, changes being both statistically significant ($P < 0.001$) and an indicator of lowered microvascular wall oxygen consumption during PgE1 infusion.

*Tissue $pO_2$*

Tissue $pO_2$ was significantly elevated to 28 ± 7 mmHg during PgE1 infusion when compared to a baseline level of 21 ± 8 mmHg ($P < 0.001$).

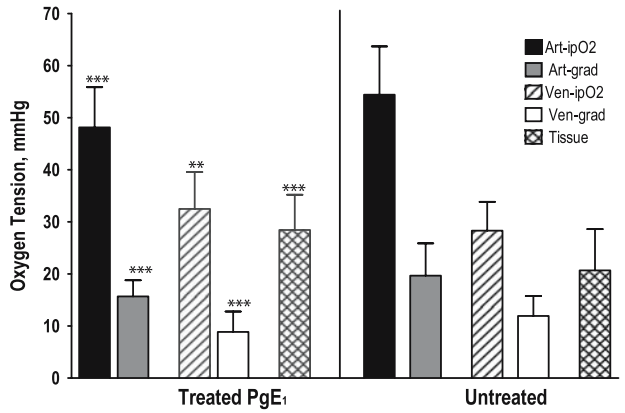


**Fig. 2** Arteriolar and venular oxygen tension in untreated and treated preparations. In untreated animals ($pO_2$ baseline) intraarteriolar (*Art-ip$O_2$*) and venular (*Ven-ip$O_2$*) $pO_2$ were 54 ± 9 and 28 ± 6 mmHg, respectively; arteriolar and venular gradient (*Art-grad*; *Ven-grad*) were 20 ± 6 and 12 ± 4 mmHg and tissue $pO_2$ (*Tissue*) was 21 ± 8 mmHg. During PgE1-infusion, intraarteriolar (*Art-ip$O_2$*) and venular (*Ven-ip$O_2$*) $pO_2$ were 48 ± 8 and 33 ± 7 mmHg, respectively; arteriolar and venular gradient (*Art-grad*; *Ven-grad*) were lowered to 16 ± 3 and 9 ± 4 mmHg, while tissue $pO_2$ (*Tissue*) was raised to 28 ± 7 mmHg. Data are presented as mean ± SD. $^{**}P < 0.01$ and $^{***}P < 0.001$

*Oxygen delivery and release in the microcirculation*

Table 1 shows the changes of flow in the microvascular network in response to PgE1 administration relative to baseline. Hb and Hct was 15.1 ± 0.9 and 48 ± 2, respectively. Overall microvascular flow through the network was estimated by averaging microvascular flow of all microvessels. Intravascular $pO_2$ in A1 and large venule (VL) vessels was used for the calculation of oxygen release to the tissue in control and PgE1-treated animals. These vessels were chosen for the calculation of oxygen release from blood to tissue because A1 arterioles represent the incoming $pO_2$ and VL the outgoing $pO_2$ within the chamber network, which makes them the most suitable vessels for the calculation of oxygen release to the tissue. Oxygen saturation in A1 and VL was 83 and 36% for control, and 76 and 40% for PgE1, respectively. The average microvascular flow (arteriolar and venular) due to PgE1-mediated dilation was significantly increased to 1.49 of baseline. Therefore, oxygen release in the PgE1-treated group was elevated to 1.12 of baseline.

## Discussion

The principal finding of this study is that the administration of a continuous intravenous infusion of PgE1 applied at a clinically relevant dosage led to a significant increase of arteriolar diameters and overall microvascular flow with no change in FCD. Even though the calculated elevation of oxygen release to the microcirculation was not significant in the face of lowered intraarteriolar $pO_2$ during PgE1 infusion, tissue $pO_2$ could be significantly improved. This highlights the importance of a significantly lowered microvascular transmural oxygen gradient as an important mechanism for improving tissue oxygenation due to decreased oxygen consumption of the microvascular wall during vasodilation.

### Microvascular flow, vessel wall oxygen consumption and microvascular oxygen delivery

In the present study, PgE1-mediated arteriolar/venular dilation, preserved FCD and increased microvascular flow significantly elevated tissue $pO_2$ above normal values when compared to untreated animals. PgE1 significantly increased microvascular flow by 49%; however, oxygen release to the tissue only increased by 12% over control, due to lowered blood $pO_2$ in the arteriolar circulation and a somewhat higher venular blood $pO_2$ after PgE1 treatment.

**Table 1** Oxygen delivery and release in the microcirculation

| | | Baseline | | | PgE1 infusion | | Changes rel. to baseline |
|---|---|---|---|---|---|---|---|
| Flow (nl/s) | Arteriolar | $3.4 \times 10^{-2} \pm 4.3 \times 10^{-2}$ | | | | | 1.65 |
| | Venular | $7.8 \times 10^{-3} \pm 1.1 \times 10^{-2}$ | | | | | 1.32 |
| | Mean microvascular | | | | | | 1.49 |
| | | | mmHg | Sat RBC | mmHg | Sat RBC | |
| Oxygen tension/saturation | | $pO_2$ arteriolar | 54.4 | 0.83 | 48.1 | 0.76 | |
| | | $pO_2$ venular | 28.3 | 0.36 | 30.2 | 0.40 | |
| Oxygen content (ml $O_2$/ml blood) | | Arteriolar | 16.9 | | 15.6 | | |
| | | Venular | 7.3 | | 8.31 | | |
| Oxygen delivery = content × mean flow | | Arteriolar | 16.9 | | 23.1 | | |
| (ml $O_2$/ml blood × normalized mean vascular flow) | | Venular | 7.3 | | 12.3 | | |
| Oxygen released by blood to tissue (ml $O_2$/s) | | | 9.61 | | 10.78 | | 1.12 |

In the face of lowered blood $pO_2$ in the arteriolar circulation and a somewhat higher venular blood $pO_2$ during PgE1 treatment, average microvascular flow was statistically, significantly increased by 49%; oxygen release to the tissue increased only by 12% over control, which was not statistically significant

Oxygen delivery = content × *Q* mean

*Sat RBC* oxygen saturation of red blood cells, *RBC* red blood cell, *Q* flow

A limiting factor for oxygen release to the tissue is oxygen consumption of the microvascular wall itself, where the rate of vessel wall oxygen consumption has been described to be directly proportional to the difference in $pO_2$ measured across the vessel wall (Eichelbronner et al. 1995; Tsai and Intaglietta 2001; Tsai et al. 1998). A physiological $pO_2$ decrease within the vessel wall is seen even under normal conditions, indicating that the cellular components of the microvasculature require energy to constrict against blood pressure and therefore consume oxygen also in resting conditions (Tsai et al. 1998). This energy expenditure is needed to maintain normal vascular tone, i.e., a moderate level of constriction required to insure that the resting tissue is not oversupplied with oxygen.

Comparing the decrease in consumption between arterial and venous sides, given the difference in wall structure, intravascular $pO_2$ and presumably baseline consumption rates, it could be expected that the arterial side would show a significantly greater change in vessel wall gradient. The arteriolar wall gradient decrease was 33% greater than the venular in terms of $pO_2$, a difference that is not statistically significant due to the variability in the data. A greater decrease in wall gradient may also be masked by the significant rise in tissue $pO_2$, which can proportionally lower the wall gradient. In an ideal experiment the wall gradient would be measured in a situation where the tissue $pO_2$, at some distance from the blood vessels is zero, a configuration not attainable in normal tissues.

Vasoactivity and maintenance of tone have been shown to increase oxygen consumption of the microvascular compartment in several tissues by Ye et al. (1990). We recently demonstrated that arginine–vasopressin induced vasoconstriction increases arteriolar vessel wall oxygen consumption in subcutaneous tissue and skin muscle of the hamster thereby significantly lowering tissue $pO_2$, whereas vasomotion, defined as a rhythmic changes of vascular smooth muscle contraction and relaxation, did not increase overall arteriolar oxygen consumption beyond the level due to pure vasoconstriction (Friesenecker et al. 2004). On the other hand, vasodilation—by reducing arteriolar tone—has been described as a means to facilitate oxygen supply to the surrounding tissue during topical application of papaverine by Shibata et al. (2005a). These studies also show that NO as an important regulator of peripheral vascular tone and therefore as a modulator of tissue oxygenation by reducing vessel wall oxygen consumption through vasodilation (Shibata et al. 2005b). The finding of the present study, that vasorelaxation decreased microvascular vessel wall oxygen gradients and increased tissue $pO_2$ suggests that lowering oxygen consumption of the microvascular compartment is an energy sparing mechanism that in combination with the improvement of microvascular flow augments tissue $pO_2$. A recent study by Shibata et al. (2006), where decreased vessel wall oxygen consumption induced by NO is related to reduced mechanical work of vascular smooth muscle, reinforces our hypothesis that PgE1-mediated improvement of tissue oxygenation may not only be attributed to the positive hemodynamic effects of increased microcirculatory flow but is also a consequence of lowered microvessel wall oxygen consumption.

A basic question is the extent of the change in oxygen consumption by the microvascular wall relative to the noted differences in vessel wall oxygen gradient. Previous studies (Friesenecker et al. 2004; Tsai et al. 1998) showed that the consumption of oxygen by the microvasculature of the organism at rest may be as much as 30% of the total oxygen consumption of the organism, and that the vessel wall gradient is directly proportional to oxygen consumption by the vessel wall. In the present experiments the arteriolar and venular vessel wall gradients decreased by 20 and 25%, respectively. It should be noted that this is an extreme lower limit because there is a portion of the oxygen gradient that is unrelated to oxygen consumption and solely due to the radial geometry. The fall of $pO_2$ in the diffusion field of a cylinder in a medium that does not consume oxygen can be found by solving the diffusion equation for this configuration (Groebe 1995). This solution shows that the $pO_2$ in the diffusion field falls off in proportion to the logarithm of the radius, and various factors dependant on vessel diameter and wall size, tissue $pO_2$, and the extent of the diffusion field due to the presence of the blood vessel. Intraluminal oxygen tension is also a factor since there is an indication that vessel wall oxygen consumption may be related to the local blood $pO_2$ (Tsai et al. 2003). Taking these factors into account shows that the passive change in $pO_2$ in the tissue of the vessel wall can be as much as 10 mmHg for vessels in the range of diameters studied (20–50 μm). A precise estimate of this parameter is difficult to obtain because it requires measurement of the radius of the tissue whose $pO_2$ is affected by the blood vessel, a parameter difficult to estimate because of the presence of capillaries in the tissue. Therefore, using the wall gradient change as a measure of changes in vessel wall oxygen consumption provides a lower limit of the actual relative change, since the baseline wall gradient due to oxygen consumption is significantly smaller.

### Clinical impact

As a result of the study it can be stated that PgE1-mediated vasodilation has a twofold positive effect on the microcirculation: not only is tissue perfusion augmented by increased microvascular flow during PgE-mediated vasodilation, but also by lowered oxygen consumption of the microvascular wall. The dosage used in the present study is a clinically relevant dosage regimen. Besides significant anti-ischemic, anti-inflammatory and antithrombotic effects (Fukuda et al. 1992), prostaglandins are described to have positive effects in patients with peripheral occlusive disease (Creutzig et al. 2004); intra-arterial infusion of PgE1 was first reported by Carlson in 1973 (Carlson and Eriksson 1973). Additionally, positive effects of PgE1 in patients with septic shock have been reported by Bihari in 1988 (Bihari and Tinker 1988) and more recently by Eichelbronner et al. (1995) and Radermacher et al. (1996).

### Limitations of the study

PgE1-induced intrapulmonary shunts (Brinkmann et al. 1997) may not serve as an explanation for significantly lowered intraarteriolar $pO_2$ in the microcirculation in the face of unchanged central arterial $pO_2$ (carotid artery). Conversely, tissue $pO_2$ increased significantly due to reduced vessel wall cell consumption of oxygen. Therefore, the finding of reduced intraarteriolar $pO_2$ is compatible with an increase in oxygen release from larger arterioles not present in the tissue of the window chamber.

### Conclusion

The present study provides an additional explanation for the positive effects of prostaglandins on tissue oxygenation beyond those proposed in earlier reports emphasizing improved microvascular rheology. It is shown that the PgE1-mediated decrease in microvascular vessel wall oxygen consumption appears to contribute significantly to the increase of tissue $pO_2$. These results support the finding that vasoconstriction is an energy-consuming process (Friesenecker et al. 2004; Tsai et al. 1998, 2003) that causes significantly lowered tissue $pO_2$ due to increased oxygen consumption of the arteriolar wall.

## Disclaimer

Prof. Intaglietta is a member of the Board of the La Jolla Bioengineering Institute, La Jolla, California 92037.

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