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Effects of Sodium Nitroprusside and Phenylephrine on Blood Flow in Free Musculocutaneous Flaps during General Anesthesia

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Background: Hypoperfusion and necrosis in free flaps used to correct tissue defects remain important clinical problems. The authors studied the effects of two vasoactive drugs, sodium nitroprusside and phenylephrine, which are used frequently in anesthetic practice, on total blood flow and microcirculatory flow in free musculocutaneous flaps during general anesthesia.

Methods: In a porcine model (n = 9) in which clinical conditions for anesthesia and microvascular surgery were simulated, latissimus dorsi free flaps were transferred to the lower extremity. Total blood flow in the flaps was measured using ultrasound flowmetry and microcirculatory flow was measured using laser Doppler flowmetry. The effects of sodium nitroprusside and phenylephrine were studied during local infusion through the feeding artery of the flap and during systemic administration.

Results: Systemic sodium nitroprusside caused a 30% decrease in mean arterial pressure, but cardiac output did not change. The total flow in the flap decreased by 40% ($P < 0.01$), and microcirculatory flow decreased by 23% in the skin ($P < 0.01$) and by 30% in the muscle ($P < 0.01$) of the flap. Sodium nitroprusside infused locally into the flap artery increased the total flap flow by 20% ($P < 0.01$). Systemic phenylephrine caused a 30% increase in mean arterial pressure, whereas heart rate, cardiac output, and flap blood flow did not change. Local phenylephrine caused a 30% decrease ($P < 0.01$) in the total flap flow.

Conclusions: Systemic phenylephrine in a dose increasing the systemic vascular resistance and arterial pressure by 30% appears to have no adverse effects on blood flow in free muscu-

locutaneous flaps. Sodium nitroprusside, however, in a dose causing a 30% decrease in systemic vascular resistance and arterial pressure, causes a severe reduction in free flap blood flow despite maintaining cardiac output. (Key words: Microcirculation; vasoconstrictor; vasodilator.)

MICROVASCULAR surgical techniques are used widely to transfer free vascularized tissue (free flaps) such as skin, muscle, bone, and bowel.¹⁻³ Despite improvements in the surgical technique during the past two decades, hypoperfusion and subsequent necrosis of tissue still are important problems.^{4,5} Although the success or failure of free flap surgery depends mainly on the skills of the surgeon, anesthetic management may also play a role.⁶ Anesthesia frequently influences the central hemodynamics and regional blood flow and therefore also may affect blood flow in the transferred tissue.⁷⁻⁹ In addition, changes in blood volume and the use of vasoactive agents during anesthesia may influence blood flow in the free flap.^{10,11}

Induced hypotension is a widely accepted technique to reduce intraoperative blood loss and thereby ensure satisfactory operating conditions, especially in microscopic interventions.^{6,12} A hypotensive technique also may reduce blood loss during the removal of extensive malignant tumors and while raising large musculocutaneous flaps.^{9,13} For this purpose, an intravenous infusion of sodium nitroprusside (SNP), which allows controlled and rapidly reversible reduction in arterial blood pressure, often is used in clinical practice.¹⁴⁻¹⁶

Although SNP may reduce blood loss during surgery,¹⁷ its effects on systemic vasodilatation and its subsequent hypotensive effect on blood flow in free flaps are poorly understood. Sodium nitroprusside decreases systemic vascular resistance and therefore may improve blood flow in the free flap and in other tissues. However, the free flap is a denervated tissue with no sympathetic tone and, therefore, already may be maximally vasodilated. If that were true, SNP might decrease vascular resistance

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more in normal innervated tissues than in the free flap, causing a "steal effect" and resulting in reduced flap flow. This hypothesis is supported by the observation in rats that denervation of skin markedly reduces SNP-induced vasodilatation compared with innervated skin.¹⁸ However, this has not been studied in free flaps.

α -Adrenergic agents, such as phenylephrine, frequently are used during anesthesia to increase blood pressure in response to hypotension. However, such agents are considered to be potentially harmful in microvascular surgery because they may increase vascular resistance (and possibly induce vascular spasm) in free flaps and decrease blood flow.^{9,19} In theory, however, an increase in perfusion pressure possibly could be more important than some increase in flap vascular resistance. Again, no data are available concerning the effects of α -agonists in free flap surgery.

The purpose of the current work was to study the effects of two vasoactive drugs, frequently used in clinical anesthetic practice, on blood flow in free musculocutaneous flaps. A porcine model was used in which human clinical conditions for anesthesia and surgery were simulated as close as possible. To differentiate between local and systemic effects of the drugs, the effects of SNP and phenylephrine were studied separately during local infusion into the flap-feeding artery and during systemic administration.

Materials and Methods

This study conformed to the Guiding Principles in the Care and Use of Animals as approved by the Council of the American Physiological Society, and the protocol was approved by the Animal Care Committee of Canton Berne. Nine large, white pigs weighing 20 to 24 kg were used in the study.

General anesthesia was induced with intramuscular injections of 10 mg/kg of body-weight ketamine followed 10 min later by 5 mg/kg metomidate, 2 mg/kg azaperone, and 0.05 mg/kg atropine, all administered intravenously. After tracheal intubation, anesthesia was maintained with 0.8% halothane (end-tidal concentration), 70% nitrous oxide in oxygen, and an intravenous infusion of fentanyl ($10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Inhaled and exhaled concentrations of nitrous oxide and halothane were monitored continuously using a multigas analyzer (model SMU 611; Hellige AG, Freiburg, Germany). Muscle relaxation was maintained with an intravenous infusion of pancuronium ($0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). The animals

were ventilated with a volume-controlled ventilator with a positive end-expiratory pressure of 3 or 4 cm water (Tiberius 19; Drägerwerk AG, Lübeck, Germany). Tidal volume was maintained at 10 ml/kg and the respiratory rate was adjusted (13 to 18 breaths/min) to maintain the carbon dioxide pressure in arterial blood between 34 and 41 mmHg (4.5 to 5.5 kPa). Abdominal aortic, pulmonary artery (thermodilution catheter; Arrow, Reading, PA), and central venous catheters were inserted *via* the left femoral artery and vein.

During surgery, the animals received Ringer's lactate ($10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). If additional fluid was needed because of blood loss during surgery, 6% hydroxyethyl starch 200-0.5 (Isohaes, Levosan, Austria) was administered to maintain central venous and pulmonary capillary wedge pressures at constant levels. The temperature of the animal was kept at $37.5 \pm 0.5^\circ\text{C}$ with two heating blankets. After surgery, which lasted approximately 5 h, the rate of the Ringer's lactate infusion was reduced to $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. The skin temperatures of the flap and the adjacent thigh were monitored continuously with a needle-probe thermometer.

Hemodynamic and Respiratory Monitoring

Mean arterial blood pressure (measured in millimeters of Mercury), central venous pressure (measured in millimeters of Mercury), mean pulmonary artery and pulmonary capillary wedge pressures (both measured in millimeters of Mercury) were recorded with quartz pressure transducers (129A; Hewlett-Packard, Andover, MA) and displayed continuously on a multimodular monitor (Hellige SMU 611) and a recorder (Hellige SMR 821). Heart rate (in beats per minute) was measured from the electrocardiogram, which was monitored continuously. Cardiac output (l/min) was measured using a thermodilution technique (the mean value of three measurements), and cardiac output module (Hellige SMU 611). Systemic vascular resistance and flap vascular resistance were calculated using standard formulas. Central venous blood temperature (in degrees Celsius) was recorded from the thermistor in the pulmonary artery catheter. Samples of blood were withdrawn from the aortic artery catheter for electrolyte, hemoglobin (in grams per deciliter), and hematocrit (expressed as a percentage) analyses.

The end-tidal carbon dioxide concentration (expressed as a percentage) was monitored continuously during the study. Samples for arterial blood gas analyses were withdrawn from the aortic catheter and analyzed

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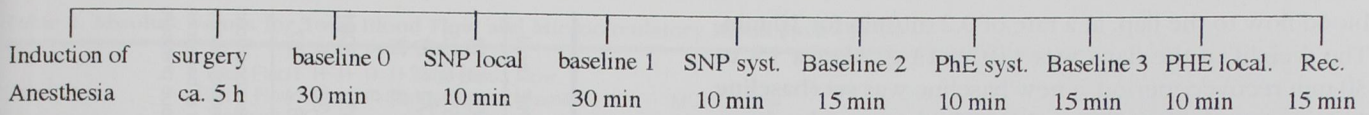


Fig. 1. The study protocol in nine pigs undergoing free flap surgery under general anaesthesia. Sodium nitroprusside (SNP) local 10 min = sodium nitroprusside ($0.7 \mu\text{g}/\text{min}$) infused locally into the feeding artery of the free flap for 10 min. SNP syst. = sodium nitroprusside infused systemically ($6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intravenously) for 10 min. Phenylephrine local = phenylephrine infused locally into the feeding artery of the free flap ($0.11 \mu\text{g}/\text{min}$) for 10 min. Phenylephrine syst. = phenylephrine infused systemically ($1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intravenously) for 10 min. Baseline 1–3 = recovery for 15–30 min after completion of the infusion of SNP or phenylephrine before the next infusion was started. Rec. 15 min = recovery for 15–30 min after completion of the infusion of phenylephrine before the final measurements were taken.

immediately (temperature corrected) in a blood gas analyzer (Radiometer, Copenhagen, Denmark).

Surgery

Surgery included raising a musculocutaneous free flap from the latissimus dorsi muscle with overlying skin and transferring it to the lower extremity using a microsurgical technique. Briefly, a skin flap that measured approximately 12×6 cm was placed over the left latissimus dorsi muscle with its long axis parallel to the axis of the pig. Transection of the pectoralis muscle followed, exposing the brachial vessels and the brachial plexus. The thoracodorsal vessels were dissected free. Dissection of the muscle was performed using an electrocautery to reduce bleeding. The brachial artery was dissected free and ligated proximally to the branching of the thoracodorsal artery. Two distal branches of the brachial artery were prepared, each approximately 3 cm long. A branch of a similar diameter to the feeding vessel on the leg was chosen for the microvascular anastomoses. The other branch was cannulated with a catheter for intraarterial infusions into the flap. All other branches were ligated. The thoracodorsal vein was transected at the confluence with the brachial vein. The pedicle measured 5 or 6 cm, and the diameter of the vessels was 1 or 2 mm. The donor site was closed primarily.

A 20-cm-long incision was made on the medial side of the right hind leg and thigh, and a 7-cm-long segment of the tibial artery was dissected free. On the lateral side of the leg, the saphenous vein was exposed. The vein was secured with sutures, transected at the level of the heel, and transposed medially through a tunnel dissected between the bone and the Achilles tendon. Any twisting or kinking of the vein was avoided. Microsurgical anastomoses were performed using 10/0 microsutures. After completion of the anastomoses, the flap was sutured into the skin incision on the leg and thigh, thus simulating reconstructive surgery on the lower extremity in patients.

Transit Time Flowmetry and Laser Doppler Flowmetry

To measure the total blood flow (TBF) in the flap, a suitably sized transit time flowmeter probe (Transonic Inc., Ithaca, NY) was placed around the feeding artery of the flap. The TBF was measured using ultrasound Doppler transit time flowmetry (Transonic).

An angled laser Doppler flowmeter (LDF) probe (PF 404, Perimed AB, Järfälla, Sweden) was sutured centrally on the muscle surface of the flap and another was sutured centrally on the skin of the free flap. Microcirculatory blood flow (MCF) was monitored continuously using two dual-channel LDF systems (Periflux 4001, Perimed AB) that allowed four simultaneous LDF measurements. The time constant of the flowmeter output amplifier was set at 3 s. The LDF signal is given in arbitrary perfusion units according to the manufacturer's specifications.

To assess the changes in normally perfused and innervated muscle and skin that occurred during drug infusion, we also placed an ultrasound Doppler probe around the contralateral femoral artery and placed LDF probes in the appropriate locations.

Microcirculatory blood flow and TBF were acquired on-line *via* a multichannel interface (Mac Pacq MP 100; Biopac Systems, Goleta, CA) with acquisition/analysis software (Acqknowledge 881 3.0, Biopac Systems) to a portable computer (Macintosh Powerbook 180C, Apple Computers, Cupertino, CA). The sampling rate was set at 20 Hz. A detailed description of the theory of LDF operation and practical details of LDF measurements have been described elsewhere.^{20,21}

Experimental Protocol

The animals were allowed to stabilize for 30 min after surgery was complete (fig. 1). Continuous monitoring of TBF, MCF, and the central hemodynamics were performed for 5 min as baseline measurements (baseline 0). Sodium nitroprusside ($0.7 \mu\text{g}/\text{min}$) was infused into a side branch of the feeding artery, without disturbing the

blood flow to the flap, at a rate of 0.2 ml/min for 10 min. The weight of the flaps was 110 ± 13 g. After a 15- to 30-min recovery period, a new baseline was set (baseline 1; determined when TBF and MCF had returned to baseline $0 \pm 5\%$) and a systemic infusion of SNP was begun at a dose of $0.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, which was increased progressively to a maximum of $6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or until the mean arterial pressure was reduced by 30%. Thereafter, SNP was infused at the constant dose for a period of 10-15 min. Approximately 15 min after the SNP infusion was discontinued, when hemodynamic data had reached the previous baseline values ($\pm 5\%$), a new baseline was set (baseline 2) and systemic infusion of phenylephrine ($1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) for 10 min was performed until the mean arterial pressure was increased by 30%. Finally, after another 15-min recovery phase, a new baseline was set (baseline 3) before phenylephrine ($0.11 \mu\text{g}/\text{min}$) was infused for 10 min into the feeding artery of the free flap at a rate of 0.2 ml/min. Fifteen minutes after the infusion was discontinued, the last measurements were made.

The doses of SNP and phenylephrine administered locally into the feeding artery of the flap were calculated from the systemic doses. The same proportion of the systemic dose was administered locally as the proportion of the cardiac output that went to the flap (TBF, a mean from six pilot experiments). At the end of the experiments, the animals were killed with an intravenous overdose of potassium chloride.

Statistical Analysis

Data are presented as the mean \pm SD. Because of the known variability of the baseline LDF signal, flow data are expressed relative to baseline, except in table 2, which shows absolute values at baseline.

Statistical analyses were performed on a Macintosh computer using the InStat 2.03 statistical program (GraphPad Software, San Diego, CA). Before each local and systemic drug infusion, a new baseline was taken and the change during that drug infusion was compared with the corresponding baseline. The nonparametric Wilcoxon test was applied to compare changes within a group. The nonparametric Mann-Whitney U test was used to compare the effects of local and systemic drug infusions on the corresponding parameter.

Results

All data from the nine experiments were included in the statistical analysis of the results. No significant

Table 1. Hemodynamic and Respiratory Data

Parameter	Unit	Baseline 0	SNP Local	Baseline 1	SNP Systemic	Baseline 2	PhE Systemic	Baseline 3	PhE Local
HR	bpm	107 \pm 16	108 \pm 16	106 \pm 17	118 \pm 18*	107 \pm 15.9	102 \pm 13	108 \pm 12	109 \pm 14
CO	L \cdot min ⁻¹	5.4 \pm 1.6	5.2 \pm 1.1	5.3 \pm 1.4	5.2 \pm 1.2	5.2 \pm 1.2	5.0 \pm 1.2	5.1 \pm 1.0	5.3 \pm 1.3
MAP	mmHg	74 \pm 6	72 \pm 6*	72 \pm 5	52 \pm 5*	76 \pm 6	95 \pm 10*	72 \pm 9†	72 \pm 7†
CVP	mmHg	8 \pm 2	8 \pm 1	8 \pm 2	7 \pm 3	9 \pm 1	10 \pm 2*	9 \pm 2	8 \pm 1†
PWP	mmHg	9 \pm 2	9 \pm 2	9 \pm 2	7 \pm 2*	9 \pm 1	11 \pm 2*	9 \pm 2	9 \pm 2
SVR	dynes \cdot cm ⁻⁵	1,051 \pm 316	1,023 \pm 275	1,031 \pm 281	739 \pm 230*	1,089 \pm 267	1,421 \pm 351*	1,028 \pm 280	1,032 \pm 309†
PaCO ₂	mmHg	34 \pm 2	35 \pm 1	35 \pm 1	35 \pm 2	35 \pm 2	36 \pm 1	36 \pm 2	36 \pm 1
Hb	g \cdot dl ⁻¹	8.7 \pm 1.1	8.3 \pm 0.7	8.6 \pm 1.1	8.8 \pm 1.0	8.6 \pm 0.9	9.7 \pm 0.9	9.4 \pm 1.2*	8.2 \pm 0.7

Central hemodynamics, respiratory parameters, and blood gases from nine pigs undergoing musculocutaneous free flap surgery under general anesthesia: during stable baseline conditions (baseline 0), during infusion of sodium nitroprusside (SNP) at $0.7 \mu\text{g}/\text{min}$ into the flap feeding artery (SNP Local), during systemic iv infusion of SNP at $6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (SNP Systemic), during systemic iv infusion of phenylephrine (PhE) at $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (PhE Systemic), and during infusion of PhE at $0.11 \mu\text{g}/\text{min}$ into the flap feeding artery (PhE Local). Measurements at baselines 1 to 3 were performed following 15-30 min of stabilization after discontinuing each drug infusion: heart rate (HR), cardiac output (CO), mean arterial pressure (MAP), central venous pressure (CVP), pulmonary wedge pressure (PWP), systemic vascular resistance (SVR), arterial CO₂ tension (PaCO₂), and hemoglobin concentration (Hb). Values are mean \pm SD. * $P < 0.01$ versus corresponding baseline (Wilcoxon test). † $P < 0.05$ versus corresponding baseline (Wilcoxon test).

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Table 2. Absolute Values for Total Blood Flow and Microcirculatory Blood Flow (MCF)

	Total Flap Blood Flow (ml/min)	Total Blood Flow Contralateral Extremity (ml/min)	MCF Control Muscle (PU)	MCF Flap Muscle (PU)	MCF Control Skin (PU)	MCF Flap Skin (PU)
Baseline 0	5.9 ± 3.5	165 ± 54	93 ± 71	109 ± 93	62 ± 29	50 ± 20
Baseline 1	5.8 ± 3.1	157 ± 52	90 ± 75	107 ± 102	56 ± 27	51 ± 20
Baseline 2	5.4 ± 3.0	150 ± 48	81 ± 75	105 ± 107	56 ± 20	51 ± 23
Baseline 3	5.0 ± 2.8	143 ± 47	79 ± 75	97 ± 77	54 ± 28	46 ± 24

Absolute values for total blood flow in the flap and in the contralateral extremity (ultrasound Doppler flow) and microcirculatory blood flow (laser Doppler flowmetry) in control and flap muscle as well as in control and flap skin at each baseline.

PU = perfusion units.

changes in any respiratory parameter (including blood gases) were noted during the experiment (table 1). The baseline laser Doppler flow values remained stable during the experiment (table 2).

Sodium nitroprusside infused locally into the feeding artery of the free flap caused a 20% increase in TBF ($P < 0.05$) and a 20% decrease in vascular resistance in the flap ($P < 0.01$; fig. 2A). The increase in TBF was not accompanied by a significant change in MCF in the flap. No systemic hemodynamic effects (table 1) or effects on flow in intact muscle and skin (fig. 2A) were observed.

Systemic SNP caused an approximately 30% decrease in mean arterial pressure ($P < 0.01$) and systemic vascular resistance ($P < 0.01$) compared with baseline, whereas cardiac output remained virtually unchanged (table 1). Furthermore, TBF in the flap decreased by 40% ($P < 0.01$) and MCF decreased by 23% in the flap skin ($P < 0.01$) and by 30% in the flap muscle ($P < 0.01$) (fig. 2B). Systemic SNP also caused a significant decrease in TBF ($P < 0.01$) and in MCF ($P < 0.01$) in the intact skin and muscle of the contralateral extremity (fig. 2B).

Phenylephrine infused locally into the flap artery caused no measurable systemic hemodynamic effects (table 1). In the flap, however, the vascular resistance increased by more than 50% ($P < 0.01$) and TBF decreased by 30% ($P < 0.01$) (fig. 3A). Microcirculatory blood flow in flap skin decreased only slightly, but in flap muscle it remained virtually unchanged (fig. 3A). Total blood flow and MCF in the intact skin and muscle of the contralateral extremity remained virtually unchanged (fig. 3A).

Systemic intravenous infusions of phenylephrine increased the mean arterial pressure ($P < 0.01$) and systemic vascular resistance ($P < 0.01$) (table 1) by approximately 30% without causing any significant changes in heart rate or cardiac output (table 1). Total blood flow in the flap, MCF in the flap, TBF in the contralateral ex-

tremity, and MCF in intact control muscle and skin were all unchanged (fig. 3B).

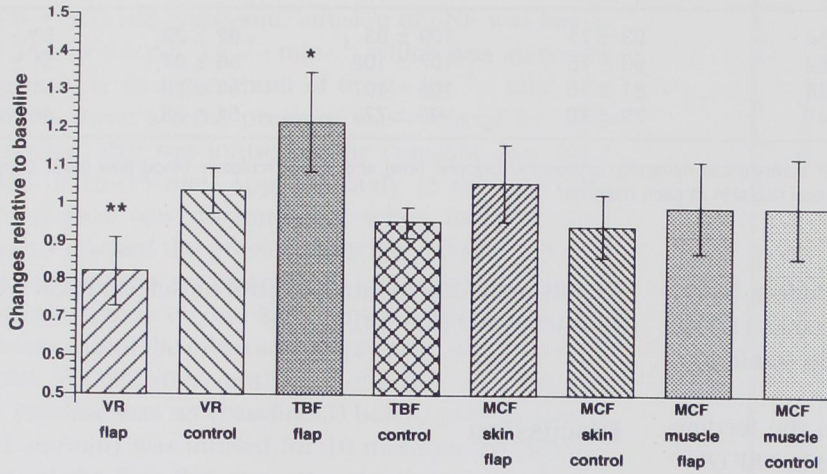
Discussion

Free flaps are different from normal tissues in several respects.^{6,9} They are subjected to a period of ischemia, because they are deprived of their blood supply from the detachment at the donor site and until completion of the two microanastomoses (usually 1 or 2 h). Furthermore, all tissues in free flaps are completely denervated (with sympathectomy of all vessels), whereas the feeding artery and the draining vein, on which the flap vessels are anastomosed, have intact innervation. However, vessels in the free flap still respond to physical and pharmacologic stimuli such as vasoactive drugs.^{6,9} In addition, there is no lymphatic drainage from the free flap, which renders it more sensitive to extravasation of fluids compared with healthy tissues.²² Thus it can be difficult for an anesthesiologist to predict what might happen to blood flow in a free flap after application of different anesthetic agents and the vasodilators and vasoconstrictors that often are used during prolonged microvascular surgery.

The pig model was chosen for this study for two main reasons. Anatomically, the vascular structure of pig skin is similar to that of humans,^{19,23,24} and pathophysiologically it also appears more relevant than rodents for human comparison, at least in the case of skin.^{19,25} In addition, the central and coronary pig circulations are remarkably similar to those of humans.²⁶ The anesthetic technique used in this study has been shown to provide stable hemodynamic conditions in flap surgery,⁸ and there is no significant difference in microcirculatory flow in the flap when halothane or isoflurane are used as long as no more than 1.5 minimum alveolar concentration halothane is used and hypovolemia can be avoided.⁸

Sodium Nitroprusside

a) local



b) systemic

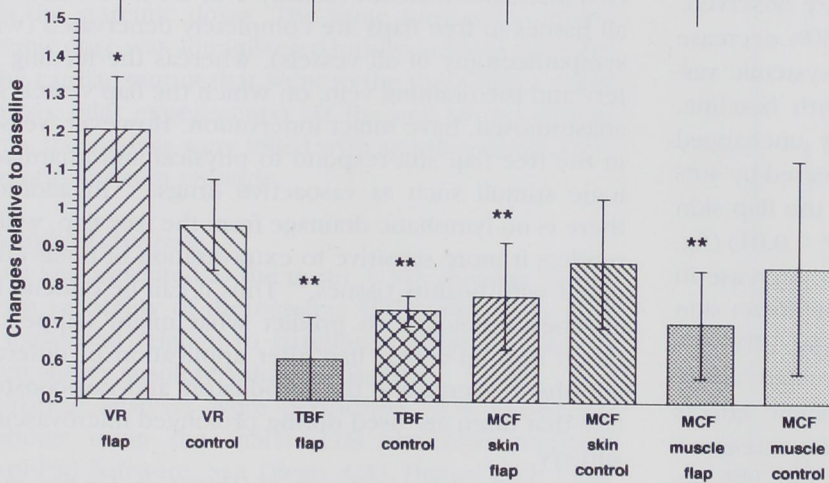


Fig. 2. Sodium nitroprusside. Data from nine pigs undergoing musculocutaneous free flap surgery under general anaesthesia. (A) Sodium nitroprusside:local. Flap vascular resistance (VR, flap), vascular resistance in the control extremity (VR, control), total flap blood flow (TBF, flap), total blood flow in the control extremity (TBF, control), and microcirculatory blood flow (MCF) as measured by laser Doppler flowmetry in the flap skin (MCF, flap skin), control skin (MCF, control skin), flap muscle (MCF, flap muscle), and control muscle (MCF, control muscle) during infusion of 0.7 $\mu\text{g}/\text{min}$ sodium nitroprusside into the feeding artery of the flap. (B) Sodium Nitroprusside:systemic. Flap vascular resistance (VR, flap), vascular resistance in the control extremity (VR, control), total flap blood flow (TBF, flap), total blood flow in the control extremity (TBF, control), microcirculatory blood flow as measured by laser Doppler flowmetry in flap skin (MCF, flap skin), control skin (MCF, control skin), flap muscle (MCF, flap muscle), and control muscle (MCF, control muscle) during systemic intravenous infusion of 6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ sodium nitroprusside. Values are plotted as mean relative changes to the baseline \pm SD. * $P < 0.05$ vs. baseline; ** $P < 0.01$ vs. baseline (by the Wilcoxon test). $\star\star P < 0.01$ for the difference between systemically and locally administered sodium nitroprusside (by the Mann-Whitney U test).

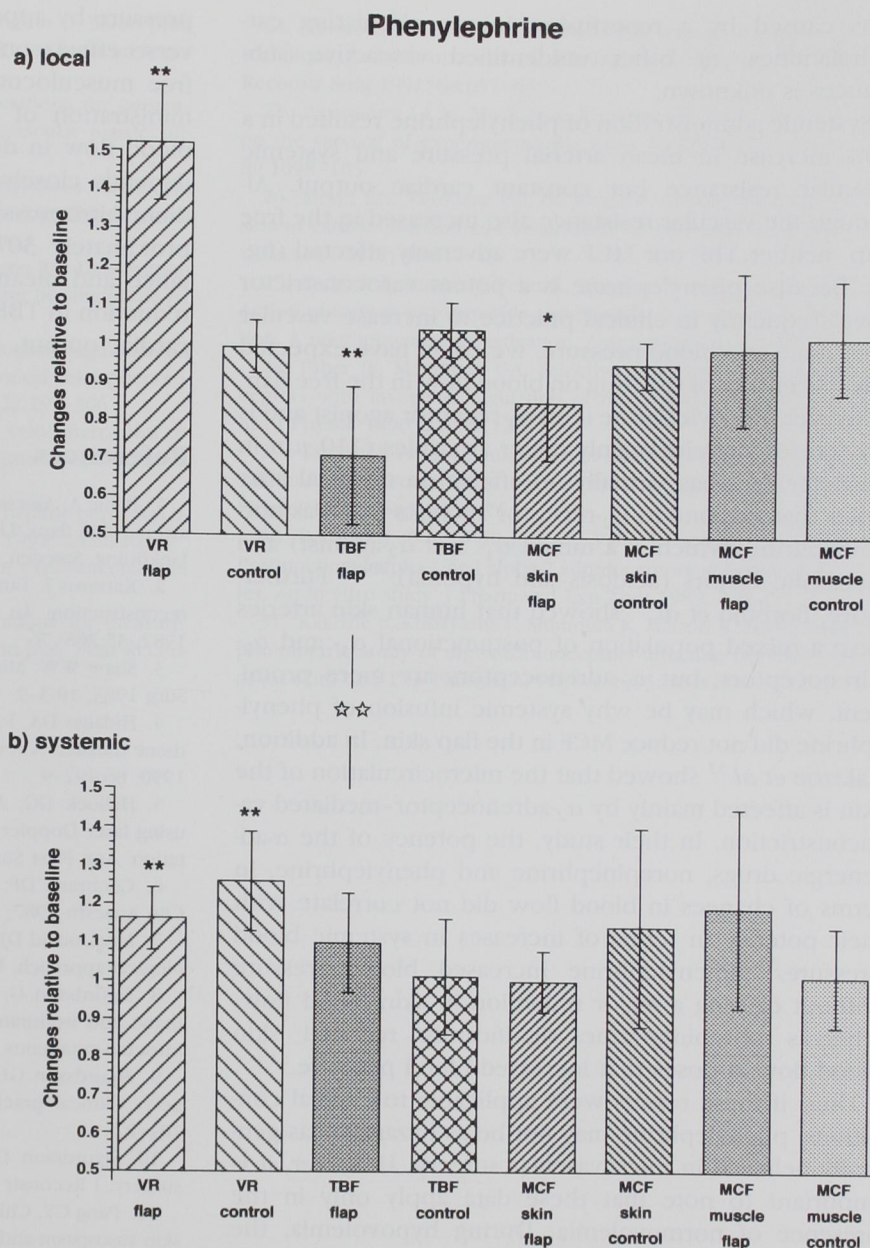
Furthermore, the animal model, which included free musculocutaneous (latissimus dorsi) flap transfer to the lower extremity, and which was developed for this study, allowed us to study changes in MCF measured with LDF and changes in TBF measured with ultrasound transit time flowmetry in innervated and in denervated skin and muscle.

Systemic administration of SNP resulted in a 30% decrease in mean arterial pressure and systemic vascular resistance, whereas cardiac output was not changed. This caused a corresponding decrease in TBF

and MCF flow in the flap (fig. 2). These findings suggest that TBF and MCF in free musculocutaneous flaps depend closely on blood pressure during SNP administration, even in the presence of adequate cardiac output. Although the SNP-induced hypotension caused a 20% increase in vascular resistance in the flap, the resistance in intact muscle and skin remained virtually unchanged and the systemic vascular resistance decreased by 30% (table 1). The difference in vascular response to SNP, a decrease in systemic vascular resistance with maintenance of regional resis-

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Fig. 3. Phenylephrine. Data from nine pigs undergoing musculocutaneous free flap surgery under general anaesthesia. (A) Phenylephrine:local. Flap vascular resistance (VR, flap), vascular resistance in the control extremity (VR, control), total flap blood flow (TBF, flap), total blood flow in the control extremity (TBF, control), and microcirculatory blood flow as measured by laser Doppler flowmetry in flap skin (MCF, flap skin), control skin (MCF, control skin), flap muscle (MCF, flap muscle), and control muscle (MCF, control muscle) during infusion of $0.11 \mu\text{g}/\text{min}$ phenylephrine into the feeding artery of the flap. (B) Phenylephrine:systemic. Flap vascular resistance (VR, flap), vascular resistance in the control extremity (VR, control), total flap blood flow (TBF, flap), total blood flow in the control extremity (TBF, control), and microcirculatory blood flow as measured by laser Doppler flowmetry in flap skin (MCF, flap skin), control skin (MCF, control skin), flap muscle (MCF, flap muscle), and control muscle (MCF, control muscle) during systemic intravenous infusion of $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ phenylephrine. Values are plotted as mean relative changes to the baseline \pm SD. * $P < 0.05$ vs. baseline; ** $P < 0.01$ vs. baseline (by the Wilcoxon test). ☆☆☆ $P < 0.01$ for the difference between systemically and locally administered phenylephrine (by the Mann-Whitney U test).



tance in intact muscle, corresponds with previous findings on the action of SNP on various vascular beds.²⁷ However, the 20% increase in vascular resistance in the free flap is explained by the finding that the SNP-induced hypotension causes a greater decrease in blood flow to the flap than to intact muscle and skin. Whether this difference in response is caused by denervation of the flap or other factors remains to be elucidated. However, Carr *et al.*¹⁸ showed that denervation of skin reduces SNP-induced

vasodilatation by nearly 30% compared with innervated skin. A comparable study has not been performed on denervated skeletal muscle.

Sodium nitroprusside administered locally into the feeding artery of the flap caused no measurable systemic effects. On the other hand, TBF in the flap increased by 20%, and the vascular resistance in the flap decreased by almost 20%. These results suggest that there was a pharmacologically reversible vascular tone in the flap vessels despite total sympathectomy. Whether this vascular tone

was caused by a reperfusion injury, circulating catecholamines, or other unidentified vasoactive substances is unknown.

Systemic administration of phenylephrine resulted in a 30% increase in mean arterial pressure and systemic vascular resistance but constant cardiac output. Although the vascular resistance also increased in the free flap, neither TBF nor MCF were adversely affected (fig. 3). Because phenylephrine is a potent vasoconstrictor used frequently in clinical practice to increase vascular resistance and blood pressure, we could have expected adverse effects of the drug on blood flow in the free flap. However, phenylephrine is an α_1 -receptor agonist and is known to constrict mainly larger arterioles (110 μm in diameter) but has virtually no effects on terminal arterioles that respond to α_2 -receptor agonists (such as norepinephrine, which is a mixed α_1 - and α_2 -agonist) and metabolic factors (acidosis and hypoxia).^{28,29} Furthermore, Borbujo *et al.*³⁰ showed that human skin arteries have a mixed population of postjunctional α_1 - and α_2 -adrenoceptors, but α_2 -adrenoceptors are more prominent, which may be why systemic infusion of phenylephrine did not reduce MCF in the flap skin. In addition, Kakizoe *et al.*³¹ showed that the microcirculation of the skin is affected mainly by α_2 -adrenoceptor-mediated vasoconstriction. In their study, the potency of the α -adrenergic drugs, norepinephrine and phenylephrine, in terms of changes in blood flow did not correlate with their potency in terms of increases in systemic blood pressure.³¹ Phenylephrine increased blood pressure without causing a major reduction in skin blood flow, whereas norepinephrine significantly reduced skin blood flow at doses that increased blood pressure.³¹

Thus, if these results were applicable to clinical conditions, phenylephrine may not be as hazardous as generally believed in microvascular surgery. However, it is important to note that these data apply only in the presence of normovolemia. During hypovolemia, the effects might be different. Furthermore, this does not mean that all α -agonists could be used safely in microvascular surgery, because, for example, norepinephrine, which is both an α_1 - and α_2 -agonist, might have entirely different effects on blood flow in free flaps.

Phenylephrine infused locally into the feeding artery of the free flap caused, as expected, a sharp increase in flap vascular resistance and consequently decreased blood flow. No systemic effects were noted.

It was concluded that the α_1 -adrenergic agent phenylephrine administered systemically in a dose that increased systemic vascular resistance and mean arterial

pressure by approximately 30% appears to have no adverse effects on TBF or microcirculatory perfusion in free musculocutaneous flaps. Furthermore, during administration of sodium nitroprusside, it appears that blood flow in denervated free musculocutaneous flaps depends closely on arterial blood pressure. When sodium nitroprusside was given at a dose causing an approximately 30% decrease in systemic vascular resistance and mean arterial pressure, there was a severe reduction in TBF and MCF in free flaps despite adequate cardiac output.

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