with no neurological sequelae, according to CT scan and neurological examination by a paediatrician.

Our three cases show that active external rewarming is an effective technique for the management of profound hypothermia (core temperature <20°C) in children. The second child was treated with active internal rewarming as an additional part of his therapy (mediastinal rewarming with heat lamps). The presenting rhythm for all three children was profound sinus bradycardia, and severe cold-induced vasoconstriction made it difficult to definitely rule out the presence of a pulse. One child's condition deteriorated into ventricular fibrillation during resuscitation at site of the accident. The children in the first two examples had extended periods of CPR (>30 min), and required epinephrine to re-establish palpable pulses. However, none of the children had afterdrop, a frequent event in which core temperature falls when skin temperature increases. Furthermore, haemodynamic deterioration with rewarming did not occur, and all patients had normal neurological outcomes.

The management of profound hypothermia with ECLS rewarming results in a stable cardiac output without concern for afterdrop and rewarming shock. Successful resuscitation of neonates with profound hypothermia (core temperature as low as 16°C) has often been achieved with combinations of active external rewarming and warmed endotracheal gas, rather than ECLS.[1,2] Other than in neonates, however, there has only been one report[3] published of normal neurological outcomes after profound hypothermia (core temperature <20°C) treated with external rewarming methods. In our experience, the Bair-Hugger device was a more effective and faster treatment for hypothermia than methods of active internal rewarming;[4] in the three cases described, rates of rewarming recorded with the Bair-Hugger device were 3·9°C/h, 4·3°C/h, and 4·4°C/h, respectively. The device has previously been used in management of patients with moderate hypothermia,[5] but not for treatment of individuals with profound hypothermia.

In the absence of a perfusing rhythm, ECLS therapy should remain the gold standard for resuscitation after profound hypothermia. In instances of severe hypothermia in children with a palpable pulse, however, active external rewarming with a Bair-Hugger device, or similar, is a viable treatment option, which is less invasive than many forms of active internal rewarming—eg, peritoneal or pleural lavage. Whether or not the ease of use and apparent risk-free profile of the Bair-Hugger device, compared with extracorporeal life support, warrants its routine use in severe paediatric hypothermia with a pulse, is untested. Active internal and external rewarming are reasonable options for management of profound hypothermia, but neither should delay consultation with a paediatric tertiary-care centre.

Conflict of interest statement
None declared.

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Nitroglycerin in septic shock after intravascular volume resuscitation

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In patients with septic shock, oxygen consumption is increased, but oxygen delivery and extraction is impaired, partly because of microcirculatory shutdown and shunting. Orthogonal polarisation spectral (OPS) imaging allows visualisation of the microcirculation. We used this technique to assess microcirculatory flow in septic-shock patients who had a mean arterial blood pressure of more than 60 mm Hg and central venous pressure greater than 12 mm Hg. The infusion of 0·5 mg of nitroglycerin intravenously then resulted in a marked increase in microvascular flow on OPS imaging. Improved recruitment of the microcirculation could be a new resuscitation endpoint in septic shock.

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Sepsis is an important cause of death, and is characterised by increased oxygen consumption, decreased peripheral vascular resistance, maldistribution of tissue blood flow, and derangement of microcirculatory perfusion. Improved oxygen delivery to tissues might lower mortality rates, especially if treatment is started without delay.[1] Orthogonal polarisation spectral (OPS) imaging produces images of the microcirculation,[2,3] and can be used as an objective bedside method to monitor the effects of treatment on microcirculatory perfusion. We tested the hypothesis that nitroglycerin, a nitric oxide donor, reverses microcirculatory shutdown that persists after intravascular volume resuscitation in patients with septic shock.

Patients 18 years or older who were admitted to the intensive care unit with septic shock, diagnosed in accordance with the Bone criteria, were considered for the study. To prevent interobserver bias, we only included patients who had been assessed by one of the clinical investigators (PS or MG). The study was approved by the medical ethics committee at the Onze Lieve Vrouwe Gasthuis Hospital in Amsterdam. In accordance with the guidelines of our hospital, informed consent is not required when standard therapy is monitored by non-invasive techniques.

Patients were resuscitated such that mean arterial blood pressure was greater than 60 mm Hg and central venous pressure greater than 12 mm Hg after infusion of crystalloids and colloids, and the lowest possible dose of dopamine. All patients received 2 mg/h of ketanserin, an inhibitor of vasoconstriction. After the pressure goals had been reached, nitroglycerin infusion was started with an intravenous loading dose of 0·5 mg, then subsequent continuous infusion of 2 mg/h. The dose was increased and fluids were infused until peripheral circulation seemed to be restored.

An OPS device (Cytoscan, Cytometrics, Philadelphia, USA) was used to produce images of sublingual microcirculation after pressure-guided haemodynamic endpoints were reached, and 2 min after initiation of 0·5 mg nitroglycerin treatment. All data were digitally recorded for later analysis. A microcirculatory flow index was calculated on the basis of semiquantitative scoring (0=no flow, 1=sludging, 2=moderate flow, 3=normal flow) of flow patterns in small (diameter 10–25 μm) medium (25–50 μm), and large (50–100 μm) microvessels. The index was validated by testing for normal flow in ten healthy volunteers.

Wilcoxon's paired rank-sum test was used to detect changes in variables. A p value less than 0·05 (two-sided) was regarded as significant.

At the end of the 6-month inclusion and assessment period, we had included eight patients. All patients showed signs of peripheral vasoconstriction—ie, cold extremities with cutis marmorata and impaired capillary refill. Median age was

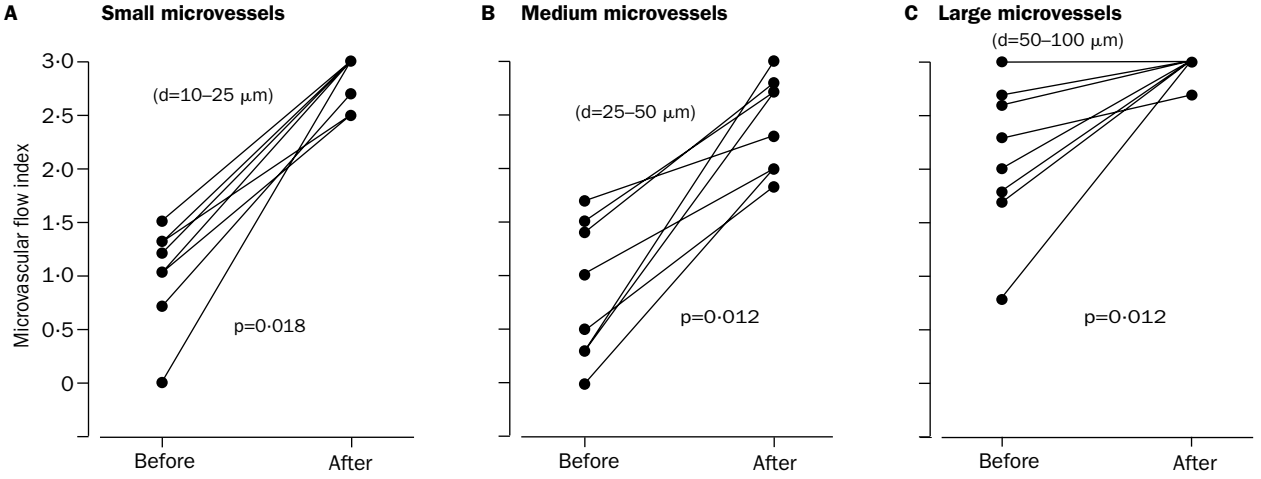

Figure 1: **Microvascular flow index before and 2 min after administration of nitroglycerin**
d=diameter. 0·5 mg bolus nitroglycerin given intravenously.

59 years (range 27–79), the median acute physiology and chronic health evaluation-II (APACHE-II) score was 27 (range 11–37). The amount of fluids (range 2·2–8·3 L) and dopamine dosages (range 4–24 γ per kg per min) required to reach haemodynamic endpoints differed between patients. Central venous pressure ranged from 11 to 25 mm Hg, and mean arterial pressure from 60 to 80 mm Hg. None of the patients received norepinephrine. Before treatment, sublingual microcirculatory flow was severely impaired, in particular, the flow in small microvessels was severely compromised (figure 1).

2 min after the initial nitroglycerin loading dose, mean arterial and central venous pressure temporarily dropped (19 mm Hg and 2 mm Hg, respectively), and there was a marked increase in microvascular flow, especially in small microvessels (figure 1). Figure 2 shows still images of patterns in a septic-shock patient after volume resuscitation and initiation of nitroglycerin treatment. Digitised video images of these changes in sublingual microcirculatory flow of a patient in septic shock are shown on our website [http://www.opsimaging.net]. After the loading dose, nitroglycerin infusion was continued at 0·5–4 mg/h with additional volume loading if required. Clinical signs improved; and seven patients were discharged from hospital alive. One patient died 6 days after treatment from a cerebral haemorrhage. One patient required renal replacement therapy.

At first glance, it seems paradoxical to give nitroglycerin for a disorder in which the expected systemic vascular resistance is low. However, during sepsis, autoregulation is disturbed, which results in a poor distribution of blood flow and inherent tissue ischaemia.[4] Microvascular weak units—ie, tissue parts that are inadequately perfused because of blood being shunted from tissues to organs—might be an explanation for the variation in findings regarding locoregional tissue perfusion in shock.[5]

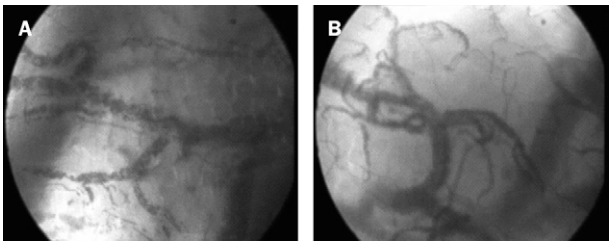

Figure 2: **Sublingual OPS images of a patient with septic shock after pressure-guided volume resuscitation**
(A) Before nitroglycerin treatment, sludged individual erythrocytes can be seen in small, medium, and large microvessels.
(B) After initiation of nitroglycerin treatment. Because of the fast flow, individual erythrocytes cannot be seen.

Thus, strategies to open the microcirculation by vasodilation are the logical next step. Our results suggest that impaired microcirculatory perfusion occurs in patients with septic shock, despite normal blood pressure attained after restoration of intravascular volume. This microcirculatory shut-down can be counteracted by cautious intravenous administration of nitroglycerin, but should not be attempted without continuous monitoring for substantial hypovolaemia. Whether these beneficial effects also apply to other microvascular beds, and whether recruitment of microcirculation will reduce cellular dysfunction, organ failure, and mortality in patients with sepsis remains to be seen. Sublingual OPS imaging seems to be a valuable tool for monitoring microcirculatory flow, and might be useful in providing new resuscitation endpoints in the treatment of patients with septic shock. However, early aggressive fluid replacement remains the cornerstone of treatment.

Contributors
P E Spronk and M J Gardien did bedside OPS measurements, C Ince, H M Oudemans-van Straaten, and D F Zandstra conceived the idea about vasodilation in sepsis. K R Mathura provided practical support and analysed the images. P Spronk did statistical analysis. P Spronk, C Ince, and H M Oudemans-van Straaten prepared the manuscript. C Ince and D F Zandstra measured flow parameters from the images.

Conflict of interest statement
None declared.

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