

Philanthropist or opportunist?

Sir—If Bill Gates did not give money to international health (Nov 23, p 1617),¹ you would criticise him for his greed; when he does give a large amount, you accuse him of self-interest. I have never met Bill Gates and have no idea what his inner motives might be. Possibly he is a genuine philanthropist. Possibly he is the “commercial opportunist” that your Editorial implies. But in either event, substantial good can be made of his recent US\$100 million gift to the Indian government to combat AIDS.

The international health-care community is fortunate to have the backing of the world's richest man. His donations will improve millions of lives. I suggest you stop focusing on his inner motives, which are unknowable, and concentrate instead on what can be made of the \$24 billion he has given to international health causes.

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- 1 Editorial. Philanthropist or commercial opportunist? *Lancet* 2002; **360**: 1617.

Nitroglycerin for septic shock

Sir—The findings of Peter Spronk and co-workers (Nov 2, p 1395)¹ confirm our results² that severe microcirculatory alterations are present in patients with septic shock and that the sublingual microvasculature can be responsive to nitric oxide, either administered directly or by local production after topical application of acetylcholine.

Although the effects of intravenous nitroglycerin, a nitric oxide donor, on the sublingual microvasculature are unquestionable in Spronk and colleagues' Research letter, we believe that use of a nitric oxide donor during severe sepsis or septic shock should not be considered on a routine basis. Administration of nitric oxide in patients with septic shock can result in profound hypotension.³ The effects of nitroglycerin on blood pressure are not mentioned in detail by Spronk and colleagues, but a 28% decrease in mean arterial pressure was previously reported by them⁴ in the first four patients they investigated.

Large amounts of nitric oxide, its byproducts, or both can exert toxic effects, including mitochondrial dysfunction leading to further impairment in oxygen delivery and

extraction. Consequently, manipulation of the nitric oxide pathway in patients with septic shock can be a risky approach. The challenging experimental data reported by Spronk and colleagues are clearly hypothesis-generating for further trials, but should not be presented as standard therapy, even with adequate fluid resuscitation.

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- 1 Spronk PE, Ince C, Gardien MJ, et al. Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet* 2002; **360**: 1395–96.
- 2 De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002; **166**: 98–104.
- 3 Vincent JL, Zhang H, Szabo C, Preiser JC. Effects of nitric oxide in septic shock. *Am J Respir Crit Care Med* 2000; **161**: 1781–85.
- 4 Spronk P, Gardien M, Ince C, et al. *Intensive Care Med* 2001; **27** (suppl 2): S251.

Authors' reply

Sir—Jean-Charles Preiser and colleagues question the routine use of nitroglycerin because of the risk of hypotension and the possible induction of mitochondrial dysfunction. Although we observed a temporary drop in blood pressure, blood flow was maintained and, in fact, increased in our patients. Space constraints meant that we were not able to include specific haemodynamic results in our Research letter, but mean arterial pressure temporarily dropped by an average of 21 mm Hg (range 13–33 mm Hg) in the eight patients we investigated. Mean arterial pressure returned to baseline level within 1 min in all patients with concomitant fluid infusion. The increase in microvascular blood flow as a result of this procedure confirms our clinical experience that resuscitation efforts should be aimed at optimising blood flow not blood pressure.

Preiser and co-workers are concerned about the possible toxic effects of large doses of nitric oxide, which could further impair oxygen delivery and extraction. In a study of their own,¹ however, where the nitric oxide donor SIN-1 was used in a canine model of endotoxic shock, they noted an improvement in oxygen extraction. If mitochondrial depression had occurred one would have expected a decrease in oxygen extraction, suggesting that the improved perfusion caused by the nitric oxide donor far outweighs the possible

toxic effect of extra nitric oxide on mitochondrial function. Furthermore, the intravenous dose in our study is similar to that of sublingual nitroglycerin in patients with angina.

The use of vasodilators such as nitroglycerin in the treatment of septic shock has been part of our standard treatment for many years. Our study was presented to our hospital ethics board as an observational study. It was not our intention to suggest that the proposed strategy should be considered standard therapy in the treatment of severe sepsis and septic shock. We showed that apparently well resuscitated patients can have almost complete microcirculatory stasis and that this condition, which Daniel De Backer and colleagues² have shown can lead to death, can be corrected by vasodilation. The importance of our study is that the rationale behind this treatment can be found in the insights obtained from animal experimentation. Such work shows that microcirculatory shunting underlies regional tissue oxygenation dysfunction, and that this condition can be corrected by vasodilatory therapy.^{3–5} Our findings suggest that conventional resuscitation procedures, while improving blood pressure, may not be successful in correcting tissue perfusion. This lack of effect on tissue perfusion may explain some of the confusion that arises in trials that aim at a better outcome by improving perfusion pressure. We are currently involved in a clinical trial to test the experimental data presented in our Research letter.

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- 1 Zhang H, Rogiers P, Smail N, et al. Effects of nitric oxide on blood flow distribution and extraction capabilities during endotoxic shock. *J Appl Physiol* 1997; **83**: 1164–73.
- 2 De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002; **166**: 98–104.
- 3 Siegemund M, van Bommel J, Volbrecht K, Dries J, Ince C. Influence of NO donor SIN-1 on the gut oxygenation in a normodynamic, porcine model of low-dose endotoxemia. *Intensive Care Med* 2000; **26**: S362.
- 4 Ince C, Sinaasappel M. Microcirculatory oxygenation and shunting in sepsis and shock. *Crit Care Med* 1999; **27**: 1369–77.
- 5 Buwalda M, Ince C. Opening the microcirculation: can vasodilators be useful in sepsis? *Intensive Care Med* 2002; **28**: 1208–17.