

challenges have great promise in diagnosis and monitoring of specific disease activities.

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- 1 Rolla G, Colagrande P, Brucino L, Bucca C, Bertero MT, Caligaris-Cappio F. Exhaled nitric oxide and pulmonary response to iloprost in systemic sclerosis with pulmonary hypertension. *Lancet* 1998; 351: 1491-92.
- 2 Husain M, Adrie C, Ichinose F, Kavosi M, Zapol WM. Exhaled nitric oxide as a marker for organic nitric tolerance. *Circulation* 1994; 89: 2498-502.
- 3 Marczin N, Riedel B, Royston D, Yacoub M. Intravenous nitrite vasodilators and exhaled nitric oxide. *Lancet* 1997; 349: 1742.
- 4 Dimberger E, Lucan H, Eichler HG, Kastner J, Pernerstorfer T, Jilma B. Effects of nitroglycerin and sodium nitroprusside on endexpiratory concentrations of nitric oxide in healthy humans. *Life Sci* 1998; 62: PL103-08.
- 5 Kharitonov SA, Alving K, Barnes PJ. Exhaled and nasal nitric oxide measurements: recommendations: The European Respiratory Society Task Force. *Eur Respir J* 1997; 7: 1683-93.

Authors' reply

Sir—Nándor Marczin and colleagues raise important methodological points about our report on exhaled nitric oxide (NO) and pulmonary response to iloprost in systemic sclerosis. We regret that we did not have room for all the methodological details.

During infusion of glyceryl trinitrate (GTN) three measurements of exhaled NO were done at 2 minute intervals, 15 minutes from the start of infusion. Exhaled NO was measured on a chemiluminescence analyser.¹ Because a substantial proportion of the NO in exhaled air originates in the nasal cavity,² patients were asked to inhale NO-free air and to perform a slow expiratory vital capacity over 15-20 s against resistance (20 cm H₂O). In this way the continuous expiratory positive mouth pressure closes the velum during expiration, reducing nasopharynx NO contamination. Exhaled air was sampled for NO analysis via a Teflon tubing side-arm attached to the mouthpiece, at a sample gas flow of 250 mL/min. NO concentration, flow, and pressure were simultaneously recorded against time and the mean value of the plateau (the last part of expiration) NO concentration was recorded.

On the basis of their experience on mechanically ventilated patients undergoing cardiac surgery, Marczin

and colleagues suggest that a large bolus of GTN is needed to obtain a transient increase in exhaled NO (tidal breath). On the contrary, GTN infusion cannot change exhaled NO, because the fractional excretion of NO is very small. We have some hypotheses to account for the different result we obtained in one patient with systemic sclerosis, methodological differences apart.

Our patient had a low endogenous NO, so that the dose of GTN required to increase the rate of signal to background noise for exhaled NO detection should have been lower than in healthy individuals. Moreover, the lack of increase in exhaled NO after GTN administration may depend on the increase in pulmonary venous admixture induced by GTN itself.³ This effect might have a more important role in mechanically ventilated cardiac patients and in healthy people than in a patient with systemic sclerosis and pulmonary hypertension, whose pulmonary vessels are presumably less sensitive to the vasodilating effect of GTN. We agree with Marczin and colleagues that technical details are equally important as clinical setting to properly explain different results.

*Giovanni Rolla, on behalf of all authors

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- 1 Kharitonov SA, Yates D, Robbins RA, Logan-Sinclair R, Shinebourne E, Barnes PJ. Increased nitric oxide in exhaled air of asthmatic patients. *Lancet* 1994; 343: 146-47.
- 2 Kimberley B, Nejadnik B, Giraud GD, Holden WE. Nasal contribution to exhaled nitric oxide at rest and during breathholding in humans. *Am J Respir Crit Care Med* 1996; 153: 829-36.
- 3 Mookherjee S, Fuleihan D, Warner RA, Vardan S, Obeid AI. Effects of sublingual nitroglycerin on resting pulmonary gas exchange and hemodynamics in man. *Circulation* 1978; 57: 106-10.

Surveillance of antifolate-resistant malaria

Sir—The epidemiology of antifolate resistance in *Plasmodium falciparum* can be monitored by molecular techniques due to a high correlation between mutations in dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) and in-vitro resistance to pyrimethamine and sulphadoxine.^{1,2} The results of James Kublin and colleagues (May 30, p 1629)³ and other studies^{4,5} reinforce the association between the genotype and phenotype.³⁻⁵

The findings of Kublin and his

colleagues in the Amazonian basin are not, however, representative and differ from the mutational patterns observed in Africa. In their series, all 11 patients with sensitive response were infected with *P falciparum* isolates that carry a wild-type DHPS and a mutant Asn-108 allele in DHFR. In Africa, sensitive response was reported with parasites that carry a wild-type DHPS and a wild-type or mutant (Asn-108 with or without Arg-59) DHFR.⁴ In the Amazon, there was no difference in the genotype in relation to the level of in-vivo resistance to sulphadoxine-pyrimethamine. In Africa, we found a tendency towards a higher level of in-vivo resistance in the presence of triple mutations in DHFR (Ile-51, Arg-59, and Asn-108).⁴ DHFR mutant codons 30 and 164 and DHPS mutant codon 540, frequently detected in the Amazon, are rare in Africa. By contrast, the mutant DHFR codon Arg-59 is common in Africa but not in the Amazon.

These genotype differences may reflect independent genetic changes in malaria parasites from different geographical origins. Before molecular analysis is used to describe the epidemiology of antifolate resistance in an endemic area, further studies that correlate the in-vivo resistance and point mutations are needed to characterise the genotype of drug-sensitive and drug-resistant parasites.

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- 1 Basco LK, Eldin de Pécoules P, Wilson CM, Le Bras J, Mazabraud A. Point mutations in the dihydrofolate reductase-thymidylate synthase gene and pyrimethamine and cycloguanil resistance in *Plasmodium falciparum*. *Mol Biochem Parasitol* 1995; 69: 135-38.
- 2 Wang P, Read M, Sims PFG, Hyde JE. Sulfadoxine resistance in the human malaria parasite *Plasmodium falciparum* is determined by mutations in dihydropteroate synthetase and an additional factor associated with folate utilization. *Mol Microbiol* 1997; 23: 979-86.
- 3 Kublin JG, Witzig RS, Shankar AH, et al. Molecular assays for surveillance of antifolate-resistant malaria. *Lancet* 1998; 351: 1629-30.
- 4 Basco LK, Tahar R, Ringwald P. Molecular basis of in vivo resistance to sulfadoxine-pyrimethamine in African adult patients infected with *Plasmodium falciparum* malaria parasites. *Antimicrob Agents Chemother* (in press).
- 5 Wang P, Lee CS, Bayoumi R, et al. Resistance to antifolates in *Plasmodium falciparum* monitored by sequence analysis of dihydropteroate synthetase and dihydrofolate reductase alleles in a large number of field samples of diverse origins. *Mol Biochem Parasitol* 1997; 89: 161-77.

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