

Dear Sir,

We thank Dr Yesildaglar *et al.* for their comments about our paper concerning the systemic effects of adding small amounts of oxygen to the CO₂ used for the pneumoperitoneum during endoscopic surgery.

We fully agree that they never performed nor published experiments concerning the effects of adding oxygen to the CO₂ used for the pneumoperitoneum. In the discussion of a rather long manuscript we deliberately chose to be brief when describing 'the hypothesis of mesothelial damage through hypoxia caused by the CO₂ pneumoperitoneum, and its prevention by adding small amounts of oxygen, as derived from experiments in rabbits and mice'. Since the concept was progressively developed by our group, references were grouped in order to give credit to previous and actual co-workers. There certainly never has been any intention to 'misleadingly quote' any of their work, and we trust that also the referees must have considered that the references referred to the concept and the group, not with the details of each previous publication.

The concept that CO₂ pneumoperitoneum enhanced adhesion formation is mediated through mesothelial hypoxia and subsequent angiogenesis is based upon the following observations. In rabbits, adhesion formation increases with the duration of pneumoperitoneum (Ordonez *et al.*, 1997; Molinas and Koninckx, 2000) and with the insufflation pressure (Yesildaglar and Koninckx, 2000), and decreases after the addition of a small percentage (3–6%) of oxygen (Molinas and Koninckx, 2000). This was observed using both CO₂ and helium as insufflation gases (Molinas and Koninckx, 2000). Similar effects were observed in mice (Molinas *et al.*, 2001). In transgenic mice partially deficient for hypoxia inducible factors HIF-1 α or HIF-2 α (Molinas *et al.*, 2003a) the effect of pneumoperitoneum-enhanced adhesions is no longer present. In mice knockout for the genes encoding for VEGF-A, VEGF-B or PlGF we could demonstrate the important role of these angiogenic factors in pneumoperitoneum-enhanced adhesions (Molinas *et al.*, 2003b). Adhesions caused by a surgical lesion with the minimum duration of the pneumoperitoneum, so-called 'basal adhesions', are mainly mediated by the plasminogen system, as demonstrated in tPA, uPA and PAI-1 knockout mice (Molinas *et al.*, 2003c). All data together strongly support the hypothesis of mesothelial hypoxia as the driving mechanism. Moreover this is logical, since 3% of oxygen at a pressure of 775 mmHg, determines a partial pressure of oxygen (PO₂) of 23 mmHg, which is the normal physiologic PO₂ in peripheral cells according to the oxygen cascade model in mammals.

According to the physics laws of gases, gases will diffuse until an equilibrium is reached, i.e. when the partial tensions are similar. Therefore, during CO₂ pneumoperitoneum some diffusion of oxygen from the blood stream into the peritoneal cavity, and of CO₂ into the blood stream must occur. We still do not know how rapid and how important this phenomenon of diffusion of oxygen is. In order to ascertain a constant pneumoperitoneum environment, we consider it prudent to

replace slowly but continuously the gas of the pneumoperitoneum, as we did.

The observations of Mynbaev *et al.* were for us unexpected (Mynbaev *et al.*, 2002). We fully admit that the hypothesis of pneumoperitoneum-induced mesothelial damage and subsequently enhanced CO₂ resorption, is not yet proven. We therefore invite Dr Yesildaglar and colleagues to disclose any data they might have and which could shed more light on this phenomenon.

Indeed the clinical implications are important. The simple addition of a small percentage (3–6%) of oxygen to the CO₂ used for the pneumoperitoneum, could decrease postoperative adhesion formation, and could decrease CO₂ resorption especially during endoscopic surgery of longer duration.

References

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