LETTER TO THE EDITOR

Reply: The underestimated effect of normobaric hyperoxia on cerebral blood flow and its relationship to neuroprotection

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Sir,

We thank Chazalviel et al. (2016) for their interest in our article (Ejaz et al. 2016) showing near-complete protection against neuronal damage and sensorimotor deficit by normobaric hyperoxia (NBO) in a rat model of brief middle cerebral artery occlusion (MCAO). Chazalviel et al. raise interesting issues regarding potential interactions between NBO and tissue plasminogen activator (tPA). To summarize, they argue that the available data from thrombo-embolic stroke models suggest that NBO when administered before tPA facilitates the latter’s thrombolytic properties, in turn increasing the chance of reperfusion and improved cerebral blood flow (CBF). Chazalviel et al. go one step further by arguing that the beneficial effects of NBO in experimental stroke may be largely, if not solely, due to this effect on perfusion, rather than to the—admittedly modest—increase in arterial oxygen content.

Although their point that NBO facilitates the thrombolytic effects of tPA is important and may account for the previously reported synergism of NBO and tPA in reducing infarct volume (Henninger et al., 2009), we believe it unlikely this to be the sole mechanism underlying the beneficial effects of NBO, and believe the latter are at least in part due to improved arterial oxygen content. Several lines of evidence support this view, as follows:

(i) Obviously, the interaction between NBO and exogenous tPA could not account for the reported beneficial effects of NBO in mechanical-based brief MCAO models (Miyamoto and Auer, 2000; Flynn and Auer, 2002; Singhal et al., 2002b; Kim et al., 2005; Liu et al., 2006, 2012; Henninger et al., 2007; Shin et al., 2007; Esposito et al., 2013; Jin et al., 2013; Ejaz et al., 2016). However, Chazalviel et al. (2016) suggest that NBO’s beneficial effects in mechanical models could occur via its interaction with endogenous tPA, preventing platelet aggregation and clotting in capillaries. This is an interesting idea, especially given the emerging role of impaired capillary perfusion from peri-capillary pericyte constriction after MCAO (Yemisci et al., 2009; Hall et al., 2014). However, this phenomenon tends to be delayed, typically occurring well beyond 1 h after onset of MCAO, or even only after reperfusion (Dalkara and Arsava, 2012), and is therefore unlikely to account for the consistently-reported strongly beneficial effects of MCAO in mechanical occlusions lasting 15–90 mins (Miyamoto and Auer, 2000; Flynn and Auer, 2002; Kim et al., 2005; Liu et al., 2006, 2012; Shin et al., 2007; Esposito et al., 2013; Jin et al., 2013; Ejaz et al., 2016). Accordingly, in the mechanical occlusion studies of Liang et al. (2015), the administration of both NBO and tPA reduced infarct volume only with very long (5 and 7 h), but not with 3 h occlusion.

(ii) In all rodent species tested so far, NBO markedly increases brain tissue PO2 (PtO2) in ischaemic areas, particularly in the penumbra (Liu et al., 2006, Shin et al., 2007, Baskerville et al., 2011). Consistent with this previous literature, we also found that NBO increased ischaemic cortex PtO2 > 2.5-fold in both Wistar and spontaneously hypertensive rats (SHRs) (unpublished observations). As brain PtO2 represents the balance between oxygen delivery and demand, these increases in PtO2 probably underestimate true improvements in neuronal oxygenation. Indeed, the penumbra exhibits extremely high oxygen extraction fraction, indicating penumbral neurones are extremely eager for oxygen, so that any increase in O2 delivery from NBO is expected to improve neuronal oxygen consumption henceforth constraining the increase in PtO2. This hypothesis could be tested using 15O-PET or novel magnetic resonance–oxygen techniques (Baron, 2016).

(iii) Importantly, both this marked increase in ischaemic brain PtO2 and the arrest in progression—and occasional reversal—
of diffusion-weighted (DWI) lesions during NBO delivery in rodents (Singhal et al., 2002a; Henninger et al., 2007) and humans (Singhal et al., 2005) take place despite no (Singhal et al., 2002a; Henninger et al., 2007) or only mild and inconsistently significant increases in perfusion (Singhal et al., 2005; Baskerville et al., 2011), except in one mice study (Shin et al., 2007).

On a more conceptual note, it may not be necessary to call on improvements in perfusion to explain why NBO blocks the progression of the penumbra to infarction. Indeed, the classic perfusion thresholds for penumbra and infarction (Astrup et al., 1981; Jones et al., 1981; Baron, 2001) in effect likely represent thresholds for oxygen delivery, i.e. CBF × arterial O$_2$ content. Thus, NBO-related higher arterial PO$_2$ could increase O$_2$ delivery above the infarction threshold even without increased perfusion, in turn preventing the penumbra from tilting to irreversible infarction. Were perfusion to increase as another effect of NBO, this dual mechanism would obviously further improve O$_2$ delivery to the penumbra.

In summary, Chazalviel et al. (2016) raise the very interesting and potentially important point that NBO administered before tPA could increase tPA’s thrombolytic effects. This paradigm fits well the clinical trial design proposed in our article (Ejaz et al., 2016), namely that NBO be delivered as early as possible, at home or in the ambulance, until a diagnosis of ischaemic stroke is made and tPA can be safely administered. This ‘pre-hospital’ paradigm is becoming even more realistic nowadays with the increasing implementation of mobile stroke units equipped with a CT scanner (Kostopoulos et al., 2012; Walter et al., 2012; Bowry et al., 2015; Cerejo et al., 2015; Wendt et al., 2015). Increasing the incidence of post-tPA reperfusion by NBO could have a major clinical impact not only on overall patients’ outcome, but also by reducing the need for transfers to comprehensive stroke centres for mechanical thrombectomy. Over and above this potentially beneficial NBO-tPA interaction, the primary role of NBO would nevertheless remain as adjunct to recanalization therapies, by directly improving oxygenation and maintaining viability of the penumbra until reperfusion occurs.

Interestingly, Chazalviel et al. also point the potential detrimental interaction of nitrous oxide with the thrombolytic effects of tPA, which could have implications for the anesthetic regimen used in patients undergoing endovascular procedures following intravenous thrombolysis.

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**References**


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