All of these cases used a mydricaine formulation standardized by Moorfields Eye Hospital, which has lower doses of adrenaline and atropine than used in this case (refer to the preceding texts).

We believe that the high dose of adrenaline used, combined with the stress and discomfort of subconjunctival injection, is the most likely cause of takotsubo cardiomyopathy in this case. There are currently multiple hypotheses attempting to describe the pathophysiology of takotsubo cardiomyopathy, including theories that it is a protective adaptation to cardiac overstimulation, with experiments in rat models showing that elevated levels of serum adrenaline can induce the effect.[2] The high concentration of vasculature in the conjunctiva further increases the risk of subconjunctival mydricaine injections resulting in systemic effects. A subconjunctival injection of 1.0 ml is extremely uncomfortable, despite topical and local anaesthetic, and is sufficient to cause significant physical and emotional stress.

As a result of this case, the use of subconjunctival mydricaine has been ceased in this hospital's emergency department and limited elsewhere within the hospital. An alternative form of controlled topical adrenaline has been proposed. We would recommend that further use of subconjunctival mydricaine should not only be judicious but also only performed in a setting where tertiary medical services can be easily accessed.

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References

1. Templin C, Ghadri JR, Diekmann J, *et al.* Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *N England J Med* 2015; **373**: 929–38.
2. Redfors B, Shao Y, Ali A, Omerovic E. Current hypotheses regarding the pathophysiology behind the takotsubo syndrome. *Int J Cardiol* 2014; **177**: 771–9.
3. Jayamanne DG, Ray-Chaudhuri N, Wariyar R, Cottrell DG. Haemodynamic responses to subconjunctival mydriatic agents (Mydricaine) used for maintenance of perioperative mydriasis in patients undergoing vitreoretinal surgery. *Eye* 1998; **12**: 792–4.
4. Steel DH, Thorn J. The incidence of systemic side-effects following subconjunctival Mydricaine no. 1 injection. *Eye (Lond)* 1999; **13**: 720–2.
5. Keembiyage RD, Newland HS, Lai C. Tachycardia and myocardial ischaemia following subconjunctival injection of mydricaine (number 02) for vitrectomy procedure [5]. *Clin Exp Ophthalmol* 2005; **33**: 105–6.

Exacerbation of macular oedema associated with hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) administers 100% oxygen at 1 to 3 atmospheric pressures to increase the partial pressure of arterial oxygen.[1] It is used for decompression sickness, carbon monoxide poisoning, burns and failing skin grafts.[1] Research in wound healing models have shown that the benefits of HBOT are facilitated by up-regulating vascular endothelial growth factor (VEGF) and subsequent angiogenesis.[2]

There is no FDA-approved indication in ophthalmic diseases. However, HBOT centres are marketing HBOT for retinal diseases such as age-related macular degeneration, diabetic retinopathy and retinal vein occlusions.[3] These processes all require *suppression* of VEGF; therefore, HBOT would theoretically be harmful. Herein, we present a patient with a ruptured retinal arterial macroaneurysm (RAM) who experienced acute development of severe macular oedema following HBOT treatment.

A 71-year-old Caucasian woman with hypertension presented with blurred vision in the left eye (OS). Past ocular history included a RAM in the right eye (OD) with central subretinal hemorrhage. Visual acuities (VA) were 20/150 OD and 20/200 OS. Fundus examination revealed macular scarring OD, and a fresh subretinal haemorrhage involving the fovea OS from a RAM as seen on fluorescein angiography (FA) (Fig. 1a).

The patient underwent pars plana vitrectomy with successful subretinal hemorrhage displacement, and VA improved to 20/150 one week after surgery (Fig. 1b). However, the patient self-referred herself to an HBOT centre after hearing radio commercials. Two to three days after the seventh treatment, the patient noted a sudden worsening of vision. VA decreased to 20/200, and there was a new, extensive and diffuse macular oedema (Fig. 1c).

The patient was instructed to discontinue HBOT, but there was no improvement of the oedema one week later, and intravitreal ranibizumab was administered. The macular oedema improved (Fig. 1d–e), but there was an increase of exudates and no further visual improvement (Fig. 1f). The examination is stable 1.5 years later.

HBOT is an FDA-approved treatment for various states of tissue hypoxia, and works by increasing

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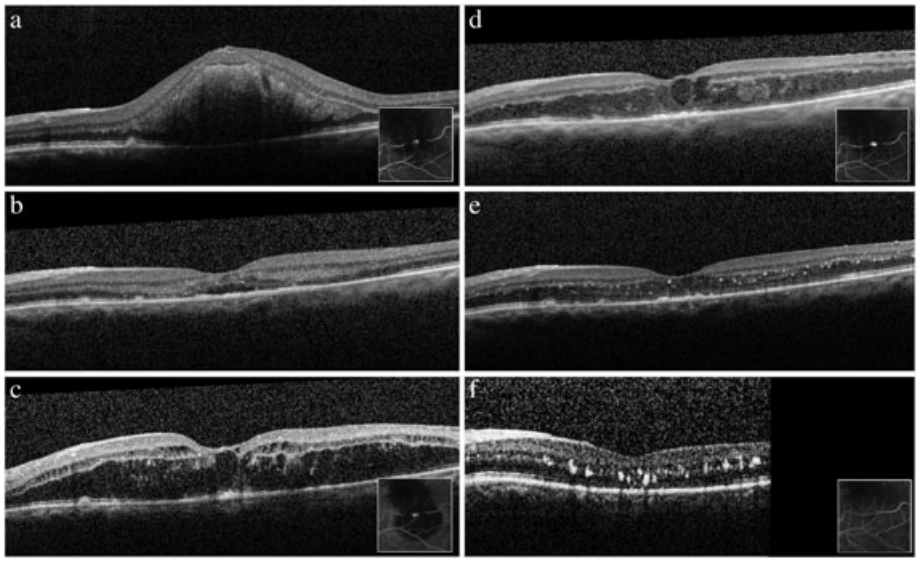

Figure 1. Macular oedema exacerbated by hyperbaric oxygen therapy (HBOT). (a) Spectral-domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering, Germany) shows subretinal hemorrhage, and the inset shows the focal hyperfluorescence of a retinal arterial aneurysm (RAM) on fluorescein angiography (FA). (b) The subretinal hemorrhage has been displaced inferiorly 1 week after pars plana vitrectomy with subretinal tissue plasminogen activator, and there is only trace residual subretinal fluid. (c) Two weeks after initiating HBOT, there is a diffuse, broad, extensive macular oedema, with persistent leakage of the RAM (inset). (d) The oedema has improved 3 weeks after ranibizumab treatment, with persistent leakage of the RAM (inset). (e) The intraretinal fluid has largely resolved after another 3 weeks, but there is an increase in exudates. (f) There is no recurrence of macular oedema 3 months after the ranibizuman injection, and the RAM has involuted (inset). The examination is stable 1.5 years subsequently with resolution of the exudates.

arterial oxygen content by application of Henry's law: the amount of gas dissolved in a liquid correlates with the partial pressure of the gas exerted on the liquid. HBOT sessions, or 'dives,' can range from one to several hours, and are often repeated daily. It is uncertain whether the hyperoxic state causes oxidative damage, but cataract and lenticular myopia have been implicated as potential complications from reactive oxygen species.[4]

Numerous *in vitro* and animal studies have shown that HBOT upregulates VEGF to facilitate angiogenesis, which is important in wound healing. Similar to the oxygen-induced retinopathy models and the pathophysiology of retinopathy of prematurity, the VEGF increase is a response to the relative ischemia that is experienced after the patient is removed from the HBOT chamber.[2] In retinovascular diseases, VEGF promotes pathologic neovascularization and is a potent vascular permeability factor. We hypothesize that the HBOT was at least partially responsible for the macular oedema in our patient, because of the abrupt onset after initiation of HBOT, unusually diffuse topography of the oedema and theoretical VEGF surge.[5]

Anecdotally, we have also experienced acute worsening of diabetic retinopathy in our patients in the 1980s when HBOT was popularized (GAW). We recommend that HBOT centres do not market HBOT for retinovascular diseases.

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References

1. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. *N Engl J Med* 1996; **334**: 1642–8.
2. Sheikh AY, Gibson JJ, Rollins MD, Hopf HW, Hussain Z, Hunt TK. Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. *Arch Surg* 2000; **135**: 1293–7.
3. Oxford Recovery Center. Treatment indications. Available at: http://oxfordhbot.com/treatment-indications (accessed November 29, 2015).
4. Palmquist BM, Philipson B, Barr PO. Nuclear cataract and myopia during hyperbaric oxygen therapy. *Br J Ophthalmol* 1984; **68**: 113–7.
5. McMonnies CW. Hyperbaric oxygen therapy and the possibility of ocular complications or contraindications. *Clin Exp Optom* 2015; **98**: 122–5.