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Evidence for an enduring ischaemic penumbra following central retinal artery occlusion, with implications for fibrinolytic therapy

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ABSTRACT

The rationale behind hyperacute fibrinolytic therapy for cerebral and retinal arterial occlusion is to rescue ischaemic cells from irreversible damage through timely restitution of tissue perfusion. In cerebral stroke, an anoxic tissue compartment (the "infarct core") is surrounded by a hypoxic compartment (the "ischaemic penumbra"). The latter comprises electrically-silent neurons that undergo delayed apoptotic cell death within 1–6 h unless salvaged by arterial recanalisation. Establishment of an equivalent hypoxic compartment within the inner retina following central retinal artery occlusion (CRAO) isn't widely acknowledged. During experimental CRAO, electroretinography reveals 3 oxygenation-based tissue compartments (anoxic, hypoxic and normoxic) that contribute 32%, 27% and 41% respectively to the pre-occlusion b-wave amplitude. Thus, once the anoxia survival time (≈2 h) expires, the contribution from the infarcted posterior retina is irreversibly extinguished, but electrical activity continues in the normoxic periphery. Inbetween these compartments, an annular hypoxic zone (the "penumbra obscura") endures in a structurally-intact but functionally-impaired state until retinal reperfusion allows rapid recovery from electrical silence. Clinically, residual circulation of sufficient volume flow rate generates the heterogeneous fundus picture of "partial" CRAO. Persistent retinal venous hypoxaemia signifies maximal extraction of oxygen by an enduring "polar penumbra" that permeates or largely replaces the infarct core. On retinal reperfusion some days later, the retinal venous oxygen saturation reverts to normal and vision improves. Thus, penumbral inner retina, marginally oxygenated by the choroid or by residual circulation, isn't at risk of delayed apoptotic infarction (unlike hypoxic cerebral cortex). Emergency fibrinolytic intervention is inappropriate, therefore, once the duration of CRAO exceeds 2 h.

Contents

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1. Introduction

Despite the optimism generated by anecdotal reports and uncontrolled studies, no treatment for central retinal artery occlusion (CRAO) has been shown to be safe and effective (Beatty and Au Eong, 2000; Noble et al., 2008; Chen and Lee, 2008; Fraser and Adams, 2009). Several years ago, the European Assessment Group for Lysis in the Eye (EAGLE) conducted a multicentre, prospective, randomized, clinical trial comparing treatment outcomes in 82 patients with non-arteritic CRAO (and no cilioretinal sparing) undergoing either local intra-arterial fibrinolysis (LIF) or standard conservative treatment within 20 h of symptom onset (Feltgen et al., 2006). This is the only gold standard trial to be undertaken to date but, in the event, safety concerns among patients undergoing LIF led to its abandonment at a stage when there was no significant difference in functional outcomes between the 2 study arms (Schumacher et al., 2010). Nevertheless, further trials are planned or recommended, not least to determine the role of