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Research Report

Effects of trauma, hemorrhage and resuscitation in aged rats

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ABSTRACT

Traumatic brain injury (TBI) is a leading cause of death in the elderly and the incidence of mortality and morbidity increases with age. This study tested the hypothesis that, after TBI followed by hemorrhagic hypotension (HH) and resuscitation, cerebral blood flow (CBF) would decrease more in aged compared with young rats. Young adult (4–6 months) and aged (20–24 months) male Sprague-Dawley rats were anesthetized with isoflurane, prepared for parasagittal fluid percussion injury (FPI) and randomly assigned to receive either moderate FPI (2.0 atm) only, moderate FPI+severe HH (40 mm Hg for 45 min) followed by return of shed blood, or sham FPI. Intracranial pressure (ICP), CBF, and mean arterial pressure (MAP) were measured and, after twenty-four hours survival, the rats were euthanized and their brains were sectioned and stained with Fluoro-Jade (FJ), a dye that stains injured neurons. After moderate FPI, severe HH and reinfusion of shed blood, MAP and CBF were significantly reduced in the aged group, compared to the young group. Both FPI and FPI+HH groups significantly increased the numbers of FJ-positive neurons in hippocampal cell layers CA1, CA2 and CA3 ($p<0.05$ vs Sham) in young and aged rats. Despite differences in post-resuscitation MAP and CBF, there were no differences in the numbers of FJ-positive neurons in aged compared to young rats after FPI, HH and blood resuscitation. Although cerebral hypoperfusion in the aged rats was not associated with increased hippocampal cell injury, the trauma-induced reductions in CBF and post-resuscitation blood pressure may have resulted in damage to brain regions that were not examined or neurological or behavioral impairments that were not assessed in this study. Therefore, the maintenance of normal blood pressure and cerebral perfusion would be advisable in the treatment of elderly patients after TBI.

Abbreviations: ARI, autoregulatory index; BP, blood pressure; CA1, 2 and 3, Cornu Ammonis regions 1, 2 and 3; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; CVR, cerebrovascular resistance; FJ, fluoro-jade; FPI, fluid percussion injury; HH, hemorrhagic hypotension; ICP, intracranial pressure; MAP, mean arterial pressure; MRI, magnetic resonance imaging; OCT, optimum cutting temperature (for embedding); PaCO2, partial pressure of carbon dioxide in arterial blood; PaO2, partial pressure of oxygen in arterial blood; PET, positron emission tomography; TBI, traumatic brain injury

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1. Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality of Americans both in the 15–25 age range and in the elderly population (Thurman et al., 1999). Experimental TBI also was associated with age-related increases in mortality (Hamm et al., 1991). Post-traumatic cerebral hypoperfusion appears to correlate with the severity of clinical TBI. Although in most patients, cerebral blood flow (CBF) is adequate for the reduced metabolic demands after TBI, there are patients in whom CBF is significantly reduced. Other groups have reported CBF values of less than 25 ml/min/100 g in patients in the first several hours after severe TBI (Bouma et al., 1991) and a subpopulation of very severely injured patients exhibited CBF levels of 15±9 ml/min/100 g (Bouma et al., 1992). Martin et al. observed cerebral hypoperfusion within the first 24 h, followed by hyperemia during days 1–3 and then vasospasm accompanied by hypoperfusion days 4–15 after severe head injury (Martin et al., 1997). Imaging studies using PET and MRI in TBI patients revealed significant increases in the numbers of ischemic brain regions in TBI patients (Coles et al., 2004). These results suggest that cerebral hypoperfusion may contribute to focal cerebral ischemia in at least some severely injured patients, a hypothesis supported by histopathologic evidence of ischemic neuronal injury in patients dying from severe TBI (Graham and Adams, 1971; Graham et al., 1989). Post-traumatic cerebral hypoperfusion correlated with worsened outcome in severe TBI patients (Hlatky et al., 2004), suggesting that posttraumatic hypoperfusion contributes to their impaired cognitive function. In addition, posttraumatic cerebral hypoperfusion may be exacerbated by reductions in systemic arterial pressure. Even mild arterial hypotension (systolic blood pressure 10–29 mm Hg below normal) was associated with significantly increased mortality after TBI (Chesnut et al., 1993; Miller, 1985).

Although CBF has been measured following experimental TBI (DeWitt et al., 1986; Lewelt et al., 1980) and hemorrhagic hypotension (HH) (Armstead, 2002; Matsushita et al., 2001; Prough et al., 2006), there are no comparable studies in aged rats. To address this gap, we measured CBF, intracranial pressure (ICP), blood gases and plasma glucose and examined neuronal injury in young adult and aged rats following fluid percussion injury (FPI) with or without HH and reinfusion of shed blood. This study was designed to test the hypothesis that, after FPI followed by HH and resuscitation, CBF would be significantly lower in aged compared with young rats.

2. Results

2.1. *Mean arterial pressure following fluid percussion injury and hemorrhage*

Mean arterial pressure at baseline did not differ among treatment groups. There were no age-related differences in MAP between rats subjected to either sham injury or moderate FPI only (Fig. 2A) for the duration of 90 min post-FPI. However, after moderate FPI+severe HH and resuscitation

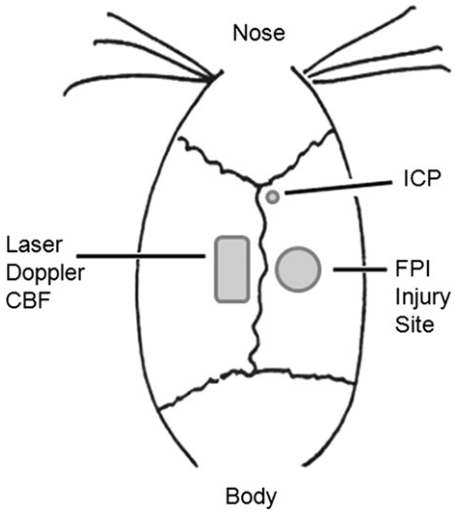

Fig. 1 – Drawing of injury site and probe placement.

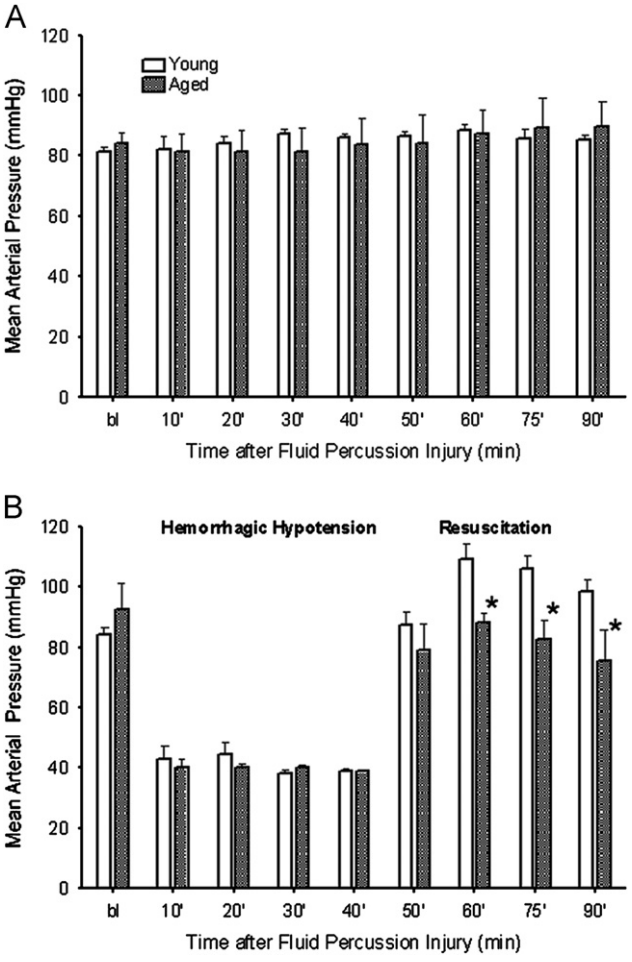

Fig. 2 – Mean arterial pressure in young and aged rats subjected to moderate FPI and severe hemorrhage. Mean arterial pressure (MAP) in young and aged rats after moderate FPI for 90 min post-FPI (A) and moderate FPI+severe HH for 45 min post-FPI followed by a 45-min resuscitation period (B). Data are expressed as mean±SEM and significance testing (*=$p<0.05$, compared to young) was performed using a t-test for the individual time points during the resuscitation phase.