Title: NEUROLOGICAL OUTCOME IN AGED RATS FOLLOWING REGIONAL CEREBRAL ISCHEMIA

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Clinical evidence suggests that aged patients have a poorer outcome and recovery following cerebral ischemia. However, these impressions are complicated by the lack of control over the ischemic challenge or subsequent anesthetic management in young vs old subjects. In these experiments we have compared the neurologic outcome of young and old rats with a model which produces regional cerebral ischemia by carotid ligation and hypotension (1).

Methods: Male Sprague-Dawley rats aged 4-5 months (young) and 27-28 months (old) were used here. These age groups correspond to a young adult and senescent rat respectively. Rats were anesthetized, intubated and ventilated with halothane in 30% oxygen, 70% nitrogen. Catheters were inserted in the right femoral artery and vein for pressure recording and drug infusions and the right subclavian vein for blood withdrawal. The right common carotid artery was isolated and a loose ligature placed around it for later clamping. At the completion of surgery the wounds were infiltrated with 0.5% bupivicaine and the inspired halothane concentration adjusted to 1.1% (1 MAC) for a 30 minute equilibration period. Vecuronium was administered as needed to maintain paralysis and rectal temperature stabilized at 37°C. After a 30 minute equilibration period the right carotid artery was clamped and hypotension induced by phlebotomy. Two graded ischemic challenges were induced in separate groups of young and old rats. Moderate ischemia was induced by maintaining the inspired oxygen concentration at 30% in nitrogen and maintaining a mean arterial blood pressure (MABP) at 30 mmHg for 30 minutes. Severe ischemia was produced by maintaining the inspired oxygen concentration at 20% and MABP at 25 mmHg for 30 minutes. Arterial PCO_2 was maintained at 35-40 mmHg by adjusting ventilation and normal pH was maintained by bicarbonate infusion. At the end of the hypotensive challenge the carotid artery was unclamped, the catheters removed, the incisions closed and the rat allowed to recover. Neurologic deficits were initially evaluated 3 hours after recovery and repeated for 3 days. Scores were rated as follows: 0 = normal, 1 = paw adduction or abnormal posturing, 2 = circling or rolling behavior marked by motor weakness or rigidity, 3 = stimulated seizure activity, 4 = unstimulated seizures, 5 = death associated with signs of stroke.

Results: No young rats died during the hypotensive period but 4 old rats died during hypotension or the recovery period. These deaths were frequently associated with some signs of respiratory distress. $PaCO_2$ was not significantly different between young and old rats. PaO_2 was 122 ± 7 (mean ± SE) and 98 ± 4 mmHg in young rats during ventilation with 30% and 20% respectively. In old rats PaO_2 averaged 87 ± 15 mmHg and 73 ± 6 mmHg during 30% and 20% O_2. Blood volumes withdrawn to produce each hypotensive level were as follows: moderate ischemia - young = 8.6 ± .5 ml (mean ± SE), old = 8.9 ± 1.4 ml (n=6); severe ischemia - young = 9.0 ± .3 ml (n=10), old = 10.0 ± 1.0 ml (n=6). The effect of regional ischemia on mortality and neurologic outcome is shown in Figure 1. As expected, the moderate ischemic episode produced less mortality and neurologic deficit in young and old rats than the more severe ischemic challenge. Both the mortality rate and the deficit score were higher in aged rats following both ischemic challenges.

Discussion: The model used in this study produces unilateral cerebral ischemic due to carotid ligation and hypotension which provide preferential perfusion of one hemisphere. Signs of stroke developed progressively in these rats and usually reached a maximum on the second day post-challenge. It is apparent from Figure 1 that the severity of stroke was dependent both on the degree of ischemia produced and the age of the rat. It is likely that the degree of hypotension, the limitation of oxygen availability and possibly an inadequate cerebrovascular response in the aged may have contributed to these differences. This is consistent with an earlier report which indicates that the aged cerebrovascular system shows an inadequate response only when an hypoxic challenge is severe (2).

References:

1. Mendelow AD, et al: The distribution of ischemic damage and CBF after unilateral carotid occlusion and hypotension in the rat. Stroke 1984; 15:704.
2. Hoffman WE, Pelligrino DA, Miletich DJ, and Albrecht RF: Brain metabolic changes in young vs aged rats during hypoxia. Stroke 1985; 16:860.

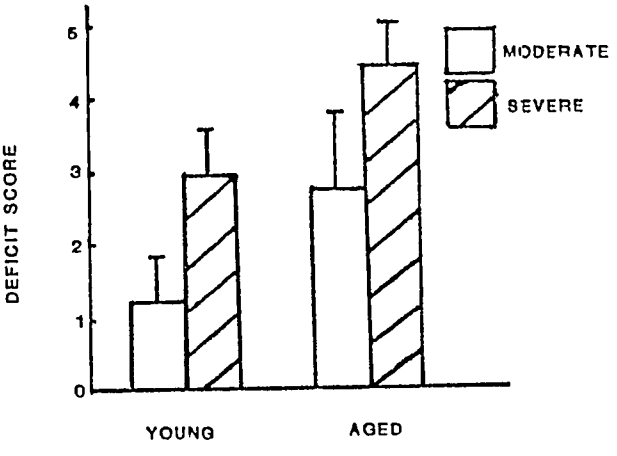

Figure 1. Deficit scores in young and old rats during regional cerebral ischemia. Old rats had higher deficit scores during both moderate and severe ischemia. Percent mortality was also greater in old vs. young rats. Moderate ischemia young = 16%, old = 50%; severe ischemia - young = 40%, old = 83%.