Research Highlight

Differences in stroke damage in aged mice may not be due to differential cerebral blood flow dynamics

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INTRODUCTION

Stroke is the leading cause of death and adult disability.[1-3] Aging is the most important nonmodifiable risk factor for stroke, and aged patients exhibit impaired stroke recovery.[4] Consistent with clinical data, findings from animal models have demonstrated that aged mice have higher mortality and worse outcomes when subjected to same duration of occlusion compared with young mice, yet paradoxically, the infarct damage is smaller in the aged mice.[5,6] Impaired recovery has been linked to several underlying mechanisms, including altered peripheral immune responses, enhanced neuroinflammation, and reductions in neurogenesis.[7-9] However, it was not known whether the discrepancy in histological outcome is associated with age-induced changes in the cerebral vasculature or cerebral blood flow.

Consistent blockage of blood flow is essential to achieve a homogenous ischemic infarct. Previous animal studies use laser Doppler flowmetry (LDF) to confirm blood flow blockage after ischemic occlusion. However, this technique has often been criticized as it not quantitative and only examines blood flow changes in a small region of the brain. As aging leads to several morphological and pathological changes throughout the vasculature, leading to atherosclerosis and small vessel disease, these changes cannot be identified by LDF. These alterations might contribute to significant stroke damage variability in aged animals. Unlike LDF, laser speckle flowmetry (LSF) provides a broader spatial, and temporal pattern of blood flow changes in the brain, allowing investigators to better examine and control cerebral blood flow changes during and following occlusion.

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COMMENT

To determine if the discrepancies in histological outcomes in aged mice were secondary to variability or differences in blood flow dynamics, we first assessed whether aged mice exhibited differential blood flow patterns after stroke compared to young mice using LSF. A structural immunohistochemical analysis of the vasculature was also performed by perfusing blood vessels with fluorescein isothiocyanate-dextran and co-labeling with the CD31 antibody. No significant difference in blood flow dynamics or microvascular density was observed between young (3-month-old) and aged (18-month-old) animals after middle cerebral artery occlusion (MCAO).

Although these results refute the hypothesis that changes in cerebral blood flow or vascular density was responsible for the smaller infarcts in aged mice, the study has provided some very interesting findings. Based on the LSF data, focal ischemia during MCAO induced a dramatic blood flow drop to the ipsilateral hemisphere as expected, but it was also associated with

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reduced blood flow in the contralateral hemisphere. This is an interesting observation as it suggests that even a focal ischemic stroke induces changes throughout the brain.

To further assess, the underlying mechanisms of smaller infarcts seen in aged mice, we investigated differences in blood-brain barrier breakdown after stroke. Somewhat surprisingly, IgG extravasation at both 24 h and 72 h after stroke was lower in aged mice compared with young mice, which likely correlated with the existence of smaller infarcts.

Despite some limitations, this is a very interesting study as it is the first to utilize LSF to investigate blood flow changes in aged animals. The mechanism responsible for the higher mortality and poorer recovery seen in aged and elderly animals remain a mystery. Age-related changes in neuroinflammation and the immune response to stroke are areas under intense investigation by a number of researchers and will hopefully be answered in the future.

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