

Both cerebrovascular and cardiac reactivity are impaired in a preclinical model of vascular cognitive impairment and dementia



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Take home message: Functional impairments in reactivity and multi-organ dysfunction could be early, significant translational biomarkers of VCID.

Introduction	Methods	Results
- Vascular cognitive impairment and dementia (VCID) is a leading cause of disability characterised by impaired cerebral blood flow (CBF). - One preclinical model of VCID, is the hyperhomocysteinemia (HHcy) induced mouse model. - HHcy is a clinical condition associated with dementia, stroke and myocardial infarction risk ^{1,2}. In the diet-based mouse model used in this study, it induces microbleeds, cognitive impairment and decreased CBF ^{3,4}. Study aim: to characterise both cerebrovascular and cardiac function and reactivity in this model for the first time, using preclinical MRI.	Animals: C57BL/6 (3-month-old) Diet inducing HHcy (TD.130867, Inotiv, US) Control diet HHcy diet 15 weeks Neuroimaging 0.8mg/kg medetomidine + 0.5% isoflurane in 0.8 L/min room air - Arterial spin labelling MRI : cerebral blood flow + cerebrovascular reactivity challenge of 10% CO₂ for 5 min Cardiac imaging 2% isoflurane in 1L/min O₂ - Electrocardiogram-triggered cine-MRI with a cardiac challenge: 1.5mg/kg dobutamine hydrochloride, imaged after 30min Behaviour Open field + Neuroscore 5 min exploratory behaviour Novel object recognition 4 hours post-familiar object adaptation Nesting Nest building over 3 hours Marble burying 10 marbles, 15 min interaction	Neuroimaging A Cerebral blood flow (CBF) was not affected by the HHcy-diet. B Hypercapnia (which increases global CBF) increased cortical CBF following 10% CO₂ inhalation at 5 min. The HHcy-diet significantly decreased this response compared to mice on the control diet, mean area under the curve represented in (C). Two-tailed t-tests, error bars show ±SEM, * indicates p<0.05. Cardiac imaging A The effect of β-adrenoceptor agonist dobutamine was significantly decreased on cardiac ejection fraction (A) and stroke volume (B) in mice on the HHcy-diet compared to control. Two-tailed t-tests, error bars show ±SEM, ** indicates p<0.01, * indicates p<0.05. Behaviour A Behaviour tests identified significant deficits in mice on the HHcy-diet through neuroscore as assessed by a modified De Simoni test⁵ (A), and marble burying (B), which assess compulsive traits and anxiety. No differences were found through anxiety and memory tests through open field (C), novel object recognition (D) and nesting tests (E). Two-tailed t-tests, all error bars show ±SEM, * indicates p<0.05. Conclusion Although the HHcy inducing diet did not lead to changes in basal CBF or cardiac function, a decreased response to reactivity challenges in both the brain and heart were found. These functional changes could precede further cognitive deficits and traditional measures of pathology. References 1. Bots, M.L. et al. (1999), Archives of internal medicine, 159(1); 2. Carey, A. and Fossati, S. (2023), Alzheimer’s and Dementia, 19(2), pp. 671–695, 3. Braun, D.J. et al. (2019), ASN Neuro, 11;. 4. Weekman, E.M. et al. (2023), Journal of Neuroinflammation, 20(1), p. 199, 5. Donath, S. et al (2016), Journal of Neuroscience, 36(31), 8132–8148.