Scottish Government Health Directorates Chief Scientist Office

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Non-invasive measurement of cerebrovascular reactivity and compliance in cerebral small vessel disease: feasibility and estimation of sample size for translational research and clinical trials.

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Aim to set up practical versions of two magnetic resonance (MR) brain scanning techniques to detect how well the small brain blood vessels were functioning (small vessel disease, SVD). We hoped to use measures of small vessel function in drug trials and studies to understand what goes wrong with the small brain blood vessels. We

Project Outline/Methodology We recruited patients who had had a stroke of the small vessels ('lacunar stroke') and performed MR scanning of the brain while the patients breathed normal air alternately with 6% carbon dioxide (CO2). The 6% CO2 makes the small blood vessels open up to increase blood flow to the brain and this can be measured by the scanner. In the first 10 patients, some patients breathed 4% and some 6% CO2 to see which gave the best signal and was best tolerated. The 6% gave better signal and was just as well tolperated as the 4%, so we used 6% therafter. On the same scan, we also measured the rate at which each heart beat passed through the brain from arteries to veins.
We also recorded blood pressure (6 times), took pictures of the blood vessels at the back of the eye while breathing air and CO2, assessed the carotid arteries in the neck and the stiffness of the arteries to the arms. The measurements were all completed in a 2-hour visit to the scanner. We asked the patients for their opinions about the procedures. We scanned all of the patients on a 1.5T MR scanner and a third of the patients were also scanned on a 3T scanner.
We measured the volume of the brain and of the visible SVD damage (white matter hyperintensities, WMH) using image analysis methods. We grouped the patients according to the amount of visible damage from SVD for statistical analysis.

Key Results We recruited and scanned 60 patients, mean age 67.8, SD 8.3, and obtained usable CO2 data on 52. No patients had problems breathing the 6% CO2 but four patients were claustrophobic (less than the usual rate for clinical indications).
The small vessel function (opening up when breathing 6% CO2) was higher in grey matter than white matter, declined with increasing age, with increased pulse pressure, carotid artery stiffness and arm blood vessel stiffness. The small vessel function also declined as evidence of damage from small vessel disease in the brain increased: as the amount of WMH increased, the small vessel function decreased in the white matter, independently of age, and blood pressure. The effect was most pronounced in the main white matter areas in the brain where the small vessel damage is commonly seen. There was little variation with increasing WMH in small vessel function in the grey matter.
We found that the stiffness in the brain increased as the amount of WMH increased.We did not see any effect of the breathing CO2 on the blood vessels at the back of the eye. We found that carotid artery stiffness measured with the easy to use ultrasound was highly consistent with stiffness measured by MR. The data provided valuable estimates of sample size for a variety of studies. Analysis of data from 3T and of tissue-level vessel function is ongoing.

Conclusions Patients tolerated this rather complex and lengthy procedure very well with few failures. Therefore the technique is suitable for use in early phase clinical trials. Vessel function declines with small vessel damage but this study does not tell us which occurs first.

What does this study add to the field? The project provides a reliable, practical and well tolerated method for assessing small vessel function, with effect size data and has already informed the design of two other funded studies.

Implications for Practice or Policy

Where to next? The method is being used to assess drug efficacy in the Lacunar Intervention Trial 1 (LACI-1) and will be used in two studies in the European Union-funded programme, SVDs@TARGET.

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