

Intensive Blood Pressure Lowering increases Cerebral Blood Flow in Older Subjects with Hypertension

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Introduction: Cerebral Blood Flow (CBF) is the key determinant of brain tissue metabolic supply, and is regulated by changes in calibre of small arteries to sustain brain perfusion across a range of blood pressure (BP). Hypertension leads to structural vascular adaptation with remodelling and hypertrophy resulting in arteriolar luminal narrowing and wall thickening, eventually compromising CBF. Hypertension leads to a rightward shift in the autoregulatory curve with an increased lower and upper limit preventing hyperperfusion but placing the brain at risk of hypoperfusion when hypotension occurs. Although BP lowering is highly effective at reducing the risk of stroke and myocardial infarction in older people, the optimal BP target in older subjects with hypertension is unclear. The studies providing evidence of benefit of BP lowering in older people mostly recruited subjects with systolic BP >160 mmHg and the evidence base for treating older patients with systolic BP in the range 140-160 mmHg is limited. Most guidelines recommend a target BP of <140/85 mmHg for hypertensive patients without previous vascular events and a target of <130/80 mmHg in patients with diabetes or previous vascular events. However BP lowering in older hypertensive patients may precipitate syncope and falls. Few studies have examined the effect of different target BP on CBF to determine whether BP lowering reduces or increases CBF in older people. In this work, we used Arterial Spin Labelling (ASL) to determine the effect of usual (< 140/85 mm Hg) and intensive (< 130/80 mm Hg) BP lowering on CBF in older subjects with hypertension and demonstrate that more intensive BP lowering increases CBF compared to usual BP lowering therapy.

Methods:

Subjects: Patients (>70 years) with uncontrolled systolic hypertension (>150 mmHg) on one or no BP lowering drugs were recruited. Subjects were excluded if they had short life expectancy, diabetes, recurrent falls, contraindication to more than one antihypertensive medications, previous stroke, myocardial infarction, angina, peripheral vascular disease, cognitive impairment (MMSE <27) or contraindication to MRI. Patients were randomised using a web based system to receive either intensive or usual treatment for 12 weeks.

BP Monitoring: Subjects were reviewed every 2 weeks, during which BP was recorded as the average of the second and third of three seated BP measurements taken in the left arm at intervals of 5 min. In the usual treatment group BP lowering therapy was increased at 6 weeks if BP readings averaged over the previous 6 weeks were >140/85 mmHg. In the intensive treatment group BP therapy was increased at two weekly intervals if BP readings were >130/80 mmHg.

MR Experiments: MR imaging was obtained on a 3T whole body Philips Achieva System (Philips Medical Systems, Best, Netherlands) using an 8 channel head coil. A T₁ weighted anatomical volume with 1 mm isotropic resolution was collected (3D MPRAGE, TE/TR 4.6/9.6ms, 240 x 240 x 180 mm³ FOV). CBF was measured in 12 slices using a FAIR [1] sequence with GE EPI readout. To avoid contrast reduction data were acquired in 3 contiguous segments with identical protocols. Each protocol contained 4 contiguous slices of 6 mm thickness, with FOV 256x256 mm², matrix size 64x64, 40 pairs, TE/TR = 26/4000 ms, inflow time 1700 ms, inversion width 48 mm and 10 ms bulk flow crusher of 14 mT/m on each axis. Quantitative T₁ maps were collected using a fast T₁ mapping Inversion Recovery (IR) sequence with GE EPI readout covering 72 transverse slices (2mm thickness, 4x4 mm² in-plane resolution, FOV 256x256 mm², TE/TR 23ms/15s). The IR curve was sampled at 12 Inversion Times (TI) beginning at 208ms and incrementing by 208 ms. The anatomical, ASL and T₁ mapping protocols were performed for each subject at 0 and 12 weeks.

Data Analysis: The ASL images were motion corrected (AIR 5.2.5) and split into tag and control image sets. The difference image dM was generated by taking the difference between the 2 sets, and magnitude image M obtained by averaging the 2 sets. Results for each segment were spatially concatenated to form dM and M volumes for each examination. T₁ maps were generated by 3 parameter fitting (T₁, M₀ and effective inversion angle) of the interrogated IR curve to the Bloch equation on a pixel by pixel basis. The anatomical images were registered into MNI space, and segmented to provide gray matter masks. The dM, M and T₁ maps were subsequently transformed into MNI space via corresponding coregistration with anatomical images. Predefined standard ROIs in MarsBaR [2] were modified to combine bilateral regions into single ROI and further masked by gray matter. The resultant ROIs and the whole gray matter ROI were applied to the T₁, dM, M and M₀ images to extract the corresponding mean value within the ROI. The CBF value in the ROI was subsequently computed based assuming blood T₁ of 1550 ms and the blood brain partition coefficient of 0.9 ml/g.

Results and Conclusions: BP fell by 26±14 / 17±9 mmHg in the intensive group and 15±14 / 5±7 mmHg in the usual BP lowering group; P=0.018 for comparison between groups. Intensive but not usual BP lowering treatment was associated with a global increase in CBF; intensive treatment (6.9±11 ml/min/100g), usual BP lowering (-2.8±9 ml/min/100g). CBF before and after treatment are shown in Fig 1 (whole grey matter) and 2 (each ROI averaged within the group), with usual treatment group marked blue and intensive treatment group marked red. The regression lines are added for each group in corresponding colour.

Discussion: Our findings suggest that the hypertension in older people is associated with a shift of the cerebral autoregulation curve to the right but also downwards and that this change is reversible by intensive BP lowering. The increase in CBF might protect against cerebral atrophy associated with hypertension. If the increase in CBF with BP lowering occurs in white matter this might reduce the risk of developing white matter lesions which are related to hypoperfusion at end of arteries in white matter. Our data suggest intensive BP lowering in older people is unlikely to substantially increase the risk of hypoperfusion syndromes.

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References: [1] Kim SG, 1995; [2] Tzourio-Mazoyer et al, 2002

Fig 1: CBF over 12 weeks across subjects

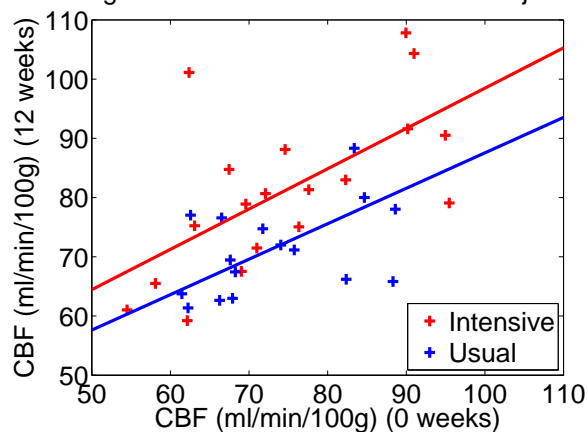


Fig 2: CBF over 12 weeks across ROIs

