

MRI measurement of transmission of arterial pulsation to the brain on propranolol versus amlodipine

Alastair JS Webb DPhil, Peter M Rothwell FMedSci

Authors:

*Dr AJS Webb, Stroke Prevention Research Unit (SPRU)

alastair.webb@ndcn.ox.ac.uk

Prof PM Rothwell, SPRU

peter.rothwell@ndcn.ox.ac.uk

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Correspondence

Dr AJS Webb

SPRU

John Radcliffe Hospital

Oxford OX39DU

United Kingdom

TEL:(44)1865231610

Abstract

BACKGROUND AND PURPOSE: Cerebral arterial pulsatility is associated with leukoaraiosis and depends upon central arterial pulsatility and arterial stiffness. The effect of antihypertensive drugs on transmission of central arterial pulsatility to the cerebral circulation is unknown, partly due to limited methods of assessment.

METHODS: In a technique-development pilot study, 10 healthy volunteers were randomised to crossover treatment with amlodipine and propranolol. At baseline and on each drug, we assessed aortic (Sphygmocor) and middle cerebral artery pulsatility (TCDtranscranial ultrasound). We also performed whole-brain, 3-tesla multiband BOLD-MRI (MB factor 6, TR=0.43s), concurrent with a novel method of continuous non-invasive BP monitoring. Drug effects on relationships between cardiac cycle variation in BP and BOLD were determined (FEAT-FSL).

RESULTS: Aortic pulsatility was similar on amlodipine (27.3mmHg) and propranolol (27.9mmHg, p-diff=0.33) whilst MCA pulsatility increased non-significantly more from baseline on propranolol (+6%, p=0.09) than amlodipine (+1.5%,p=0.58). On MRI, cardiac frequency BP variations were significantly more strongly associated with BOLD on propranolol than amlodipine.

CONCLUSIONS: We piloted a novel method of assessment of arterial pulsatility with concurrent high-frequency BOLD-MRI and non-invasive BP monitoring. This method was able to identify greater transmission of aortic pulsation on propranolol than amlodipine, which warrants further investigation.

Introduction

Cerebral arterial pulsatility is associated with white matter hyperintensities¹ and cognitive decline² and largely determined by central arterial pulsatility and arterial stiffness.¹ No therapies have been specifically developed to affect cerebral arterial pulsatility, but such effects may explain the greater reduction in stroke risk with calcium channel blockers than beta-blockers, despite similar BP reductions.³⁻⁴

Cerebral arterial pulsatility is usually measured by transcranial Doppler (TCD),⁵ with good temporal but limited spatial resolution whilst current MRI sequences have good spatial but limited temporal resolution. Furthermore, there are practical difficulties in continuous blood pressure (BP) measurement during MRI. We piloted a novel method of continuous BP measurement during high-temporal resolution MRI (multiband-BOLD),^{6,7} and determined its potential utility by assessing transmission of arterial pulsations on amlodipine versus propranolol.

Methods

10 healthy adult subjects were randomised (according to CAMARADES recommendations for non-clinical studies⁸) to 1 week of daily amlodipine 10mg or Propranolol-LA 160mg in a crossover design, with a 2-week washout. This physiological protocol was assessed by the Medicines and Healthcare products Regulatory Authority. At baseline and on each drug, carotid-femoral pulse wave velocity (cfPWV) and aortic BP (Sphygmocor) were measured.¹ Transcranial Doppler ultrasound (TCD, DWL-Doppler Box) was performed with a handheld 2MHz probe on the same side as carotid applanation, at 50mm or the depth of the optimal waveform. Gosling's pulsatility index ($MCA-PI = (systolic\ CBFV - diastolic\ CBFV) / mean\ CBFV$) and MCA transit time were calculated.¹ All waveforms were visually inspected.

On a 3T Siemens Verio scanner, a volume-acquisition T1 MPR (1.5x1.5x1.5mm voxels) and a 12 minute multiband BOLD-MRI (multiband factor=6, 30 slices, 3x3x3mm voxels, TE=40ms, TR=0.43s, Supplemental Figure I)⁶⁻⁷ were acquired. Continuous, non-invasive brachial BP

was simultaneously acquired by a novel method (figure 1). Cardiac cycles were marked at the maximum of the second differential of BP.

Multiband BOLD sequences were motion corrected (MCFLIRT-FSL) to a presaturated BOLD volume, spatially smoothed (FEAT-FSL⁹), registered to T1 (FNIRT-FSL⁹), and then the MNI-152 brain for group analysis (FNIRT-FSL⁹). Non-physiological artefactual components were identified and removed manually by independent component analysis.⁹ Voxel-to-voxel differences in pulse arrival time were measured by event-related summation of each timeseries to the peripheral BP marker (figure 2), phase-shifting voxels by differences in peak arrival time with interpolation by piecewise cubic hermitte interpolation.

For each voxel, power spectra (Welch, 350 volume segments, 50% overlap, nfft 512 volumes) and mean-squared coherence with BP were derived. Correlation between cardiac frequency BP and BOLD signal were determined on each treatment and compared between treatments (FSL-FEAT).

Results

Of 5 men and 5 women (median age=29, range=18-41) recruited, all completed the protocol, half receiving amlodipine first. Both drugs reduced aortic BP, pulsatility and PWV and cerebral blood flow velocity similarly (Table 1), although MCA-PI increased non-significantly more with propranolol.

The coherence (frequency-specific relationship) between the BOLD signal and the peripheral BP at the cardiac cycle frequency was greatest in the ventricles and venous sinuses, but was also present throughout grey matter. Averaging BOLD responses for each voxel across all cardiac cycles produced identifiable arterial waveforms (figure 1). The peripheral cardiac cycle frequency BP waveform was more strongly associated with BOLD signal in grey matter on propranolol than amlodipine (figure 2). This was unchanged when excluding individual subjects from the analysis.

Discussion

We simultaneously acquired non-invasive, continuous BP and high-frequency BOLD MRI, demonstrating a direct relationship at the frequency of the cardiac cycle. This relationship was stronger on propranolol than amlodipine, despite similar effects on aortic BP and pulsatility.

Cerebral artery pulsatility is associated with chronic white matter disease,^{1,3} potentially due to increased transmission of aortic pulsatility to the brain through stiff vessels.¹ However, investigation of dynamic cerebral blood flow changes is limited by poor temporal resolution of standard MRI sequences, low spatial resolution of TCD and practical difficulties in continuous BP measurement during MRI scanning. We used a recently-developed high-frequency MRI sequence,⁶⁻⁷ and developed a novel method of concurrent, continuous BP monitoring. With refinement, this technique could allow detailed assessment of transmission of rapid fluctuations in systemic BP on region-specific cerebral blood flow. Indeed, we found a stronger association with the cardiac cycle waveform on propranolol than on amlodipine. This may reflect less dampening of systemic BP which could expose the brain to greater arterial pulsatility. This is a potential explanation for differences in cerebrovascular physiology and stroke risk between the two drugs^{4-5,10} that warrants further investigation.

Our study has a number of limitations. Firstly, subjects were healthy volunteers with less arteriopathy than more elderly patients at a greater risk of stroke. As such, the effects of drugs in this study can not be extrapolated to clinical populations. Secondly, BOLD is affected by blood flow, blood oxygenation and blood volume. However, the associations we demonstrated with cardiac frequency BP variation reflect BOLD variation at a higher frequency than neurovascular coupling and is therefore likely to be dependent primarily upon blood flow. Thirdly, the BP measurement method is susceptible to artefactual slow drifts in BP, which were filtered out offline. This has minimal impact upon the high-frequency BP fluctuations we addressed, but limits the technique for investigating slower fluctuations in BP. Fourthly, the stronger association between cardiac cycle frequency BP fluctuations and the BOLD signal

on propranolol superficially follows a different pattern to the distribution of greatest cerebral pulsation, likely reflecting highest absolute brain perfusion in the grey matter, and limiting the sensitivity of the analysis for effects on white matter perfusion. This may reflect correlations between BP and BOLD not directly dependent upon the magnitude of BP pulsatility but this pattern of cerebral pulsation has also been demonstrated using a surrogate of peripheral BP.¹¹ Finally, given a TR=0.43, heart rates above 70bpm result in aliasing of the cardiac pulsation. Only one subject had an excess mean resting heart rate and excluding this individual did not alter the results (data not shown). However, in a broader population multiband imaging with a shorter TR¹¹ would limit aliasing.

We piloted a novel method of concurrent, continuous non-invasive BP measurement during high-frequency BOLD MRI to assess transmission of arterial pulsatility to the brain, demonstrating a stronger association on propranolol than amlodipine. This needs further development but with refinement could enable systematic MRI-based assessment of rapid BP fluctuations effects on the cerebral circulation.

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Disclosures: The multiband-BOLD pulse sequence was used under an agreement with the sequence developers at the University of Minnesota.

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Figure 1. Methodology. A) Brachial BP cuffs on each arm are sequentially inflated to ~10mmHg above DBP (balancing comfort and optimisation of the waveform) via semi-rigid plastic tubing. The two transduced waveforms are high-pass filtered ($>0.04\text{Hz}$), calibrated to contralateral oscillometric BPs in the non-monitored arm, weighted with a triangular-window during overlaps and summed. B) Examples of BP and BOLD voxel time series, showing arterial pulsations in ventricles and grey matter.

Figure 2 Associations between multiband BOLD signal and peripheral arterial pulsation. A) Coherence map and cardiac cycle-averaged BOLD responses. B-D) Z-statistics from general linear modelling are shown for Amlodipine, Propranolol and for voxels with stronger associations (corrected cluster $p < 0.05$) on propranolol versus amlodipine respectively.

Table 1. Physiological indices

Measure	Baseline	Amlodipine		Propranolol		Difference	
		Value	p	Value	p	Value	p
Aortic:							
SBP (mmHg)	96.6	91.6	0.01*	91.2	0.002*	0.4	0.76
DBP (mmHg)	69.5	64.3	0.002*	63.3	<0.001*	1.0	0.48
Pulse pressure	27.1	27.3	0.88	27.9	0.49	0.6	0.67
PWV (m/s)	5.5	5.3	0.15	5.2	0.03*	0.1	0.66
Mean MCA:							
Transit time	172	154	0.03*	174	0.91	19.6	0.26
Peak Velocity	93.1	93.2	0.98	89.1	0.55	4	0.20
Trough Velocity	50.0	49.6	0.90	46.6	0.31	3.1	0.06
Pulsatility Index	0.67	0.68	0.58	0.71	0.09	0.02	0.25