Magnetic Resonance Imaging Measurement of Transmission of Arterial Pulsation to the Brain on Propranolol Versus Amlodipine

Alastair J.S. Webb, DPhil; Peter M. Rothwell, FMedSci

Background and Purpose—Cerebral arterial pulsatility is associated with leukoaraiosis and depends on central arterial pulsatility and arterial stiffness. The effect of antihypertensive drugs on transmission of central arterial pulsatility to the cerebral circulation is unknown, partly because of limited methods of assessment.

Methods—In a technique-development pilot study, 10 healthy volunteers were randomized to crossover treatment with amlodipine and propranolol. At baseline and on each drug, we assessed aortic (Sphygmocor) and middle cerebral artery pulsatility (TCD transcranial ultrasound). We also performed whole-brain, 3-tesla multiband blood-oxygen level dependent magnetic resonance imaging (multiband factor 6, repetition time=0.43 s), concurrent with a novel method of continuous noninvasive blood pressure monitoring. Drug effects on relationships between cardiac cycle variation in blood pressure and blood-oxygen level dependent imaging were determined (fMRI Expert Analysis Tool, fMRIB Software Library [FEAT-FSL]).

Results—Aortic pulsatility was similar on amlodipine (27.3 mm Hg) and propranolol (27.9 mm Hg, P diff =0.33), while MCA pulsatility increased nonsignificantly more from baseline on propranolol (+6%; P=0.09) than amlodipine (+1.5%; P=0.58). On magnetic resonance imaging, cardiac frequency blood pressure variations were found to be significantly more strongly associated with blood-oxygen level dependent imaging on propranolol than amlodipine.

Conclusions—We piloted a novel method of assessment of arterial pulsatility with concurrent high-frequency blood-oxygen level dependent magnetic resonance imaging and noninvasive blood pressure monitoring. This method was able to identify greater transmission of aortic pulsation on propranolol than amlodipine, which warrants further investigation. (Stroke. 2016;47:1669-1672. DOI: 10.1161/STROKEAHA.115.012411.)

Key Words: amlodipine ■ blood pressure ■ central arterial pulsatility ■ MRI ■ stroke

Cerebral arterial pulsatility is associated with white matter hyperintensities1 and cognitive decline2 and is largely determined by central arterial pulsatility and arterial stiffness.3 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 β-blockers, despite similar blood pressure (BP) reductions.3,4

Cerebral arterial pulsatility is usually measured by transcranial Doppler,5 with good temporal but limited spatial resolution, whereas current magnetic resonance imaging (MRI) sequences have good spatial but limited temporal resolution. Furthermore, there are practical difficulties in continuous BP measurement during MRI. We piloted a novel method of continuous BP measurement during high temporal resolution MRI (multi-band–blood-oxygen level dependent imaging [MB-BOLD])6,7 and determined its potential utility by assessing transmission of arterial pulsations on amlodipine versus propranolol.

Methods

Ten healthy adult subjects were randomized (according to CAMARADES recommendations for nonclinical studies8) to 1 week of daily amlodipine 10 mg or propranolol-LA 160 mg in a cross-over 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 and aortic BP (Sphygmocor) were measured.1 Transcranial Doppler ultrasound (DWL-Doppler Box) was performed with a handheld 2 MHz probe on the same side as carotid applanation, at 50 mm or at the depth of the optimal waveform. Gosling’s pulsatility index (middle cerebral artery–pulsatility index, MCA-PI=(systolic cerebral blood flow velocity–diastolic cerebral blood flow velocity)/mean cerebral blood flow velocity) and MCA transit time were calculated.1 All waveforms were visually inspected.

On a 3T Siemens Verio scanner, a volume-acquisition T1 multiplanar reconstruction (1.5×1.5×1.5 mm voxels) and a 12-minute multi-band BOLD-MRI (multiband factor=6, 30 slices, 3×3×3 mm voxels, echo time=40 ms, repetition time=0.43 s; Figure I in the online-only Data Supplement)9,10 were acquired. Continuous, noninvasive 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 (motion correction FMRIB linear image registration tool [MCFLIRT]-FSL) to a presaturated BOLD volume, spatially smoothed (fMRI Expert Analysis Tool, fMRIB Software Library [FEAT-FSL]), registered to T1 (FMRIB non-linear image registration tool [FNIRT]-FSL), and then the MNI-152 brain for group analysis (FNIRT-FSL). Nonphysiological artefactual components were identified and removed manually by independent component analysis. Voxel-to-voxel differences in pulse arrival time were measured by event-related summation of each time series to the peripheral BP marker (Figure 2), phase shifting voxels by differences in peak arrival time with interpolation by piecewise cubic hermite 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 was 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.

Figure 1. Methodology. A, Brachial blood pressure (BP) cuffs on each arm are sequentially inflated to ≈10 mm Hg above diastolic blood pressure (DBP; balancing comfort and optimization of the waveform) via semirigid plastic tubing. The 2 transduced waveforms are high-pass filtered (>0.04 Hz), calibrated to contralateral oscillometric BPs in the nonmonitored arm, weighted with a triangular window during overlaps, and summed. B, Examples of BP and blood-oxygen level dependent imaging (BOLD) voxel time series, showing arterial pulsations in ventricles and gray matter. MRI indicates magnetic resonance imaging.

Figure 2. Associations between multiband BOLD signal and peripheral arterial pulsation. A, Coherence map and cardiac cycle-averaged blood-oxygen level dependent imaging (BOLD) responses. B–D, Z-statistics from general linear modeling are shown for amlodipine, propranolol, and voxels with stronger associations (corrected cluster P<0.05) on propranolol versus amlodipine, respectively.
Both drugs reduced aortic BP, pulsatility and pulse wave velocity, and cerebral blood flow velocity similarly (Table), although MCA-PI increased nonsignificantly 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 gray 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 gray matter on propranolol than amlodipine (Figure 2). This was unchanged when excluding individual subjects from the analysis.

**Discussion**

We simultaneously acquired noninvasive, 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, potentially because of increased transmission of aortic pulsatility to the brain through stiff vessels. However, investigation of dynamic cerebral blood flow changes is limited by poor temporal resolution of standard MRI sequences, low spatial resolution of transcranial Doppler, and practical difficulties in continuous BP measurement during MRI scanning. We used a recently developed high-frequency MRI sequence 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 exposes the brain to greater arterial pulsatility. This is a potential explanation for differences in cerebrovascular physiology and stroke risk between the 2 drugs that warrants further investigation.

Our study has several limitations. First, 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 cannot be extrapolated to clinical populations. Second, 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 on blood flow. Third, the BP measurement method is susceptible to artefactual slow drifts in BP, which were filtered out offline. This has minimal impact on the high-frequency BP fluctuations we addressed, but limits the technique for investigating slower fluctuations in BP. Fourth, 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 gray 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 on the magnitude of BP pulsatility, but this pattern of cerebral pulsation has also been demonstrated using a surrogate of peripheral BP. Finally, given a repetition time=0.43, heart rates above 70 bpm 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 TR would limit aliasing.

We piloted a novel method of concurrent, continuous noninvasive 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. The authors report no conflicts.

**References**
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SUPPLEMENTAL MATERIAL

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

AJS Webb, PM Rothwell
Supplemental Figure I. Multiplexed-EPI pulse sequence illustration. (Left) multiband RF pulse composed of 3 single band RF pulses that have frequency offsets among them. (Upper right) two multiband RF pulses that run sequentially with a readout gradient between them to separate the echoes as in the SIR technique. Extra gradients in the slice direction were added at the same time as the phase-encoding gradient to modulate the phase of multiple slices that were simultaneously excited by the multiband RF to help to separate the slices, as in the blipped controlled aliasing technique. (Lower right) the sum of 3 slices acquired with FOV/3 shift between the slices and the same images separated.

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磁共振成像测定比较普萘洛尔与氨氯地平对动脉搏动向脑传递的影响

Magnetic Resonance Imaging Measurement of Transmission of Arterial Pulsation to the Brain on Propranolol Versus Amlodipine

(Stroke. 2016;47:1669-1672. 河北医科大学附属唐山工人医院神经内科 李欣 杨富玲 译 曹亦宾 校)

Alastair J.S. Webb, DPhil; Peter M. Rothwell, FMedSci

背景和目的：脑动脉搏动取决于中心动脉搏动和动脉僵硬度，与脑白质疏松有关。降压药物对中心动脉搏动向脑循环传递的影响尚不清楚，部分原因是因为评估方法有限。

方法：在一项技术开发试点研究中，10名健康志愿者被随机分到氨氯地平组和普萘洛尔组的交叉治疗组。在基线和接受每种药物治疗时，评估中心动脉搏动（无创中心脉波分析仪）和大脑中动脉的搏动（经颅超声）。我们也做了全长3.0T 多频段血氧水平依赖磁共振成像（多频段系数6，重复时间 =0.43 s），同时采用一种新方法进行持续的无创血压监测。测定了药物对心动周期血压变异与血氧水平依赖磁共振成像之间相关关系的影响（fMRI 专家分析工具，fMRIB 软件库）。

结果：主动脉搏动在服药期间变化不大（27.3 mmHg vs. 27.9 mmHg, P diff=0.33）是相似的，然而大脑中动脉搏动在服用普萘洛尔时的基线增加值（+6%；P=0.09）显著高于服用氨氯地平时（+1.5%；P=0.58）。在磁共振成像上，发现心脏周期血压变异与血氧水平依赖磁共振成像之间关系在服用普萘洛尔时比服用氨氯地平时更密切。

结论：我们初步研究了一种以高时间分辨率磁共振成像与无创血压监测方式评估动脉搏动传递的新方法。这种方法成功确定了对主动脉搏动的传递影响，普萘洛尔大于氨氯地平，这结论还需要进一步研究证实。

关键词：氨氯地平；血压；中心动脉搏动；磁共振；卒中

方法

按照交叉设计，10名健康成年受试者被随机分配（根据CAMARADES关于非临床研究的建议）到每天氨氯地平 10 mg 组或普萘洛尔-LA 160 mg 组，疗程 1 周，中间有 2 周的洗脱期。这个背景和目的：脑动脉搏动取决于中心动脉搏动和动脉僵硬度，与脑白质疏松有关。降压药物对中心动脉搏动向脑循环传递的影响尚不清楚，部分原因是因为评估方法有限。

方法：在一项技术开发试点研究中，10名健康志愿者被随机分到氨氯地平组和普萘洛尔组的交叉治疗组。在基线和接受每种药物治疗时，评估中心动脉搏动（无创中心脉波分析仪）和大脑中动脉的搏动（经颅超声）。我们也做了全长3.0T 多频段血氧水平依赖磁共振成像（多频段系数6，重复时间 =0.43 s），同时采用一种新方法进行持续的无创血压监测。测定了药物对心动周期血压变异与血氧水平依赖磁共振成像之间相关关系的影响（fMRI 专家分析工具，fMRIB 软件库）。

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线性图像注册工具（FMRIB non-linear image registration tool，FNIRT）-FSL] 后再被注册到用于群体分析的 MNI-152 脑 (FNIRT-FSL）。通过独立成分分析人工识别并去除非生理性的人为成分。脉搏到达时体素-体素的差异采用与外周 BP 标记一致的每个时间序列的事件相关总和进行测定（图 2），相位移动体素通过峰值到达时间差异和分段式三次埃尔米特（hermitte）插值法插值进行测定。

对于每个体素，都推导出了功率谱（Welch，350 容积段，50% 的重叠，nfft 512 容积）和与血压的均方一致性。确定每种治疗时心动周期频率 BP 与 BOLD 信号之间的相关关系，并进行治疗之间的比较（FSL-FEAT）。

结果

纳入的 5 名男性和 5 名女性受试者（平均年龄 = 29 岁，范围 = 18–41 岁），都完成了研究方案。半数首先接受氨氯地平治疗。两种药物降低主动脉 BP、动脉搏动和脉搏波速度以及脑血流速度的效果相似（表），但接受普萘洛尔治疗时 MCA-PI 有非显著性的升高。心动周期频率上的 BOLD 信号与外周 BP 之间的一致性（频率特异性关系）在脑室和静脉窦处最大，而且也见于整个灰质。对所有心动周期中每个体素 BOLD 响应平均后产生了可识别的动脉波形（图 1）。外周心动周期频率 BP 波形与灰质 BOLD 信号的相关性在普萘洛尔治疗时较氨氯地平治疗时要强（图 2）。从分析中排除个别受试者后，这一结果没有改变。

讨论

我们同步采集了无创的连续性 BP 和高频率 BOLD MRI，证实了两者在心动周期频率下的直接联系。这种联系在接受普萘洛尔治疗时
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平均MCA

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注：SBP：收缩期血压；DBP：舒张期血压；PWV：脉搏波速度；MCA：大脑中动脉。

较接受氨氯地平治疗时更强，尽管两者对主动脉 BP 和动脉搏动有相似的效果。

脑动脉搏动与慢性脑白质病变有关，潜在的原因可能是因为僵硬的血管可以增加主动脉搏动向脑的传递。然而，研究动态血管血流变化却受限于常规 MRI 浏览的时间分辨率差、低频多普勒的空间分辨率低及在 MRI 扫描过程中持续测量 BP 存在的实际困难。我们使用了一种最近开发出的高频 MRI 浏览序列，并且开发了一种同步持续 BP 监测的新方法。通过技术改进，这种方法应该能实现对脑的频谱 BP 快速波动向区域特异性血流的传递进行详细的评估。的确，我们发现与心动周期波形的联系在接受普萘洛尔治疗时较接受氨氯地平治疗时更强。这一结果表明，降低程度较小的体循环 BP 可能使脑暴露在较大的动脉搏动之下。这对两种药物之间在脑血管生理和卒中风险方面的差异是一个潜在的解释，但尚需进一步研究。

本研究有一些局限性。第一，受试者为健康志愿者，动脉病变少于年龄更大且卒中风险更高的患者。因此，该研究发现的药物影响不能外推到临床人群。第二，BOLD 受到血流、血液氧合以及血容量的影响。然而，我们证实的与心脏频率 BP 变异之间的联系反映的是在超过神经血管耦合的频率情况下的 BOLD 变异，因此很可能主要取决于血流。

我们试用了一种在高频 BOLD MRI 扫描期间同时持续性无创性 BP 测量的新方法评估动脉搏动向脑的传递，证实接受普萘洛尔治疗时较接受氨氯地平治疗时的相关性较强。这种新方法尚需进一步的开发，随着不断改进，将会使以 MRI 为基础的检查能系统地评估 BP 波动对脑循环的影响。

参考文献