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 (TCDtranscranial ultrasound). We also performed whole-brain, 3-tesla multiband blood-oxygen level dependent magnetic resonance imaging (multiband factor 6, repetition time=0.43s), 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.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 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 (multiband–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 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 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 (1.5×1.5x1.5 mm voxels) and a 12-minute multiband BOLD-MRI (multiband factor=6, 30 slices, 3x3x3 mm voxels, echo time=40 ms, repetition time=0.43 s; Figure I in the online-only Data Supplement)6,7 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]9), registered to T1 (FMRIB non-linear image registration tool [FNIRT]–FSL 9), and then the MNI-152 brain for group analysis (FNIRT–FSL 9). Nonphysiological 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 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.
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,\(^1,3\) potentially because of 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 transcranial Doppler, 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 2 drugs\(^4,5,10\) 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.\(^13\) 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\(^11\) 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.

**Acknowledgments**

We gratefully acknowledge the Cardiovascular Clinical Research Facility, the Acute Vascular Imaging Centre, and Michael Kelly from...
the Oxford Centre for functional Magnetic Resonance Imaging of the Brain (fMRIB).

Sources of Funding
P.M. Rothwell has National Institute for Health Research and Wellcome Trust Senior Investigator Awards and receives funding from the Oxford Biomedical Research Centre. A.J.S. Webb had a Medical Research Council Clinical Training Research Fellowship.

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
Magnetic Resonance Imaging Measurement of Transmission of Arterial Pulsation to the Brain on Propranolol Versus Amlodipine
Alastair J.S. Webb and Peter M. Rothwell

Stroke. 2016;47:1669-1672; originally published online May 3, 2016; doi: 10.1161/STROKEAHA.115.012411
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/47/6/1669

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/05/03/STROKEAHA.115.012411.DC1
http://stroke.ahajournals.org/content/suppl/2017/07/10/STROKEAHA.115.012411.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
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.

Reproduced with permission from Xu et al. Neuroimage 2013;83:991-1001
脑动脉搏动与脑白质高信号病变和认知能力减退有关且在很大程度上取决于中心动脉搏动和动脉僵硬度。目前尚未专门开发出影响脑动脉搏动的治疗方法,但是这种影响可以解释钙通道阻滞剂较 β-阻滞剂更能降低卒中风险,尽管两种药物降低血压的效果相似。

脑动脉搏动通常采用时间分辨率好但空间分辨率有限的经颅多普勒(transcranial Doppler,TCD)测定,而当前的磁共振成像(magnetic resonance imaging,MRI)序列却有良好的空间分辨率但时间分辨率有限。此外,在 MRI 扫描过程持续地测量血压有些实际困难。我们试用了一种能在高时间分辨率 MRI[ 多频段 - 血氧水平依赖成像(multiband-blood-oxygen level dependent imaging,MB-BOLD) ] 扫描过程中进行持续性 BP 测量的新方法,并通过评估氨氯地平与普萘洛尔作用下动脉搏动的传递确定了其潜在的用途。

**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。此背景和目的: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和普萘洛尔的交叉治疗组。在基线和接受每种药物治疗时,评估主动脉(无创主动脉脉波分析仪)和大脑中动脉的搏动(经颅超声)。我们也做了全脑 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。结果:主动脉搏动在服用氨氯地平时(27.3 mmHg)和服用普萘洛尔时(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)非显著性地高于服用氨氯地平时 (+1.5%; P=0.58)。在磁共振成像上,发现心脏频率血压变异与血氧水平依赖磁共振成像的相关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同期高频血氧水平依赖磁共振成像与无创血压监测方式评估动脉搏动的新方法。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,这一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
线性图像注册工具（FMRIB non-linear image registration tool, FNIRT）- FSL®后再次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 (hermite) 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。确定每种治疗下心动周期频率 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 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
表 生理学指标

<table>
<thead>
<tr>
<th>测量</th>
<th>测量基线</th>
<th>氨氯地平</th>
<th>普萘洛尔</th>
<th>普萘洛尔，氨氯地平差异性</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>数值</td>
<td>P值</td>
<td>数值</td>
<td>P值</td>
</tr>
<tr>
<td>主动脉</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>96.6</td>
<td>0.01*</td>
<td>91.2</td>
<td>0.002*</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>69.5</td>
<td>0.002*</td>
<td>63.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>脉搏压</td>
<td>27.1</td>
<td>0.88</td>
<td>27.9</td>
<td>0.49</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>5.5</td>
<td>0.15</td>
<td>5.2</td>
<td>0.03*</td>
</tr>
<tr>
<td>主动脉</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>通过时间</td>
<td>172</td>
<td>0.03*</td>
<td>174</td>
<td>0.91</td>
</tr>
<tr>
<td>峰速度</td>
<td>93.1</td>
<td>0.98</td>
<td>89.1</td>
<td>0.55</td>
</tr>
<tr>
<td>谷速度</td>
<td>50.0</td>
<td>0.90</td>
<td>46.6</td>
<td>0.31</td>
</tr>
<tr>
<td>搏动指数</td>
<td>0.67</td>
<td>0.58</td>
<td>0.71</td>
<td>0.09</td>
</tr>
</tbody>
</table>

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 
1,3, 肥胖的原因可能是因为血管硬化使主动脉搏动向脑的传递增强 
1,3, 而且, 研究结果表明脑白质变化可受到常规 MRI 序列的时间分辨率差、经颅多普勒空间分辨率低以及在 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的高频 MRI 序列 6,7, 并且开发了一种同步持续 BP 监测的新方法。随着技术不断改进, 这种方法应该能实现对体循环 BP 快速波动区域特异性脑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使用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 可能会使大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 
4,5,10, 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人群。因此, 这一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 BOLD 的变化, 因此很可能主要取决于血流。第三, 这种 BP 测量方法容易受到离线时过滤掉的人为缓慢 BP 漂移的影响。这种情况虽然对我们处理的高频 BP 波动影响不大, 但使这种技术用于研究较慢 BP 波动受到限制。第四, 接受普萘洛尔治疗时心动周期频率 BP 波动与 BOLD 信号的相关性增强这一现象表面上不同于最大脑动脉搏动的分布模式, 有可能反映出神经的最高绝对脑灌注, 而限制对脑白质灌注的影响分析的敏感性。这可能反映了 BP 与 BOLD 信号之间的不同影响不包括直接对 BP 搏动的影响, 但这种模式的脑动脉搏动已经在采用注射 ATP 作为刺激方法的实验中得到了证实。最后, 考虑到重复时间 t0 =0.43 s, 心率 70 次 / 分以上可以导致心脏搏动的混叠 (aliasing)。仅 1 例受试者平均静息心率过快, 排除这个样本后结果没有改变 (数据未显示)。然而, 在一个更广泛的人群中, 有更短重复时间的多频段成像会限制混叠。

我们试用了一种在频段 BOLD MRI 扫描期间同时持续性无创性 BP 测量的新方法评估主动脉搏动对脑的传递, 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显著增加。这种新方法尚需进一步的开发, 随着不断改进, 将会使以 MRI 为基础的检查法系统地评估快速 BP 波动对脑生理的影响。

参考文献