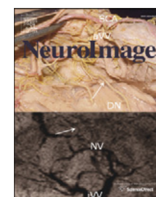
NeuroImage 118 (2015) 301–312

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg



Full length Article

Venous cerebral blood volume increase during voluntary locomotion reflects cardiovascular changes

Bing-Xing Huo [a], Stephanie E. Greene [a], Patrick J. Drew [a,b,*]

[a] Center for Neural Engineering Department of Engineering Science and Mechanics
[b] Department of Neurosurgery Pennsylvania State University, University Park, PA 16802, USA

ARTICLE INFO

Article history:
Received 8 January 2015
Accepted 3 June 2015
Available online 6 June 2015

Keywords:
Neurovascular coupling
Locomotion
Imaging
Frontal cortex
Somatosensory cortex

ABSTRACT

Understanding how changes in the cardiovascular system contribute to cerebral blood flow (CBF) and volume (CBV) increases is critical for interpreting hemodynamic signals. Here we investigated how systemic cardiovascular changes affect the cortical hemodynamic response during voluntary locomotion. In the mouse, voluntary locomotion drives an increase in cortical CBF and arterial CBV that is localized to the forelimb/hindlimb representation in the somatosensory cortex, as well as a diffuse venous CBV increase. To determine if the heart rate increases that accompany locomotion contribute to locomotion-induced CBV and CBF increases, we occluded heart rate increases with the muscarinic cholinergic receptor antagonist glycopyrrolate, and reduced heart rate with the β_1-adrenergic receptor antagonist atenolol. We quantified the effects of these cardiovascular manipulations on CBV and CBF dynamics by comparing the hemodynamic response functions (HRF) to locomotion across these conditions. Neither the CBF HRF nor the arterial component of the CBV HRF was significantly affected by pharmacological disruption of the heart rate. In contrast, the amplitude and spatial extent of the venous component of the CBV HRF were decreased by atenolol. These results suggest that the increase in venous CBV during locomotion was partially driven by peripheral cardiovascular changes, whereas CBF and arterial CBV increases associated with locomotion reflect central processes.

© 2015 Elsevier Inc. All rights reserved.

Introduction

Local cerebral blood flow is controlled centrally by local neural activity via neurovascular coupling (Attwell et al., 2010; Hillman, 2014; Logothetis, 2008), but also can be affected by peripheral cardiovascular changes, which are buffered to varying degrees by cerebral autoregulation (Lassen, 1959; Lucas et al., 2010; Tzeng and Ainslie, 2013). Understanding the relative balance of central and peripheral contributions to the cerebral hemodynamic response is critical for drawing inferences from hemodynamic signals across behavioral states and comparing healthy versus diseased populations (D'esposito et al., 2003; Iadecola, 2004, 2013). However, there is an incomplete understanding of how systemic cardiovascular changes impact cerebral blood flow (CBF) and volume (CBV) increases.

Sensory evoked hemodynamic changes are typically thought of as a linear convolution of the stimulus with a hemodynamic response function (HRF) (Boynton et al., 1996; Glover, 1999; Vazquez and Noll, 1998). It is important to determine if the HRF reflects purely central processes, such as neural and/or astrocytic control (Attwell et al., 2010; Hamel, 2006; Hillman, 2014; Petzold and Murthy, 2011), or if the HRF is affected by changes in the cardiovascular system, such as increases or decreases in heart rate (Chang et al., 2009). Because CBV increases are generated by the dilation of both arteries and veins (Drew et al., 2011; Kim et al., 2007; Kim and Kim, 2011; Lee et al., 2001; Silva, 2005; Zong et al., 2012), in order to interpret CBV signals it is essential to understand how cardiovascular state affects both types of vessels. Arteries and veins will be affected by blood pressure differentially, as arteries have active autoregulatory responses (Faraci and Heistad, 1990; Harder, 1984), while veins passively change their diameters in response to pressure changes (Boas et al., 2008; Buxton et al., 1998; Edvinsson et al., 1983; Mandeville et al., 1999; Zheng and Mayhew, 2009). Consistent with these observations, measurements of the responses of individual cerebral arteries and veins in anesthetized mice, where the heart rate is lowered relative to the awake animal, have shown that anesthesia completely blocked the dilation of cerebral veins to sensory stimulation that was normally present in the awake animal (Drew et al., 2011). Fluctuations in cardiovascular and respiratory processes can affect resting and sensory-evoked cerebral hemodynamic signals (Birn et al., 2008a,b, 2009; Chang et al., 2009; Shmueli et al., 2007), and blood pressure can affect BOLD (blood-oxygen level dependent) signals (Kalisch et al., 2001; Wang et al., 2006). Imaging modalities that permit subject motion, such as near-infrared spectroscopy (NiRS) (Ferrari and Quaresima, 2012; Piper et al., 2014) may also

* Corresponding author at: Department of Engineering Science & Mechanics, Department of Neurosurgery W-317 Millennium Science Complex Pennsylvania State University, University Park, PA 16802.
E-mail address: pjd17@psu.edu (P.J. Drew).

http://dx.doi.org/10.1016/j.neuroimage.2015.06.011
1053-8119/© 2015 Elsevier Inc. All rights reserved.

be sensitive to cardiovascular changes accompanying movement. These results suggest that in addition to changes in blood vessel diameter evoked by central processes, changes in cardiovascular state may also contribute to the hemodynamic response.

The largest, normal physiological perturbations in the cardiovascular system take place during exercise, making exercise a natural test case for investigating the significance of cardiovascular changes in affecting cerebral hemodynamic signals. Exercise increases heart rate, cardiac output and systemic blood pressure (Mitchell, 1985; Yancey and Overton, 1993). While there is a large, but contradictory, body of literature on the effects of exercise on CBF in humans (Ogoh and Ainslie, 2009), the imaging techniques available in animal models have allowed a better understanding of the cerebral hemodynamic changes during exercise, as well as their microvascular basis. During voluntary locomotion in mice, increases in CBV and CBF are largely localized to the forelimb/hindlimb (FL/HL) representations in the primary somatosensory cortex (SI), with little change in the frontal cortex (FC) (Huo et al., 2014). The increases in CBV and CBF are linearly related to locomotion, and are well-captured by HRFs (Huo et al., 2015) similar to the one used in BOLD-based fMRI (Boynton et al., 1996; Glover, 1999). The CBV HRF can be decomposed into arterial and venous components (Huo et al., 2015; Silva et al., 2007). The locomotion-evoked arterial component of the CBV HRF is largest in the cortical FL/HL representation, while the spatial distribution of venous component of the CBV HRF is more uniform across frontal and parietal cortical surface (Huo et al., 2015). Because average neural activity and hemodynamic signals in FC decouple during locomotion (Huo et al., 2014), it is conceivable that other physiological processes, such as cardiovascular changes, contribute to locomotion-evoked CBV and CBF changes.

Here, we tested if the disruption of normal cardiovascular changes accompanying voluntary locomotion affected locomotion-evoked CBV and CBF HRFs. If pharmacological occlusion or reduction of the heart rate increases during locomotion altered the locomotion-evoked HRFs, then systemic cardiovascular processes contribute to the observed changes in CBV and CBF, and thus any evoked changes in cerebral hemodynamic signals cannot be entirely attributed to central (neural and astrocytic) processes. We blocked muscarinic acetylcholine receptors with glycopyrrolate, which increases heart rate and cardiac output (Seifert et al., 2010), elevates resting blood pressure (Hamner et al., 2012), and blocks parasympathetic outflow. In humans, glycopyrrolate can block exercise-induced CBF increases (Seifert et al., 2010) (but see Rokamp et al., 2014). We blocked β_1-adrenergic receptors with atenolol, which reduces heart rate and blood pressure (Fitzgerald et al., 1978; Joyner et al., 1986) and decreases cardiovascular output (Joho et al., 2006). Neither glycopyrrolate nor atenolol crosses the blood-brain barrier (Franko et al., 1962; Neil Dwyer et al., 2012). Using laser Doppler flowmetry (LDF) and intrinsic optical signal (IOS) imaging, we found that the CBF HRF and the arterial component of the CBV HRF to locomotion were not significantly affected by these pharmacological disruptions of normal cardiovascular fluctuations. In contrast, the amplitude of the venous component of the locomotion-evoked CBV HRF was significantly decreased under the influence of atenolol. Our findings indicate that during normal behavior, a substantial amount of the venous component of the CBV HRF could be driven by cardiovascular changes.

Methods

Animals

All experimental procedures were performed in accordance with the Institutional Animal Care and Use Committee of the Pennsylvania State University, University Park and NIH guidelines. A total of 13 male C57BL/6 J mice (Jackson Laboratory) were used. Mice were housed individually and kept on a 12-hour light/dark cycle.

Surgery

Mice were 4 to 10 months old (23–33 g) at the time of surgery. All surgical procedures were performed under isoflurane anesthesia. Mice were implanted with head bolts, and either bilateral or unilateral reinforced thinned-skull windows for IOS and LDF measurements. Detailed surgical procedures for creating reinforced thinned-skull windows have been described previously (Drew et al., 2010; Huo et al., 2014, 2015; Shih et al., 2012). We attached a custom-machined titanium head bolt to the dorsal aspect of the exposed skull, posterior to lambda. We then installed chronic, coverslip-reinforced thinned-skull windows spanning both frontal and parietal cortices, bilaterally in 10 mice, and unilaterally in 3 others. Black dental acrylic was used to minimize reflected light. In the three mice with unilateral thinned-skull windows, self-tapping 3/32" #000 screws were placed into the skull contralateral to the windows over the frontal (+2.0 mm A-P and 1.0 mm M-L from bregma) and parietal (−0.5 mm A-P and 2.0 mm M-L from bregma) cortices for use as electrocortogram (ECoG) electrodes. The screws were connected via stainless steel wires (A-M Systems, #793600) to an electrical connector for differential ECoG measurements.

Experiments

Mice were head-fixed on top of a spherical treadmill (60-mm diameter) covered with anti-slip tape. The treadmill had one rotational degree of freedom. The animal's velocity was recorded using an optical rotary encoder (Gao and Drew, 2014) (US Digital, E7PD-720-118) attached to the axle of the treadmill. All data were collected using custom-written software in LabView 8.6 (National Instruments). For CBV measurements ($n = 13$), four 530 nm LEDs (Thorlabs, M530L2-C1) (Bouchard et al., 2009), with ± 10 nm filters (Thorlabs, FB530-10), uniformly illuminated the area of the thinned skull window(s). Because 530 nm is an isobestic point of hemoglobin (Prahl, 2006), CBV increases due to arterial and venous dilations cause a decrease in reflectance (Huo et al., 2015). Intrinsic images (256×256 pixels, 27–43 μm/pixel) were captured using a CCD camera (Dalsa, Pantera 1 M60)(Huo et al., 2014, 2015) at an acquisition frequency of 30 frames/s (for ~3 minutes) for heart rate measurements (Fig. 1), or at 3 frames/s (for ~33 minutes) for locomotion-driven CBV HRF measurements. A camera (Microsoft, LifeCam Cinema) was used to monitor the animal's behavior. In this experimental setup, instrumentation noise in measures of reflectance has a root-mean square (RMS) amplitude of ~0.01% (Huo et al., 2014), which is ~100x smaller than the spontaneous ongoing fluctuations in hemodynamic signals that are found in awake rodents (Huo et al., 2014, 2015) and ~1000× smaller than the locomotion evoked signals measured here (Huo et al., 2014, 2015). For CBF measurements, a laser Doppler flowmeter (LDF) (Oxford Optronix, OxyFlo) probe was positioned at a 30-degree angle over the frontal or parietal cortex of the left hemisphere ($n = 7$) of animals with bilateral thinned-skull windows. CBF was only measured in one location per trial. For simultaneous LDF and IOS measurements, a 530 ± 5 nm filter was attached to the CCD camera to block light emitted by the LDF probe. Because the LDF probe partially obscured the window over the left hemisphere, on trials where CBF measurements were made, only the right hemisphere was included in calculating the spatial spread of the arterial and venous signals. ECoG was recorded differentially from screws in the frontal and parietal cortices, amplified (DAM80, WPI Inc.), and band-pass filtered between 0.1 Hz and 200 Hz (Brownlee Precision, Model 440). The measured CBF and CBV signals report fractional, not absolute, changes in cerebral blood flow and volume, respectively.

Sterile saline (Teknova), glycopyrrolate (50 μg/kg in saline, Sigma-Aldrich), and atenolol (2 mg/kg in saline, Sigma-Aldrich) were intraperitoneally injected into all of the 13 mice. The animal was allowed to acclimate to the treadmill for at least 30 minutes prior to the injection. Only one injection was made for each animal per day. The interval

Download English Version:

https://daneshyari.com/en/article/6025126

Download Persian Version:

https://daneshyari.com/article/6025126

Daneshyari.com