Investigating water exchange across the BBB as a mechanism for the slow time constant of blood volume

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Motivation

IRON (increased relaxation for optimized neuroimaging) fMRI using exogenous contrast agent has increased functional sensitivity and spatial specificity with respect to BOLD signal[1,2], and achieved comparable spatial resolution within current resolution limitations[3,4]. IRON contrast reflects changes in cerebral blood plasma volume (CPV)[5]. In order to understand the physiology of functional activation, and to further optimize experimental designs, a detailed understanding of IRON signal kinetics is needed.

The temporal evolution of CPV has been examined in anesthetized rats[5] and awake monkeys[1]. It was found that the impulse response functions (IRF) for BOLD and IRON contrasts could be accurately described by the same two time constants, a fast (~ 4.5 sec), and a slow (~ 13.5 sec). For BOLD, these were consistent with the responses of blood oxygenation (fast) and blood volume (slow). For IRON, they were presumably related to arterial (fast) and capillary/venous (slow) dilations. During prolonged stimulation, signal decomposition suggested that changes in CPV reduce the BOLD effect by 40%, and that the slow time constant contained 80% of the IRON signal strength.

IRON contrast linearity has been explicitly and generally demonstrated[1,2,6]. According to the Windkessel model[7], the slow time constant arises from slow venous relaxation of stress. In this abstract, we investigate an alternative model for the slow capillary/venous changes in CPV, and one that is linear with CBF.

Background

Intracranial pressure (ICP) is determined by the sum of pressures exerted by the intracranial compartments (parenchyma, CSF, and CBV). According to the Monro-Kellie doctrine of ICP homeostasis, an increase in one intracranial compartment can only occur at the expense of another. In the autoregulatory regime[8,9], as cerebral perfusion pressure (CPP) falls, CBF remains approximately constant, and CBV may not change[10,11], or may increase by more than 50% for CPP ~ 60mmHg[12,13]. In fact, increases in the diameter of capillaries have been observed[14,15].

Model

Pressure balance across the capillary wall: ICP is small compared to pressures inside capillaries and small venules. At steady state, this pressure differential is balanced by tension in vessel walls. As arterioles swell to regulate blood flow during functional activation, additional pressure is shifted onto the downstream compartment. Hence, downstream vessels will swell until the additional intraluminal pressure is balanced by an increase in wall tension. Writing the average capillary/venous intraluminal pressure (P_{CV}) in terms of the product of CBF (F) and resistance (R_{CV}), the pressure difference across vessels walls in this compartment can be written as $\Delta P(t)=P_{CV}(t)-P_w(t)=F(t)R_{CV}(t)/2-P_w(t)$. In terms of CPV (V), we further assume that $R_{CV} \propto V^{-\alpha}$ and $P_w \propto V^{\beta}$; laminar flow corresponds to $\alpha = 2$, and a value of $\beta = 1$ implies a quadratic relationship between wall pressure and radius. Using these relationships and rearranging terms, the pressure difference can be written in terms of relative changes in flow, f(t) = F(t)/F(0), and volume, v(t) = V(t)/V(0):

$$\Delta P(t)=P_{CV}(0)\left(f(t)/v^{\alpha}(t)-v^{\beta}(t)\right).$$

This formulation represents the balance of forces on the vessel wall, but equations are similar to those produced by a Windkessel formulation[7]. For instance, the relationship between functional changes in flow and volume when $\Delta P=0$ closely resembles measured values[16], $f(\infty)=v^{\alpha+\beta}(\infty)$.

Water extraction across the capillary wall: Downstream vessels do not respond passively to pressure changes in the same way as a balloon; a physical quantity other than intraluminal pressure must define the rate of blood volume changes. The Windkessel description of this response assumed that changes in intravascular (IV) volume displaced extravascular (EV) volume, presumably by displacing low-pressure fluid like CSF or CPV in very large veins. Here, we investigate the consequences of the assumption that the sum of IV and EV volumes is always constant. Under this condition, increases in IV volume can only occur by extracting EV water through the blood brain barrier (BBB). The rate of net flow across the membrane depends upon the driving pressure (ΔP), the surface area (S), and the permeability of the membrane expressed as the hydraulic conductivity (L_p), according to the Starling equation $dV(t)/dt=L_pS(t)\Delta P(t)$. Inserting $\Delta P(t)$ above into the Starling equation, and linearizing the resultant expression for small fractional changes in flow and volume ($v=1+\Delta v/v$, $f=1+\Delta f/f$), we get

$$\frac{d}{dt}\left(\frac{\Delta v}{v}\right)=-\frac{(\alpha+\beta)\Delta v}{\tau\ v}(t)+\frac{1}{\tau}\frac{\Delta f}{f}(t), \text{ with } \tau=\frac{T_{MTT}F(0)}{LS(0)P_{CV}(0)},$$

where the mean transit time (T_{MTT}) is the ratio V(0)/F(0). This differential equation describes changes in CPV as an exponential function of time with a driving term dependent upon CBF. For a step change in CBF at time zero, the solution is simply $(\Delta v/v)(t)=(\alpha+\beta)^{-1}(\Delta f/f)(t)\,e^{-t/\tau}$, so that relative changes in CPV are smaller and slower than relative changes in CBF, as has been shown in anesthetized rats[17], and the time constant is determined by membrane permeability. Assuming a mean transit time of 3 seconds, a baseline value for CBF of 0.6 ml/g/min, a baseline pressure of 15 mm Hg in the capillary/venous compartment, and a surface area of 100 cm^2/g, the value of L_p required to explain the data is about 10^{-6} cm/sec/mmHg.

Discussion and Future Work

The BBB hydraulic conductivity has been measured in different preparations with different methods. The use of boluses of hypertonic solutions in humans, has led to values of 10^{-9} cm/sec/mmHg[18]. It is not clear if increases in blood flux due to hypertonic solutions were accounted for in these studies, which could lead to underestimation of L_p. In studies of cat's brain capillaries, where changes of ICP were mechanically applied through an opening in the skull, L_p was found to vary within 10^{-7}-10^{-8} cm/sec/mmHg[19], still 1 to 2 orders of magnitude slower than our model would imply. Nevertheless, Eichling and colleagues[20] have shown that the half-time for water extraction in the brain of rhesus monkeys at baseline CBF is ~ 31 sec, a value on the same order of magnitude as the slow CPV time constant.

It has been suggested that most of the activation-related increase in CPV comes about by exchange of water between the capillaries and the endothelial cells surrounding them, such that the outside diameter of the vessels would remain constant[21]. An intermediate compartment, as proposed by Turner, might be compatible with a larger value of Lp, as required for this model, but it also apparently provides a very limited buffer for volume changes.

According to measured values of hydraulic conductivity, water extraction appears to be too slow to explain the large observed CPV changes. Nevertheless, refined models for dynamic transport across a flexible, permeable membrane are required, and additional measurements of CPV kinetics and ICP in models with varied BBB permeability would help determine the role of water exchange during CPV transitions.

References [1]Leite et al, NeuroImage 2002; [2]Leite and Mandeville, NeuroImage 2006; [3]Leite et al, ISMRM 2004; [4]Leite et al, ISMRM 2005; [5]Mandeville et al, MRM 1998; [6]Lu et al, NeuroImage 2005; [7]Mandeville and Marota, JCBFM 1999; [8]Powers, Ann Neurol 1991; [9]Derdeyn et al, Brain 2002; [10]Schumann et al, Brain 1998; [11]Zaharchuk et al, Stroke 1999; [12]Grubb et al, J Neurosurg 1975; [13]Ferrari et al, Am J Physiol 1992; [14]Villringer et al, Circ Res 1994; [15]Hudetz, Microcirc 1997; [16]Grubb et al, Stroke 1974; [17]Mandeville et al, MRM 1999; [18]Bradbury, Circ Res 1985; [19]Coulter, Am J Physiol 1958; [20]Eichling et al, Circ Res 1974; [21]Turner and Thomas, ISMRM 2006.