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Control of brain blood flow by capillaries: a simulation study in an anatomically accurate large human vascular network

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1. Introduction

Blood micro-circulation plays a central role in the local adaptation of cerebral blood flow to neural activity. A growing body of evidence indicates that neurons, glia and cerebral blood vessels, acting as an integrated unit, have a crucial role in mediating the activation-induced changes in blood flow. In particular, the smooth muscle cells surrounding the arterioles, and possibly pericytes, at capillary level, convert the bio-chemical signals that originate from this integrated unit into changes in vascular diameter, thus regulating blood flow by modulating vascular resistance (Hamilton et al. 2010).

However, the role of capillaries in the control of cerebral blood flow is still controversial (Hamilton et al. 2010). In particular, it is at present not clear whether the capillary dilatation experimentally observed *in vivo* by several groups is a passive consequence of upstream arteriolar dilatation via an alteration in perfusion pressure or the result of an active regulation of the capillary diameter via contraction/relaxation of pericytes (Hamilton et al. 2010). Answering this question by experimental means is extremely challenging. For example, the penetration depth of the most recent intravital two-photon microscopy techniques (typically $\sim 500\,\mathrm{mm}$) does neither allow to investigate the cortical layers of highest capillary density, which are located approximately in the middle third of the cortex (Lauwers et al. 2008) nor those where the fastest capillary dilation occurs (Tian et al. 2010).

By contrast, Hamilton et al. (2010) have pointed out that modelling using anatomically accurate representations of the intracortical vascular network will be valuable for generating predictions as to the likely impact of pericyte-mediated capillary diameter regulation.

Our group has recently performed the first numerical simulations of blood flow in an anatomically accurate large human intra-cortical vascular network ($\sim 10{,}000$ segments), using a 1D non-linear model taking into account the complex rheological properties of blood flow in microcirculation (i.e. Fahraeus, Fahraeus–Lindquist and phase separation effects; Lorthois et al. 2011a). This model predicts blood pressure, blood flow and hematocrit distributions, volumes of functional vascular territories, regional flow at local, voxel and network scales, etc. Using the same approach, we have studied the flow re-organisations induced by arteriolar vasodilations, highlighting the hemodynamic component of various functional neuroimaging techniques (Lorthois et al. 2011b).

In this paper, the variations in cerebral blood flow induced by global or localised capillary vasodilations are studied.

2. Methods

The methodology for simulating blood flow in the intra-cortical vascular network of a secondary cortex region extending over $7.7\,\mathrm{mm}^2$ along the lateral part of the collateral sulcus has been presented in detail and validated elsewhere (Lorthois et al. 2011a). It is used to calculate the flow and hematocrit in each segment and the pressure at each node. Of course, the computed values of these parameters depend on the boundary condition prescribed at frontiers capillary nodes, and two relevant conditions, providing a lower- and upper-bound limit to the network behaviour, have been determined: a zero flow condition (Case 1) and a self-consistent constant pressure condition adjusted such that the net flux contributed by all the frontiers capillary segments is null (Case 2).

To study the active role of intra-cortical capillaries, the diameters either of every capillary in the network (global) or of capillaries in a restricted area (localised) are multiplied by a constant factor f_{vaso}. This restricted area is randomly chosen in the high capillary density cortical layer, with a spatial extent in the direction parallel to the cortical surface fixed to $600\,\mu\mathrm{m}$, typically corresponding

to the periodicity of the vascular organisation in the cortex (Lauwers et al. 2008).

3. Results and discussion

The relative variations of the regional blood flow induced by global capillary vasodilations as a function of f_{vaso} are displayed in Figure 1 for both boundary conditions studied. In both cases, the results can accurately be fitted by a simple model of two resistances connected in series and subjected to a constant pressure drop. Despite the architectural and rheological complexity, the second resistance, representing the capillary network, behaves as a single Poiseuille resistance, the variation of which is inversely proportional to the fourth power of f_{vaso} (see Figure 1). In both cases, a two-fold increase in capillary diameter increases blood flow by a factor ~ 5. This is much greater than previous estimates from the relative importance of capillary and arteriolar resistance in models with simplified network structure and rheology, where a factor between 1.18 and 2.98 had been found (Hamilton et al. 2010). This is also greater than the increase induced by a two-fold global vasodilation of the arteriolar trees (Lorthois et al. 2011b).

However, this simple approach cannot account for the heterogeneities of flow variations throughout the network, the flow increasing by a factor of more than 9 in a significant proportion of vessels (data not shown).

In case of local vasodilations, a general augmentation of the flow in the vasodilated area is observed (Figure 2). This augmentation is larger than above: a 2-fold increase in diameter can result in a 10-fold increase in the most central capillaries (see Figure 2(B)). It is generally associated with
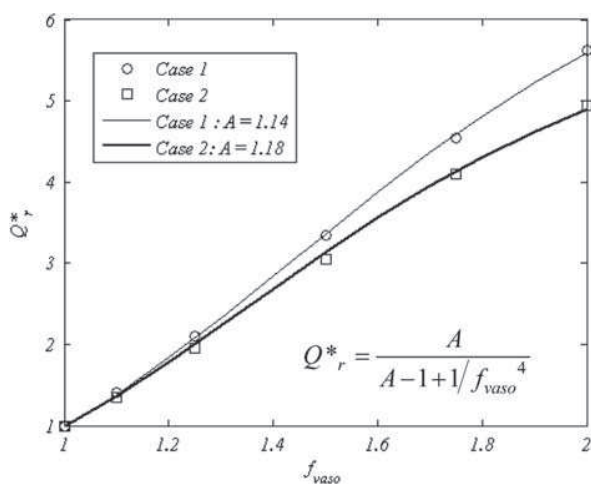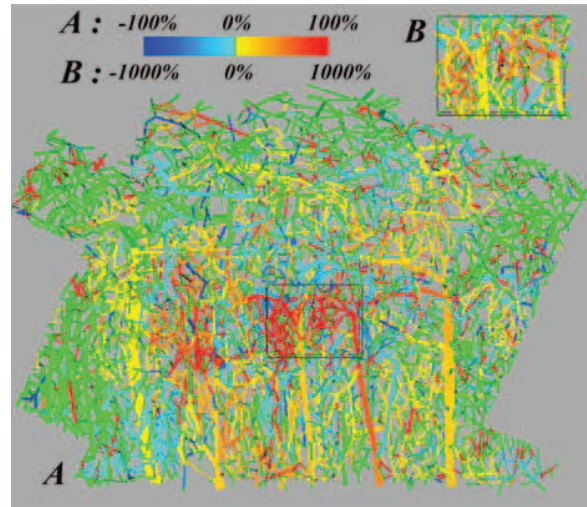

Figure 2. Flow rate variations in individual vessels induced by a two-fold increase of the diameters of the capillaries situated in the box.

a decrease in pressure and an increase in hematocrit. Outside the vasodilated region, a $\sim 300\,\mu m$ wide surrounding area exhibits a decrease in flow rate. Further away, significant variations spread as far as $\sim 1\,mm$ from the centre of the vasodilated region.

4. Conclusions

The above results demonstrate that pericyte-mediated regulation of blood flow at capillary level would be efficient for neuro-vascular coupling. By contrast to a regulation situated at the level of arterioles (Lorthois et al. 2011b), the changes in blood volume can be highly localised in space, with the potential to be as close as possible of areas of neuronal activation. However, the changes in blood flow are much more diffuse. This imposes limits on the ultimate spatial resolution of hemodynamically based brain functional imaging techniques.

$$Q^*_r = \frac{A}{A - 1 + 1/f_{vaso}^4}$$

Figure 1. Regional blood flow normalised to its baseline value as a function of f_{vaso}. Symbols: numerical results; lines: best fit according to a two-series resistance model (see inserted equation).

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