Variations in cerebral haemodynamics and capillary transit time heterogeneity in patients before and after carotid endarterectomy

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Target Audience: Scientist and Clinicians with an interest in perfusion MRI

Introduction: Cerebral Blood Flow (CBF) and Mean Transit Time (MTT) are frequently used in Dynamic Susceptibility Contrast (DSC) MRI to assess cerebral ischemia[1]. MTT above an ischemic threshold is commonly used as a marker of disease progression[1], however, the microscopic distribution of transit times within the underlying capillary network is often not considered. Recent studies have demonstrated the potential for evaluating capillary transit time heterogeneity (*CTH*) in ischemic vascular disease[2,3]. The Singular Value Decomposition (SVD)[4] method, while commonly used, cannot reliably estimate the true transit time distribution (TTD), and thus evaluate the *CTH in vivo*. By contrast, the Control Point Interpolation (CPI) method can reliably and non-parametrically estimate TTD *in vivo*[5,6]. This work evaluates the extent to which additional useful information is available from *CTH* measurements compared to the more commonly used parameter MTT.

Material and Methods: *In vivo data:* DSC data were acquired both pre- and post- carotid endarterectomy (CEA) from 17 patients (age: 69.7±10.4 years; M:F=12:5) with carotid atherosclerotic disease under a National Research Ethics Committee approved protocol. MRI data were acquired on a Siemens 3T Trio scanner with Diffusion Weighted Imaging (DWI) and GRE-DSC: TR/TE=1.5s/30ms. 78 volumes, 128x128x22 matrix, 1.7x1.7x5mm^3 voxels. An intravenous bolus injection of 0.1 mmol/kg Magnevist® was performed followed by a 20 ml saline flush. DSC images were analysed using the control point interpolation (CPI) method [5] that estimates the tissue residue function ($R(t)$) from a set of control points and then cubic spline interpolation is used to generate a smooth residue function. The transit time distribution ($h(t)$) was calculated from the residue functions using[2], $h(t) = -dR(t)/dt$. The capillary transit time heterogeneity[2] of the transit time distribution was used for evaluation of haemodynamics.

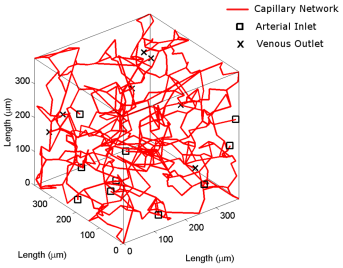

Figure 1: *The artificial tissue capillary network model with 10 arterial inlets and 7 venous outlets in cube of dimensions 375 μ.*

Simulations: One hundred different artificial capillary networks were randomly generated each measuring 375x375x375 cu.um based on a method by Su at al.[7] Figure 1 shows an example of the simulated capillary network. After solving the equations for the transit time distributions as in Park and Payne[8], network properties were varied to observe the effect on the estimated haemodynamic parameters. MTT and *CTH* were calculated for each network. Three properties were varied in these simulations: 1) changing the pressure difference across the network, 475 Pa-4250 Pa (equivalent to changing CBF in range of 10-90ml/100g/min, representing major arterial occlusion), 2) changing the number of inlets to the network 10, 6, 4, 3 and 2 (equivalent of arteriolar occlusion) and 3) randomly occluding a percentage of capillary vessels within the network, 5% to 20% (capillary occlusion).

Analysis: Principal component analysis (PCA) was performed independently on MTT and *CTH* values from individual patients and simulated capillary network data, while varying specific capillary network properties. PCA decomposes the data into independent principal components (e.g. PC1 and PC2) that represent the major axes of variation in the data along with the variability explained by each component. The variability value, *Var,* ranges from 0 to 1 where zero means no variability in data along the direction of PC1 and a value of one represents that all the variation in the data is explained by PC1. The slope of the major (*Slp1*) and minor (*Slp2*) PC was calculated to quantify the changes in haemodynamics in patients pre and post CEA and also to measure variations in haemodynamics among patients. Student paired t-tests were used to measure the statistical significance ($p<0.05$) for changes in *Var*, Slp1 and Slp2 pre- and post-CEA.

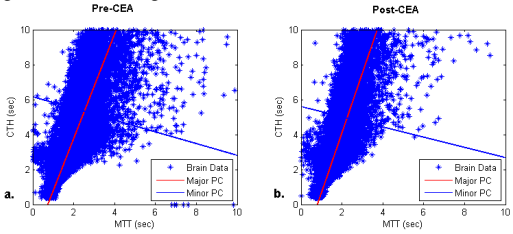

Figure 2: *MTT and CTH estimated for one of the representative subject (patient 17) used for principal component analysis both pre- and post- CEA. The major PC explains most of the variability in data (pre-CEA: 85% and post-CEA: 88%).*

Results: The mean *Var* in patients was 0.84±0.02 (pre-CEA) and 0.84±0.03 (post-CEA) with no significant differences ($p>0.05$). No significant change in *Slp1* (pre-CEA: 2.92±0.31, post-CEA: 3.05±0.33, $p>0.05$) or *Slp2* (pre-CEA: -0.35±0.04, post-CEA: -0.33±0.04, $p>0.05$) was observed after CEA. Figure 2 shows the estimated major and minor PCs using PCA for one representative patient. Figure 3 shows result of simulations performed in 100 different artificial capillary networks investigating the effects of occlusion in a major artery (Figure 3a), an arteriole (Figure 3b) and within the capillary network (Figure 3c). In all three scenarios, increased degree of vascular occlusion was correlated with an increase in both MTT and *CTH* and also an increase in the variability in of both MTT and *CTH*. Table 1 shows the value of *Var*, *Slp1* and *Slp2* in the three conditions.

Table 1: *Value of Var and slope of PC1 and slope of PC2 for 100 random capillary networks simulating artery, arteriolar and capillary occlusion*

Simulations	*Var* in PC1	*Slp1*	*Slp2*
Artery	0.82	1.07	-0.93
Arteriole	0.77	1.13	-0.88
Capillary	0.69	1.88	-0.53

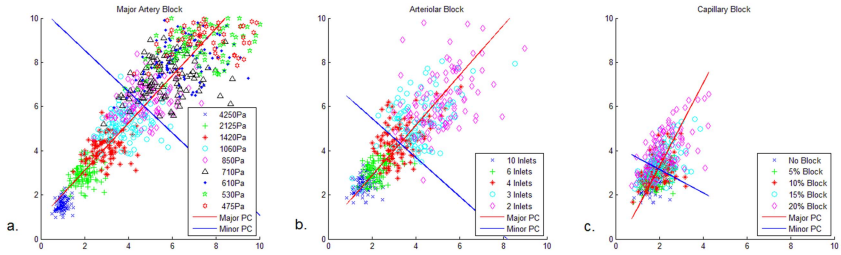

Figure 3: *Artificial capillary networks (n=100) with occlusion in a) the major artery, b) arteriole and c) within the capillary network. Major and minor principal component from the PCA analysis illustrating the direction of variability in the data.*

Discussion: In this study PCA has been used to evaluate the variations in *CTH* and MTT in patients both pre- and post-CEA. The results showed that more than 80% of the variability in the data (pre-CEA: 84±0.02%, post-CEA: 84±0.03%) can be represented with only one principal component; demonstrating a strong correlation between two parameters, MTT & *CTH*. The estimated slope of PCs were also found to be consistent across all the seventeen patients and showed no significant variation after surgical intervention. Similar finding were observed with simulation of 100 different random artificial capillary networks. A linear increase in *CTH* was observed with increase in MTT under three different simulated conditions; major arterial, arteriolar and capillary occlusion.

Conclusion: In a patient cohort undergoing carotid endarterectomy, variations in both MTT and *CTH* were observed with DSC perfusion imaging, but the two parameters were found to be highly correlated suggesting that *CTH* was unable to explain any further variability in tissue haemodynamics beyond that observed with MTT. Simulations of various sites of vascular occlusion in realistic vascular networks suggest that the correlation of MTT and *CTH* is a natural feature of the capillary bed.

References: 1.Astrup *et al. Stroke* 1981; 12: 723–5. 2.Ostergaard *et al. JCBFM* 2013; 33: 635–48. 3. Mouridsen *et al. JCBME* 2014. 4.Wu *et al. MRM* 2003; 50: 164–74. 5.Mehndiratta *et al. Neuroimage* 2013; 64: 560–570. 6.Mehndiratta *et al. MRM* 2013. 7.Su *et al. Microcirculation* 2012; 19: 175–87. 8.Park & Payne. *Interface Focus* 2013; 3.