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VISUALIZING THE CORTICAL MICROCIRCULATION IN STROKE PATIENTS

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While the cortical microcirculation can readily be observed and quantified in experimental models of focal cerebral ischemia, human ischemic stroke has heretofore been largely inaccessible to these observations. In this issue of CCM, Barcena and co-authors (1) have taken the first steps to fill this gap in our knowledge by reporting, in a small but carefully conducted clinical investigation, the direct visualization of the cortical microcirculation in 6 patients (ages 46–69) with major hemispheric infarcts of sufficient severity to warrant decompressive craniectomy to reduce elevated intracranial pressure and manage malignant cerebral edema. The 5 control subjects in this series were considerably younger patients (ages 20–45) who required craniotomy for deep lesions -- non-ruptured aneurysms (2 cases), meningiomas (2 cases), and III ventricular tumor (1 case) – that were assumed to have left the overlying cortex unaffected.

The method used in this study was sidestream dark-field imaging (SDF) – a technique pioneered by Dr. Ince, a co-author of the present article (2). SDF, a successor to the method of orthogonal polarization spectral imaging, has been widely applied to study the superficial microcirculation of accessible organs (e.g., skin, tongue, skeletal muscle, and serosal surfaces of pleura, kidney, and ileum). The method has been especially useful in characterizing abnormalities of the sublingual microcirculation in the settings of myocardial infarction (3), heart failure (4), hypothermic circulatory arrest (5), cardiogenic shock (6), septic shock (7), and high altitude (8).

Using the SDF method, the authors assigned a visually based microvessel flow grade (none, intermittent, sluggish, or continuous) and assessed the proportion and density of perfused microvessels in the observed field (1). In control subjects, they observed continuous microvascular flow, while cortical microvessels in the central ischemic zone of the stroke patients showed intermittent or absent flow. While nearly all microvessels were perfused in control brains, the proportion of perfused vessels was reduced by one-third and perfused vessel density index was lower by about one-half in the central ischemic zone of the stroke patients. Although the method used here did not permit measurement of microvascular flow velocity, a recent SDF study of the sublingual and ileal-serosal microcirculatory beds has demonstrated a tight linear correlation of capillary microvascular flow index and capillary flow velocity (9).

As has been extensively reviewed (10), microcirculatory derangements in ischemic stroke have many potential underlying causes, including *intravascular* obstruction by stagnant red cells, adherent leukocytes, aggregated platelets, fibrin masses, and/or endothelial swelling; as well as active vasoconstriction; and/or extrinsic microvascular compression from edema and elevated intracranial pressure. The SDF method used in the present study (employing a wavelength in the hemoglobin-absorption range) imaged only the intravascular contents, not the vessel wall. Furthermore, the method was limited in its ability to distinguish cortical arterioles and venules as the rapid flow rate in the former exceeded the ability of the method (with its 25 frames per second imaging rate) from measuring flow velocity directly. Microvessel type, however, is important: for example, our own experimental studies of focal ischemia by confocal microscopy have revealed that, during the early moments of postischemic recirculation, cortical *venules* (but not arterioles) specifically develop prominent foci of vascular stagnation associated with thrombus-like aggregates and adherent corpuscular structures consistent with neutrophils (11).

An essential question raised by studies of this type concerns the nature of *reperfusion* itself. The present study evaluated the cortical microcirculation at only a single surgical time-point (range 24 – 120 hours post-stroke) after craniectomy and dural opening (1). It is possible that the antecedent thrombolytic therapy and surgical decompression had afforded at least a modicum of microvascular reperfusion at the time of the SDF observations. One notes with particular interest that in this series, 5 of the 6 stroke patients received thrombolytic therapy. Intriguingly, in the single patient who did *not* receive thrombolysis, the proportion of perfused vessels (PPV) was markedly lower (17%) than in the thrombolysed group (range 51–74%). If these observations were confirmed, they would provide a mechanistic correlate to the clinical improvement seen after thrombolytic therapy in patients with acute ischemic stroke (12) by showing that thrombolytically induced large-vessel reopening is, in fact, accompanied by improved *microvascular* hemodynamics.

In experimental focal cerebral ischemia, we have shown that high-dose albumin therapy (ALB) is markedly neuroprotective (13), and recent evidence suggests that this effect is mediated in part by intravascular mechanisms. Thus, when a stable thrombus is produced in a rat cortical arteriole by laser irradiation, microvascular flow velocity (MFV) measured by in vivo two-photon microscopy distal to the thrombus falls to 10–13% of control levels and is unaffected by saline-placebo administration; however, following ALB administration MFV increases substantially despite persistence of the thrombus (14). In this model, sub-lytic doses of the thrombolytic agent, reteplase, lead to a small rise in MFV distal to the arteriolar thrombus, but this effect is further augmented when ALB is co-administered (15). These results support an effect of thrombolytic therapy on the cerebral microcirculation and suggest that ALB therapy may be adjunctively beneficial. This conclusion is supported by a recent exploratory efficacy analysis of data obtained in the first stage of a large randomized multicenter clinical trial of ALB therapy in patients with acute ischemic stroke – the ALIAS (Albumin in Acute Stroke) Trial: namely, in a target population of stroke patients treated with thrombolysis, those patients who also received high-dose ALB showed a 10% higher proportion of favorable 3-month neurological and functional outcome than those thrombolysed patients who received saline-placebo (46.7% vs. 36.6%) (16). Taken together, these observations emphasize the potential importance of the cerebral *microvasculature* as a therapeutic target in stroke.

One must be cautious in over-generalizing the findings of this study, remembering that the patients studied here had a malignant, space-occupying form of ischemic stroke. It is possible that the microcirculatory events in milder forms of ischemic stroke may differ considerably from the findings reported here. Nonetheless, the authors of the present article

are to be congratulated on their pioneering observations and should be encouraged to extend their investigations to a larger series.

Acknowledgments

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References

1. Barcena JP, Goedhart P, Ibañez J, et al. Direct observation of human microcirculation during decompressive craniectomy following stroke. *Crit Care Med*. 2010 [e-pub ahead of print].
2. Ince C. The microcirculation is the motor of sepsis. *Crit Care*. 2005; 9 (Suppl 4):S13–19. [PubMed: 16168069]
3. Lam K, Sjauw KD, Henriques JP, et al. Improved microcirculation in patients with an acute ST-elevation myocardial infarction treated with the Impella LP2.5 percutaneous left ventricular assist device. *Clin Res Cardiol*. 2009; 98:311–318. [PubMed: 19280085]
4. den Uil CA, Lagrand WK, Spronk PE, et al. Low-dose nitroglycerin improves microcirculation in hospitalized patients with acute heart failure. *Eur J Heart Fail*. 2009; 11:386–390. [PubMed: 19211570]
5. Elbers PW, Ozdemir A, Heijmen RH, et al. Microvascular hemodynamics in human hypothermic circulatory arrest and selective antegrade cerebral perfusion. *Crit Care Med*. 2010; 38:1548–1553. [PubMed: 20473147]
6. den Uil CA, Lagrand WK, van der Ent M, et al. Impaired microcirculation predicts poor outcome of patients with acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J*. 2010; 31:3032–3039. [PubMed: 20829210]
7. Morelli A, Donati A, Ertmer C, et al. Levosimendan for resuscitating the microcirculation in patients with septic shock: a randomized controlled study. *Crit Care*. 2010; 14:R232. [PubMed: 21182783]
8. Martin DS, Goedhart P, Vercueil A, et al. *Exp Physiol*. 2010; 95:880–891. [PubMed: 20418348]
9. Dubin A, Pozo MO, Ferrara G, et al. Systemic and microcirculatory responses to progressive hemorrhage. *Intensive Care Med*. 2009; 35:556–564. [PubMed: 19127356]
10. del Zoppo GJ, Mabuchi T. Cerebral microvessel responses to focal ischemia. *J Cereb Blood Flow Metab*. 2003; 23:879–894. [PubMed: 12902832]
11. Belayev L, Pinard E, Nallet H, et al. Albumin therapy of transient focal cerebral ischemia: in vivo analysis of dynamic microvascular responses. *Stroke*. 2002; 33:1077–1084. [PubMed: 11935064]
12. Ahmed N, Wahlgren N, Grond M, et al. Implementation and outcome of thrombolysis with alteplase 3–4.5 hours after an acute stroke: an updated analysis from SITS-ISTR. *Lancet Neurol*. 2010; 9:866–874. [PubMed: 20667790]
13. Belayev L, Liu Y, Zhao W, et al. Human albumin therapy of acute ischemic stroke: marked neuroprotective efficacy at moderate doses and with a broad therapeutic window. *Stroke*. 2001; 32:553–560. [PubMed: 11157196]
14. Nimmagadda A, Park HP, Prado R, et al. Albumin therapy improves local vascular dynamics in a rat model of primary microvascular thrombosis: a two-photon laser-scanning microscopy study. *Stroke*. 2008; 39:198–204. [PubMed: 18032741]
15. Park HP, Nimmagadda A, DeFazio RA, et al. Albumin therapy augments the effect of thrombolysis on local vascular dynamics in a rat model of arteriolar thrombosis: a two-photon laser-scanning microscopy study. *Stroke*. 2008; 39:1556–1562. [PubMed: 18323493]
16. Hill MD, Martin RH, Palesch YY, et al. The Albumin in Acute Stroke (ALIAS) Part 1 Trial: an exploratory efficacy analysis. *Stroke*. 2010 [e-pub ahead of print].