Appendix Figures

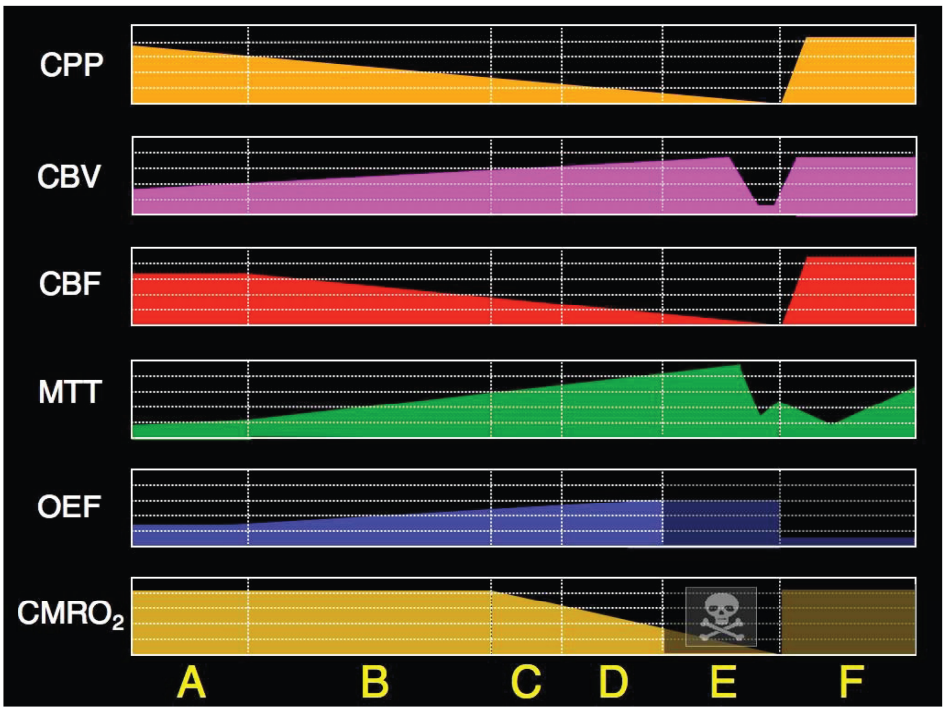

Figure A1

Figure A1. Hemodynamic changes that may occur in major anterior circulation occlusions. Cerebral perfusion is driven fundamentally by regional cerebral perfusion pressure (CPP). In response to mild decreases in CPP, precapillary resistance vessels dilate, in order to reduce cerebrovascular resistance. This is manifested by an increase in cerebral blood volume (CBV). If the reduction in vascular resistance is sufficient to maintain normal cerebral blood flow (CBF), this condition may be considered to be a compensated reduction in CPP (A). Note that

mean vascular transit time (MTT), which is the quotient of CBV divided by CBF, is increased in this condition.

With more severe reductions in CPP, autoregulatory vasodilation is insufficient to maintain normal CBF (B) CBF falls below normal levels, and therefore brain tissue experiencing this condition (and also hemodynamic conditions C through E) may be called "underperfused." MTT continues to increase, and this has the following protective effect upon the brain. When blood spends more time in gas-permeable capillaries, brain cells are able to extract a greater proportion of the blood's oxygen. As a result of this increase in oxygen extraction fraction (OEF), the brain's required oxygen supply is maintained, and the cerebral metabolic rate of oxygen consumption, CMRO2, is preserved. OEF and CMRO2 can be measured by PET, and ongoing developments in MRI technology hold the promise of measuring these quantities in the future.

If CPP falls further, OEF is maximized, and the brain's supply of oxygen begins to fall short of its metabolic needs (C). CMRO2 begins to fall, and lactate accumulates as a result of anaerobic glycolysis. However, a sufficiently mild drop in CMRO2 neither threatens tissue viability, nor results in clinically detectable electrical dysfunction. The conditions defined by (B) and (C) are sometimes called "benign oligemia."

A further reduction in CPP results in neuronal electrical failure (D), and therefore the possibility of a clinically observable neurologic deficit. However, the CBF threshold for electrical function is below the threshold for tissue viability, and

therefore some electrically silent tissue may persist indefinitely as such, without threat to its survival.

A sufficient reduction in CBF causes infarction (E). Importantly, the time that it takes for ischemic damage to become irreversible is inversely related to the severity of the ischemia. A complete cessation of blood flow causes cell death in minutes, whereas tissue may survive a less severe reduction in CBF for hours, before being rescued by reperfusion. The irregular graphs of CBV and MTT reflect the hypothesis in (E) reflect the hypothesis that, when CPP is extremely low, the elevation of CBV that is usually seen in ischemic may be reversed, and CBV may fall below normal, either because blood vessels collapse, or because extremely slow blood flow results in intravascular thrombosis. The phenomenon of CBV reduction has been incompletely researched, and it is not clear how often it occurs.

Reperfusion of previously ischemic tissue frequently occurs spontaneously, and may also result from therapeutic intervention. Following reperfusion, autoregulatory impairment often results in persistent vasodilation following restoration of normal CPP, a condition called post-ischemic hyperperfusion (F). CBV and CBF are both elevated above normal levels. Their quotient, MTT, may be either elevated or decreased, although the latter seems more common. Figure adapted by William A. Copen, MD from Powers WJ, et al. [1 2]

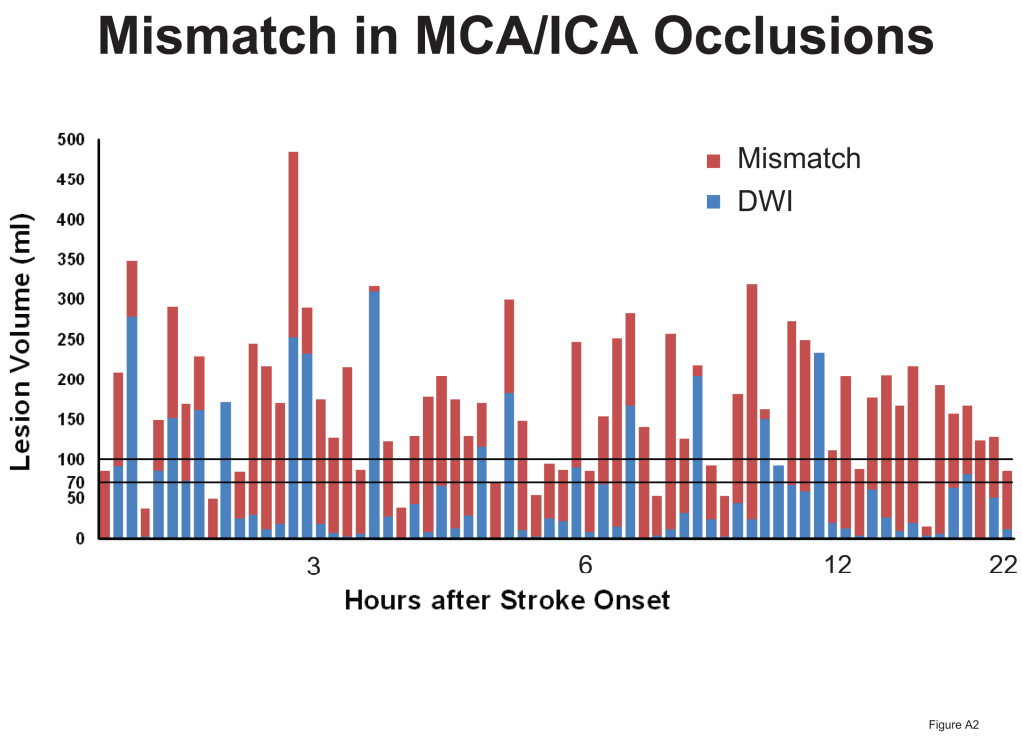

Figure A2. DWI/MTT mismatch volumes of 68 consecutive patients with anterior circulation occlusion in order of time after stroke onset. Abnormal DWI volume of each patient is depicted as a blue bar. Red bars represent DWI/MTT mismatch. Horizontal lines demarcate volumes of 70 ml and 100 ml. Time since stroke onset is in hours. All patients with DWI lesion volume 70 ml or less had at least a 100% mismatch. There was no significant correlation between time from stroke onset and DWI lesion volume or between time and mismatch volume. DWI: Diffusion weighted imaging; MTT: Mean transit time. [3 4]

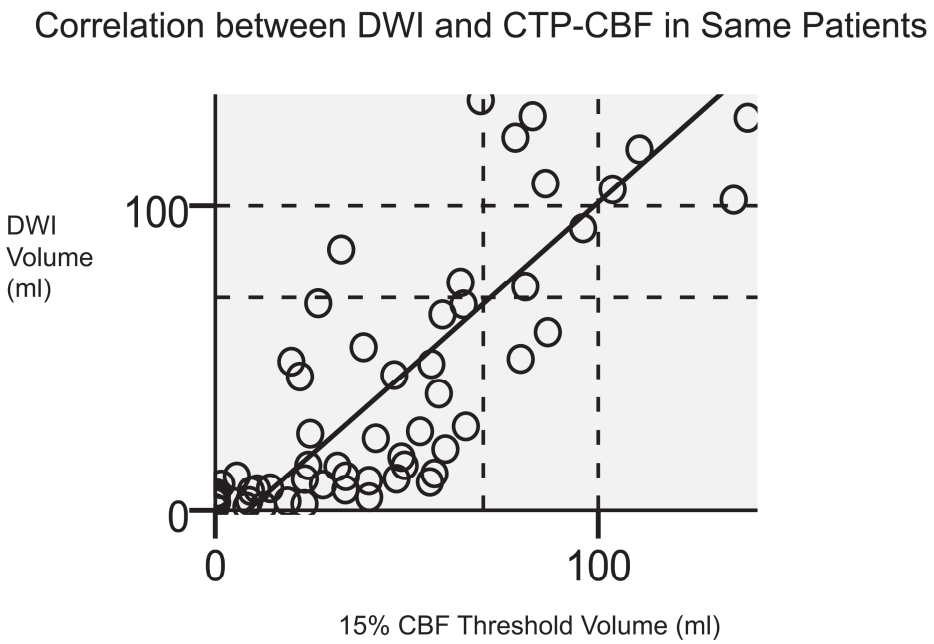

Figure A3

Figure A3. Comparison of DWI and CTP-derived cerebral blood flow estimates of core infarct volumes in the same patients with major anterior circulation occlusions. Analyses were performed on admission CTP and DWI of 62 stroke patients presenting with a large anterior circulation arterial occlusion on CTA. Infarct core was semi-automatically segmented on the admission DWI. A 15% thresholds was applied to the CBF map. Shown here are all patients with apparent core infarct volumes of less than ~150 ml on DWI or CBF. There was a high correlation between the 2 measurements (R2=0.87, slope=1.11 for CBF; p<0.001). However, as illustrated here, there was a wide discordance between the DWI and CBF measurements in individual patients. From Souza, Lev , Franceschi , Hi , Gonzalez,

Schaefer. Thresholded CTP Maps Can Accurately Determine Infarct Core When DWI Is Unavailable, and Have Similar Specificity in Identifying Patients Unlikely to Benefit from Thrombolysis. Data presented at 2011 Radiological Society of North America Annual Meeting.

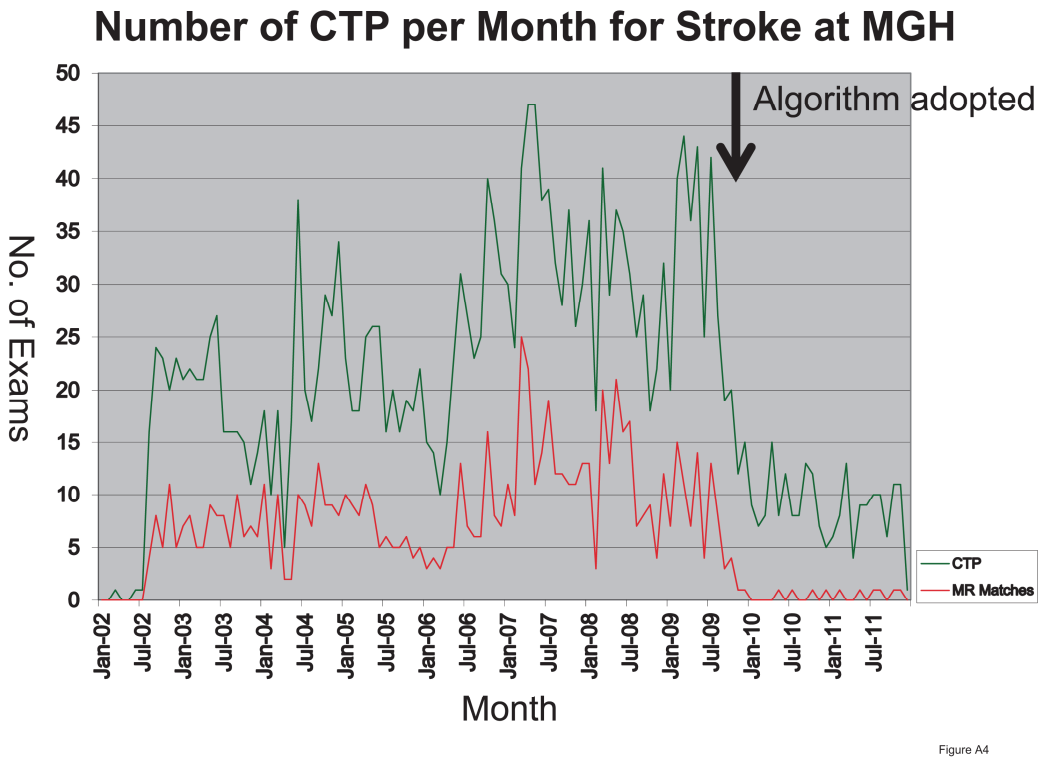

Figure A4. Monthly CT perfusion studies performed at MGH. The graph shows the number of CTP studies performed per month for stroke (green line) from July 2002 through December 2011. The red line shows the number of MRIs that were also performed on the same patients who had had CTP studies done. After we adopted this algorithm the number of CTPs dropped sharply (arrow).

Appendix Figure References

1. Powers WJ, Press GA, Grubb RL, Jr., et al. The effect of hemodynamically significant carotid artery disease on the hemodynamic status of the cerebral circulation. Annals of Internal Medicine 1987;**106**:27-34.
2. Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. Annals of Neurology 1991;**29**:231-40.
3. Copen WA, Rezai Gharai L, Barak ER, et al. Existence of the diffusion-perfusion mismatch within 24 hours after onset of acute stroke: dependence on proximal arterial occlusion. Radiology 2009;**250**:878-86.
4. Hakimelahi R, Yoo AJ, He J, et al. Rapid identification of a major diffusion/perfusion mismatch in distal internal carotid artery or middle cerebral artery ischemic stroke. BMC Neurol 2012;**12**:132.