From Time is brain to Physiology is brain: a case for reflection in acute stroke treatment decisions

This scientific commentary refers to ‘Perfusion computed tomography to assist decision making for stroke thrombolysis’, by Bivard et al. (doi:10.1093/brain/awv071).

The ischaemic penumbra, defined as severely hypoperfused, functionally impaired yet salvageable tissue, has been established as the key target for acute stroke therapy for more than three decades (Muir et al., 2006). However, the penumbra has a limited lifespan and, unless reperfused early, it progresses to become part of the irreversibly damaged tissue referred to as the ‘core’. The core therefore grows over time, incorporating first the most hypoperfused portions of the penumbra, and then progressively less hypoperfused portions, until none remains. How fast this process occurs varies greatly from subject to subject, mainly because of variable pial collaterals and the occurrence of spontaneous reperfusion (Fig. 1). On a mechanistic basis, reperfusion therapy—such as with intravenous thrombolysis using recombinant tissue plasminogen activator (rt-PA)—would be expected to be of no benefit, and potentially harmful, in cases with large core or no penumbra (Marchal et al., 1993).

Despite this underlying heterogeneity, clinical trials of intravenous rt-PA, the only currently licensed therapy in stroke, have evolved rather divergently from this mechanistic approach. In populations not selected on the basis of physiological brain imaging, the benefits of thrombolysis decrease with increasing time from stroke onset, and become undetectable ~4.5 h post-onset (Lees et al., 2010). At a mechanistic level, this is not surprising given the above-described time and space evolution (hence ‘Time is Brain’). Hitherto, physiological imaging has exclusively been evaluated in later time windows where the margin of benefit is much smaller. Setting up a trial to evaluate the benefit of add-on physiological imaging in the 0–4.5 h time-window presents an ethical and logistical challenge when a beneficial treatment is already available. Alongside a number of significant methodological issues, this challenge has been a major factor in the disappointing results of such trials (Alawneh and Baron, 2014). One interesting report, however, is the prospective DEFUSE study, which found that patients with the so-called ‘target mismatch’ profile on MRI, i.e. presence of penumbra but no large core, benefitted significantly from reperfusion-induced thrombolysis administered in the 3- to 6-h window, whereas this was not true of patients with the ‘no mismatch’ or ‘large core’ profiles—the latter being apparently harmed (Albers et al., 2006). Supporting findings emerged from the follow-up DEFUSE2 study using endovascular therapy (Lansberg et al., 2012).

In this issue of Brain, Bivard et al. report the results of a study in which they tested post hoc the effects of intravenous therapy in an earlier and shorter time window, using CT perfusion instead of MRI (Bivard et al., 2015). Institutional arrangements allowed the authors to obtain consent prior to treatment. Their study, although observational, further supports the idea that clinical outcomes and safety of thrombolysis can be improved with imaging-based selection, and is the first to address this issue using CT perfusion.

The investigators describe a cohort of consecutive acute stroke patients, all potential candidates for thrombolysis, i.e. following a priori exclusion of those with medical contra-indications or a large hypodense lesion on non-contrast CT, over a 5-year period in a tertiary stroke centre in Australia. More than 600 patients fulfilled the study criteria and underwent selection for intravenous therapy on the basis of a visual assessment of whole-brain CT perfusion images as provided by vendor software. More than half of these (n = 366) were visually categorized as having the ‘target mismatch’ profile and therefore received intravenous therapy. Post hoc quantitative analysis was then used to re-categorize the entire cohort according to precise imaging criteria, as described in previous physiological imaging studies (Fig. 1): (i) ‘target’ mismatch: perfusion lesion-core mismatch ratio >1.8 and perfusion lesion volume >15 ml, core <70 ml; (ii) large core >70 ml; and (iii) no ‘target’ mismatch: perfusion lesion-core mismatch ratio <1.8 or volume <15 ml, core <70 ml.

They then compared the outcome of thrombolysed versus non-thrombolysed patients within each CT perfusion category. Comparisons were adjusted for several major variables influencing outcome in univariate analyses, including core and hypoperfusion volumes.

There are three key findings in the study. Firstly, patients with a target mismatch who received treatment had significantly greater chances of achieving no or minimal disability than those who did not receive treatment (adjusted odds ratios 23.1 and 13.8, respectively), with a strikingly low symptomatic intracerebral haemorrhage (ICH) rate (~2%). Secondly, patients with a large core did not benefit from therapy and had a significantly higher incidence of symptomatic ICH (25%). Thirdly, no-mismatch patients fared worse with treatment despite demographic factors...
Figure 1 The three main pathophysiological profiles used by Bivard et al. to categorize acute stroke patients, as originally defined using PET with $^{15}$O-labelled compounds to generate quantitative maps of cerebral blood flow (CBF, left column) and the cerebral oxygen metabolic rate (CMRO$_2$, right). Validated tissue compartments including penumbra (reduced cerebral blood flow but relatively preserved CMRO$_2$) and core (markedly reduced CMRO$_2$) were used to characterize the three profiles of ‘target mismatch’, ‘large core’ and ‘no mismatch’ (Muir et al., 2006). Consistent with the strikingly distinct spontaneous outcomes associated with these profiles (Marchal et al., 1993), Bivard et al. provide evidence from their cohort that the target mismatch group, i.e. patients with significant penumbral tissue and a small core, benefit the most from intravenous thrombolysis administered within 4.5 h of stroke onset, while the no-mismatch and large core groups do not benefit and may even be harmed. Modified from Marchal et al. (1993).

Biasing the treated group to better outcomes.

Interestingly, major reperfusion (assessed with magnetic resonance $\sim$24 h post-treatment) was achieved in 62% of the treated target mismatch patients versus 19% in the untreated target mismatch group. This further confirms that early tissue reperfusion is probably the strongest predictor of response to therapy, and that the target mismatch profile identifies a subgroup of patients very likely to reperfuse early if rt-PA is given within 4.5 h.

The authors also compared their data set with historical controls, which is not ideal but reasonable given the observational nature of the study. Reassuringly, despite a potential negative bias in that the study patients had more severe strokes and a longer onset-to-treatment time driven by delays in transfer to the tertiary centre compared to historical controls, outcomes in the imaging-selected treated group were significantly better. This was despite a $\sim$30% error rate in visual as compared to quantitative patient selection, which meant that some patients with quantitative mismatch did not in fact receive treatment. Effectively, using the post hoc quantitative categorization, the difference compared to the historical, non-contrast CT-only selected group was even greater. That patients with the no-mismatch profile have little to gain from intravenous therapy and may even come to harm further argues against the commonly held view that thrombolysis may be ‘safe’ in such patients. Finally, the large core profile group did not benefit from treatment either, and furthermore showed a very high incidence of symptomatic ICH as compared to the historical group. Importantly, this was despite a priori exclusion of patients with a large hypodense area on non-contrast CT, indicating that the latter does not safely exclude all large core cases. As the proportion of patients receiving thrombolysis increases, the resource and safety implications of an incorrect label of stroke may become enormous.

Overall 58% of patients were treated on the basis of presence of mismatch visually, while target mismatch was in fact present in $\sim$52% of patients overall. Although excluding 48% of potential rt-PA candidates (i.e. primary contra-indications apart) may appear a lot, treating only those likely to respond and excluding the unlikely responders and those potentially harmed is standard decision-making in emergency medicine.

Fewer than 2% of patients screened were excluded because of imaging-related issues such as movement artefacts and contrast injection failure, highlighting the strength of CT over magnetic resonance-based acute imaging modalities. This could potentially facilitate recruitment into clinical trials of newer stroke therapies. Another strength of the Bivard et al. study is the short door-to-needle time (51 min), which is better than the recommended target worldwide (Jauch et al., 2013) and than that achieved, on average, in most centres not using perfusion imaging. It is also reassuring that the investigators found no significant renal or radiation safety issues, which have been causes of concern with CT perfusion previously. With optimization of acquisition protocols, as with CT imaging allowing simultaneous whole-brain coverage and angiography (Agarwal et al., 2013), radiation doses can be minimized.

There are also some limitations to this study. The main one is the lack of a randomized comparison between groups, although groups were fairly well matched for most baseline characteristics. This limitation means that the results cannot be construed as formal evidence. Where the groups differed, in fact, the differences would be expected to bias the results against the authors’ conclusions. Thus, their findings appear fairly robust. There was a substantial error rate in visual classification relative to
post hoc quantitative assessment across all three CT perfusion profiles, illustrating the well-known intrinsic limitations of visual assessment based on vendor displays. Ultra-fast and reliable quantitative processing software that can be incorporated into daily practice is therefore needed if the findings from this study are ever to be tested formally in prospective studies or applied in routine practice.

Another caveat is the lack of consensus in the literature about optimum thresholds and processing methods to identify the penumbra and core using CT perfusion. Although the imaging definitions applied in this study have a sound basis from previous work, this is another area that needs clarification. Additionally, not all patients underwent CT angiography, so vessel occlusion site data are incomplete. A further point relates to lacunar strokes (n = 37), a group belonging to the no-mismatch profile that did not respond to thrombolysis, and for which no subgroup analysis is presented. Post hoc analyses of the early thrombolysis trials claimed that patients with lacunar infarcts benefitted just as much as others. It therefore remains unclear what the optimal treatment strategy for this group would be.

In summary, the study by Bivard et al. makes a strong case for CT perfusion-based selection for thrombolysis in an early time window. Although only a randomized comparison would establish the conclusions of this work beyond reasonable doubt, the study findings are convincing. Emerging randomized trial evidence with CT perfusion-based phenotyping for intravascular interventions (Campbell et al., 2015) and newer thrombolytic agents (Parsons et al., 2012) showing unprecedented rates of good outcomes further support the case. Perhaps heterogeneity of findings in early trials will be clarified in due course by physiological imaging-based studies. The use of CT perfusion to select the responders to intravenous therapy beyond 4.5 h is another area in need of prospective studies.

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doi:10.1093/brain/awv120

References


Progranulin protects against the tissue damage of acute ischaemic stroke

This scientific commentary refers to ‘Multiple therapeutic effects of progranulin on experimental acute ischaemic stroke’, by Kanazawa et al. (doi:10.1093/brain/awv079).

Stroke is one of the commonest causes of death, and survivors often suffer debilitating impairments of speech, memory, movement, swallowing and other neurological functions. About 80% of strokes are ischaemic, due to thrombosis or embolism. The resultant loss of oxygen to the affected tissue depletes cells of energy and initiates a series of biological events that...