

Perfusion imaging in ischaemic stroke

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Abstract

Perfusion imaging allows the blood flow to the tissue to be imaged. It is currently widely applied to the management of acute ischaemic stroke. Using either Computerised Tomography or Magnetic Resonance Imaging techniques, perfusion maps can be created in a short enough time to allow their routine use in clinical practice. Perfusion Imaging enables the physician to directly estimate the tissue at risk which can be salvaged with reperfusion, enabling appropriate patient selection. Perfusion imaging however has its limitations which need to be kept in mind when these studies are interpreted. Although perfusion imaging is widely used, the evidence to support its routine use in acute stroke is somewhat sparse and therefore there are no clear cut guidelines as to its role in this context. The work in progress using permeability mapping and molecular imaging techniques will further augment the place of these techniques in the overall management of acute stroke. There are very few centres in Pakistan offering routine perfusion imaging prior to thrombolysis.

Introduction

Although blood flow to the brain was first imaged using angiographic techniques over 60 years ago it was not possible to accurately measure in vivo brain perfusion until the development of radionuclide techniques in the late 1960s.¹ Clinical applications of brain perfusion imaging using radio labelled albumin macroaggregates appeared soon afterwards² but its application in the setting of acute cerebral ischaemia was impractical. The development of first Magnetic Resonance (MR) and later Computerised Tomographic (CT) techniques to measure brain perfusion has brought this modality to every day clinical applications.^{3,4} The technology has now evolved to the extent that these examinations can be completed in a very short time enabling their use in routine stroke imaging.^{5,6}

The role of perfusion imaging in stroke

Perfusion imaging has been applied to a range of conditions,⁷ but it is most widely applied in the setting of cerebral vascular disease especially acute ischaemia. With the publication of the the National Institute of Neurological Disorders and Stroke recombinant Tissue Plasminogen

Activator Stroke Study [NINDS]⁸ and the European Cooperative Acute Stroke Study [ECASS]⁹ results in 1995, the role of imaging in stroke underwent a paradigm shift. The emphasis shifted from confirmation of infarction and exclusion of haemorrhage to the detection of the 'tissue at risk' that may be rescued with restoration of circulation. Perfusion imaging is currently the only test available in clinical departments that can answer this question.

Imaging of cerebral infarction in the first hour after the onset of clinical symptoms is a challenge. On MR imaging this is achieved by employing Diffusion Weighted Imaging (DWI). However DWI only shows areas that are already irreversibly damaged. On CT there is no equivalent of the DWI and although the CT may be abnormal in the first hour the signs are subtle and difficult to recognise.¹⁰ In both instances perfusion imaging provides the information required for effective decision making.

Perfusion Parameters in Stroke Imaging

Perfusion is defined as the amount of blood (volume) flowing through any tissue (mass) per unit time. It is usually expressed as millilitres per gram per minute (mL/Gm/min). In the normal brain, auto regulation of the vasculature maintains cerebral blood flow (CBF) to the grey matter between 50-60 mL/100Gm/min.¹¹ CBF is the primary perfusion parameter that is studied. When CBF falls to approximately half of normal (35mL/100gm/min or less), protein synthesis in neurons stops completely however the neurons are functional and will survive if the CBF does not fall any further.¹² When the CBF falls to approximately a third of normal (20mL/100gm/min or less) neuronal function is lost but the neurons may still be viable.⁴ This is the tissue at risk and can be salvaged if appropriate measures to restore the CBF are instituted. Irreversible cell death occurs when CBF falls to less than 20% of normal (10mL/100gm/min or less).¹³

Cerebral blood volume (CBV) is the volume of blood per unit brain mass. Normal CBV is 4-5 mL/100gm. In early ischaemia with the dilatation of the capillary bed the CBV rises slightly or is maintained at a near normal level despite the falling CBF. When CBV starts to fall irreversible cell death has occurred.⁴

Two parameters of transit times are usually employed depending on the exact calculation methodology

Table 1. Interpretation of perfusion data in the first three hours of stroke onset. Adapted from Tomandl et al.⁶

Pathological Condition	TTP/MTT	Perfusion Finding	
		rCBF	rCBV
Normal	Normal	Normal	Normal
Arterial Stenosis or occlusion with excellent compensation	Prolonged	Normal	Normal
Oligemic tissue that will survive	Prolonged	Moderately reduced	Normal or slightly elevated
Tissue at risk	Prolonged	Markedly reduced	Normal or slightly reduced
Tissue that is irreversibly damaged	Strong prolongation or may not be measurable	Severely reduced	Severely reduced

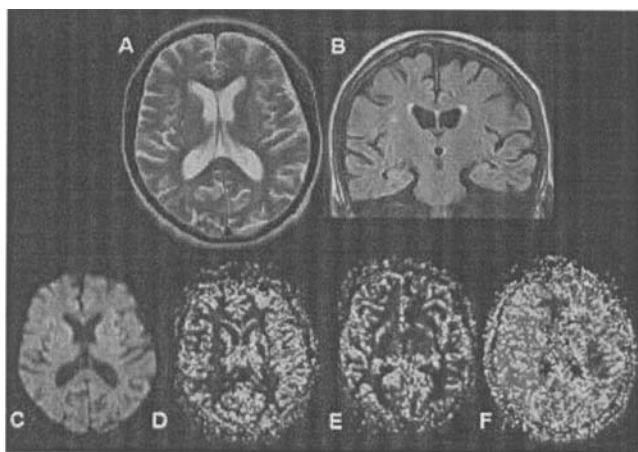


Figure 1. MR of the brain with diffusion and perfusion images demonstrating the ischemic penumbra. A 60-year-old male with acute onset of left-sided hemiparesis for 30 minutes. A: T2-weighted axial image is within normal limits. B: Coronal FLAIR images also within normal limits. C: b1000 Diffusion-weighted image shows no significant diffusion restriction. D: CBF map showing asymmetry with reduced blood flow in the right temporal and parietal lobes. E: CBV map showing asymmetry with some increased CBV in the corresponding area. F: MTT map demonstrating marked prolongation of MTT. Findings are those of impending infarction with no restriction of diffusion, reduced blood flow, or preserved blood. [From Hussain Z et al (7)]

employed. These are Mean Transit Time (MTT) and Time to Peak (TTP). MTT is the interval between arterial inflow and venous outflow and TTP is the time from the beginning of the contrast injection to the peak enhancement within a region of interest.⁴ Transit times become prolonged early in the course of the ischaemic event and increases to immeasurable levels as the infarct progresses.

MTT/TTP are the most sensitive for acute infarct and generally show the largest defects on perfusion maps but have the poorest correlation to eventual infarct size. CBV defects have the best correlation to eventual infarct size.¹⁴ CBF defects are the most specific for acute infarction. The methodology for calculating these parameters is different between CT and MR perfusion studies; there is a close correlation between the values obtained from the two modalities.¹⁵ The data whether obtained from CT or MR has the same clinical relevance and may be used interchangeably in clinical decision making. (Table 1) (Figure 1)

Although it is possible to calculate absolute values for CBF and CBV there are methodological constraints and these therefore in most clinical applications use relative

values comparing the 'normal' from the 'abnormal' side based on the patient's symptoms. These relative values are denoted by prefixing a small case r to the abbreviations (rCBF, rCBV). The rCBF and rCBV accurately reflect the absolute values and are adequate for clinical applications.¹⁶

MR Perfusion Imaging

MR Perfusion Weighted Imaging (PWI) may be performed with or without an intravenous (iv) injection of a gadolinium based contrast agent. Although clinical applications of PWI without iv contrast using a technique called arterial spin labelling have been described,¹⁷ it is still largely experimental and difficult to implement, especially on intermediate or low field strength units (1.5T or less). Contrast based PWI is the standard for clinical imaging. Sequential acquisitions are carried out after an iv injection and perfusion maps are generated by the software which is now well standardised. The operator has to identify the input artery, usually the middle cerebral artery. This sets the arterial input function (AIF) and sets the time ranges. Other than these two steps, the calculations are automated and reproducible. Tissue at risk is calculated by comparing the DWI maps with the PWI maps. DWI/PWI mismatch is the tissue at risk or penumbra. Usually rCBF or rCBV maps are employed for this purpose as MTT/TTP may be abnormal even without any infarction (Table 1).⁵

Not only can tissue at risk be identified with DWI/PWI mapping, MR angiography adds another dimension to the overall stroke imaging. It rapidly identifies patients that will need more aggressive interventions rather than just iv thrombolysis.

CT Perfusion Imaging

CT perfusion imaging is carried out after the injection of iodinated contrast medium. The same slice is repeatedly scanned and the rate of change of attenuation is plotted. On conventional spiral scanners only a single slice can be covered. On multi detector row CT (MDCT) more slices may be covered depending on the number of rows. The major limitation of CT perfusion imaging is that only the latest 64+ detector row CT scanners can achieve near complete coverage of the brain. Most scanners only cover

Table 2. Comparison of CT and MR imaging for the evaluation of acute stroke. Adapted from Sirinavasan et al. ⁵

Characteristic	CT	MR Imaging
Availability	Good, getting much better	Fair, Getting better
Examination time	5-10 minutes	15-30 minutes
Imaging Volume for perfusion study	2-4 cms	Entire Brain
Ability to exclude haemorrhage	Excellent	Good but may require expert interpretation
Ability to detect early irreversible infarction	Good (needs perfusion mapping)	Excellent (using DWI)
Risks to patient		
Radiation	Ionising radiation and associated risks	No Radiation
Contrast Agent	Iodinated contrast mandatory, risks of allergic and toxic effects	May not be required if canner able to perform spin labelled imaging. Gadolinium based contrast has significantly lower allergic and toxic effects at the doses administered.
Environment	No special risks, easy to monitor patient, no absolute contraindications	Magnetic fields, restricted access, difficult to monitor patient, absolute contraindications (pacemakers)

1 to 4, 10mm slices of the brain and therefore substantial perfusion defects may be missed unless multiple boluses are used.¹⁸ The operator sets regions of interest over the input artery and the draining vein. The rest of the calculations are usually automated.⁵

As there is no DWI equivalent in CT scanning the tissue at risk is calculated by rCBV/rCBF mismatch, as CBV has the closest correlation to DWI abnormalities.¹⁵ Like MR imaging it is now possible to have a 'one stop' imaging with CT scanning with the one scan providing anatomic, perfusion as well as angiographic information.¹⁹

CT or MR?

The comparative merits and disadvantages of CT and MR are listed in Table 2. As far as the clinical applicability of the perfusion parameters is concerned there is not much to choose between them.¹⁵ The choice therefore is based on local availability and logistics. Due to the wide availability of CT and its high sensitivity to the presence of haemorrhage, most patients being considered for thrombolysis will have a CT first. If an angiogram and a perfusion image can be obtained in an additional 10 minutes without moving the patient it would be the ideal scenario.⁶

Limitations of Perfusion Imaging

Some of the limitations such as the limited coverage on CT perfusion have already been discussed earlier in the article.

The major limitation of MR perfusion imaging is related to the arterial input function (see above). As the acquisitions are dependent on a T2* signal drop it may not be possible to visually confirm the adequacy of the injection and therefore it is mandatory to plot a time activity curve to confirm that the bolus profile was satisfactory. Dispersion of the bolus leads to clinically significant errors in the

calculation of CBF.²⁰ CBV calculations may be more robust. Although relative values (rCBV, rCBF) may be less prone to bolus dispersion, as they depend on a comparison, if the two sides have symmetrical defects the maps will be erroneously normal. This is also true if the injection is either erroneously timed (or not given at all) so that the acquisition is completed before the bolus arrives.

Current Recommendations for the Use of Perfusion Imaging in Stroke

Although many studies have demonstrated that perfusion imaging provides additional information, systematic reviews of the published literature have failed to determine its exact role in either diagnosis or treatment stratification in acute stroke.^{21,22} There is no universal agreement as to the sensitivity or specificity of the mismatch or its role in selecting patients for thrombolysis. In view of these facts there are no clear cut recommendations. Common sense would suggest that while more data is accumulated patients should benefit from the additional information if it can be obtained within a reasonable length of time so that treatment is not delayed.

The Future

The stage is set for the next paradigm shift in imaging. MR permeability studies looking at the integrity of the blood brain barrier are already undergoing clinical trials.²³ The early data suggests that disruption of the blood brain barrier may be a helpful sign in predicting haemorrhage in acute stroke.²⁴ Developments in molecular imaging are targeting the molecular cascade in the development and evolution of the penumbra. New developments as well as better data to support the already established technologies is likely to have a significant impact leading to improvements in outcomes for stroke

sufferers.

Situation in Pakistan

Although the availability of MR and CT units capable of carrying out state of art stroke imaging is growing, very few of these are in acute hospitals where acute neurological emergencies are handled. As an example in Karachi, of over 20 centres with either a MR or a CT scanner only 2 units offer routine perfusion imaging. There has to be a serious rethink of the health care strategies to make healthcare more accessible and relevant for the people of Pakistan.²⁵

Summary

Perfusion imaging adds additional important information in the setting of acute ischaemic stroke. It may be obtained by several means. In clinical practice it is obtained either by MR or CT after the administration of iv contrast. It helps define the tissue at risk and may be helpful in appropriate selection of patients suitable for thrombolysis. Both of the most widely applied techniques (CT and MR) have their limitations and pitfalls which need to be considered when interpreting the images.

References

1. Kennady JC, Taplin GV. Albumin Macroaggregates for brain scanning: Experimental basis and safety in primates. *J Nucl Med.* 1965;6:566-81.
2. Briz-Kanafani S, Garcia-Montemayor E. Perfusion brain scans and the anatomic lesions encountered: A correlation. *AJNR.* 1970;109(4):686-691
3. Le Bihan D. Diffusion Perfusion MR imaging of the brain: From structure to function. *Radiology* 1990;177:328-29.
4. Koenig M, Koltz E, Luka B, Vanderink DJ, Spittler JF, Heuser L. Perfusion CT of the brain: Diagnostic approach for early detection of ischemic stroke. *Radiology* 1998;209:85-93.
5. Srinivasan A, Goyal M, Al Azri F, Lum C. State of Art imaging in acute stroke. *Radiographics.* 2006; 26:S75-S95.
6. Tomandl BF, Klotz E, Handschu R, Stemper B, Rienhardt, Huk WJ, et al. Comprehensive imaging of ischemic stroke with multi section CT. *RadioGraphics* 2003;23:565-92.
7. Hussain Z, Sajjad Z, MR Perfusion Imaging. *Pak J Neurol Sci* 2006;1: 162-66.
8. Tissue Plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995;333:1581-87.
9. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA.* 1995;274: 1017-25.
10. Roberts HC, Dillon WP, Furlan AJ, Wechsler LR, Rowley HA, Fischbein NJ, et al. Computed tomographic findings in patients undergoing intra-arterial thrombolysis for acute ischemic stroke due to middle cerebral artery occlusion: results from the PROACT II trial. *Stroke.* 2002; 33: 1557-65.
11. Heiss WD. Ischemic penumbra: Evidence from functional imaging in man. *J Cereb Blood Flow Metab* 2000;20:1276-93.
12. Mies G, Ishimaru S, Xie Y, Seo K, Hossmann KA. Ischemic thresholds of cerebral protein synthesis and energy state following middle cerebral artery occlusion in rat. *J Cereb Blood Flow Metab* 1991;11:753-61.
13. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia. : The ischemic penumbra. *Stroke* 1981;12:723-25.
14. Karonen JO, Liu Y, Vanninen RL, Ostergaard L, Kaarina Partanen PL, Vainio PA, et al. Combined perfusion- and diffusion weighted MR imaging in acute ischemic stroke during the 1st week: a longitudinal study. *Radiology* 2000;217: 886-94.
15. Eastwood JD, Lev MH, Wintermark M, Fitzek C, Barboriak DP, Delong DM, et al. Correlation of early dynamic CT perfusion imaging with whole brain MR diffusion and perfusion imaging in acute hemispheric stroke. *Am J Neuroradiol* 2003;24:1869-75.
16. Grandin CB, Duprez TP, Smith AM, Oppenheim C, Peeters A, Robert AR, et al. Which MR derived perfusion parameters are the best predictors of infarct growth in hyper acute stroke? Comparative study between relative and quantitative measurements. *Radiology* 2002; 223: 361-70.
17. van Laar PJ, van der Grond J, Hendrikse J. Brain perfusion territory imaging: methods and clinical applications of selective arterial spin-labeling MR imaging. *Radiology.* 2008;246: 354-64.
18. Mayer TE, Hamann GF, Baranczyk J, Rosengarten B, Klotz E, Wiesmann M, et al. Dynamic CT perfusion imaging of acute stroke. *AJNR Am J Neuroradiol.* 2000; 21: 1441-49.
19. Smith WS, Roberts HC, Chuang NA, Ong KC, Lee TJ, Johnston SC, et al. Safety and feasibility of a CT protocol for acute stroke: combined CT, CT angiography and CT perfusion imaging in 53 consecutive patients. *AJNR Am J Neuroradiol.* 2003; 24: 688-90.
20. Calamante F, Gadian DG, Connelly A. Quantification of perfusion using bolus tracking magnetic resonance imaging in stroke: assumptions, limitations and potential implications for clinical use. *Stroke.* 2002;33: 1146-51.
21. Kane I, Sandercock P, Wardlaw J. Magnetic resonance perfusion diffusion mismatch and thrombolysis in acute ischaemic stroke: a systematic review of the evidence to date. *J Neurol Neurosurg Psychiatry.* 2007; 78: 485-91. Epub 2006..
22. Keir SL, Wardlaw JM. Systematic review of diffusion and perfusion imaging in acute ischemic stroke. *Stroke.* 2000;31: 2723-31.
23. Kassner A, Roberts TP. Beyond perfusion: cerebral vascular reactivity and assessment of microvascular permeability. *Top Magn Reson Imaging.* 2004; 15: 58-65.
24. Kassner A, Roberts T, Taylor K, Silver F, Mikulis D. Prediction of hemorrhage in acute ischemic stroke using permeability MR imaging. *AJNR Am J Neuroradiol.* 2005; 26: 2213-17.
25. Sajjad Z. Multi-slice CT Scanning, Editorial. *Pak J Neur S* 2006; 1: 4-5.