REVIEW ARTICLE

ACUTE STROKE: BASIC CONCEPTS AND USE OF IMAGING FOR CLINICIANS

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In this article we review basic and some advanced concepts of stroke imaging. The benefits and caveats of both CT and MRI are stressed and we attempt to familiarize the reader with current concepts regarding collateral brain circulation, its nature, and its importance in acute stroke.

Key-word: Brain, ischemia, collateral circulation.

Stroke is a clinical condition with varied symptoms generally related to inadequate blood flow to a part of the brain. The term "stroke" does not imply an etiology. Strokes are mostly due to ischemia (90%) or hemorrhage (5-10%) (1). Other causes such as arteriovenous malformations and tumors may occasionally (2%) cause stroke symptoms. Because treatment for intracerebral hemorrhage must occur immediately (i.e. surgical decompression) and because it precludes treatment for ischemic stroke (anticoagulation, thrombolysis), its early detection is paramount. Since CT is exquisitely sensitive for detection of hemorrhage, it is extensively used as the initial imaging study in stroke patients (2). Recent data show that intracerebral hemorrhage is more common than previously believed with about 70,000 such cases happening every year in the USA (3). Large intracerebral bleeds carry a 32% mortality rate which has remained unchanged for many decades. Intracerebral hemorrhages will not be addressed in this review.

Ischemic stroke occurs in nearly 800,000 individuals per year in the USA resulting in over 140,000 deaths (4). The treatment of stroke is based on the "brain is time" paradigm which as we will see later, is not completely correct (1). Stroke has been categorized based on its temporal evolution. But since treatment needs to be instituted as fast as possible, we cannot wait for a patient's clinical evolution to make the correct diagnosis. In the past, ischemic stroke was broadly divided into TIA (transient ischemic attack) and infarction. The traditional definition of TIA was time-driven; that is, symptoms resolved within 24 hours. That definition is no longer used because by 24 hours, treatment of true stroke is not possible and patients may improve due to transfer of function (brain plasticity) and still have an infarct. Therefore, TIA is now a tissue-driven definition in which the patients must have normal DWI (diffusion-weighted imaging) and symptoms need to resolve within one hour of onset (5). If one images all patients with TIAs, DWI shows lacunar and small infarcts in 35-70% of them (6). These patients cannot be considered as having had a TIA and are better categorized as having small volume infarctions which generally, and regardless of treatment, have a good prognosis (7). Approximately 45% of cerebral infarctions can be categorized as minor (segmental arterial branch occlusions) and 20% as lacunar (arising from occlusion of the deep perforating arteries). These two types of infarctions carry a good prognosis and will not be discussed here. The following discussion centers on major infarctions (35%) and on the role of collateral circulation. Over one-half of major infarctions are due to occlusion of the MCA (middle cerebral artery) and most are from emboli that arise from disease at the level of the common carotid artery bifurcation in the neck (8). It is critical to mention here that timely systemic (intravenous) thrombolytic treatment transforms about 30% of major infarctions into minor ones and that intra-arterial thrombolysis in those who fail systemic treatment will transform another 30% of major into minor ones. Thus, by adequately treating patients one could transform up to 60% of major infarcts into minor ones which have a good prognosis (R. Gilberto Gonzales, personal communication).

Imaging of acute stroke

Because of its extreme sensitivity and specificity in the diagnosis of acute brain hemorrhage, CT continues to play an important role in the evaluation of the acute stroke patient (1, 8). However, its ability to depict infarctions is only about 60% within the 3-6 hours that follow onset of symptoms. Thus, if used in treatment trials it is estimated that up 50% of patients are treated unnecessarily a finding that may reflect the significant success of early trials which were only CT-driven. Hemorrhage or low density in over 1/3 of the MCA territory precludes thrombolysis. The "1/3 rule" was empirically arrived at by estimating that the volume of territory supplied by the MCA is normally about 300 ml and in our opinion estimating the volume of the involved territory is difficult and impractical. Other CT signs of acute MCA infarction include the "hyperdense MCA" (reflecting intraluminal clot), blurring with low density of the gray matter in the insular cortex ("insular ribbon" sign) and basal ganglia all off which reflect cytotoxic edema, and sulcal effacement (1).

The greatest revolution in stroke imaging was the advent of DWI (9). DWI is sensitive to the imbalance between extracellular and intracellular water (cytotoxic edema) and it becomes positive in most patients in less than 1 hour after stroke symptom onset. As water migrates into the complex intracellular space and the extracellular space size is reduced by cell swelling, the ability of water molecules to randomly move (called Brownian motion) decreases giving raise to restriction of the

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apparent diffusion coefficient (ADC). Note that the diffusion coefficient is called "apparent" because its true magnitude cannot be calculated with current clinical techniques. By comparison, cytotoxic edema seen as gray matter T2 high signal intensity on conventional MR imaging is seen in less 80% of infarctions at 24 hours. The success of DWI is based on the facts that it can be rapidly obtained stopping macroscopic motion (thus it is helpful in unstable patients who cannot hold still for prolonged periods of time), it is easy to interpret, it reliable and reproducible, and its post processing is fast and easy (10). Of course, lack of intra-arterial flow-related enhancement (signal) on MRA, intravascular high FLAIR signal, and intravascular contrast enhancement help confirm the diagnosis vessel occlusion or severe stenosis on conventional MR imaging (11). Regardless of this, no one should attempt to image acute stroke patients without DWI. It is important to remember that DWI is ideal for the acute period but that the abnormal signal depicted by it generally disappears by 10-15 days. This phenomenon does not imply that the underlying tissues revert to normal, on the contrary, they remain abnormal and this "pseudo-normalization" is considered a caveat and artifact in DWI of subacute infarctions (12).

The second most important MRI advance (but equally important for CT) was the development of brain perfusion sequences (8, 13). In both modalities, perfusion imaging is based on the same principle, that is, the passage of intravascular contrast through the capillary bed produces a loss of signal intensity in the case of MRI and a gain in density in CT. Thus, the amount of signal/density is proportional to the contrast getting to a specific regions and proportional to cerebral blood flow. In order to obtain perfusion images, MR units with echo planar capability and CT with spiral capabilities are needed. A compact bolus of contrast (in MRI contrast followed by saline solution and in CT only iodinated contrast) at a rate of 3-5 ml/sec is given generally in the right antecubital vein and from an automatically generated TTP map (time-to-peak) other parametric maps such as the CVB (cerebral blood volume), MTT (mean transit time), and CBF (cerebral blood flow) can be calculated. All maps are "relative" and not quantitative in regards to the parameters being measured. In ischemic stroke, alterations in rCBF are seen in over 90% of patients

with both MR and CT perfusion. However, circulation abnormalities are more obvious and easier to visually detect on the TTP and MTT maps. Defects seen on those two maps need to be confirmed on the rCBF one.

The tissue "penumbra" is defined as that part of the brain at risk for stroke due to impaired and deficient blood supply but which can still be salvage with appropriate therapy (14). By imaging, the penumbra is the perfusion defect which can be separated from the core of the infarct as seen on the DWI, that is, a perfusion/diffusion mismatch. Patients with penumbras must be acutely and even chronically treated to save those tissues. Patients without penumbra (no diffusion/perfusion mismatch) should not be treated regardless of the size of the infarct because all of the affected tissue is considered to be irreversibly damaged. The following type's mismatches can be seen on MRI:

1. Perfusion defect> DWI abnormality: means a penumbra is present and since the core of infarct may progress to involve the entire penumbra, treatment is indicated (Figs. 1 and 2).
2. DWI abnormality with accompanying high rCBV and defect on MTT/TTP: means presence of a penumbra with collateral circulation (see below), there is a chance of core progression and acute or chronic treatment is indicated (Fig. 3).
3. Perfusion defect and normal DWI: means no infarct but tissue is at risk due to inadequate perfusion; there is a chance of future stroke and treatment must be given.
4. DWI abnormality > perfusion defect: means early and generally spontaneous re-perfusion, core may decrease in size or remain stable. No acute treatment is needed (Fig. 4).
5. DWI abnormality = perfusion defect: means there is no penumbra, no collateral circulation, and the infarct core will remain stable. No immediate treatment is needed.

Susceptibility-weighted imaging (SWI) also has the ability (perhaps even earlier than DWI) of detecting acute infarctions (15). After an arterial occlusion there is always physiological dilation of veins and arteries in the ischemic territory. SWI exquisitely depicts deoxygenated venous blood in dilated veins in ischemic
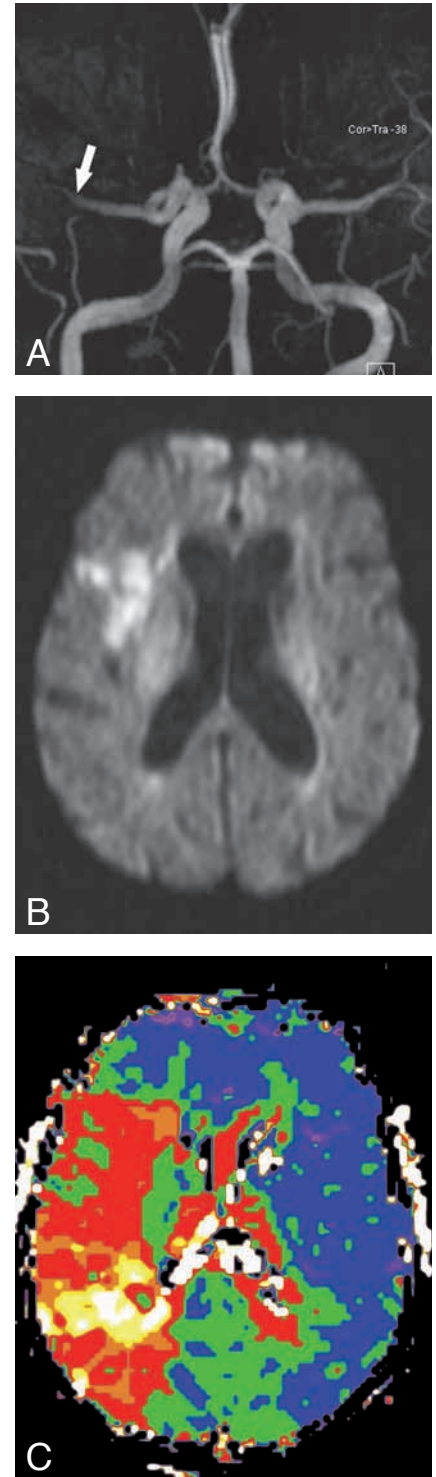
Fig. 1. — A. Frontal MRA view shows occlusion of the right middle cerebral artery (MCA, arrow). B. Axial DWI shows areas of high signal which showed restriction on ADC map (not shown) in the deep regions of the right MCA territory. C. TTP MRI map shows delayed arrival of blood in the entire MCA territory. The mismatch between the perfusion and DWI abnormalities represents the ischemic penumbra. The large volume of the penumbra in this patient indicates that treatment would be beneficial to prevent infarct core from growing.
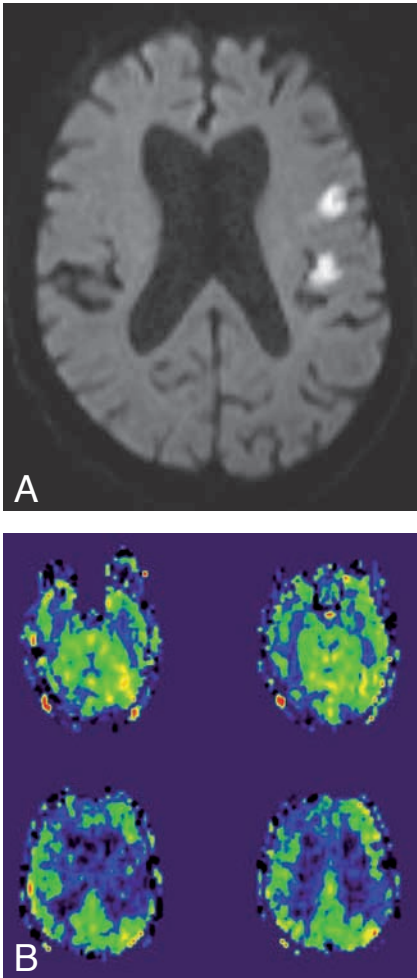
Fig. 2. — A. Axial DWI shows two small bright infarcts in the territory supplied by the left middle cerebral artery. B. Arterial spin label CBF map shows large defect in that same vascular territory indicating the presence of a significant ischemic penumbra.

zones. In our experience the area containing these dilated veins approximates that of the penumbra seen on perfusion studies. The problem with SWI is that it takes about 5-6 minutes to obtain and many stroke patients are unstable and unable to hold still that long.

Malignant infarction

The concept of malignant cerebral infarction is a recent one. These are patients in whom a large volume of infarcted tissue occurs without any collateral circulation and who will develop significant edema and mass effect leading to death in most unless a decompressive craniectomy to relief the mass effect is done (Fig. 5). Its definition varies slightly but infarcts with volumes greater than 70-100 ml can be considered as
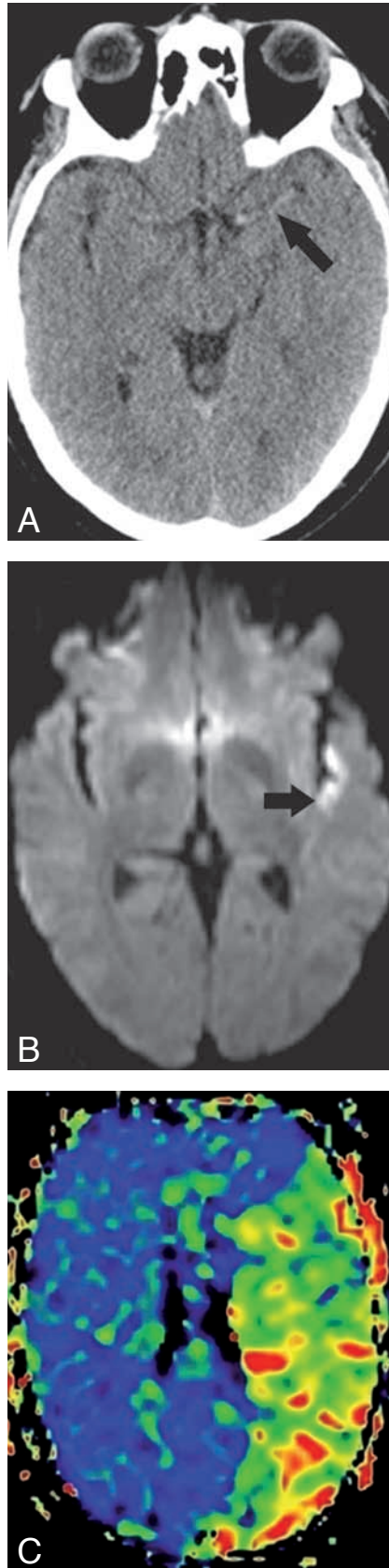
malignant (that is why treating patients with infarcts involving over 1/3 of the MCA territory is not always indicated). The volume of the infarct
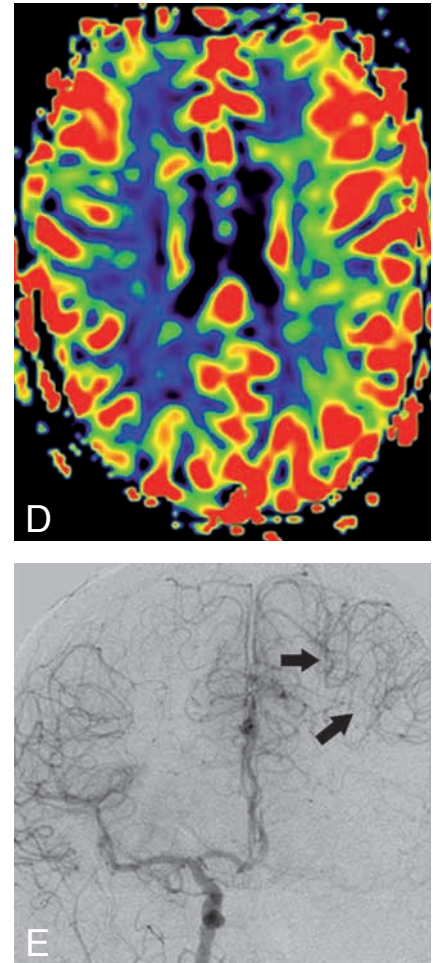

Fig. 3. — A. Axial CT shows a hyperdense (arrow) left middle cerebral artery (MCA). B. Axial DWI shows only a small infarction (arrow) in posterior left insular cortex. C. TTP MRI map shows slow arrival of blood (green) in the entire left MCA territory. The diffusion/perfusion mismatch indicates a large ischemic penumbra. D. rCBV MRI map shows that blood volume is slightly increased (red) in the affected area suggesting presence of collateral circulation a fact that explains the small size of the infarct despite a large vessel occlusion. E. Frontal view from catheter angiogram shows extensive collaterals (arrows).

core must be estimated using DWI or occasionally the area of low CT attenuation may be used as some studies have shown a correlation between it and the DWI core. The treatment is usually a hemicraniectomy in patients less than 60 years of age which reliefs the mass effect caused by swelling (16).

Collateral circulation

As previously stated, all brain stroke treatment protocols are based on the premise that "brain is time"
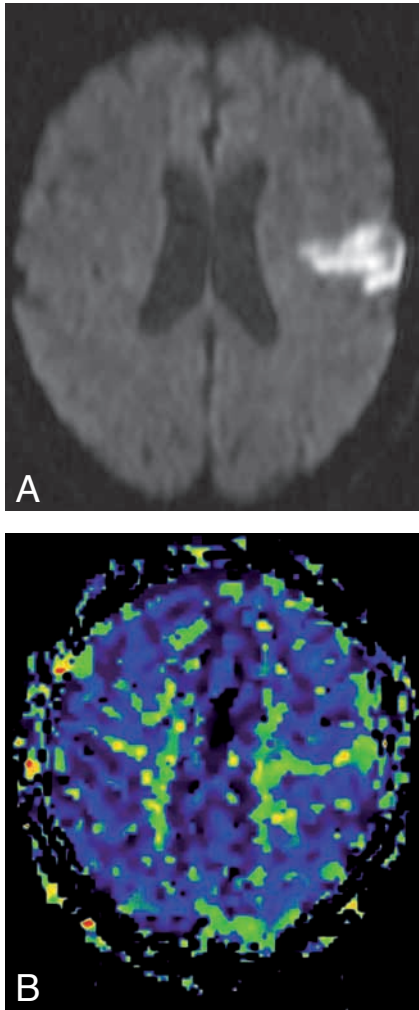
Fig. 4. — Axial DWI shows infarction in the left posterior frontal region. B. rCBF MRI map shows that perfusion defect (green) is much smaller than the diffusion abnormality indicating partial reperfusion of the affected region.

Fig. 5. — A. Axial ADC map shows a large area of dark restricted diffusion in the territory of the right middle cerebral artery. B. One week later, DWI shows massive extension of the infarction which contains areas of low signal suggesting hemorrhage and significant mass effect with midline shift to the left compatible with a malignant infarction.

1. Compensatory: collaterals incited by this mechanism appear very fast and involve the circle of Willis and the leptomeningeal network; they form adapt the mechanism of arteriogenesis.
2. Hemodynamic: this mechanism leads also to the immediate formation of collaterals via arteriogenesis. The circle of Willis is also involved in their formation.
3. Metabolic: this mechanism leads to slower collateral formation via arteriogenesis and angiogenesis via some leptomeningeal arteries.
4. Neural: this mechanism is responsible for the slowest collateral formation via angiogenesis and mostly involves the deep striatal arteries.

Compensatory and hemodynamic mechanisms are responsible for collateral formation in acute stroke while metabolic and neural related collaterals mostly occur in chronic ischemia such as moyamoya. Arteriogenesis refers to the enlargement of pre-existing arteries induced by physical forces such as shear stress and volume. Angiogenesis refers to the formation new arteries from pre-existing ones due to chronic hypoxia. At least in animals, arteriogenesis is modulated by 3 proteins (Canq1, Civg1, and HSg1) controlled by genes located in chromosome 7 (19-21). The existence and role if any of these genes in humans, is under investigation. Once brain collateral circulation has been established its integrity may be threatened by: hypotension, dehydration, clot fragmentation, hyperthermia, hyperglycemia, hyperviscosity, infections, cardiac failure, and renal and pulmonary insufficiencies and thus careful control of stroke patients in an intensive care setting is needed (22). The most important factor in the development of collaterals is however, the integrity of the circle of Willis. A complete circle of Willis is found in about 60% of the population meaning that all communicating arteries are present and functional in case of arterial occlusions (23). In the rest, the circle of Willis is incomplete and does not function adequately as an immediate source of collateral arterial circulation.

As mentioned before, collaterals are formed by arteriogenesis. In this mechanism, enzymes such as metalloproteases deconstruct the arterial wall extracellular matrix and allow increased shear stress to stretch the blood vessel (24). These enzymes

which is not completely true. In reality, "time is collateral circulation" and thus, to some degree, "brain is collaterals." This means that although we want to treat stroke patients as soon as possible the window of opportunity is not entirely time dependent. It is well known that patients with initial NIHSS (National Institutes of Health Stroke Scale) scores over 15 due poorly regardless of type of therapy. The reason for this is that in them, very little or no collateral circulation is present (1). Additionally, collateral circulation seems to predict the success of treatment. In one study, the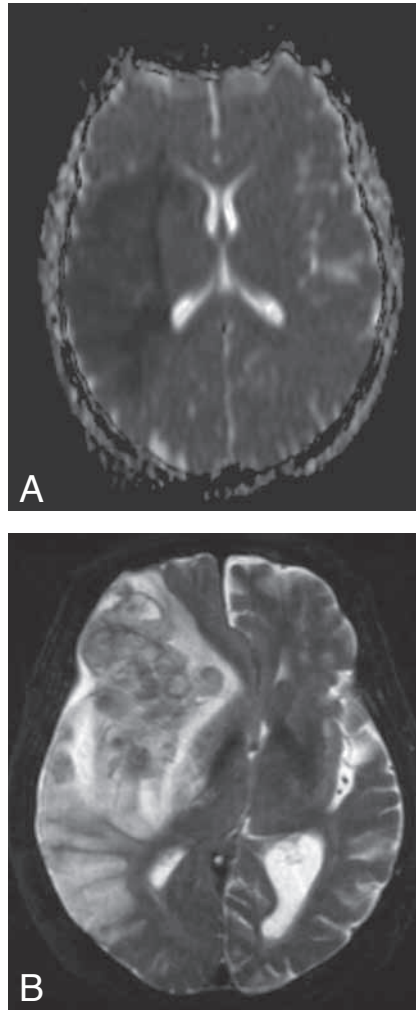 degree of collateral circulation as seen on catheter angiography determined the rate of successful recanalization after endovascular therapy and thus the outcome (17).

Broadly, collateral circulation is a subsidiary arteriole-to-arteriole network that stabilizes CBF when the primary conduits fail (18). Collateral circulation may be intracranial (primary from the circle of Willis or secondary via other intracranial anastomoses) or extracranial (from branches of the external carotid arteries). Intracranial collaterals open up first while extracranial ones take time to develop. The development of collateral arteries depends on 3 mechanisms as follows:

are produced as the result of ischemia in tissues surrounding arteries. The cells in the deconstructed blood vessels secrete cytokines which travel in the systemic circulation to the bone marrow stimulating it to produce endothelial precursor cells. These cells then enter the systemic circulation and find their way to the affected artery lodging in the spaces previously created between the native cells. Endothelial precursor cells then mature and become endothelial cells.

Imaging has been extensively used to study collateral brain circulation including PET, SPECT, and Doppler sonography. On conventional contrast enhanced MRI 2 findings have been correlated with the presence of collateral circulation: intravascular enhancement sign and intravascular hyperintensity on FLAIR images (so called "ivy" sign). These findings generally imply slow arterial flow and because passage of blood through collaterals is slower than through native arteries, the findings imply at least some degree of collaterals. Catheter angiography, CT angiography, and MR angiography may also show arteries in territories beyond proximal arterial occlusions implying presence of collaterals (Fig. 3). The presence of leptomeningeal collaterals seen on CTA is a strong predictor of functional outcome in stroke patients with large vessels occlusion (25). On MR perfusion, prolonged transit times and delayed MTT with high rCBV in infarcted or at risk areas corresponds, to some degree, with the presence of collaterals.

Arterial spin label angiography (ASL) is a new technique which may also help to identify collaterals (26, 27). This MR technique uses an inversion pulse to continuously or non-continuously label water spins in blood flowing through the arteries in the neck. After a time delay, the head is imaged recovering a very small amount of signal in the capillary bed with respect to the background brain. This sampling must be repeated about 60 times to recover a 1-2% change in signal intensity between capillaries and brain. ASL results in CBF maps which may be quantitative or not depending on the MR system being used. ASL may show what appears to be paradoxically increased perfusion in regions of ischemia (Fig. 6). This sign called "paradoxical hyperperfusion" correlates with presence of collateral circulation. The recovery of signal in these cases is greater because of the slowness of blood flow in collaterals.
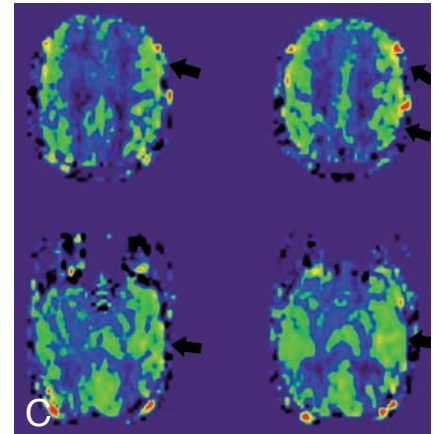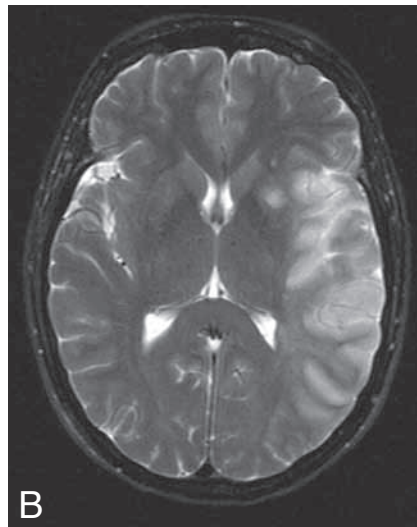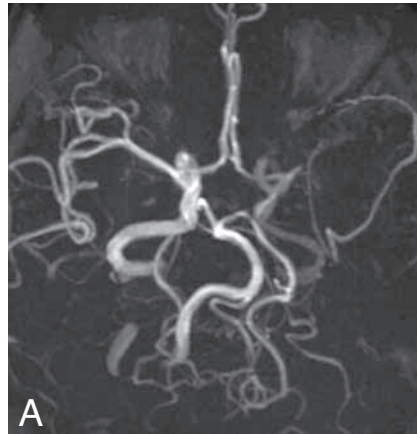

A

B

Based on these observations, some investigators have attempted to treat collaterals at same time as treating the infarction (22). Stimulation of parasympathetic fibers in the sphenopalatine ganglion may increase CBF by 40% or more but data are early and controversial. Direct and indirect (partial aortic occlusion with balloons, external blood pressure cuffs) expansion of blood volume has been found to be beneficial in some patients. Chronically, statins may improve collateral formation by stimulating endothelial cell proliferation (20). Maintaining an adequate systemic blood pressure is very important in collateral formation and in preventing strokes.

Hemorrhagic transformation of infarction

These terms refer to development of new hemorrhage in a previously ischemic region, a complication that generally occurs within 72 hours of symptoms. It is generally due to arterial reperfusion into a damaged territory (normal pressure breakthrough).

C

Fig. 6. – A. Base view of MRA shows occlusion of the left middle cerebral artery. B. Axial T2 MR image shows edema involving predominantly the gray matter (cytotoxic edema) in the left temporal region. C. ASL CBF maps show slightly increased (paradoxical) perfusion in the affected regions (arrows).

Most hemorrhagic transformations involve the MCA circulation and were previously thought to occur in 15% of patients but it is now known that its incidence is much less (3.5%) (28) (Fig. 7). Nowadays, the most common cause of it is previous intravenous thrombolytic treatment. Because hemorrhagic transformation carries a poor prognosis, several techniques have been employed in an attempt to predict which patients will undergo it. Hemorrhagic transformation is more common in patients with poor collaterals and lack
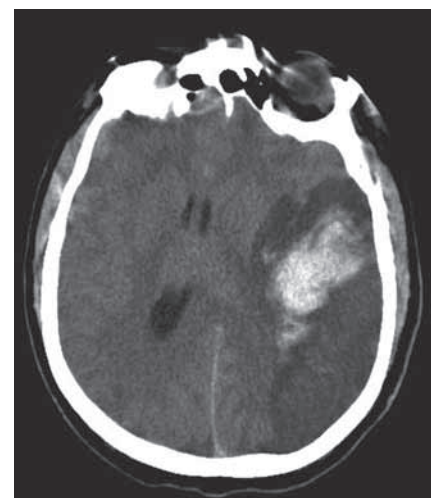

Fig. 7. – Axial CT shows large left middle cerebral artery infarction with post thrombolysis hemorrhagic transformation.

Table I. – Benefits of CT and MRI in acute stroke imaging.

	Presence of hemorrhage	Occlusion of large artery	Mapping of ischemic core	Mapping of penumbra
CT	++	++ (CTA)	+ (CTA, CTP)	+
MRI	+	+	++ (DWI)	++

of arterial recanalization. This observation has been confirmed by a larger study of 222 patients undergoing catheter angiography as part of intra-arterial recanalization procedures (29). Permeability studies using MRI with contrast have shown that infarcted regions with increased permeability are at high risk for hemorrhagic transformation (30, 31). However, it should be noted, that petechial and small hemorrhages in an infarcted zone are generally clinically silent, generally do not affect the patients' outcome, and do not preclude additional treatment.

Practical issues

Unfortunately, less than 10% of patients arrive within the allowable time window for stroke therapy to emergency departments. Early morning stroke is a common presentation and since patients do not feel pain they do not see the need a go to the hospital immediately. Since these patients do not know when the stroke occurred, MR FLAIR images may shed some light in this regard since abnormalities on FLAIR take about 3 hours to develop. Intravenous thrombolysis may be given up to 4.5 post stroke; intra-arterial thrombolysis up 6 hours, and mechanical clot retrieval employed up to 9 hours post ictus (32). These broad guidelines apply only to infarcts involving the anterior circulation and not the vertebrobasilar system.

Which is the best imaging choice when the acute stroke patients arrive at the hospital is controversial and both CT and MRI have strong proponents. The advantages of CT are: it is readily available most anywhere, it is superb at detecting hemorrhage, CTA rapidly identifies patients with major vessel occlusions which may be directly stratified to intra-arterial treatments, and CT perfusion may be easily obtained to identify the penumbra. Supporters of MRI cite the following advantages: direct identification of infarcted core by DWI, MRA identifies major arterial occlusions, perfusion studies include the entire brain (something not possible with many CT scanners), and identification of blood with gradient echo or susceptibility-weighted sequences. The reality is that the choice of modality will be dictated by what is available, the type of trial patients are enrolled in, and personal and institutional preferences. The best imaging choice may be combination of both CT and MRI taking advantage of their benefits (Table I). The ideal combined protocol includes a non-contrast CT for detection of hemorrhage, a CTA for detection of large vessel occlusion and MRI with DWI for mapping the infarcted core and whole brain perfusion for determining the extent of the penumbra.

Conclusion

A cerebral infarction is composed of 3 zones: the core, the penumbra, and surrounding area of oligemia. Imaging and treatment of stroke is geared towards salvaging the penumbra and the oligemic regions and preventing the core from enlarging. Presence of hemorrhage and large size infarcts (>100 ml) preclude treatment and carry a poor prognosis. Although it is true that "brain is time", up until now brain attack studies have not taken into consideration the presence or absence of collateral circulation and early data indicate that patients with collaterals have a better outcome regardless of treatment. The use of CT or MRI in acute stroke patients is a matter of availability, treatment protocol, and personal and institutional preferences. The most useful protocol is probably a combination of both modalities. New techniques such as ASL MRI perfusion may allow for measurement of collateral circulation detecting those patients who carry a better outcome. Genes controlling collateral circulation have been detected in mice and probably exist in men too.

References

1. Gonzalez R.G.: Imaging-guided acute ischemic stroke therapy: from "time is brain" to "physiology is brain." *AJNR*, 2006, 27: 728-735.
2. Symons S.P., Culen S.P., Buonanno F., Gonzalez R.G., Lev M.H.: Noncontrast conventional computed tomography in the evaluation of acute stroke. *Semin Roentgenol*, 2002, 37: 185-191.
3. Andaluz N., Zuccarello M.: Recent trends in the treatment of spontaneous intracerebral hemorrhage: analysis of a nationwide inpatient database. *J Neurosurg*, 2009, 110: 403-410.
4. http://www.strokecenter.org/patients/about-stroke/stroke-statistics.
5. Easton J.D., Saver J.L., Albers G.W., Alberts M.J., et al.: AHA/ASA scientific statement. Definition and evaluation of transient ischemic attack. *Stroke*, 2009, 40: 2276-2293.
6. Bertrand A., Oppenheim C., Lamy C., Rodrigo S., et al.: Comparison of optimized and standard diffusion-weighted imaging at 1.5T for the detection of acute lesions in patients with transient ischemic attack. *AJNR*, 2008, 29: 363-365.
7. Torres-Mozqueda F., He J., Yeh I.B., Lev M.H., et al.: An acute ischemic stroke classification instrument that includes CT or MR angiography: the Boston acute stroke imaging scale. *AJNR*, 2008, 29: 1111-1117.
8. Cullen S.P., Symons S.R., Hunter G., Hamberg L., et al.: Dynamic contrast-enhanced computed tomography f acute ischemic stroke: CTA and CTP. *Semin Roentgenol*, 2002, 37: 192-205.
9. Schaefer P.W., Romero J.M., Grant P.E., Wu O., et al.: Diffusion magnetic resonance imaging of acute stroke. *Semin Roentgenol*, 2002, 37: 219-229.
10. Wessels T., Wessels C., Ellsiepen A., Reuter I., et al.: Contribution of diffusion-weighted imaging in determination of stroke etiology. *AJNR*, 2006, 27: 35-39.
11. Romero J., Schaefer P.W., McDonald C., Schwann L., Gonzalez R.G.: Conventional magnetic resonance imaging in acute stroke. *Semin Roentgenol*, 2002, 37: 206-211.
12. Lansberg M.G., Thjis VN., O'brien M.W., Ali J.O., et al.: Evolution of apparent diffusion coefficient, diffusion-weighted, and T2 signal intensity of acute stroke. *AJNR*, 2001, 22: 637-644.
13. Schaefer P.W., Romero J.M., Grant P.E., Ona W., et al.: Perfusion magnetic resonance imaging of acute stroke. *Semin Roentgenol*, 2002, 37: 230-236.
14. Schaefer P.W., Ozsunar Y., He J., Mamberg L.M., et al.: Assessing tissue viability with MR diffusion and perfusion imaging. *AJNR*, 2003, 24: 436-443.
15. Mittal S., Wu Z., Neelvalli J., Haacke E.M.: Susceptibility-weighted imaging: technical aspects and clini-

cal applications, part 2. *AJNR*, 2009, 30: 232-252.

16. Huttner H.B., Schwab S.: Malignant middle cerebral artery infarction: clinical characteristics, treatment strategies, and future perspectives. *Lancet Neurol*, 2009, 8: 949-958.

17. Bang O.Y., Saver J.L., Kim G.M., Chung C.S., et al.: Collateral flow predicts response to endovascular therapy for acute ischemic stroke. *Stroke*, 2011, 42: 693-699.

18. Lebeskind D.S.: Collateral circulation. *Stroke*, 2003, 34: 2279-2284.

19. Wang S., Zhang H., Dai X., Sealock R., Faber J.E.: Genetic architecture underlying variation in extent and remodeling of the collateral circulation. *Circ Res*, 2010, 107: 558-568.

20. Chalothorn D., Faber J.E.: Statin-dependent variation in collateral circulatory function in mouse hindlimb. *Physiol Genomics*, 2010, 42: 469-479.

21. Wang S., Zhang H., Wiltshire T., Sealock R., Faber J.E.: Genetic dissection of the Canq1 locus governing variation in extent of the collateral circulation. PLoS ONE 7:e31910. doi:10.1371/journal.pone.0031910.

22. Shuaib A., Butcher K., Mohammad A.A., Saqqur M., Liebeskind D.S.: Collateral blood vessels in acute ischaemic stroke: a potential therapic target. *Lancet Neurol*, 2011, 10: 909-921.

23. De Silva K.R.S., Silva R., Gunasekera W.S.L., Jayesekera R.W.: Prevalence of typical circle of Willis and the variation in the anterior communicating artery: a study of a Sri Lankan population. *Ann Indian Acad Neurol*, 2009, 12: 157-161.

24. Van Royen N., Piek J.J., Shcpaer W., Fulton W.F.: A critical review of clinical arteriogenesis research. *JACC*, 2009, 55: 17-25.

25. Lima F.O., Silva G.S., Lev M.H., Camargo E.C., et al.: The pattern of leptomeningeal collaterals on CT angiography is a strong predictor of long-term functional outcome in stroke patients with large vessel intracranial occlusion. *Stroke*, 2010, 41: 2316-2322.

26. Van Laar P.J., van der Grond J., Hendrikse J.: Brain perfusion territory imaging: methods and clinical application of selective arterial spine-labeling MR imaging. *Radiology*, 2008, 246: 353-364.

27. Chng S.M., Petersen E.T., Zimine I., Sitoh Y.Y., et al.: Territorial arterial spin labeling in the assessment of collateral circulation. *Stroke*, 2008, 39: 3248-3254.

28. Mullins M.E., Lev M.H., Schellingerhout D., Gonzalez R.G., Schaefer P.W.: Intracranial hemorrhage complicating acute stroke: how common is hemorrhagic stroke on initial CT scan and how often is initial clinical diagnosis of acute stroke eventually confirmed? *AJNR*, 2005, 26: 2207-2212.

29. Bang O.Y., Saver J.L., Kim G.M., Chang C.S., et al.: Collateral flow averts hemorrhagic transformation after endovascular therapy for acute ischemic stroke. *Stroke*, 2011, 42: 2235-2239.

30. Lin K., Kazmi K.S., Las M., Babb J., et al.: Measuring elevated microvascular permeability and predicting hemorrhagic transformation in acute ischemic stroke suing first-pass dynamic perfusion CT imaging. *AJNR*, 2007, 28: 1292-1298.

31. Bang O.Y., Buck B.H., Saver J.L., Alger J.R., et al.: Prediction of hemorrhagic transformation after recanalization therapy using T2*-permeability magnetic resonance imaging. *Annals Neurol*, 2007, 62: 170-176.

32. Wechsler L.R., Jovin T.G.: Intravenous recombinant tissue-type plasminogen activator in the extended time window and the US Food and Drug Administration. *Stroke*, 2012, 43: 2517-2519.