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Perfusion Imaging In Acute TBI

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One paragraph synopsis:

Traumatic Brain Injury (TBI) is a significant problem world-wide and neuroimaging plays a critical role in diagnosis and management. Recently, perfusion neuroimaging techniques have been explored in TBI to determine and characterize potential perfusion neuroimaging biomarkers to aid in diagnosis, treatment and prognosis. In this article, CT bolus perfusion, MRI bolus perfusion, MRI ASL perfusion, Xenon-CT were reviewed with a focus on their application in acute TBI. Future research directions were also discussed.

Keywords

Concussion; Traumatic Brain Injury; TBI; perfusion

INTRODUCTION

Traumatic Brain Injury (TBI) is a major healthcare issue affecting 1.7 million people, hospitalizing 275,000 people and resulting in 52,000 deaths annually in the United States and the incidence of emergency room visits related to TBI is on the rise.[1-3] It is estimated that 3.2 million people are living with long-term disability from TBI.[4] The most common causes of TBI include motor vehicle accidents, falls, sports-related injury and assault in the civilian population[1-3] and explosion related injury in the military.[5] Neuroimaging plays a key role in the diagnosis, treatment and prognosis of TBI.

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The American College of Radiology has provided Appropriateness Criteria to help referring physicians make the most appropriate decisions on imaging examinations. As an example, for a moderate or severe acute closed head injury (Glascow Coma Scale < 13), the most appropriate initial neuroimaging study is a noncontrast Computed Tomography (CT) scan.[6] A noncontrast CT scan can diagnose injuries such as an epidural hematoma that require emergent neurosurgical intervention. However, there are limitations associated with non-contrast CT scans. For example, early CT scans have been found to underestimate the size of parenchymal contusions.[7] For this reason, short interval follow up CT scans may be beneficial. In addition, early conventional non-contrast CT imaging does not show secondary ischemic changes related to cerebral edema and intracranial hypertension, which is responsible for nearly half of TBI-related deaths after admission.[8]

In recent years, the field of neuroimaging has advanced beyond structural imaging to functional tissue characterization including cerebral perfusion. Perfusion is physiologically defined as the flow of blood per unit volume of tissue. The term "tissue" emphasizes the fact that this specifically means capillary blood flow. Perfusion imaging is commonly utilized in clinical practice in the setting of stroke since it has the ability to distinguish normally perfused cerebral parenchyma from ischemic penumbra from infarcted tissue.[9-12] Recently, perfusion neuroimaging techniques have been explored in TBI to determine and characterize potential perfusion neuroimaging biomarkers to aid in diagnosis, treatment and prognosis. Following TBI, it is thought that alterations in the cerebrovascular parameters may lead to secondary injuries.[13] The ability to improve clinical outcomes following TBI may rely on the ability to detect potentially salvageable tissue known as "traumatic penumbra" and secondary ischemic events.[14-16] The purpose of this article is to review perfusion imaging techniques in TBI including bolus perfusion CT, bolus perfusion MRI, arterial spin labeling (ASL) perfusion MRI and stable Xenon perfusion CT. This article will conclude with a discussion of future research techniques.

PERFUSION IMAGING IN CT

Introduction

The underlying basis for perfusion CT (PCT) is conservation of flow. In order to measure flow, a non-diffusible tracer (i.e., an agent that remains in vasculature) is administered intravenously. Bolus Perfusion imaging is performed on a multidetector CT scanner in the axial plane typically with a 4 mL/second contrast injection rate.

With regards to image processing, the PCT images are used to create time-enhancement curves registered to each pixel in the data set. From the time-enhancement curves, processing software can generate key parameters including regional cerebral blood volume (rCBV), mean transit time (MTT), and regional cerebral blood flow (rCBF), which has been validated to stable xenon CT.[17]

The CBV map is calculated from the area under the time-enhancement curves and represents the blood volume within the arterioles and venules of a given parenchymal tissue volume with units of mL of blood per 100 grams of brain tissue. The MTT represents the average time that it takes for blood to flow from the arterial input through the brain tissue and to the

venous drainage and has units in seconds. MTT is calculated by a mathematical process called deconvolution.[18-20] The MTT requires a reference arterial input function (AIF), which commonly uses a region of interest drawn around the anterior cerebral artery. Time to peak is the time from the arrival of contrast into the AIF to the peak of the time-enhancement curve for each voxel. The T_{max} is calculated from the time to peak where TMax = 0 for normal perfused tissue without delay.[21] Finally, CBF is the volume of blood flowing through a given volume of brain tissue over a certain time period and has units of mL of blood per 100 grams of brain tissue per minute (Figure 1).

The central volume principle describes the relationship between a compartment volume, blood flow through the compartment and the mean transit time through the compartment.[12] According to the central volume principle, the MTT is equal to the rCBV divided by the rCBF.[22] The cerebral parenchyma viability is completely dependent on CBF. Alterations in CBF can have influence upon electrical and metabolic neuronal activity. Cerebral autoregulation plays a role in ensuring that there is adequate CBF despite alterations in systemic pressure.

Bolus CT Perfusion applied to TBI imaging

Wintermark et al. explored PCT on admission CT scans and found perfusion abnormalities associated with juxtadural collections, cerebral edema and intracranial hypertension.[23] In Wintermark's study which included 48 patients who had cerebral contusions diagnosed on delayed follow-up imaging, 19 of the 48 contusions were seen on the initial noncontrast CT images (sensitivity of 39.6%) and 42 of the 48 were seen on the perfusion CT images (sensitivity of 87.5%). The 42 perfusion abnormalities were noted to occur in the same location as the contusion on delayed CT. The difference in the sensitivity of noncontrast CT and PCT was statistically significant (p-value < 0.001). The specificity of perfusion defects for cerebral contusion in the setting of severe trauma was 93.9%.[23] In the setting of cerebral contusions, focal cortical-subcortical perfusion abnormalities of increased MTT, decreased rCBF and decreased rCBV were noted (Figure 2).[23] Areas of vasogenic edema could either show increased perfusion or decreased perfusion and areas of cytotoxic edema showed decreased perfusion.[23] In the setting of juxtadural collections, decreased rCBF was found to be decreased in the immediate vicinity of epidural hematomas (Figure 3).[23,24] In Wintermark's study, increased MTT, decreased rCBF and decreased rCBV were observed in the setting of intracranial hypertension (Figure 4).[23]

Even with no visible intracranial injury on admission head CT, perfusion imaging with acute reductions in blood flow and blood volume are associated with worse outcomes.[24] In patients with severe TBI, PCT was found to show additional information in 60% of patients and alter management in 10% of patients.[25]

Areas of hypodensity on CT may be necrotic or viable and PCT may help distinguish between these possibilities.[26] PCT also provides insight into the cerebral vascular autoregulation, which may be used to guide therapy and monitor treatment efficiency.[26]

Challenges in CT Perfusion

One of the key challenges is the radiation dose that accompanies PCT. Radiation safety is of paramount importance and the aim of every institution should be to keep radiation dose as low as reasonably achievable (ALARA). It has been suggested that PCT should be performed at 80 kVp and 100mAs, to maximize the contrast enhancement and decrease the radiation dose.[27]

Another risk of PCT is the intravenous administration of contrast material, which can result in renal impairment or allergic reaction.

PERFUSION IMAGING IN MRI

Cerebral perfusion in MRI can be performed via two main approaches. The first method is through the exogenous intravenous administration of a nondiffusible contrast agent such as gadolinium-based contrast agents.[28] The second method is through endogenous magnetic labeling of arterial blood water as a diffusible flow tracer in arterial spin labeling (ASL) MR perfusion.[28]

BOLUS PERFUSION MRI

Introduction

In bolus perfusion MRI imaging, also known as bolus tracking, an exogenous, non-diffusible contrast agent such as gadolinium-based contrast agents is administered intravenously.[28] Within non-diffusible brain perfusion imaging there are two main categories including Dynamic Susceptibility Weighted Contrast (DSC) and Dynamic Contrast Enhancement (DCE) imaging.[28]

In DSC, the gadolinium-chelate bolus causes transient decrease in signal intensity by the T2* effect of the contrast bolus during initial pass through vasculature.[28] This results in decreased signal with increased contrast. A typical DSC bolus MRI sequence requires an intravenous injection rate of a gadolinium-based contrast agent at approximately 4 mL/second. A gradient-echo echo-planar sequence is performed with a total scan time of approximately 1-2 minutes during the injection of the contrast bolus.

In DCE, the gadolinium-chelated bolus causes T1 shortening within the blood-pool and within any area that accumulates because of leakage outside of vessels. This results in increased signal with increased contrast.[28]

As previously discussed in DSC imaging, as the contrast bolus arrives, a transient signal drop in T2* occurs. A plot of the contrast concentration curve over time, $C(t)$, is called the time-concentration curve. A plot of the signal intensity over time is called the time-intensity curve. It should be noted that the time-intensity curves in bolus perfusion MRI are logarithmically related to the time-concentration curves.[11] The rest of the calculations in bolus perfusion MRI imaging are similar to those described above for PCT.

Bolus MRI applied to TBI imaging

In one study of TBI in a military population by Liu et al, voxelwise analysis of regional cerebral blood flow (rCBF) maps demonstrated scattered perfusion defects in the cerebellum, cingulate gyrus, cuneus and temporal gyrus in TBI patients compared to normal controls.[29] This study also demonstrated correlations of the perfusion defects with verbal memory, reaction time and self-reported stress.[29]

In another study by Garnett et al, DSC was performed in 18 patients with subacute TBI (mean of 10 days following TBI)[13]. Six of the 18 patients had visible contusions on conventional MRI imaging and each of these six patient had significantly reduced rCBV in the contused regions.[13] Five of the 18 patients were noted to have reduced rCBV in areas where a contusion was not identified on conventional imaging. These five patients were not more significantly injured than the remaining patients, but were found to have worse clinical outcomes.[13]

Challenges in Bolus MRI imaging

In general, performing an MRI scan in the setting of trauma can be difficult. Patients may be hemodynamically unstable. Since MRI scans are inherently long, patients may not be able to be cleared for MRI. Furthermore, trauma patients may be unable to complete the MRI safety questionnaire due to unconscious state or may have known contraindications to MRI. For this reason, MRI in the setting of trauma is inherently challenging.

Arterial Spin Labeling (ASL)

Introduction: Arterial Spin Labeling (ASL) is a non-invasive MR imaging technique that offers quantitative information on the CBF and perfusion. The technique was successfully implemented for the first time in a rat CBF model by Williams et al.[30] ASL uses radio-frequency (RF) pulses to invert water proton spins by 180° in the regions inferior to the brain slice of interest. A “labeling” image is acquired as these tagged protons flow along the cerebral vascular and enter the slice; another “control” image is sequentially obtained in the same slice, but without the RF inversion; the difference between the labeling and control image is used to create a map of CBF and perfusion as highlighted by endogenous proton spins. ASL signal is affected by physiological parameters including labeling efficiency, arterial blood T1 and T2, blood transport time through vessels and tissue, and magnetization transfer effects.[30-33]

ASL-based CBF measurements have been validated against traditional radiotracer perfusion techniques, including HMPAO SPECT[34], PET[35], and Xe-CT[36]. This versatile technique also generates reproducible results that are confirmed by multicenter clinical trials.[37] ASL has multiple attractive features compared to other perfusion imaging techniques. ASL uses endogenous water protons as opposed to contrast agents and avoids radiation exposure making it ideal for imaging in pediatric and pregnant patients.[38] In addition, ASL modeling allows quantification of absolute CBF, which can be used to carry out longitudinal studies, as well as comparison studies between different MRI scanners.

ASL applied to TBI imaging: Since its inception, ASL has been widely used in various clinical applications including stroke, arteriovenous malformations, dementia, epilepsy, CNS tumors and infections.[39] ASL has also been used in several TBI perfusion studies in animals and human subjects.

In 2002, Kochanek et al performed one of the pioneer animal experiments using ASL investigating the effect of TBI on CBF in rats after controlled cortical impact (CCI).[40] They measured T1 relaxation times in a slice through the plane of injury using continuous ASL imaging at one year post injury and found a 80% reduction in CBF in the ROIs immediately next to the lesion when comparing CCI subjects to sham-surgery subjects.[40] Despite significant tissue loss in both ipsilateral and contralateral hemispheres, they did not find widespread reduction in CBF, which they attributed to remodeling of the brain to maintain constant CBF outside the primary lesion.[40]

The chronic effects of mild TBI (mTBI) on regional CBF and neuropsychological function were studied by Ge and colleagues[41] using a True FISP ASL labeling sequence on a 3T scanner. Comparing 21 patients with clinical diagnosis of mTBI to healthy controls, the authors found a statistically significant decrease in CBF in mTBI patients in bilateral thalami and caudate nuclei, but not in putamen or frontal white matter. Moreover, the CBF changes were positively correlated with the changes in processing, response speed, memory, verbal fluency, and executive function of the mTBI subjects. This remarkable study correlated quantitative CBF measurements to neuropsychological impairment, making an important connection between brain physiology to common clinical symptoms of patients.

Kim et al[42] studied the resting CBF in 27 patients with chronic moderate to severe TBI and compared them to matched controls. They discovered a global, nonuniform hypoperfusion with prominent regional decreases in the thalami and posterior cingulate gyri, where the greatest volume losses also occurred. They suggested that structural lesions contribute to chronic CBF changes; in particular, signal loss in posterior cingulate gyri may explain the attention deficit commonly experienced by TBI patients.

Doshi et al.[43] expanded the scope of TBI research using ASL to include ER patients who suffered from mTBI in the early stages, with time delay to scan ranging between 3 hours and 10 days. Using ASL and susceptibility weighted imaging, they found increased rCBF in the caudate, putamen and ventral pallidum of the mTBI subjects. Although there is a wide distribution of delayed scan times among subjects, the increase in rCBF contrasts sharply with the decreased CBF found in previous studies, which the authors attribute to the early vs. chronic phase of TBI injury and to the mild vs. severe degrees of injuries.

In a recent study, MRI was performed on both contact sports athletes (i.e., football players) and non-contact sports athletes (i.e., volleyball players).[44] There was no difference in the volumes of the cortex, white matter, basal ganglia, thalami or hippocampi between the two groups.[44] However, the football players had significantly lower CBV than the volleyball players in the hippocampi and thalami, which suggests that CBV may be a more sensitive metric for detecting TBI.[44]

Challenges in ASL imaging: One technical challenge of applying ASL to TBI imaging lies in its inherently low signal-to-noise ratio (SNR) and temporal resolution.[45] Since the signal from labeled inflow water protons constitutes only 0.5-1.5% of the total tissue signal, ASL is an inherently low SNR technique. SNR can be improved by averaging over repeated acquisitions, increasing magnetic field strength, reducing subject movement, and using fast-imaging techniques such as Echo-Planar Imaging (EPI) and phase-array receiver coils for parallel imaging. However, EPI can suffer from image distortion in regions with high magnetic susceptibilities. Newer pulse sequences, such as turbo-ASL[46] and single-shot ASL[47], can shorten acquisition times, but the interpretation of the signal is more complicated.

In the previous section "ASL applied to TBI imaging", we highlight apparent discrepancies between results published by different research groups in terms of the changes of ASL signals and CBF associated with TBI. CBF appears to increase in certain brain regions e.g. caudate and putamen in the acute phase immediately after impact.[43] It has been shown at the cellular level that cortical impact causes neuronal loss, axonal injury, blood brain barrier (BBB) disruption and microscopic hemorrhage between days 1 and 28 post-TBI.[48] The acute CBF change may reflect the brain's autoregulatory mechanism to maintain constant perfusion by a compensatory increase in blood flow. During the chronic phase of moderate to severe TBI cases, there is a global decline in perfusion, especially in thalami and posterior cingulate gyri, accompanied by volume loss in the lesions.[42]

Additional research is needed to elucidate the physiological transition between the early and chronic phases in mild and severe TBI. In addition, the exact mechanism underlying cognitive impairment from TBI is yet to be discovered.[38] Clearly ASL alone cannot capture the complex physiological changes in an injured brain along time and space axes; the armamentarium of neuroimaging techniques reviewed thus far must work together to collect information on the white and grey matter changes, CBF/ CBV, BBB permeability, microvascular capacity, and oxygen delivery and metabolism rates after an injury occurs, thereby constructing a comprehensive and consistent framework to describe the physiological basis of TBI in vivo.

Stable Xenon Perfusion CT

Introduction: Another form of perfusion CT imaging is performed by inhalation of stable Xenon gas instead of injecting iodinated contrast. In Xenon Perfusion CT, images are acquired during both a wash-in phase and a wash-out phase of the Xenon gas. One protocol that has been studied in multiple trials includes a 13-17 minute protocol consisting of four axial slices each measuring 5 mm thick with 20 mm of spacing between slices.[49-51]

Xe-CT applied to TBI imaging: In one study of 90 patients who suffered TBI, Xe-CT performed 1-3 days post-TBI was correlated with outcomes.[52] MTT was measured with a region of interest including the average of the right and left hemispheres measured at the level of the basal ganglia.[52] Discriminate analysis based on a cut-off MTT value of 6.85 seconds predicted good outcomes (good recovery and moderate disability) and bad outcomes (severe disability, vegetative state and death) with an accuracy of 70.6%.[52]

In another study, stable Xe-CT imaging was used within 12 hours of severe TBI to determine whether neurologic outcome measured by Glascow Outcome Scale (GOS) could be predicted by early CBF.[51] Xe-CT was able to distinguish GOS 1-2 (dead or vegetative state) from GOS 3-5 (severely disabled to good recovery) with a receiver operating characteristic (ROC) curve area under the curve (AUC) of 0.92 at 6 hours and 0.77 at 12 hours.[51] This finding emphasizes the importance of early perfusion imaging after TBI.

Challenges in Stable Xenon CT: The most significant challenge in recent years is that stable Xenon of medical quality is largely unavailable in the U.S. For this reason, clinical and research of Xe-CT is on hold at this time.

FUTURE PERFUSION RESEARCH

Neuroprotective strategies have resulted in positive outcomes in animal research. However, such pre-clinical successes have failed to translate into improved clinical outcomes in clinical TBI trials.[53-56] One possible explanation for this is the fact that there is more heterogeneity in TBI in clinical settings as compared to consistent models in animal research.[51,53,57] The importance of early perfusion changes has been recognized in TBI for its prognostic value.[23,51] Thus, one area of further research should be in early post-TBI perfusion changes.

The benefits of early perfusion are well-known and commonly utilized in seizure localization through the use of technetium-99m-hexamethylpropylene amine oxime (Tc-99m HMPAO). Tc99m-HMPAO is taken up rapidly within the brain (30-60 seconds) and its long half-life allows for high quality scanning up to 4 hours after the injection. The distribution of the tracer at the time of the imaging provides a snapshot of the blood flow at the moment of tracer injection. Despite the known utility of performing ictal single photon emission computed tomography (SPECT) imaging with Tc-99m HMPAO for seizure localization[58], a recent systematic review article of SPECT imaging at TBI revealed 19 longitudinal and 52 cross-sectional studies only found a single study that was performed within 12 hours of the TBI.[59,60] This study showed hypoperfusion after TBI and found that the hypoperfusion correlated with amnesia.[60]

An ongoing Department of Defense funded TBI study is investigating early perfusion changes in the acute phase of TBI.[61] In this study, an animal model with precision cortical impact is followed by Tc-99m HMPAO tracer administration with subsequent SPECT-CT imaging within the half-life of the tracer. The experimental design reflects the realistic scenario of brain injury sustained by a soldier in combat who receives the radiopharmaceutical injection and subsequent SPECT-CT imaging within a few hours. In our TBI animal experiments, decreased perfusion was seen at the cortical impact site (Figure 6), consistent with hypoperfusion observed by other research groups.[61] A limitation of this technique is the poor spatial resolution of SPECT-CT. Future experiments will soon be conducted with high spatial resolution collimators.

The considerable heterogeneity in TBI poses a challenge at identifying an effective treatment at an individual level;[62] however, perfusion imaging creates new opportunities for

detection of injuries that might otherwise go unnoticed with conventional imaging. Through perfusion imaging, more specific diagnoses can be made and coupled with more specific treatments. Future research may involve building normal age-stratified perfusion imaging scans. With a normative database, computer-aided diagnosis and machine learning (ML) could be performed yielding a more refined diagnosis through etiological, symptom-based or prognostic classifications of TBI.[63-66] ML refers to the process of training a computer algorithm to "learn" from past experience where perfusion parameters (e.g., CBV values) are matched to particular outcomes (e.g., Glascow Outcome Scale). An integrated approach that combines optimal structural imaging, perfusion imaging, clinical parameters may direct future treatment directions.

CONCLUSION

TBI is a significant problem world-wide and neuroimaging plays a critical role in diagnosis and management. In this article, CT bolus perfusion, MRI bolus perfusion, MRI ASL perfusion, Xenon-CT were reviewed with a focus on their application in TBI. Future research directions were also discussed.

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Key points:

1. Noncontrast Computed Tomography (CT) scan is the most appropriate initial neuroimaging study for a moderate to severe closed head injury.
2. Perfusion Computed Tomography (PCT) has a higher sensitivity for detecting cerebral contusions than noncontrast CT examinations.
3. Future research in perfusion imaging may improve the diagnosis, prognosis and management of acute TBI.

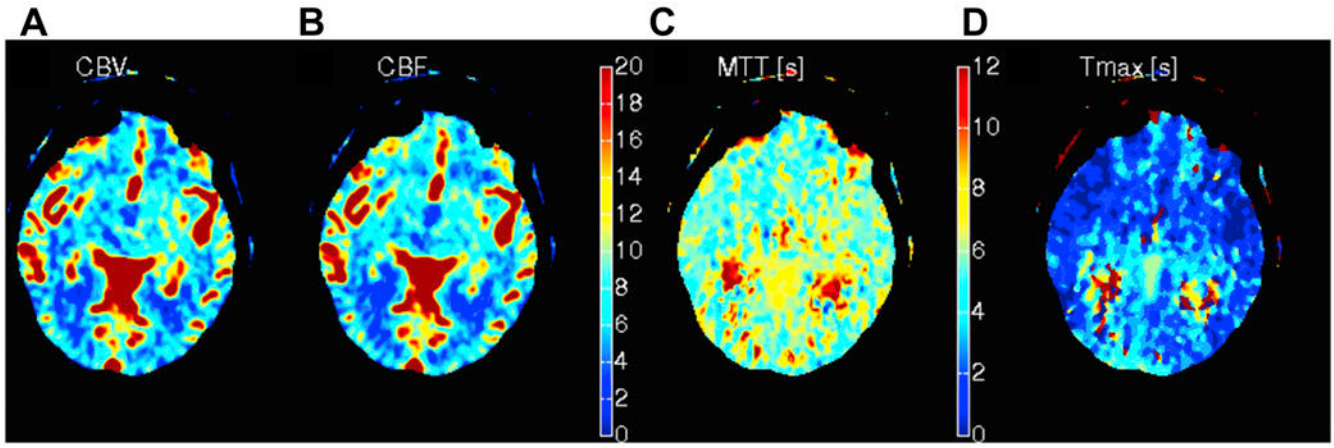

Figure 1:
Normal CT Perfusion images showing (A) rCBV, (B) rCBF, (C) MTT and (D) T_{max}.

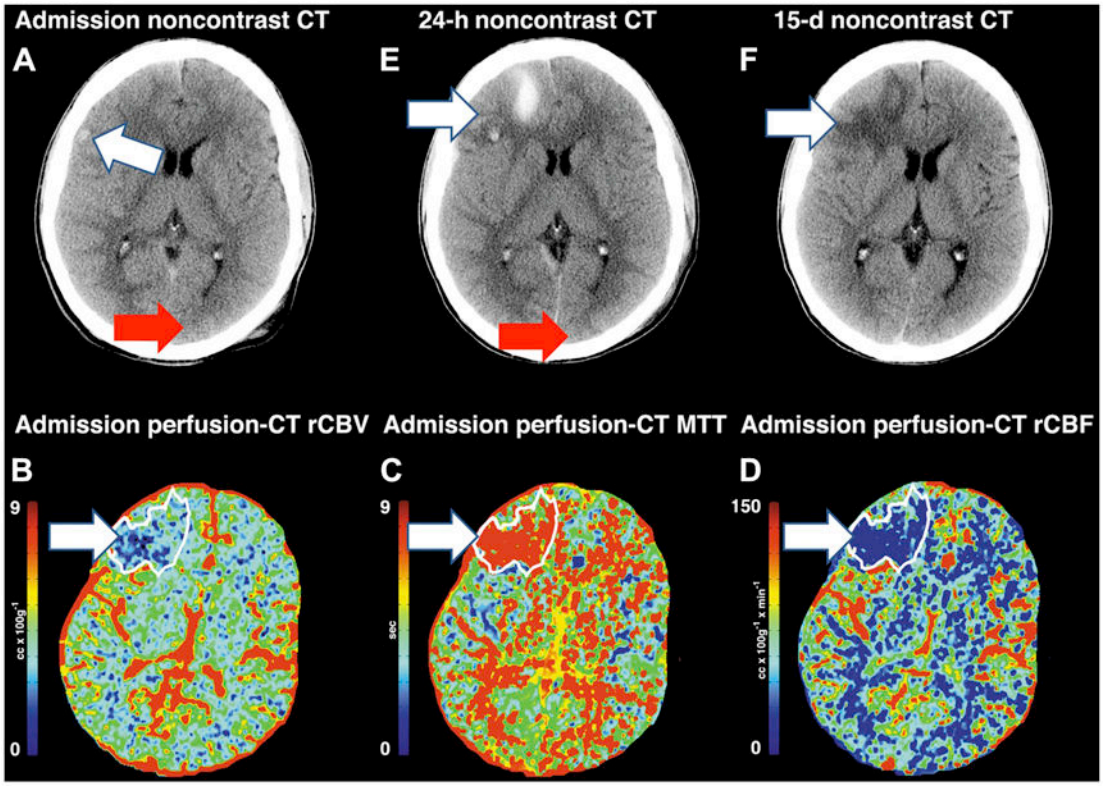

Figure 2:

Contrast-enhanced and perfusion-CT images from a patient with severe TBI. (A) Noncontrast CT at admission demonstrates a small hemorrhagic contusion in the right frontal lobe (arrow). Admission perfusion-CT images demonstrate a large territory of decreased rCBV (B), increased MTT (C) and decreased rCBF (D). Follow-up noncontrast CT at 24 hours (E) demonstrates increased areas of hemorrhagic contusion in the right frontal lobe where the perfusion abnormality was seen. Follow-up noncontrast CT at 15-days (F) demonstrates evolving hemorrhagic contusion and encephalomalacia in the right frontal lobe, which corresponds to the same distribution that is seen on the perfusion-CT.

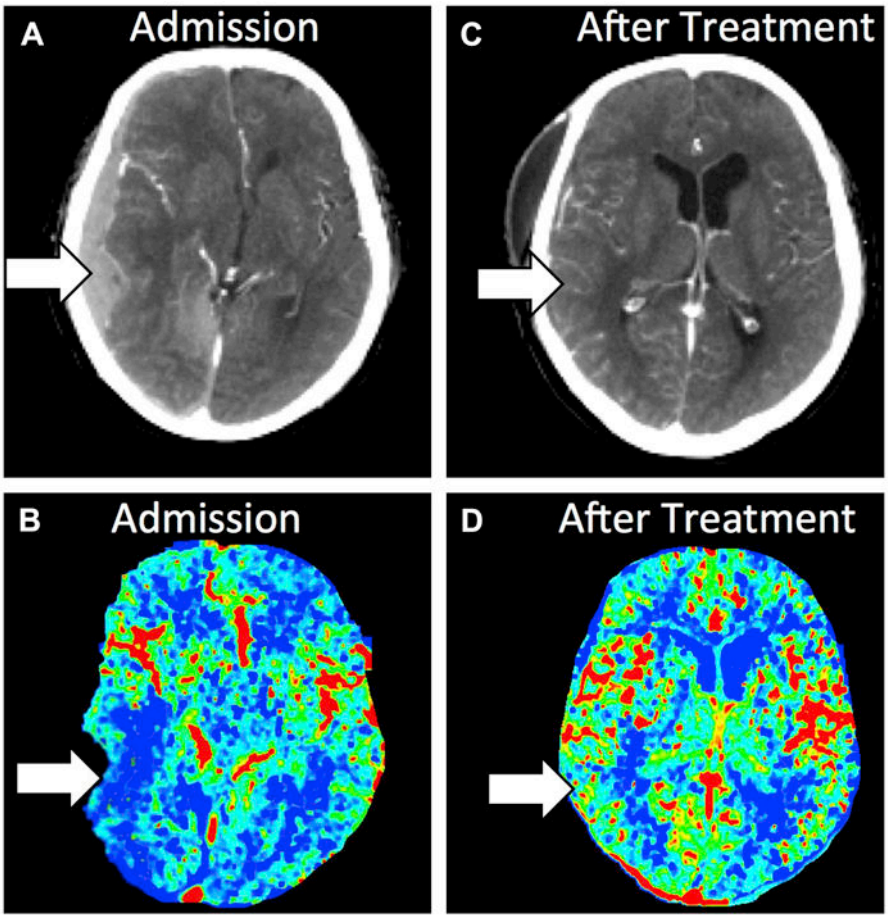

Figure 3:

Contrast-enhanced and PCT images from a patient with severe TBI. (A) Contrast-enhanced CT imaging at admission demonstrates a right-sided subdural hematoma causing mass effect on the underlying brain and midline shift. (B) rCBF PCT imaging at admission demonstrates decreased rCBF in the right temporal lobe. (C) Contrast-enhanced CT image after surgical evacuation of the hematoma demonstrates resolution of the right-sided subdural hematoma, mass effect and midline shift. (D) rCBV PCT imaging after surgical evacuation of the right-sided hematoma demonstrates normalization of the rCBF in the right temporal lobe.

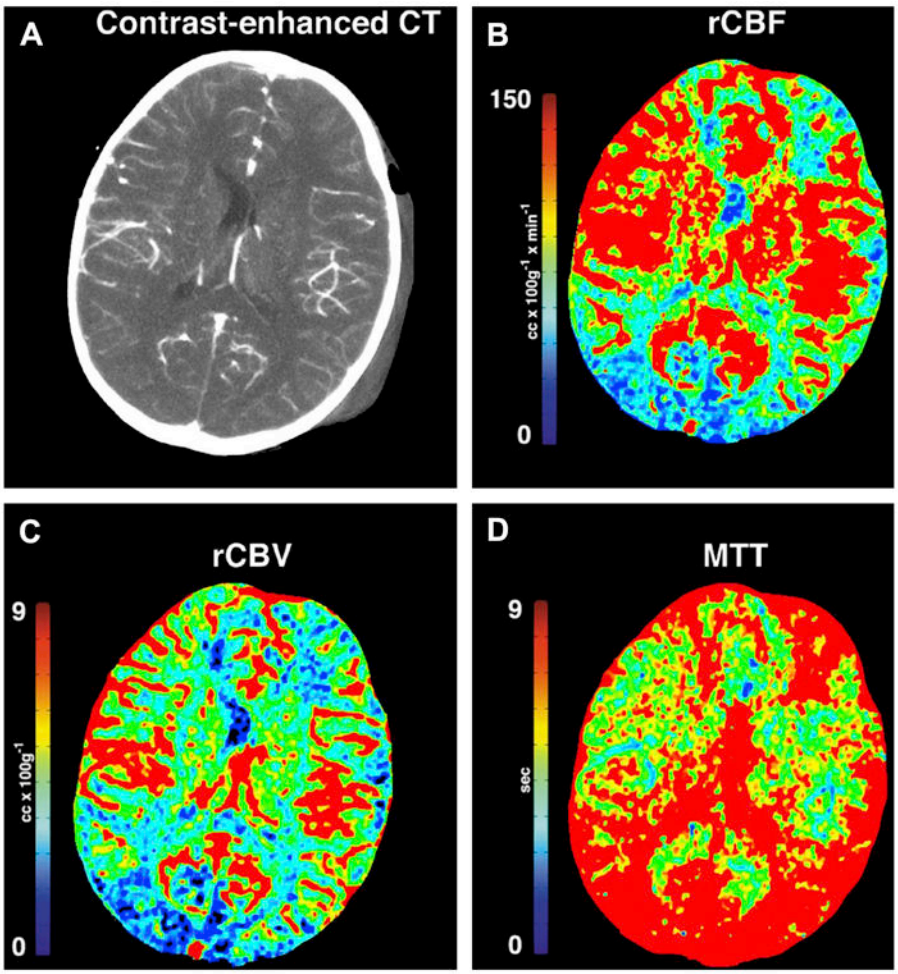

Figure 4:

Contrast-enhanced and PCT images of a case of TBI with intracranial hypertension. The contrast enhanced CT (A) demonstrated left-sided scalp hematoma. The rCBF (B) and rCBV (C) trended toward lower values especially in the occipital lobes. The MTT (D) demonstrated significantly higher values, reflecting altered cerebral autoregulation after TBI.

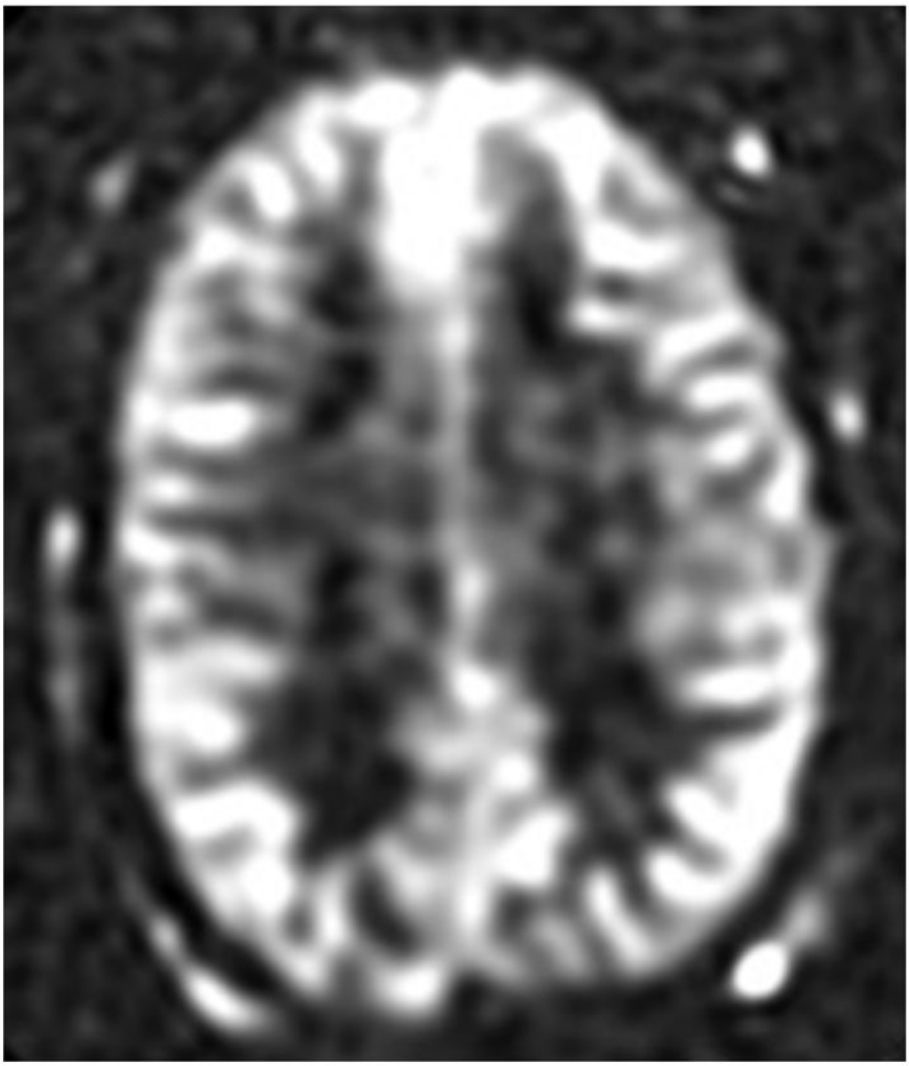

Figure 5:
Normal noncontrast arterial spin labeling (ASL) sequence.

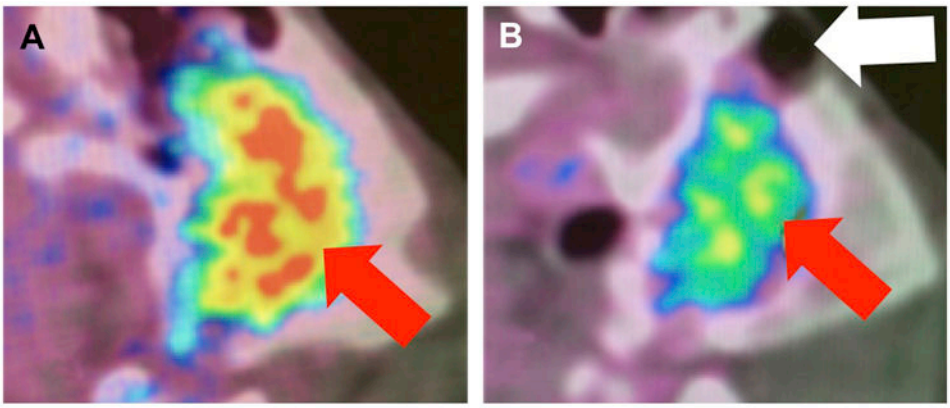

Figure 6:

Two Tc-99m-HMPAO images of a Molecular Neuroimaging of Cerebral Blood Flow Abnormalities due to Traumatic Brain Injury (TBI) in a Swine Model (*Sus acrofa*). Control (A) illustrates normal perfusion (red arrow). The 1-hour post-TBI (B) illustrates craniectomy site (white arrow) at the top of the image with hypoperfusion seen in the underlying brain (red arrow).