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Application of perfusion-weighted magnetic resonance imaging as an imaging biomarker in clinical practice: A review from bench to bedside

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ABSTRACT

Despite substantial advances in disease management in the previous years, survival from many common cancers remains poor. It is expected that decision and cost-effectiveness analyses will become an integral component in assessing the indications for initial brain imaging, including the evaluation for metastatic disease, and the efficiency of follow-up of known primary Attention to the mentioned issues and applying PW-MRI provides suitable situation in which one can calculate certain vascular parameters. In our opinion revolutionary progress in the medical imaging techniques provides situations in which brain surgery could be replaced by techniques such as PW-MRI in near future. A tissue and this reduction is due to T2* as well as presence of the contrast media in the tissue. At the beginning signal intensity will extremely dropped, then it increases to its basic state.

KEY WORDS: perfusion-weighted magnetic resonance, biomarker, imaging.

1. INTRODUCTION

Despite substantial improvements in treatment over the past few decades, survival from many common cancers remains poor (Group, 2005). Concurrent advances in molecular cell biology have identified key ontogenesis and tumor suppressor genes that have a role in tumor growth and metastasis. Patho physiological processes that are common to most solid tumors have become targets for supplementary therapeutics that act on specific biological pathways and might improve clinical outcome. Targeted therapies make cytostasis rather than considerable tumor shrinkage (O'Connor, 2008). Minimum improvement in overall response, defined from measures of tumor shrinkage, has been observed in many clinical trials of agents that inhibit growth factors; membrane bound receptors, and novel targets of downstream signaling pathways. This definition introduces a distinction between a test or tool that is either positive or negative and a variable that is measured by the tool. It places a major emphasis on the measurement used as a marker of a biological state. In order to, an imaging biomarker is a biologic feature, or biomarker detectable in an image. In medicine, an imaging biomarker is a characteristic of an image pertinent to a patient's disease. For example, a number of biomarkers are often used to determine risk of lung neoplasm. The lesion itself helps as a biomarker; nonetheless, the minute details of the lesion serve as biomarkers as well, and can collectively be used to assess the risk of neoplasm. Some of the imaging biomarkers used in lung nodule evaluation include size, speculation, calcification, cavitation, location within the lung, rate of growth, and rate of metabolism. Each piece of information from the image represents a possibility. Speculation increases the probability of the lesion being cancer. A decreased growth indicates benignity. These variables can be added to the patient's history, physical exam, laboratory tests, and pathology to reach a proposed diagnosis. Imaging biomarkers can be measured using several techniques, such as, X-ray, CT, and MRI. Magnetic resonance imaging and spectroscopy of human subjects in vivo have enjoyed over 30 years of steady progress (Gore, 2011). Currently, MRI is well established as the single most useful imaging modality available in radiological practice, especially for the detection and characterization of soft tissue pathologies such as solid tumors in cancer. MRI yields delicate three dimensional images non-invasively, with high spatial resolution and high contrast, and the quality and acquisition times of images continue to improve as technological innovations such as parallel imaging, compressed sensing and higher field strengths are introduced. However, in parallel with these developments, other modalities (most notably X-ray CT, ultrasound and nuclear imaging) have also shown dramatic advances, and developments in one analytic method seem often to catalyze improvements in other domains (Rostamzadeh, 2014; Kalra, 2004). Furthermore, the applications of imaging methods have also changed from conventional radiological diagnosis to addressing other types of problem in biomedical research and patient management. Current tendency in the use and nature of imaging build on growths in other fields such as genomics and molecular biology, and the types of application and procedures have transformed compared to previous years. For example, imaging is progressively was assessing function rather than just anatomy (e.g. for studies of the brain), or to characterize individual phenotypes for targeted drug therapies. Much better use is made of quantitative measurements from images rather than subjective judgments, and pre-clinical imaging of animal models of disease has increased dramatically with the development of specialized instrumentation (Levenson, 2014). Of specific note has been the appearance of molecular imaging to assess specific cellular and molecular processes in living tissues.

Lucignani states that, by accepting the concept that an imaging biomarker is not a tool or a method but a measurable variable that is in turn an indicator of normal or pathogenic processes, it is recognized the use of imaging biomarkers transforms the role of molecular and anatomical imaging from technical to fully clinical. This alteration likewise proposes the choice of the imaging biomarker may become the prerogative of the diagnostic imaging specialist, selecting the most appropriate biomarker for each particular clinical question. This means moving molecular and anatomical imaging from the present status as an aid or support in the diagnostic process to a decision-making level with respect to the choice of the most appropriate procedure for the optimization of the individual patient's care. Imaging biomarkers may be the only way to measure rapidly the management responses in genetically dissimilar subcategories of patients presenting with similar symptoms. In order for techniques using imaging biomarkers to be introduced successfully into regular and routine clinical practice, there has to be a sound evidence base for their clinical utility. Some researchers mentioned "As radiologists and images become focused on the technical, anatomical, and pathophysiological significance of imaging and its interpretation it will be easy to neglect the assessment of its relative clinical value using appropriately designed studies that could determine diagnostic performance and efficacy". Enthusiasm for a novel sequence or method has to be tempered with realism. Morcos and Weir confirm that "It is significant to limit the imaging strategy to what is clinically vital and to resist the lure of creating impressive… images just because it is possible". There has to be a valid clinical reason for performing a particular technique and also a referring clinician who will act appropriately on the results. Medina, state that, although mastering the technical and interpretive aspects of the various imaging techniques is important, maintaining a proper clinical perspective through the use of sound studies aimed at determining efficacy and the effect imaging has on clinical outcome is fundamental to the advancement of the field and the well-being of patients. Society is increasingly demanding proof that imaging has an impact on patient outcome and is questioning the burden of its cost on the healthcare delivery system. In helping an imaging method for clinical use, radiologists should deliver, among other key components, complete decision analysis and cost-effectiveness analysis to determine the impact that imaging has on health outcome, cost and quality of life. Strict adherence to evidence-based medicine principles will help advance the field and provide the best healthcare for patients. Imaging with advanced CT and MR scanners opens new horizons in the evaluation of cerebral hemodynamic. The evaluation of cerebral blood volume and flow can now be performed routinely during the diagnosis and subsequent management of brain neoplasms. What clinical role this information will have awaits careful investigation employing evidence-based practice. The application of decision and cost-effectiveness analyses to radiology will remain difficult because the effects of imaging on patient outcome are relatively indirect (Blackmore, 1999). It is anticipated that decision and cost-effectiveness analyses will become an integral component in assessing the indications for initial brain imaging, including the evaluation for metastatic disease, and the efficiency of follow-up of known primary brain neoplasms.

Physical basics of perfusion-weighted magnetic resonance imaging (PW-MRI): Perfusion-weighted image (PWI) from endogenous and exogenous detectors used to display the hemodynamic status, to extract parameters' quantity such as hemodynamic, cerebral blood volume (CBV), cerebral blood flow (CBF) and the mean transition time (MTT). Potential applications include tissue characteristics after acute stroke and neurological conditions are applied to evaluate tumor conditions. Vascular perfusion process is a biological procedure, in which glucose and oxygen transfer to the brain by nerve cells in the capillaries of the circulatory system. In impaired perfusion almost occur all brain diseases such as strokes definitive neuro degeneration and neoplasm. Nowadays, blood flow imaging is used as a diagnostic procedure. Applying H_2O_{15}, during a positron emission tomography (PET) scan along with newsworthy tracers; one can calculate changes in the blood flow. PW-MRI is used for evaluation of brain perfusion in many disorders such as acute cerebral stroke, brain tumors and neuronal degenerative diseases. Unlike angiography that deals to determine the blood flow in large vessels, PW-MRI, which is capillary sensitive, is applied to reveal leakage of blood from the capillaries. Measurement of tissue perfusion depends to the ability of the target tissue in a constant and rapid detection of the changes in the concentration of tracer (Szabo, 2001).

Overall PW-MRI can be performed via three techniques in wide use to derive one or more perfusion values:

Techniques include:

- Dynamic susceptibility contrast (DSC) MR perfusion
- Dynamic contrast enhanced (DCE) MR perfusion
- Arterial spin labelling (ASL) MR perfusion

Derived values include:

- Time To Peak (TTP)
- Mean Transit Time (MTT)
- Cerebral Blood Volume (CBV)
- Cerebral Blood Flow (CBF)
- Negative Enhancement Integral (NEI)
- k-trans

PW-MRI techniques that are based on increasing the contrast using DSCI are very common for assessment of hemodynamic changes in the following cases: acute cerebral stroke, brain trauma, tumor imaging, and researches. These techniques are based on the passage of drugs and contrast of arterial and capillary bed; while crossing signal changes caused by bolus contrast. In normal circumstances, if the blood brain barrier (BBB) is not damaged; contrast media remains in the lumen of the artery and capillary network, and do not leak toward the extra-vascular space. During movement of the contrast media in the blood vessels, a small amount of the drug causes a sort of non-uniformity in the magnetic field that reduces transverse relaxation time of the tissue. This non-uniformity in the magnetic field can be recorded by T2- and T2*- weighted, spin echo and gradient echo sequences (Szabo, 2001).

PW-MRI procedure: In order to have images in PW-MRI it is necessary that the contrast media is injected rapidly; since we must sure that a suitable combination of the blood and contrast media is happened. A branuel (gage 18 or even 16) should be implemented and administered into the elbow region of the patient by a powerful and compatible MRI rapid injector. The device must inject 5ml/sec of the contrast media providing a dose of 0.2 mMol/kg (or lesser in a 3Tesla system). We also need having a high temporal resolution (< 2 seconds). For PW-MRI the following sequences are the best: GRE T2* single shot- EPI and T2W SE- EPI. The SE-EPI provides high quality images that its sequences are very sensitive to the effects of changing in the magnetic susceptibility. These could even obtain from very tin capillaries with diameter of 5 micrometers. GE-EPI sequences have more sensitivity for larger vessels (> 7 mm). Therefore, SE-EPI sequences have more inherent sensitivity in comparison to the GE-EPI for the vessels in the micrometer scale. The GE-EPI sequences are mainly used in clinical studies. Due to the high sensitivity of these sequences to the changes in magnetic susceptibility and reduction of the effects of signal that passes through the area; the bolus contrast is more sensitive. Thus, in this conditions one need a lower dose of the contrast media. This property is not only used for small vessels, but also could perform for larger vessels and veins in the brain. An alternative option for T2 and T2* -weighted is to apply sequences of T1-weighted (increased signal) which are more sensitive to susceptibility effects (signal losing).

Since relaxation effect is stronger than the effect of magnetic susceptibility, high-contrast T1-weighted images need a low percentage of the contrast media (≈ 10%). This let one to repeat the study. Another reason to use T1-weighted sequences is that it will better illustrate the destruction of the BBB than those obtained by T2 and T2*-weighted sequences. Intensity reduction due to contrast transmission lets one to depict a graph of signal intensity versus time for an individual voxel in the region of interest (ROI) as a function of time. The graph can be converted as contrast media concentration versus time. The amount of contrast media concentration values in all voxels along with maps of perfusion and hemodynamic changes in CBF and CBV can be calculated. Additionally one is also able to find MTT, time to peak (TTP), cerebral blood flow (CBF), and cerebral blood volume (CBV). These parameters are depended to the following characteristics of the contrast media: injection speed, amount and concentration of the drug, vascular volume, and cardiac output of the patient. As a result, the hemodynamic parameters cannot be same for different patients in various situations. CBV in comparison to intravascular space is a part of each imaged voxel; therefore, vessels' blood volume (VBV) is evaluated based on the brain tissue volume. The unit for VBV measurement is ml of blood per 100 gram of tissue. Since brain tissue density is roughly the same as water density, one can count it 1 ml/g for the brain tissue. However, in practice, one uses percentage of this unit. Usually, brain CBV is 3%-5%; which is slightly lesser than the CBV for capillaries' blood and veins' blood. Variation of CBV is related to the automatic changes in diameter of the vessels. Relative CBV is defined as the area of a curve planned for concentration versus time. Identifying a reference voxel, that 100% is composed of blood, *e.g.* superior sagittal sinus; one will be able to calculate absolute CBV. CBF is defined as quantity of arterial blood that reach brain tissue each time, and its unit is ml/min/100gr. Specifically CBF for the white and gray media of the brain is 15 ml/min/100gr and 60 ml/min/100gr; respectively. CBF is controlled by factors that are responsible for nutrition of the brain arterioles. CBF is the main parameter responsible for carrying nutrition materials to and banish redundant materials from nerve cells. CBF less than a threshold point shows infarction in the ROI. MTT, in second, reveals the average time of transmitting of blood from arterial environment. The arterial environment is consisting of infinite arteries that have no definite length and diameter. Therefore, MTT has different values for various tissues. Recorded MTT for normal brain tissue is 3-5 sec; however, in infarction it increases. In MR images the high MTT is shown in red color, the medium MTT in yellow and the normal one in green. Based on the mentioned issues, one can conclude that the following formula explains relation between CBV, CBF, and MTT.

CBF = CBV/MTT: Maximum TTP, in second, is defined as maximum time to have the highest concentration of the contrast media after injection start time. Two factors affected on the pulse intensity: contrast media reaching time and injection process. In DSCI-MRI, Gadolinium (Gd) is a basic material producing T2-weighted images when it transits across the brain arteries for the first time. Gd causes a transient reduction in T2*-weighted signal (T2* shortening) which depends on the Gd concentration. In this procedure using fast pulse sequence, fifty consequent images are created during 70 to 120 seconds of the contrast media injection. We should notice that pulse intensity decreases when contrast media reach the tissue; therefore, the effect of T2* reduction in tissue is shown when the

contrast media is in the vessels. At the beginning, a fast reduction is seen in the pulse intensity, after that the pulse increases to its basic state. The reason for these changes is that blood flow normally exits the contrast media from tissues. Applying DSC-MRI one is capable to measure parameters such as CBV in different vascular conditions. Measurement of endothelial membrane permeability, membrane area, and extracellular space (ECS) need qualitative analysis respecting contrast media leakage from arterial space to ESS. Using T2- or T2*-weighted images for contrast media leakage evaluation has some limitations. Although some MR techniques explain this; but they affected of nonlinear signal changes as well as image susceptibility and tissue relaxation. Hence, T1- weighted images mainly are used in order to acquire vascular information when contrast media is injected. Having T1-weighted images; one can evaluate contrast media concentration and analysis of the data by standard models. During MRI when bolus is used to identify the volume of the bolus in the ROI; there is need to have a high temporal resolution of 5 seconds or less. This short time destructs the spatial resolution; since the scan time is too small. Nowadays, many of the MR centers use single shot gradient echo sequences. The modern MR equipment provide situation in which one can create images with matrixes of $256^{x}256^{x}256$ in 5 seconds. Relationship between signal changes and contrast media concentration is nonlinear and depends to the tissue's T1 for each voxel. Thus, it is necessary to prepare some T1-weighted images before contrast media injection from the ROI that decrease the image reconstruction time (Heiss and Sobesky, 2008).

Clinical application of PW-MRI:

Intracranial neoplasms: Vascular morphology and the degree of angiogenesis are significant elements in evaluating dissimilar tumor types and confirming the biologic fierceness of intracranial neoplasms. Tumor angiogenesis can be indirectly assessed using perfusion MR imaging-derived in vivo maps of cerebral blood volume that depict the overall tumor vascularity. MR imaging capacities of relative cerebral blood volume have been shown to correlate with both orthodox angiographic measurement of tumor vascular density and histologic evaluation of tumor neovascularization. Increased tumor vascularity, however, is not synonymous with malignancy. Numerous intracranial neoplasms, especially those that are extra-axial such as meningiomas or choroid plexus papillomas, can be vascular but benign in biologic behavior. In patients receiving antiangiogenesis cancer therapies that directly attack tumor vessels, perfusion MR imaging is a noninvasive method to assess changes in the relative cerebral blood volume of the tumor during treatment and thus can be used to monitor the efficacy of therapy. Conventional MR imaging is limited by its nonspecificity and inability to allow differentiation between tumor recurrence and therapy related necrosis. Findings of perfusion MR imaging have been shown to correlate better with clinical responses of patients undergoing antiangiogenic therapy (Sobesky, 2005).

Infarction: PW-MRI explains blood circulation through vessels in the live tissues. In the defected conditions, nutritive and wasted materials may transit via vessels' membrane. PW-MRI technique could imaged hemodynamic condition of vessels surface. It also provides higher contrast in comparison to other MRI techniques. PW-MRI could show the blood current of the tissue more clear than other conventional MRI techniques. Therefore, applying PW-MRI it is possible to illustrate a pattern of the damaged brain tissues. Disorders in the perfusion of microscopic arteries can demonstrate using PW-MRI technique. Hence, PW-MRI is suggested as a unique technique that can guide treatment planning of infarction in the brain tissues; since it could show disorders in the perfusion of the tissues. Although the damaged brain tissues are not repairable, but an on time thrombotic or nerve protective treatment may survive the damaged tissues. Studies report applying PW-MRI technique in evaluation of perfusion using intravenous thrombotic intra arterial can improve the treatment of the infarction. Studies reports if MTT is greater than 6 seconds, the damaged tissues in infarction will recover when patient is treated by intravenous plasminogen (Heiss and Sobesky, 2008).

Brain tumor: PW-MRI is capable to illustrate arteriogenesis of brain tumor and determine permeability of the vessels. Both arteriogenesis and permeability are premonition of malignancy; as they are symbols showing presence and grade of the tumor. Vessels of the brain tumor have critical roles not only for providing oxygen and nutritive materials, but also they prepare a plan for tumor penetration as well as hypoxic and necrosis conditions. Determination of the complex biological process for tumor arteriogenesis in order to obtain insight regarding metastatic malignancies and conflict against tumor growth is an important issue. PW-MRI is trying to provide a noninvasive and strength replacement for diagnosis of tumor arteriogenesis and permeability. To recognize possible imaging biomarkers in oncology, it is valuable to study specific questions pertinent to cancer that we may wish to address by dissimilar imaging methods. For example, we may wish to characterize the phenotype and state of some solid tumors by assessing, for example, the blood perfusion and/or oxygenation of the tissue, both of which are highly relevant in considering certain classes of therapy. We may wish to assess whether specific therapeutic targets (e.g. EGFR, VEGF, HER2) are over-expressed by the tumor, and whether a targeted drug or antibody essentially changes this level of expression. We also want to know early in the course of therapy whether a tumor responds to the treatment, before there are gross changes in tumor size or clinical manifestations (Heiss, 2009).

Artifacts and errors in PWI:

Unknown contrast: There is a relation between contrast media concentration and changes in the tissues relaxation time. Studies reveal that based on the contrast media types, vessels and tissue there are certain CBF. Although researchers calculated the CBF for normal conditions; it can be different in pathological situations. A delay in transition of bolus contrast media from ROI may cause an error in the estimated CBF. The error may vary for different regions. There are calculating methods available to identify and correct these kinds of errors. While in DSCI studies 1-2 seconds delay in bolus will result 40% of underestimation in MTT, for the CBF studies it will make 60% of the overestimation. These sorts of delays are frequently seen in patients with brain vascular disorders such as infarction, neoplasm, vessel occlusion, collateral circulation. In these patients perfusion maps evaluate accounting probability of the calculated error (Zaharchuk, 2007).

Effect of contrast media presence: While we know that in DSCI the effect of maximum intensity of contrast media is seen a few minutes after the bolus injection; studies demonstrate that effect of the contrast media remains even 2 hrs after the injection in arterial tissue around the region. This could affect on the MR signals in the 2nd injection. When MRI performs accompanying several injections one must calculate the effect of the remained contrast media in the ROI. If the effect of the remained contrast media is not count, we will face with an overestimation on pulse intensity in the calculations. To reduce the effect of remained contrast media, one should give the patient a very low dose of the contrast media before the examination. Thereafter, the main protocol can be performed. In this condition we have a signal that is fused with the signal of the remaining contrast media which clearly need adjustment for correct calculation (Kane, 2007).

Voxel shift: During the bolus injection it uses EPI sequences, as there is need a high resolution for PW-MRI. EPI sequences have artifacts that disturb the perfusion map when one applies imaging with calculations. The EPI artifacts are mainly due to using images with low width for each pixel (≈10 Hz/pixel) during coding process of the phase. This produces the following artifacts: chemical shift, magnetic susceptibility, and displacement of image's dimensions in the borderline of two tissues. These artifacts are not seen in DSCI, while they are shown in EPI sequences. As contrast media have paramagnetic characteristics, one sees a dislocation of the magnetic field; while bolus contrast is transferred from the ROI. This may cause error in diagnosis of vessels and the time of pulse receiving in the pixels of the borders of the vessels. Having these artifacts one may face with a wrong CBV, especially for the first time of the contrast media transition; since the contrast media concentration is maximum in the presence of the bolus. Thus, applying EPI sequences one must notice that the signal near to the border is an artifact and that also this artifact includes the measured arterial input function (AIF). Therefore, regions that are selected for AIF measurement should be far from the wall of the large vessels (Le Fur, 2010).

Patient movement: Movement artifact is one of the most important artifacts in DSCI technique. Probability of the patient move is high during the DSCI, because of the rapid contrast media injection. Loss or destruction of the data, due to the movement artifact, depends to the amplitude of the movement as well as capability of the MR system for image reconstruction. If movement was done only during the bolus injection, the data are still usable; as it takes a few seconds for contrast media to reach the brain. Although, one must notice that do not use the primary data, obtained after the first injection, for reconstruction. One can use primary images obtained before the contrast media injection to adjust the effect of very small movements; however, this is not a suitable method for all movements. The reason for this issue is that always due to the spatial resolution, a maximum of special covering is obtained and usually there is a time between the two sequential slices. Hence, adjustment of the movement effect in the planned slice is possible.

Perfusion MR imaging provides hemodynamic info that matches conventional structural imaging and is increasingly used in clinical practice to diagnose, manage, and understand brain tumors. Relative cerebral blood volume maps derived from perfusion MR imaging data provide quantifiable estimates of regional blood volume that can be used to grade gliomas, distinguish different brain tumor types, and distinguish tumors from non-neoplastic lesions. There are a few minor limitations of the dynamic contrast enhanced perfusion MR imaging technique—susceptibility artifacts, relative rather than absolute quantification of cerebral blood volume, and the inaccurate estimation of cerebral blood volume in patients in whom the blood–brain barrier has been severely disrupted or destroyed. Despite the minor likely drawbacks of the method, inclusion of perfusion MR imaging as part of a unchanging evaluation of brain tumors can lead to improved diagnostic accuracy, understanding of tumor pathophysiology, and detection and quantification of tumor angiogenesis. With further effort, perfusion MR imaging could be used to assess current and novel cancer treatments that target blood vessels. Finally, the measurement of perfusion provides an indirect access to brain metabolism through the tight coupling between oxygen consumption and delivery. CBF is therefore a more direct estimate of brain function than the use of the blood oxygenation level-dependent (BOLD) contrast, which arises from a complex interplay between CBF, CBV, and oxygen extraction, with influences from hematocrit and basal oxygenation levels. Functional perfusion imaging is more challenging to perform than BOLD fMRI, as its contrast-to-noise ratio is lower, yet provides a better localization of activation than BOLD. The combination of both methods provides additional insight into oxygen metabolism during functional

activation. Oxygen metabolic responses using a combination of BOLD and ASL perfusion MRI are particularly well suited to study pharmacological responses in the brain. CBF has found another application when combined with resting-state fMRI to study functional connectivity in various neurodegenerative diseases. Validation of a new imaging technique involves the following steps:

- Demonstration of its technical feasibility, including assessment of its reproducibility and precision. For comparison among studies, a common standardized protocol is necessary.
- Establishment of normal and abnormal values as studied in different clinical situations. For accurate interpretation of study results, sensitivities, specificities, and positive and negative predictive values compared to a gold standard must be known.
- Assessment of the clinical utility of both positive and negative tests. The clinical utility of an imaging study is related to how the results of that study can be used to benefit patient management. Relevant outcomes of a negative test (i.e., suspected pathology is not present) may be avoidance of more invasive diagnostic tests or avoidance of ineffective therapy. Relevant outcomes of a positive test (i.e., suspected outcome is present) may also include avoidance of a more invasive test plus the institution of specific, effective therapy.

Furthermore, the advancement of medical imaging technology, including an increase in the use of functional and molecular imaging, provides a wealth of new information to be used in preclinical and clinical decision making. Imaging biomarkers removed from the available imaging modalities have become progressively important in medical product growth, disease diagnosis and treatment planning. The forecast is that the role of imaging biomarkers will only continue to increase. Methods of advanced image processing and analysis can provide powerful tools for the discovery and characterization of imaging biomarkers. Future advancements in medical science and industry are likely to benefit significantly from the increased availability of imaging biomarkers as well as theoretical and software tools for the processing and analysis of the images from which the biomarkers are being extracted (Kearse Jr, 1994).

2. CONCLUSION

Researchers demonstrate that signal intensity decreases when contrast media enters to a tissue and this reduction is due to T2* as well as presence of the contrast media in the tissue. At the beginning signal intensity will extremely dropped, then it increases to its basic state. The main reason for this is that blood current normally exits the contrast media from ROI. The speed of the changes is different for various tissue types. Measurement of parameters such as endothelial membrane's permeability, membrane area and ESS need quantitative analysis respecting contrast media leakage from vessels to EES. Using T2- or T2*- weighted images for evaluation of contrast media leakage is difficult; however, in some techniques those procedures affected by nonlinear changes in the signals, magnetic susceptibility, and tissue relaxation. Relationship between signal variation and contrast media concentration is nonlinear and depends to T1 of the base tissue in each voxel. Thus, one should prepare a series of T1-weighted images before the contrast media injection in ROI; which saves time of the reconstruction. Although in DSCI, maximum of the contrast media intensity is seen a few minutes after the bolus injection; but the effect of contrast media remains around the ROI even 2 hours later. The remained contrast media affects on the signal intensity; hence, to reduce error in the received signals one must decreases contrast media dosage of the first injection. Attention to the mentioned issues and applying PW-MRI provides suitable situation in which one can calculate certain vascular parameters. In our opinion revolutionary progress in the medical imaging techniques provides situations in which brain surgery could be replaced by techniques such as PW-MRI in near future.

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