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Role of imaging modalities in evaluation of stroke; towards molecular imaging probes

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ABSTRACT

MRI scanners show a spatial resolution of 250 µm in-plane (small lenticel empirical devices permit for 50 µm isotropic voxels for in vivo evaluation) infinite profundity infiltration along with significant good soft tissue contrast. Extracting any new epitomizing technology to the imaging of children has a number of safety interests that must be aimed. However the lack of ionizing radiation makes MRI particularly suitable for a stroke patient. These treatments must be tailored to the individual biochemical set-up or disease stage of each respective patient with the support of diagnostic data. Equipped with these patient-specific data, a therapy regime is selected, taking into account the different molecular defects for each disease as well as the particular clinical history and condition of a patient. Neuroradiological tools such as CT or MRI have become an indispensable part of the examination and work-up of patients with acute cerebrovascular insults.

KEY WORDS: Molecular imaging, central nervous system (CNS) diseases, positron emission tomography (PET).

1. INTRODUCTION

Clinical MRI scanners show a spatial resolution of 250 µm in-plane (small lenticel empirical devices permit for 50 µm isotropic voxels for in vivo evaluation) infinite profundity infiltration along with significant good soft tissue contrast (Heyn, 2006). Those mentioned above about the condensation of molecular epitomizing targets in the micromolar range is challenging and requires sophisticated imaging strategies(Gharib Salehi, 2016). Progresses in MRI plan to decrease the lower examination limit are feasible only to some extent (Heyn, 2006). Therefore biophysical amplification. Mechanisms to enhance the signal from the label are necessary. For MRI, two different classes of contrast agents exist: agents that influence mainly the signal in T2W (negative contrast agents, reducing the signal) or in T1W Images (affirmative opposition factors, enhancing the symptom) (Kiessling, 2007). For both cases, some procedures have been developed to reinforce symptoms. Generally, both of the cases take advantage of either too vast relaxivity searches, background decrease (SNR optimization) by activation of low– relaxivity searches by the aimed molecular signal (persuaded alteration in relaxivity) or discourse tissue reposition. The latter is feasible with a very limited number of highly expressed molecular signals (e.g. fibrin for thrombosis imaging). The bio – distribution of molecular epitomizing searches must be more specific in detecting and distinguishing disease than the morphological information acquired using anatomical imaging alone (Kiessling, 2007). MRI has a lot of characteristics that make it a powerful device to search issue function as well as to epitomize cellular and molecular procedures (Fatehi, 2016). However, although descriptive epitomizing with MRI is well established epitomizing functional and molecular procedures with MRI has only recently been introduced into clinical practice and many applications are still in the pre-clinical stage of development. Adapting Adapting any new epitomizing to the imaging of has some safety interests that must be addressed. however the lack of ionizing radiation makes MRI particularly suitable for a stroke patient(Fatehi, 2016).

Epidemiological and radiological characteristics of stroke: Stroke is the second-leading cause of death in adults aged 15 years and over worldwide, the fourth-leading cause of disease burden as measured in disability adjusted life years, and the leading cause of acquired disability in adults in most regions. Globally, an estimated 5.7 Million people died because of stroke in 2005. The estimated direct medical cost of stroke in the United States was $25 billion in 2007. The symptoms and the imaging and histopathologic findings following ischemic stroke result from insufficient flow of blood to the brain parenchyma. Most commonly, This decrease in blood current is a result of obstraction of an arterial branch supplying a part of the brain in the absence of adequate collateral circulation (Easton, 2009).

Systemic factors, such as hypoperfusion because of sustained severe hypotension, can also lead to irreversible ischemic damage in the brain tissue. An occlusion of a blood vessel is typically due to arterial or paradoxical embolism, due to a local thrombotic event that is triggered by rupture of an atherosclerotic plaque or due to prothrombotic conditions. If the reduction in blood flow is of sufficient severity and duration, a series of events occurs at the cellular level that leads to irreversible changes. These events include the release of excitatory

neurotransmitters and inflammatory mediators, influx of calcium to the cells, the generation of free-oxygen radicals, the depolarization of the cellular membrane, and the loss of the membrane integrity. A concept of the neurovascular unit comprising neurons, astrocytes, microglial cells, and microvascular structures has emerged recently in the study of ischemic injury. The interactions and signaling between these components appears to play a pivotal role in the response of the tissue to the ischemic insult. If adequate blood supply is not restored in the appropriate time, the affected tissue becomes infarcted, undergoes necrosis and shows scarring with accompanying, potentially permanent neurological deficits. Ischemic stroke is a vascular disease that is caused by insufficient flow of blood to the brain tissue. In general, stroke results from a Thrombotic obstarction of an intracranial artery. Reperfusion following recanalization or elapse of the obstraction, or modified parallel current is a necessary but not enough situation for a desireable clinical result with the time from the onset of ischemia to the reperfusion being a pivotal determinant. Thus, therapies that target the prerequisites of reperfusion, such as intravenous thrombolysis (IVT) and intra-arterial interventions are of special interest. Imaging has a central role in the evaluation of patients with acute stroke. Typically, a multimodal computed tomography (CT) or stroke MRI is performed. Both methods enable the detection of intracranial hemorrhage, allow the approximation of the extent of reversible and irreversible ischemic changes and provide anatomical information on the cerebral and cervical vasculature. These data can be applied to bode the clinical result and the danger of hemorrhagic convolution and to triage the patients to different therapeutic approaches. Multimodal CT, especially parameters derived from CT angiography (CTA) and CT perfusion (CTP) studies, holds promise in achieving these goals with increased accuracy (Hachinski, 2006).

Comparison of imaging methods in stroke imaging: Traditionally CT examinations of the brain have been performed by imaging sequential axial slices with or without intravenously administered iodinated contrast-agent. These imaging modalities are called contrast-enhanced Computed tomography (CECT) and non-contrast (increased) computed tomography (NCCT) (Chalela, 2007). Both of these conditions provide anatomical and structural information on the intracranial space. CECT is not typically included in the acute ischemic stroke imaging protocols. The introduction of multi-detector technology in the past two decades has enabled the use of thinner section-widths and fast envelopement of large epitomizing masses. This technology has eventuated to the progress of CTA and CTP. CTA prepares detailed descriptive data on the mental vasculature. CTP transmit functional data on the hemodynamic basis of the vasculature at the tissue (capillary) level and allows the detection and characterization of ischemic brain parenchyma. The second modality acquired in a multimodal protocol is typically the CTA. In general, a volume from the aortic arch up to the vertex of the skull is covered, and thin-section slices of isotropic spatial resolution are calculated 117. This method enables the reconstruction of two-dimensional (2D) reformatted images in arbitrary planes, maximum intensity projection (MIP) images and three-dimensional (3D) images and provides detailed information on the cerebral vasculature that is comparable with that obtained using digital-subtraction angiography (DSA). Both intracranial and extracranial vessels can be evaluated in a single study. Thus, the vascular anatomy and the collateral circulation can be visualized, the pathology of the vessel wall that alters the diameter of the vessel lumen can be evaluated, and intravascular thrombi can be identified. CTA can detect large- and small vessel occlusions and stenosis highly accurately (95-99%) both intracranially and extracranially. The location and the volume of the thrombi are independent prognostic factors in acute ischemic stroke with proximal, high-volume clots predicting poor clinical outcomes compared with distal, low-volume clots. This finding is related to the rate of recanalization, which is lower in proximal-vessel positions. In addition, the location and volume of the clot limits the effectiveness of IVT in dissolving the occluding thrombus. This information can be used to guide therapeutic decision making and the choice between IVT, intra-arterial interventions or refraining from revascularization therapy. The final imaging modality obtained in a typical multimodal protocol is CTP. A perfusion study enables the quantification of capillary, tissue-level blood flow. CTP is a dynamic imaging modality where the first pass of a bolus of iodinated contrast factor is pursued though the brain parenchyma by replicated scanning of the mass of interest immediately after the infusion 165. This method provides insight into the physiology and pathophysiology of cerebral hemodynamics. Based on a tracer kinetic model, CTP allows the calculation of a variety of parameters that reflect different aspects of the hemodynamic state (Davis, 2008):

- Cerebral Blood Flow (CBF) indicates the volume of blood moving through a brain volume (mass) of interest per unit time ([CBF] = ml/100 g/min).
- Cerebral Blood Volume (CBV) describes the total volume of blood in a given brain volume (mass) of interest ([CBV] = ml/100 g). This volume includes the intracellular, intravascular and extravascular interstitial spaces.
- Mean Transit Time (MTT) describes the average difference in time between the arterial inflow and the venous outflow of a brain region-of interest ([MTT] = s). This time is dependent on the average distance travelled. MTT can be calculated from the CBF and CBV with the central volume principle: MTT = CBV/CBF.

- Time to Peak (TTP) is defined as the time from the beginning of the arterial enhancement to the peak of the enhancement curve ([TTP] = s).

In essence, to evaluate the CBF and MTT from raw measurement information gained using a CT scanner, two mathematical approaches have been used: the deconvolution and non-deconvolution methods. Non-deconvolution methods are based on the application of Fick's principle of conservation of mass to a given region of interest. The CBF can be calculated using the maximum slope technique. Non-deconvolution methods make use of simplifying assumptions that decrease the accuracy of the results. Deconvolution methods attempt to correct the effect of contrast delay and dispersion. There are multiple deconvolution techniques, and the singular value decomposition (SVD) has gained widespread acceptance. Deconvolution methods enable the creation of accurate, quantitative perfusion parametric maps. The concept and calculations have been legalized in humans applying xenon – CT positron emission tomography (PET) and MRI and in animals, using microsphere studies. The main purpose of a stroke perfusion article is to offer an evaluation of the viability of the ischemic tissue, i.e, to identify the irreversibly damaged tissue (the infarct core), the tissue that is at risk for progression to infarction if reperfusion is not achieved (the penumbra) and the normally perfused or hyperemic tissue.

This classification stems from experimental studies that characterized two functional thresholds for CBF: 1) below which cortical function ceases without an increase in extracellular potassium or reduction in pH (the penumbra) and 2) below which there is disruption of cellular integrity (the core). These thresholds have been correlated with advanced neuroimaging findings-the perfusion parametric maps-to define a more clinically relevant operational penumbra, which identifies hypo perfused but potentially salvageable tissue. In the simplest terms, the operational penumbra is the mismatch (subtraction) volume between the CBF or MTT (or TTP) and the CBV (or DWI), in which the CBV (or DWI) lesion reflects the infarct core and the CBF or MTT (or TTP) lesion reflects the boundaries of the hypo perfused penumbral tissue. This concept was initially validated for MRI, and later MRI and CT results were correlated (see section 2.2.4 for a discussion of the DWI-PWI mismatch in MRI). However, Standardization or confirmation of of the quantitative perfusion parameter map avails has not been achieved for acquisition and post-processing across different vendor platforms or even across different platforms from the same vendor. Thus, plenty of absolute threshold avails have been suggested for different perfusion parameters in multiple articles. Applying relative avails obtained by comparing to the contralateral, uninvolved side can, in part, circumvent this problem. However, even the relative values vary with post-processing technique, and the interpreter must be familiar with the software and hardware used. The perfusion parameters that determine the core and the halation in the best way, remain under discussion. This task is challenging, as both regions are dynamic in character because of the nature of the disease process.

Novel information demonstrate that properly threshold relative and total MTT values optimally recognize the risk halation and that threshold CBF values may assess the core more accurately than CBV cut-offs. Depending on the post-processing technique used, relative MTT thresholds ranged between 150 and 249% and relative CBF values were between 16 and 44%. Relative CBVs ranged between 56 and 60%. Some researchers have been validated for CTP parametric maps, which provide another method for quantifying CTP findings in the anterior circulation including calculation of the perfusion mismatch. CTP can serve as a substitute signal for stroke intensity and as an autonomous clinical result. Multiple studies utilizing a variety of imaging methods have established a strong correlation between the size of the core upon admission and the clinical outcome. Patients with a core lesion volume 70-100 ml show poor outcomes regardless of therapy or recanalization status. It is unclear how large a clinically significant penumbra should be. An arbitrary mismatch ratio (e.g. defined as Volume MTT/Volume CBV) –cut-off of 1.2 or 2.0 has been used in most studies. The degree of early reduction in CBF and CBV and, interestingly, the size and severity of the DWI lesion are correlated with the risk of a hemorrhagic complication. CTP can identify potentially salvageable brain tissue in the context of IVT. A major disadvantage of CTP in most currently used scanners is the limited z-axis coverage. According to a recent report, 75 mm of z-axis coverage was required to reliably detect a perfusion mismatch ratio of 2.0 in the anterior circulation, whereas 50 mm was sufficient when a ratio of 1.2 was used. Newer 256- and 320-row scanners can achieve whole-brain coverage. CTP is insensitive to acute lacunar and small, deep white-matter lesions 194, 195. CTP may overestimate the size of the CBV lesion. In contrast, CBV and CBF may underestimate the core due to post-ischemic hyper perfusion. If not properly threshold, the MTT and CBF imperfections include a zone of reflexive benignant oligemia that is not in danger of developing to disruption. CTP involves an intravenous injection of 35-60 ml of iodinated contrast material. However, this procedure does not appear to increase the incidence of contrast-induced nephropathy 201. The patient also receives a dose of ionizing radiation. If the CTP protocol has been set-up correctly, the dose is slightly higher than that used for NCCT.

The complex post-processing may be prone to operator errors, which can be counteracted with training and quality control. MRI has proven itself to be a revolutionary and evolutionary tool, maybe even more so than CT. While the advantages of its non-ionizing nature are evident, the examinations were initially extremely time

consuming and ill-suited to acutely ill patients. It would be the manifestation of echo – planar epotimizing that was the solstice not just fir stroke but also for many zones that need an enhancement in epotimizing speed and a reduction in overall acquisition time. Actually, echo – planar purposed that dissemination and perfusion weighted imaging (PWI) MRI would be eventually clinically possible. Conventional MRI has been in use from the start But more to show the attendance of appointed ischemic wounds that will be hypo intense on T1 and hyper on T2, because water reposition these conventional techniques are still used for the follow-up of patients where they remain the standard. Diffusion weighted imaging (DWI) technique are MRI techniques that image water movement. These techniques are now more than 20 years old. Thus, the protons were given a bump and if they propel more or less would deliver more or less symptom back. The procedure was initially very sentient to motion and it was only with the development of clinically available echo-planar scanners that this technique could translate from the lab to the clinical site. Once it was clinically applied to patients with acute stroke, it showed itself to have a high sensitivity and specificity. As in animal models the capacity for detection of acute ischemic changes starts minutes after stroke onset only.

Comparison studies have shown DWI to be far superior to CT. Of interest also is the capacity of DWI volumes to correlate with clinical status and outcome; this implies that at least for studies implicating drugs it can be used as a surrogate marker of ischemia. It is also known that diffusion lesions tend to grow with time and this can be used more when using the so-called diffusion-perfusion mismatch. The diffusion – perfusion inconformity is a rather simple pattern but which clinically act at times: one suggests that at an early time point the diffusion wound is the core and around that the hypo injected zone demonstrates the penumbra. The problem is that from a historical perspective at least the penumbra is a physiological definition of an area between thresholds of dysfunction and definitive damage, Thresholds of ischemia are also present in the diffusion image and most certainly on the ADC maps: while this has not been as well reproduced in humans as in the animal models it seems that there is a definable threshold. Also, another zone where DWI has assisted to do a lot of development is its capability to place more accurate the wounds: this can even allow alteration between wounds that are made as a result of a more distal or a more proximal cause. Those that have a more proximal origin will be more distributed widely with at times a starry sky appearance of the emboli on the DWI images. For patients who some-times wake-up with a stroke, a mismatch between FLAIR and DWI can be sought: if the lesions are of same size, it is highly probably that the lesion is more than the allowed therapeutic window. PWI techniques have been available for a long time using MRI scanners. These techniques can be per-formed in a multitude of ways.

The most repetitious methods is to apply T2 epiyomizing procedures: images are repeated too fast using echo – planar technology and images covering the whole brain are done: a gadolinium based chelate is then injected and when this enters into the blood there is a decrease in contrast that is due to the induction of local changes in magnetic susceptibility: this will allow to calculate maps of mean transit time as well as of relative cerebral blood flow and volume. Additionally, T1-weighted techniques can be used but are far less common but could be advantageous. Another technique that has been available for a number of years but has been underutilized is the so-called arterial rotation labelling procedure: this depends on the tagging of blood current at the cervical rate with making maps of cerebral blood current at the distal cerebral level. This allows obtaining perfusion maps without any contrast agent, which could cause toxic allergic or nephrologic problems. Also with advances in MRI technology, it has been possible to obtain multi-slice data sets covering the whole brain. The impediment is fewer symptoms but there are a lot of privilege of ASL besides the non-utilization of contrast such the feasible show of parallels and selective demonstration of vascular territories. Thus, conflicting series have demonstrated information that is a little conflicting with either agreement or overestimation of hypoperfusion; this may be due in part to the lower signal but also due to a lack in consensus on the use of technical parameters used for ASL in clinical practice across vendor platforms. While contractual T2 epitomizing has been acting a main role in epitomizing of bleeding and petrifactions, the manifestation of so called susceptibility – weighted epitomizing has altered this even further: indeed, these SWI images now allow to obtain high-resolution images of e.g. the brain. While good for the detection of bleeding these results could also ameliorate our knowledge about the attendance of trans-cerebral veins in acute stroke. MR Angiography (MRA) techniques: these techniques have evolved greatly over the last decade. At first images based on either time of flight or phase conflict procedures were utilized. These did not include any conflict factor but used. Multimodal MRI suggests an alternative procedure to study critical stroke.

A typical stroke MRI protocol includes: DWI, PWI, MRA, gradient-echo (GRE) and fluid-attenuated inversion recovery (FLAIR) imaging. GRE and FLAIR are used to detect intracranial hemorrhage, and MRA provides information on major-vessel patency. DWI is used to detect the ischemic process and to characterize the extent of the infarct core. PWI allows the assessment of cerebral hemodynamics using the perfusion parameters described in section. The DWI-PWI mismatch estimates the size of the operational penumbra. MRI is superior to NCCT in sensitivity and accuracy of detection of acute ischemia and hemorrhage. The anatomical and pathophysiological information obtained with CTA and CTP and the clinical utility of these data are comparable to MRI. Theoretically,

CTP provides better approximation of the true quantitative perfusion values. As with CTP parameters, DWI can overestimate the size of the infarct core but appears superior to any CT option (Kane, 2007).

Future of molecular imaging: Multimodal CT is readily available, is faster and cheaper to perform, is less sensitive to motion artifacts and has fewer contraindications. However, MRI typically has better z-axis coverage and does not include disposal to ionizing radiation or iodinated conflict - factors. Since therapeutic choices have appeared for critical ischemic stroke there has been an enhanced pressure to expand devices for an early diagnosis. Indeed, the era when stroke was synonymous with death or lengthy stays in recovery are now far gone. The main diagnostic tool over the first decades when treatment was initiated was CT (Herschman, 2003). Indeed, the early thrombolysis trials were done based on the use of unenhanced CT alone. This was in a way enough to evacuate hematoma or a mass as well as to show early intense ischemia but was unfortunately inadequate for a more accurate work-up. Also, the use of MRI was restricted in the early phase due to the fact that it could only detect T2changes in the late phase and also due to the fact that early scanners were closed and that patients could not take the long examination times. Thus, there was a first technological revolution when MRI saw the development of early clinical echo-planar scanners; this allowed implementing sequences such as diffusion and perfusion that allowed modeling the first human penumbra. Actually, these procedures which had been in expansion for a while had been almost inconceivable to utilize clinically due to time limitations and duet sensibility to motion(Fatehi, 2016a). The two techniques that got a boost from echo-planar technology were DWI and PWI techniques. DWI, which was indeed a revolution, was initially met by much resistance due to a multitude of factors: on the one hand radiologists were not enthusiastic about performing emergency MRI and on the other hand neurologists doubted its capacity to adequately represent the neuronal damage and thus be an equivalent if not replacement of an accurate clinical examination. This led to a delay in the adequate utilization of these tools (Massoud and Gambhir, 2003). Then the development of CT techniques such as CT perfusion made the acceptance of multimodality imaging much more widespread. With treatment modalities becoming more and more sophisticated with intravenous and intra-arterial thrombolysis as well as mechanical techniques being proposed such as the MERCI device or the current modern stent-rievers, it has become possible to open vessels that could not be before. Thus, in a lot of situations the pragmatic issue initially located by MRI procedures has been dominated and more and more centers tend to suggest the procedure in first attempt. In other places, MRI will still be done but either in cases where it is unclear or as a follow-up method. The major problem could be some times blood: even though in theory MRI procedures are known to have a high level of susceptibility to the detection of hemosiderin and blood degradation products, it is sometimes a question of experience with the appearance of acute hemorrhage that is an issue when using the method. Much data points to the fact that both techniques can be used almost equally but may also be used together: in some instances CT will be used primarily to exclude hemorrhage and perfusion and angiographic techniques will demonstrate hemodynamics and occlusion with an MRI done as follow-up; MRI scan also be used when there is a clinically very strong suspicion of stroke but with no real CT parameters; on the other hand when using MRI in first intention, very often CT can be used to detect early hemorrhage or pooling of contrast in case an intra-arterial intervention has been done. Thus, both techniques tend now to become complementary and not so much exclusive (Hoffman and Gambhir, 2007).

2. CONCLUSIONS

Molecular Imaging is one out of three pillars of molecular medicine, i.e. the translation of basic molecular biology into medicine. The other two are *in vitro* diagnostics and knowledge driven healthcare. To specify genetic preparation, *in vitro* genomic or proteomic screening techniques will be applied, such as DNA – chip technologies or mass spectroscopy. IT devices will be compulsory as complicated molecular data, be it in vivo or *in vitro* diagnostic, has to be integrated by IT and has to be supplemented by knowledge bases to leverage it into clinical applications. This means diagnostic data has to be converted into meaningful medical knowledge. The financial feasibility and medical practicability of molecular medicine including comprehensive diagnostics are debatable. The trial and error method will certainly continue to be the most reasonable approach for cost effective therapies without side effects. However, this is not the case with highly potential therapy regimes (i.e. therapies with a potential for serious side effects), cost intensive (molecular) treatment schemata (such as cell- or gene therapy) or therapies of chronic diseases. In such examples, a logical treatment selection based on general diagnostic information is a crucial agent for impressive and cost susceptible patient care. One of the main cost drivers in medicine is inappropriate treatment over a prolonged time. From a medical point of view, many arising molecular therapy concepts are based on individualized drugs. These treatments must be tailored to the individual biochemical set-up or disease stage of each respective patient with the support of diagnostic data. Equipped with these patient-specific data, a therapy regime is selected, taking into account the different molecular defects for each disease as well as the particular clinical history and condition of a patient. Neuroradiological tools such as CT or MRI have become an indispensable part of the examination and work-up of patients with acute cerebrovascular insults. The patient who comes into the emergency department must be examined as quickly as possible since factors as time to needle play a more and more

important role. What type of imaging is used is very often dependent on local organizational factors (Weissleder and Mahmood, 2001).

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