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"ROLE OF SPECTROSCOPY IN MAGNETIC RESONANCE IMAGING: A CLINICAL REVIEW"

Radiology

R. Adityan — 1st Year Student, M.Sc., Radiology and Imaging Technology, The Tamilnadu Dr.MGR Medical University, Chennai

Dr. Sajith Selvaganesan* — MBBS., MD (Radiology) Assistant Professor, Department of Radiodiagnosis, Pondicherry Institute of Medical Sciences, Pondicherry.*Corresponding Author

ABSTRACT

Magnetic Resonance Spectroscopy (MRS) is used in diagnostic imaging for disease metabolism evaluation. The ^{1}H MRS is highly used because of the abundance, high sensitivity, etc. The various clinical implementation includes whole-brain MRS is used in measuring metabolites of different brain areas simultaneously. The breast MRS is used in malignant and benign tumors differentiation by the total choline compound. The prostate MRS is used to map the metabolites like citrate, choline, and creatinine. For spinal cord MRS, the myoinositol and N acetyl aspartate were considered markers for various diseases. The MRS uses nuclei like ^{31}P, ^{23}Na, and ^{1}H for metabolic and biochemical evaluation of cardiac muscles. The liver MRS spectrum has mainly methylene group of lipid, methyl groups of choline, and water. The MRS measures choline, creatinine, lactate, and lipid peaks in uterine leiomyoma and myometrium. Hence there are organ-specific metabolites used as a reference to map the metabolic process by using spectroscopy, making it one of the commonly preferred technique.

KEYWORDS

Magnetic Resonance Spectroscopy, Clinical application, Peak values.

BACKGROUND OF THE REVIEW

Magnetic Resonance Spectroscopy is a highly considered medical imaging technique in the neuroradiological interpretation of various pathologies. Several review articles were published about the spectroscopies of breast, brain, prostate pathologies, and various other body parts. This review article discusses about the physics behind spectroscopy and clinical application in the breast, brain, and prostate. We also focussed on spectroscopies of the spinal cord, cardiac imaging, musculoskeletal imaging, liver imaging, and gynecological imaging.

INTRODUCTION

Magnetic Resonance Spectroscopy (MRS) is a non-invasive technique used clinically to evaluate the disease metabolism. (G. Lin & Chung, 2014) This technique is helpful for clinicians in interpreting neuronal viability, neurotoxins, etc., within the volume of interest. (Hollingworth et al., 2006) The clinical implementation of MRS has increased drastically nowadays due to advancements in pulse sequence and hardware, leading to an enhanced temporal and spatial resolution of the MRS spectrum. Usually, the Magnetic Resonance Imaging (MRI) images were visualized as greyscale images for interpretation, whereas the MRS spectrum has various peaks or resonances of different chemical structures. These chemical structures have a varying inherent electronic environment that drives the nuclei to resonate at various frequencies. This resonance frequency is called chemical shift and expressed as parts per million (ppm). (G. Lin & Chung, 2014) The MRS spectra can be acquired from nuclei like 1-Hydrogen (^{1}H), 31-Phosphorus (^{31}P), etc. The ^{1}H MRS is highly used because of the abundance, high sensitivity, etc. (Faghihi et al., 2017) whereas ^{31}P MRS is used in evaluating cellular energy states. (Ruiz-Rodado et al., 2021) The standard brain MRS shows spectra of N-acetyl aspartate (NAA), Myoinositol, choline, and creatinine containing compounds. (Hsu et al., 2001; J et al., 2018; Jain et al., 2018) NAA represents neuron health and it is considered a good metabolite, whereas choline represents a tumor, and lipid is seen in necrotic tumors. (Umamaheswara Reddy et al., 2014)

Like routine clinical MRI, MRS does not produce higher fat and water signals, which instead creates a frequency spectrum with the minute signal from the metabolites. The weak signal intensity, demands a higher magnetic field. Hence, most clinical MRS studies use 1.5 tesla (T) or 3T MRI systems. The clinical advantages of 3T are the higher signal-to-noise ratio (SNR) and ability to acquire precise spectra from smaller voxels etc. (Faghihi et al., 2017) Even though 3T has several advantages over 1.5T, the field strength does not determine the spectra information. So, MRS can be clinically performed either in 1.5T or 3T MRI scanners. In recent days, notable advancements in the spatial and spectral resolution are reported by using 7T scanners. (Öz et al., 2014)

SPECTROSCOPY ACQUISITION TECHNIQUE

Bottomley et al. acquired the first MRS of the human brain with frequency selected water suppression and slice selective spin-echo excitation in a 1.5T scanner. In the 1980s, many spatial localization techniques for signal acquisition came to an advent in which Stimulated Echo Acquisition Method (STEAM), Point Resolved Spectroscopy (PRESS) or Spin Echo Full Intensity Acquired Spectroscopy (SPECIAL) were used nowadays with broadband pulse and slice selection to localize a voxel. (Al-Iedani et al., 2017; Gonçalves et al., 2019)

Due to the broadband pulse, a water suppression like Chemical Shift Selective Saturation (CHESS) or Variable Power Radiofrequency Pulses with Optimized Relaxation Delays (VAPOR) is needed before excitation for acquiring a clear spectrum. Also, Water Suppression by Gradient Tailored Excitation (WATERGATE) combines gradients and water-selective pulses used in selectively dephasing bulk water signals while retaining a full spin-echo from metabolites. (Gonçalves et al., 2019)

SINGLE VOXEL AND MULTI VOXEL SPECTROSCOPY

Single Voxel Spectroscopy (SVS) is a voxel placed in an area that is suspicious of metabolic damage due to the disease. (Faghihi et al., 2017) The SVS gives a high-quality spectrum with excellent peak separation and higher SNR. The total acquisition time of SVS takes approximately 3 – 5 minutes. (J et al., 2018) The SVS is performed in a single focal lesion or diffuse disease. The SVS has several advantages like good shimming, auto water reference acquisition, lesser scan time, etc. (J et al., 2018; Öz et al., 2014) The major disadvantage is that information about the spatial heterogeneity of the normal brain tissue and the lesion is not available; hence, in many cases, the contralateral acquisition of healthy brain tissue is acquired after acquiring pathological area for normal reference data that is time-consuming. (Mathur et al., 2019; Öz et al., 2014)

Multi Voxel Spectroscopy (MVS) is used in which a more extensive volume coverage is divided into several small voxels to produce individual spectra of the voxels. (Faghihi et al., 2017) The scan time of two-dimensional imaging is 5 – 8 minutes, whereas for three-dimensional imaging is 7 – 15 minutes. (J et al., 2018) The major disadvantage of this technique is the spectral loss because of improper lipid and water suppression due to insufficient shimming as it covers a larger area. Therefore adequate knowledge is necessary to select the appropriate technique. (Öz et al., 2014) PRESS and STEAM techniques were used in SVS and MVS. (Sharma & Jagannathan, 2019) The schematic representation of SVS and MVS were illustrated in Figure 1.

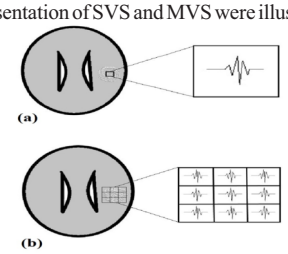

Figure 1: Schematic representation of SVS and MVS planning in a brain pathology. **(a)** Represents SVS voxel with a single spectra acquired in it whereas **(b)** represents MVS in which multiple smaller voxels with separate spectra placed in a volume.

TIME OF ECHO

There are various parameters altered in optimizing the MRS acquisition in which the most important one is the Time of Echo (TE). These parameters determine the appearance of the MRS spectrum and diagnostic information extracted from them. The clinical MRS uses a TE of 18 milliseconds (ms) to 288 ms. In this range, the TE is divided into Short TE (18-45 ms) and Long TE (120 – 288 ms), highlighting different aspects of the MRS spectrum. (Cianfoni et al., 2011; Tivaskar et al., 2021)

The short TE is used to detecting metabolites with shorter T2 relaxation time like macromolecules, myoinositol, mobile lipids, etc. Nevertheless, the drawbacks of short TE is increased overlapping peaks, especially lipid and lactate as lipid is the most critical marker in diagnosing the tumor's metabolic condition, water contamination with spectral distortion due to the eddy current's effect, irregular baseline, the artefactual appearance of elevated N acetyl aspartate (NAA), background noise due to lipid and water contamination etc. From the clinical point of view, short TE is used in brain tumor characterization. (Cianfoni et al., 2011; Kousi et al., 2012; Tivaskar et al., 2021) The short TE's SNR is higher due to the lesser T2 dephasing and high signal intensity. (Hattingen et al., 2007)

Long TE is used in metabolite detection with longer T2 relaxation time with undistorted baseline acquisition. The lipid, lactate peaks were acquired clearly. However, the drawbacks are that spectra obtained with long TE are less informative as short T2 metabolites can be missed, the artefactual elevation of choline creatinine ratio, etc. (Cianfoni et al., 2011; Isobe et al., 2002; Kousi et al., 2012; Carles Majós et al., 2004) From the clinical point of view, long TE spectra are used to quantify and detect NAA, Choline, and creatinine. (Darweesh et al., 2014) The long TE's SNR is lesser than short TE, but there is the best reproducibility in long TE. (Inglese et al., 2006)

The TE is one of the essential parameters in MRS acquisition as it is altered to obtain different diagnostic information and diagnostic peak ratios for pathology evaluation. (Cianfoni et al., 2011; A. P. Lin & Ross, 2001) The short and long TE's, have their potential advantages as well as disadvantages. Hence MRS with both the TE's are performed to avoid misdiagnosis. (Cianfoni et al., 2011; Kousi et al., 2012) The appropriate knowledge in MRI physics as well as chemistry phenomena is vital in interpreting the MRS spectra and avoiding pitfalls. (Cianfoni et al., 2011)

CLINICAL APPLICATIONS

BRAIN, BREAST, AND PROSTATE

The whole-brain MRS is used in measuring metabolites of different brain areas simultaneously. (Klietz et al., 2019) Functional neuroimaging (combination of diffusion & perfusion-weighted imaging with MRS) is used in functional tissue assessment, tumor functionality, tumor grading, etc. (Hasan et al., 2019; C. Majós et al., 2011) The role of MRS in psychiatry is significant as it gives information about the psychological process of the brain with the help of two and three-dimensional MRS in interpreting various psychological disorders. (Dager et al., 2008) The MRS has also contributed to the correct assessment of diseases like demyelination, inflammatory changes, malformation of the brain, ischemia, follow-up imaging, brain tumors, etc. (Cianfoni et al., 2011; Kaddah & Khalil, 2016) The peaks of the metabolites were not altered after the administration of gadolinium-based contrast media. (A. P. Lin & Ross, 2001; Smith et al., 2000) The reduction in NAA, choline, creatinine and choline creatinine ratio are seen in radiation injury of brain. (Sundgren, 2009) The various metabolites and related diseases of the brain are given in table 1.

Table 1: Metabolites and their impact in various brain diseases. (Chaudhary & Bano, 2011; Faghihi et al., 2017; C. Majós et al., 2011; Ruiz-Rodado et al., 2021; Van Der Graaf, 2010; Verma et al., 2016)

METABOLITE	PEAK VALUE (ppm)	ELEVATED PEAK	DECREASED PEAK	ABSENCE OF PEAK
Lipid	0.9 (methyl proton)	Necrosis, Inflammation, Lymphoma (absence of necrosis), Anaplastic &atypical meningioma, Glioblastoma, Metastatic lesion etc.	-	-
	1.25 - 1.3 (methylene proton)		-	-
Lactate (Doublet Peak)	1.33	Hypoxia, Stroke, Multiple Sclerosis, and Higher grade Tumour.	-	Low grade brain tumour.
Alanine	1.47 / 3.93	Central neurocytoma, Meningioma, etc.	-	-
Acetate	1.92	Brain Abscess.	-	-
Succinate	2.42	Brain Abscess, Neurocysticercosis.	-	-
N-acetyl Aspartate	2.01	Canavan disease, Autism spectrum disorder in paediatrics.	Glial tumours, Stroke, Multiple sclerosis, Epilepsy, Neurocytoma, Alzheimer's dementia	Glial tumours, Meningioma,
N-acetyl aspartyl Glutamate	2.04	-	-	-
Glutamate (GLX)	2.2-2.4Glx	Meningioma, Helps in differentiating Oligodendroglioma (elevated peak) from astrocytoma (low peak), Epilepsy.	-	-
Glutamine (GLX)	3.6-3.8			-
Creatinine (Cr)	3.03 (methyl protons)	-	Glial tumours, meningotheliomatous meningioma, brain metastases, Peritumoral oedema in glioma	-
	3.93(methylene protons – Phospocreatinine)	-		-
Choline (Cho)	3.2 / 3.52	Glial tumours, Stroke, Radiation induced necrosis, Peritumoral oedema in glioma, Multiple sclerosis, Lymphoma, Meningioma, Neurocytoma, Inflammation, Hypothalamic glioma	-	-
Taurine	3.25/ 3.43	Metastatic renal cell carcinoma, Pituitary micro adenoma, and Medulloblastoma.	-	-
Myoinositol	3.5 - 3.61	Grade II Glioma (LOW GRADEGLIOMA), Alzheimer 'sdementia, Astrocytosis, Gliosis	(HIGH GRADE TUMOUR) Anaplastic astrocytoma (Grade - III) and Glioblastoma multiforme (Grade – IV)	-
Glycine	3.55	Central neurocytoma, Ependymoma, Glial tumours, Glioblastoma (helps in differentiating it from metastatic lesion), and Medulloblastoma	-	-
Glucose	3.43 – 3.8	Slightly visible in Low grade glioma.		

The hunter's angle is a way to analyze the metabolite ratio like NAA: Cho, NAA: Cr, Cho: Cr. (J et al., 2018) The NAA: Cho ratio is used in detecting high-grade glioma in response to treatment. (Ruiz-Rodado et al., 2021) The Cho: Cr ratio of greater than 1.5 indicates the presence of tumor. (Hollingworth et al., 2006) The Cho: NAA ratio characterizes the lesion as benign and malignant, further classified as high or low grade. (Chandrasekharan et al., 2020) The NAA: Cr ratio is higher in neoplastic brain lesions. (Kaddah & Khalil, 2016)

The breast MRS is used in malignant and benign tumors differentiation based on the total choline compound (tCho) as the malignant tumors have higher tCho and insufficient for detection in benign tumors. (Begley et al., 2012; Shin et al., 2012) The SVS is commonly preferred following contrast media injection. (Begley et al., 2012) Roebuck et al. had suggested that using tCho is a potential marker for diagnosing breast malignancy, and this team first reported the qualitative approach. (Begley et al., 2012) The tCho is detected in pathological areas and observed in normal breast tissues of lactating females and healthy subjects in lesser concentration. (Sharma & Jagannathan, 2019) However, in lactating females lactose peak was also detected, which is not detected in breast cancer patients. (Sharma & Jagannathan, 2019)

Among most males, prostate is the secondly diagnosed cancer site in the world. The MRS is used to map the metabolites like citrate, choline, creatinine with localization, staging, and guiding treatment selection and planning in prostate cancer. (Filip G. Claus, Hedvig Hricak, 2004; Mathur et al., 2019) The choline and citrate peaks are closer to each other, causing difficulty in interpretation. The citrate concentration is usually high in the healthy prostate's peripheral area, than in central or transition zones, whereas in malignant pathology, it is lower. (Filip G. Claus, Hedvig Hricak, 2004; Mathur et al., 2019)

SPINAL CORD (Hock et al., 2013)
The degenerative changes, traumatic injury, neoplastic disorders, etc., can cause metabolic or microstructural changes in the spinal cord that may cause an impact on the daily life. MRS has been implemented for evaluation after its huge acceptance in brain interpretation to avoid various invasive techniques for disease evaluation. The MRS needs expertise in clinical application as it has some challenges like reduction in SNR and line shape distortion of the MRS spectrum from the susceptibility changes of different surrounding anatomical structures. Lesser SNR leads to improper quantification and improper water suppression because of the cerebrospinal fluid flow. Patient movement in millimeters can severely affect the MRS Voxel as the dimensions are in the range of millimeters.

For an adequate SNR and shimming, good voxel placement is necessary. Initially, for the voxel placement, a high resolution T2 weighted turbo spin echo sequence of the spinal cord is acquired. Cooke et al. used triggering to compensate for the cerebrospinal fluid flow. Additionally, in some studies, electrocardiograms or pulse oximeters were used. Also, in some other studies triggering was avoided to reduce acquisition time.

The Myoinositol and NAA were considered markers for various diseases. Various studies of the cord shows the reduction of NAA: Cr ratio for multiple sclerosis patients. Post brachial plexus root re-implantation, there is an elevation in the Myoinositol creatinine ratio. For traumatic injury patients, decreased NAA: Cr ratio and increased Myoinositol creatinine ratio are observed.

CARDIAC IMAGING (Hudsmith & Neubauer, 2009)
The MRS uses nuclei like ^{31}P, ^{23}Na, and ^{1}H for metabolic and biochemical evaluation of cardiac muscles. ^{1}H MRS is used in evaluating creatinine, lactate, etc., whereas ^{31}P MRS for adenosine triphosphate (ATP) and phosphocreatine detection. ^{23}Na MRS is used in myocardial sodium assessment. Mostly the MRS is conducted in ^{31}P MRS, with its first implementation in the 1980s. The localization techniques like depth-resolved surface coil spectroscopy (DRESS), image-selected in vivo spectroscopy (ISIS), and 3-dimensional chemical shift imaging (3D-CSI) were used in myocardial voxel placement. The spectral localization with optimum point spread function (SLOOP) enables curved voxel placement in quantifying the myocardium accurately. The ^{31}P MRS phosphocreatine (PCr) to ATP ratio shows the energetic heart state. The ^{23}Na MRS for evaluating the viability and infarction of myocardium. The ^{23}Na signal is elevated in case of scarring. For ischemic heart disease, the ^{31}P MRS shows decreased PCr level due to decreased oxygenation. The , ^{31}P MRS of heart failure patients shows decreased PCr to ATP ratio and a collateral decrease of PCr & ATP, whereas ^{1}H MRS shows decreased creatinine levels in dilated cardiomyopathy. In inherited cardiomyopathy patients, ^{31}P MRS shows decreased PCr to ATP ratio in asymptomatic younger patients.

LIVER (ter Voert et al., 2011)
The liver is the secondary common metastatic cancer invading site. Currently, histopathological analysis is considered the golden standard for cancer suspicion. Nevertheless, invasive procedures may have some disadvantages too. The MRS gives tumor pathophysiology with metabolism mapping, which helps in evaluating the tumor stage and grading. The ^{1}H MRS spectrum has mainly three peaks of methylene group of lipid, methyl groups of choline, and water. There is decreased creatinine level in tumors and other pathologies. The lactate peak is often noted in tumors. The ^{31}P MRS is also used, which shows elevated PCr levels in tumors.

MUSCULOSKELETON (MSK)
The musculoskeletal areas are composed of tissues with variable lipid and water content. Due to the higher availability of lipids in the MSK region, a long TE is used to avoid other metabolite's contamination. The MSK MRS is conducted with both ^{1}H and ^{31}P nuclei. Nevertheless, ^{1}H is highly preferred because of its sensitivity and abundance. The MRS of MSK malignant bone and soft tissue tumors show an increased level of choline. Hsieh et al. stated that decrease in tumor size, there is a decrease in choline levels. (Subhawong et al., 2012) The Dixon and MRS are used in the fat quantification of muscles. The high-speed T2 corrected multi-echo (HISTO) sequence as MRS sequence with an acquisition time of 15 seconds for fat quantification even in pediatric patients. (Li et al., 2019)

GYNECOLOGY
The MRS is limited in the adnexal evaluation due to bowel and respiratory motions. The MRS measures choline, creatinine, lactate, and lipid peaks in uterine leiomyoma and myometrium. Some pathology has lipid peak which is not visible in a healthy subject. The higher lipid in the uterus's cervix is a malignancy indicator. The lactate peak indicates the higher possibility of multiple and degenerated leiomyoma. (Celik et al., 2004) The MRS is still in its preliminary stage for ovarian tumor quantification. The Cho to Cr ratio provides differentiation between malignant and benign adnexal tumors which paves the way to appropriate surgical planning. (Ma et al., 2015)

CONCLUSION
The MRS helps in evaluating various pathological processes aiding way towards appropriate surgical planning and treatment non-invasively. In recent days, MRS is applied in various parts of the body to rule out its efficiency, and it is considered one of the fundamental techniques for mapping human metabolites. So, adequate knowledge is needed in the appropriate usage of MRS techniques in clinical implementation.

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