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²³Na MRI: From Research to Clinical Use

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Introduction

Many exciting new variations of MRI have been tested in MR research, but only a few find their way to clinical use. Sodium (²³Na) MRI is one of those techniques that at first glance appeared to be very promising. ²³Na MRI has the potential to extend MR imaging beyond anatomical imaging by providing information on physiology and cellular metabolism. Signal strength is related to disease specific changes in the tissue. This type of ‘disease specific’ contrast can compensate for the much lower signal to noise ratio of these techniques. The contrast between ischaemic (1) and healthy cardiac tissue and between benign tissue and malignant tumors (2) is based on significant changes in Tissue Sodium Concentration (TSC). For stroke in humans an increase in TSC was recorded of 50%(3).

The feasibility of ²³Na MRI on human subjects has been demonstrated as far back as 1989 (4) and the image contrast obtainable in stroke(3), cancer and edema (2) has also been demonstrated some time ago. In spite of this, ²³Na MRI has yet to find a wider acceptance as a possible clinical tool. The technical difficulty of obtaining ²³Na scans can only be part of the reason. If it had been deemed worth it commercially, the MR scanner manufacturers would have found a way to simplify the procedure to almost a push button solution. Apparently, the progression of ²³Na MRI from research to clinical use was halted by a failure to create a demand for the great potential of ²³Na MRI.

Currently ²³Na MRI appears to have been rediscovered. Even though the technical advances since the early 90's have been incremental, a threshold has been reached by reducing scan times to the point where the addition of a ²³Na MRI to an existing ¹H-MRI protocol becomes an option for studies on patients rather than just very patient volunteers.

An overview of recent advances in the use of ²³Na-MRI for clinical MR research will illustrate the very significant consequences of the reduction of the length of a ²³Na scan from more than 45 minutes in earlier attempts to less than 15 minutes at 1.5T. Now ²³Na-MRI is no longer a stand-alone modality with ¹H-MRI used only as a scout image. Instead, ²³Na-MRI is used as an add-on to improve specificity of established ¹H-MRI protocols. To understand what kind of information ²³Na-MR can and cannot add to an MRI exam we have to explore the properties of this nucleus and what imaging techniques we can use to observe it.

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²³Na-MRI techniques

The signal to noise ratio (SNR) of ²³Na-MRI is much lower than that of ¹H-MRI, mainly because of the difference in abundance between water protons and sodium ions in the body and also because of the lower gyro-magnetic ratio. The short longitudinal relaxation time, T₁, in the order of 25-30 milliseconds (ms) allows fairly rapid repetition rates and this partially compensates for the low SNR, even when repetition rate, TR, is chosen relatively long to allow quantification of TSC without T₁ relaxation corrections. The transverse relaxation time, T₂, of sodium is very fast and is bi-exponential in most biological tissues and in gels. Part of the sodium experiences anisotropic interactions with proteins. In very ordered environments such as cartilage or gels this can lead to a short T₂ in the order of 1-2 ms for 60% of the signal and a longer T₂ in the order of 20-30ms for 40% of the signal. In most biological tissues the fraction of the fast relaxing component is less than 60%, but still large signal losses can occur as a result of T₂ relaxation. For quantification of TSC short TE in the order of 0.2-0.4 ms is required to reduce those T₂ losses to less than 5-10% of the total signal. This requirement for a short TE together combined with the need for small receiver bandwidths for better SNR, makes it difficult to use gradient recalled echo sequences with little T₂ losses and good SNR.

One method to overcome this problem is to use 3D projection imaging (PI) methods. In 3D-PI sequences there is no need for a selective pulse and no need for slice select gradient refocusing or phase encode gradient pulse. Thus, the signal acquisition can start very shortly after the excitation pulse with an effective TE that is only limited by the pulse duration and the switching time between transmit and receive.

To reduce the large number of excitations needed for a complete 3D image with PI using constant projection gradients during readout, the projections can be twisted by using time varying gradients. This method has been successfully applied to quantitation of TSC in humans (2,3).

Neither the increase in intracellular sodium concentration, nor an increase in extracellular space is entirely unique for cancer. In perfused ex-vivo organs and in some animal models intra and extra cellular sodium can be separated with shift reagents that remain exclusively extracellular, but so far all suitable shift reagents are toxic and thus of no use for human studies. The Triple Quantum Filtered (TQF) ²³Na-MRI technique has been suggested as an alternative way to separate intra- and extra-cellular sodium. TQF certainly provides some suppression of extracellular signals, thus accentuating the tumor specific changes in the intracellular sodium, but the price in Signal to Noise ratio (SNR) of such filters is very high, leading to much longer scan times and reduced resolution and T₂ dependencies of the TQF signals further complicate quantification.

Without a reliable means to exclusively quantify intra-cellular sodium we can still use ²³NaMR imaging of the total tissue sodium to our advantage, but only in combination with an optimized comprehensive ¹H-MRI protocol (see Figure 1). To appreciate what type of information is added by ²³Na MRI adds to an MRI exam we need to understand the origin of the disease specific contrast delivered by measurement of TSC with ²³Na-MRI.

²³Na-MRI and heart disease

In a dog model of acute ischemia the TSC increase right after reperfusion was in excess of 200% of the baseline myocardial TSC. The increase in sodium in older infarcts is less pronounced, typically about 50%. The origin of this increase is unknown. Ex-vivo hearts from rats with four-week old myocardial infarcts (MI) showed normal intracellular sodium content and an increase in the extracellular volume fraction of the scar tissue. Whether increase in the extracellular space is the dominant mechanism leading to the increased sodium signals

observed in human hearts with non-acute myocardial infarcts is not known. The most interesting feature from a clinical point of view would be the intracellular sodium concentration in at-risk areas around the MI, rather than the TSC in non-viable tissue. Elevated intracellular sodium in myocytes could well be one factor leading to arrhythmias, particularly under stress.

²³Na-MRI to monitor therapy

Lack of substrate and oxygen can cause very significant changes in tissue sodium content. As soon as the energy dependent Na^+/K^+ -ATPase stops pumping sodium out of the cell, passive sodium influx from the extracellular environment will rapidly raise the intracellular levels of sodium several fold. This effect is exacerbated if a stress on the cells increases the permeability of the cell wall for sodium ions.

The acute effect of a therapy that causes cell death on an appreciable scale should therefore be easy to monitor with ²³Na-MRI. The effect of the Highly Focused Ultrasound (HIFUS) ablation of uterine fibroids could be seen in ²³Na-MRI images taken within 24 hours of therapy. Long-term effects of such therapies may be more difficult to predict. In a limited number of patients with breast cancer pre-operative systemic chemotherapy the effect of the therapy in responders showed as a decline in the tumor TSC along with a decline in lesion size. In this application of ²³Na MRI it is important to have a reference or a quantification method to make comparison of the results of baseline images and multiple post-chemo therapy images possible.

²³Na-MRI and cancer

Proliferating cells have an abnormally high sodium content, because the normally very low intracellular sodium concentration of about 10-15 mmol/l is elevated as a result of altered Na^+/H^+ transport kinetics (5) and pH. Outside the cells continuous perfusion of living tissue will ensure a constant sodium concentration of approximately 140 mmol/l. Thus, an increase in the extracellular partial tissue volume through the increased vascularization (angiogenesis) and the increased interstitial space in tumors will also lead to an increase in tissue sodium concentration (TSC) in tumors.

Using a quantitative ²³Na-MRI technique, a 50% increase of TSC relative to non-involved contra-lateral tissues was found in malignant brain tumors (2). Likewise, in malignant breast tumors an increase of 50% in TSC was found relative to non-involved glandular tissue and benign lesions. This information could augment the specificity of Contrast Enhanced (CE)-MRI. The unique sensitivity of ²³Na-MRI to both extra-cellular volume and intracellular changes related to cell proliferation can provide information that is supplemental to a full coverage high resolution CE-MRI scan (see Figure 1).

Conclusion

If we want to retain the best possible resolution in ²³Na MRI, we must look at other relatively high-resolution ¹H-MR techniques such as Fluid Attenuated Inversion Recovery (FLAIR)-MRI, CE-MRI or Diffusion Weighted (DW)-MRI to distinguish non-cancer-high-TSC tissues from malignant tumors. This goes for any clinical application of ²³Na-MRI. The protocol will be different for each particular application and in each application we have to examine whether ²³Na-MRI has enough added value to justify the extra scan time and effort. But in doing so we must not forget that practically all MRI exams consist of a series of scans and only the whole set will yield the desired diagnostic sensitivity and specificity. Thus we cannot expect that ²³Na-MRI can compete with this in an exam consisting of only a scout image and a ²³Na-MRI.

This is where the reduced scan time for ^{23}Na MRI has made an impact. The total scan time for a protocol yielding for a good diagnostic quality set of ^1H -MR images and a ^{23}Na image can be limited to less than an hour. This is a really important factor in continued patient recruitment even for repeat MRI scans on the same patients. Quantitative imaging of TSC used in longitudinal studies in stroke (3) or to monitor treatment in cancer may prove to be one of the more interesting uses of ^{23}Na -MRI. If we consistently use ^{23}Na -MRI in synergy with ^1H -MRI we may learn a lot about progressive changes in TSC related to edema, ischemia or cancer.

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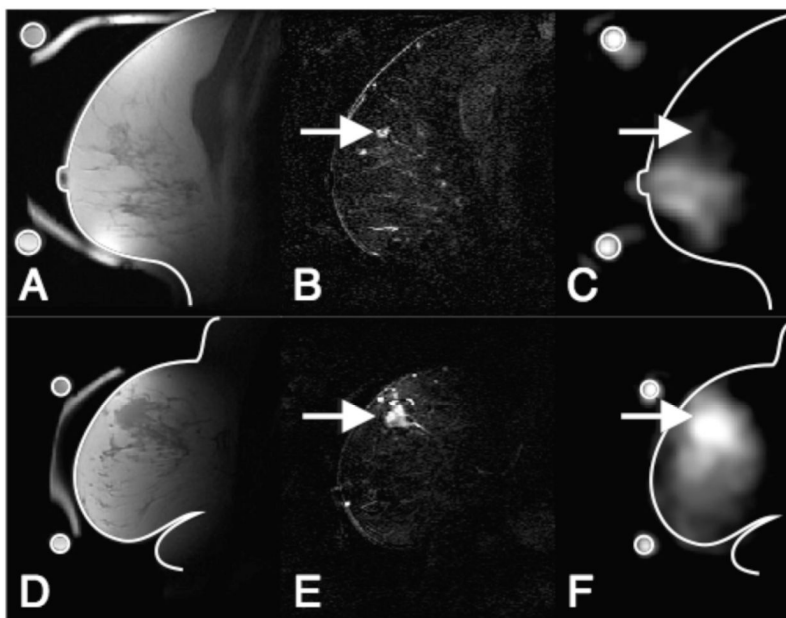


Figure 1.

Registered ^1H and ^{23}Na -MRI breast images of a benign (ABC) and a malignant breast lesion (DEF). Images ABC are from a 55 year-old woman with proliferative fibrocystic changes and sclerosing adenosis (benign). Images DEF are from a 54 year-old woman with an infiltrating poorly differentiated ductal carcinoma (T3, malignant). A,D) T1 weighted ^1H -MRI showing anatomical details B,E) Difference images of pre and post Gd injection CE ^1H -MRI showing enhancement in the lesion indicated by arrows C,F) ^{23}Na images with arrows to the position of enhancing lesions. Outlines of the breast and a ring shaped phantom, containing a 150 mMol/l saline solution, taken from images A and D are superimposed on the ^{23}Na images for position reference. The ^{23}Na images show hyperintensity in the Gd positive region of the malignant case but not in the benign case.