# Sodium Magnetic Resonance Imaging: From Research to Clinical Use

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## INTRODUCTION

Many exciting new variations of magnetic resonance imaging (MRI) have been tested in magnetic resonance research, but only a few have found their way to clinical use. Sodium ($^{23}$Na) MRI is one of those techniques that at first glance seemed to be very promising. Sodium MRI has the potential to extend MRI beyond anatomic 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/noise ratio (SNR) of these techniques. The contrast between ischemic [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 of 50% was recorded [3].

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

Currently, $^{23}$Na MRI seems to have been rediscovered. Even though the technical advances since the early 1990s have been incremental, a threshold has been reached by reducing scan times to the point at which the addition of $^{23}$Na MRI to an existing proton-MRI ($^{1}$H) protocol becomes an option for studies on patients rather than just very patient volunteers.

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

## SODIUM-MAGNETIC RESONANCE IMAGING TECHNIQUES

The SNR of $^{23}$Na MRI is much lower than that of $^{1}$H MRI, mainly because of the difference in abundance between water protons and sodium ions in the body and also because of the lower gyromagnetic ratio. The short longitudinal relaxation time ($T_1$ in the order of 25-30 milliseconds (ms)) allows fairly rapid repetition rates, partially compensating for the low SNR, even when repetition time is set relatively long to allow the quantification of TSC without $T_1$ relaxation corrections. The transverse relaxation time ($T_2$) of sodium is very fast and is biexponential in most biologic 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 $T_2$ (1 to 2 ms for 60% of the signal) and a longer $T_2$ (20 to 30 ms for 40% of the signal). In most biologic tissues, the fraction of the fast relaxing component is less than 60%, but still, large signal losses can occur as a result of $T_2$ relaxation. For the quantification of TSC, short echo time (0.2 to 0.4 ms) is required to reduce those $T_2$ losses to less than 5% to 10% of the total signal. This requirement for a short echo time, combined with the need for small receiver bandwidths for a better SNR, makes it difficult to use gradient-recalled echo sequences with little $T_2$ loss and a good SNR.

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

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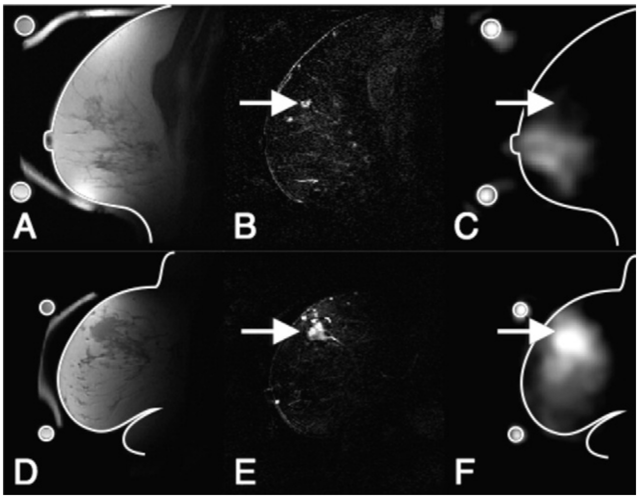

**Fig 1.** Registered $^{1}H$ and $^{23}Na$ magnetic resonance images of a benign (A, B, C) and a malignant (D, E, F) breast lesion. Images A, B, and C are from a 55-year-old woman with proliferative fibrocystic changes and sclerosing adenosis (benign). Images D, E, and F are from a 54-year-old woman with an infiltrating, poorly differentiated ductal carcinoma (T3, malignant). (A, D) $T_1$-weighted $^{1}H$ magnetic resonance image showing anatomic details. (B, E) Difference images of contrast-enhanced $^{1}H$ magnetic resonance imaging before and after gadolinium injection showing enhancement in the lesion, indicated by arrows. (C, F) $^{23}Na$ images, with arrows indicating the positions 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 gadolinium-positive region of the malignant case but not in the benign case.

To reduce the large number of excitations needed for a complete 3-D image with projection imaging using constant projection gradients during readout, the projections can be twisted by using time-varying gradients. This method has been successfully applied to the 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, intracellular and extracellular 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 $^{23}Na$ MRI technique has been suggested as an alternative way to separate intracellular and extracellular sodium. Triple quantum filtering certainly provides some suppression of extracellular signals, thus accentuating the tumor-specific changes in the intracellular sodium, but the price in SNR of such filters is very high, leading to much longer scan times and reduced resolution, and $T_2$ dependencies of the triple-quantum-filtered signals further complicate quantification.

Without a reliable means to exclusively quantify intracellular sodium, $^{23}Na$ MRI of the total tissue sodium can still be used to advantage, but only in combination with an optimized comprehensive $^{1}H$ MRI protocol (Figure 1). To appreciate what type of information $^{23}Na$ MRI adds to an MRI examination, it is necessary to understand the origin of the disease-specific contrast delivered by the measurement of TSC with $^{23}Na$ MRI.

## SODIUM-MAGNETIC RESONANCE IMAGING AND HEART DISEASE

In a dog model of acute ischemia, the TSC increase immediately 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 4-week-old myocardial infarcts 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 nonacute myocardial infarcts is not known. The most interesting feature from a clinical point of view is the intracellular sodium concentration in at-risk areas around myocardial infarcts, not the TSC in nonviable tissue. Elevated intracellular sodium in myocytes could well be one factor leading to arrhythmias, particularly under stress.

## SODIUM-MAGNETIC RESONANCE IMAGING TO MONITOR THERAPY

Lack of substrate and oxygen can cause very significant changes in tissue sodium content. As soon as the energy-dependent $Na^{+}/K^{+}$–adenosine triphosphatase 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 stress on the cells increases the permeability of the cell walls for sodium ions.

The acute effect of therapy that causes cell death on an appreciable scale should therefore be easy to monitor with $^{23}$Na MRI. The effect of the highly focused ultrasound ablation of uterine fibroids could be seen in $^{23}$Na magnetic resonance images taken within 24 hours of therapy. The long-term effects of such therapies may be more difficult to predict. In a limited number of patients undergoing preoperative systemic chemotherapy for breast cancer, the effect of the therapy in responders showed a decline in the tumor TSC, along with a decline in lesion size. In this application of $^{23}$Na MRI, it is important to have a reference or a quantification method to compare the results with baseline images and multiple images after chemotherapy.

## SODIUM-MAGNETIC RESONANCE IMAGING AND CANCER

Proliferating cells have an abnormally high sodium content, because the normally very low intracellular sodium concentration of about 10 to 15 mmol/L is elevated as a result of altered $Na^+/H^+$ transport kinetics [5] and pH. Outside the cells, the 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 increased TSC in tumors.

Using a quantitative $^{23}$Na MRI technique, a 50% increase in TSC relative to noninvolved contralateral tissues was found in malignant brain tumors [2]. Likewise, in malignant breast tumors, an increase of 50% in TSC was found relative to noninvolved glandular tissue and benign lesions. This information could augment the specificity of contrast-enhanced MRI. The unique sensitivity of $^{23}$Na MRI to both extracellular volume and intracellular changes related to cell proliferation can provide information that is supplemental to a full-coverage, high-resolution, contrast-enhanced MRI scan (Figure 1).

## CONCLUSION

To retain the best possible resolution in $^{23}$Na MRI, it is necessary to use other relatively high-resolution $^1$H MRI techniques, such as fluid-attenuated inversion recovery MRI, contrast-enhanced MRI, and diffusion-weighted MRI, to distinguish noncancer, high-TSC tissues from malignant tumors. This goes for any clinical application of $^{23}$Na MRI. The protocol will be different for each particular application, and in each application, it is necessary to determine whether $^{23}$Na 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 examinations consist of a series of scans, and only the whole set will yield the desired diagnostic sensitivity and specificity. Thus, we cannot expect that $^{23}$Na MRI can compete with this in an examination consisting of only a scout image and a $^{23}$Na MRI scan.

This is where the reduced scan time for $^{23}$Na MRI has made an impact. The total scan time for a protocol yielding a set of $^1$H magnetic resonance images of good diagnostic quality and a $^{23}$Na image can be limited to less than 1 hour. This is a very important factor in continued patient recruitment, even for repeat MRI scans on the same patient. 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 $^{23}$Na MRI is consistently used in synergy with $^1$H MRI, much may be learned about progressive changes in TSC related to edema, ischemia, or cancer.

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