Abstract

As for other organs, nuclear magnetic resonance (NMR) of skeletal muscle can be repeated as many times as needed, making it perfectly suited for a non-invasive longitudinal monitoring of neuromuscular patients during clinical trials. The aim of the thesis is to investigate the sensitivity of novel NMR outcome measures (OM) aiming to quantify pathological changes in the dystrophic muscle. Muscular dystrophy (MD) refers to a heterogeneous group of diseases with progressive muscle wasting and associated weakness characterized by variable degrees of necrosis, regeneration, ionic homeostasis disturbances, chronic inflammation, and, ultimately, resulting in the replacement of muscles by fibro-fatty tissue. My focus was on the evaluation of ^{23}Na NMR and advanced ^{1}H transverse relaxation time (T_2) techniques as early, sensitive OM. ^{23}Na NMR measures the tightly controlled sodium concentrations and distribution in skeletal muscle tissue. This biophysical information can be used to assess ion homeostasis and cell integrity. However, ^{23}Na NMR suffers from a low sensitivity and *in vivo* concentration compared to ^{1}H. Alterations in the muscle ^{1}H T_2, commonly interpreted as an indicator of disease activity, are linked to a variety of non-specific events like oedema, inflammation, or necrosis that precede the actual muscle replacement by fat.

Protocols including different ^{23}Na NMR and ^{1}H T_2 methods were implemented to evaluate healthy and dystrophic skeletal muscle tissues of animal models and patients. First, a non-localized ^{23}Na NMR protocol was developed in order to reduce the usually long acquisition times of ^{23}Na NMR and it was validated on healthy subjects under different vascular filling conditions. The ^{23}Na NMR approach was more sensitive than standard global ^{1}H T_2 to monitor acute changes in extracellular volume fractions of the leg. Our ^{23}Na NMR protocol permits the monitoring of total and intracellular weighted ^{23}Na signal in less than 15 minutes. In the context of MD, these OM offer novel options to investigate ion channel/transporter impairments, membrane integrity, or even, indirectly, fibrosis formation.

Murine models represent a valuable tool to study the pathological progress of MD and to test possible therapeutic interventions. Additionally, the specificity of NMR techniques to monitor certain pathologies can be validated on well-described murine models. Here, a new murine model for dysferlinopathy named *MMex38* was characterized by standard NMR techniques. Severity of disease activity and progression was reflected by the significant fatty replacement, showing for the first time in mice some similarity with the phenotype observed in humans. A comprehensive protocol including the ^{23}Na and ^{1}H T_2 OM demonstrated hydro-ionic homeostasis disturbances in different murine MD models.

In a natural history study on Duchenne muscular dystrophy (DMD) patients in Erlangen, different NMR imaging and spectroscopy methods were combined to evaluate their sensitivity to monitor the pathological processes of MD at an early stage of the disease. We demonstrated that DMD patients exhibit elevated total sodium concentrations and ^{23}Na intracellular weighted signal as well as water T_2 at the early disease stage preceding the fibro-fatty infiltration. Intracellular sodium accumulations did not systematically parallel water T_2 increases. This work provides evidence that ^{23}Na NMR could offer a sensitive outcome measure able to monitor specific alteration of the dystrophic muscle at a very early stage.