Combining MR-Elastography and diffusion tensor imaging to measure the in vivo anisotropic elasticity of skeletal muscles of Mdx and healthy mice.

Eric Chuan Qin[1,2], Lauriane Juge[3], Simon Lambert[3], Ralph Sinkus[3], and Lynne Bilston[1,2]

[1]*Neuroscience Research Australia, Randwick, NSW, Australia,* [2]*Prince of Wales clinical school of medicine, UNSW, Randwick, NSW, Australia,* [3]*INSERM U773/Hôpital Beaujon, Centre de Recherche Biomédicale Bichat Beaujon (CRB3), Clichy, France*

Introduction:

Duchenne Muscular Dystrophy (DMD) is a high incidence hereditary muscular disease (affecting 1/3500 boys, or between 400 and 600 live male births each year in the United States alone [3]) that weakens the muscles which can result in major disability and premature death. Currently the gold standard in detecting and monitoring abnormal changes in muscle tissues is muscle biopsy, which is invasive and painful. In this study we used a novel imaging technique which combines diffusion tensor imaging (DTI) with magnetic resonance elastography (MRE) to non-invasively investigate the anisotropic shear moduli ($\mu_{\parallel}$, $\mu_{\perp}$) of the skeletal muscles of Mdx mice (a mice model for DMD) and healthy wild type mice in vivo. This technique could potentially provide additional parameters in detecting abnormal changes in muscular diseases (DMD, myositis), and allow early diagnosis and monitoring of such diseases.

Methods:

MRE can assess tissue stiffness in vivo by measuring mechanical wave propagation [1]. Synchronised motion-sensitive MR gradients are used to track wave propagation throughout a tissue region. DTI can estimate the local fibre direction by calculating the diffusion of water molecules in different spatial directions. By combining these two techniques, the shear modulus parallel and perpendicular to the local fiber orientation can be calculated assuming a transversely isotropic model [2]. In this study, 7 weeks old Mdx mice (n=7, C57BL/10ScSn-Dmd^{mdx}/J, JAX, USA) and aged matched wild type mice (n=7, C57BL/10ScSnJ) were scanned using a 7T Bruker PharmaScan spectrometer with a custom made MRE transducer. Ten slices were acquired in the sagittal plane covering the gatrocnemius and plantaris muscles of the right hind leg of the mice. For MRE, a mechanical excitation of 1000 Hz was used with a modified spin-echo pulse sequence [2]. The wave motion was captured at 8 time points (TR/TE = 691/13.5 ms, matrix size = 64x64, voxel size = 0.3x0.3x0.3 mm^3). DTI data were collected from the same slices using the following parameters: 6 gradient directions, 0.3mm isotropic voxel size, b-factor = 560). The anisotropic shear moduli were reconstructed and the anisotropic ratio ($\mu_{\parallel}/\mu_{\perp}$) was compared between the Mdx and the control mice. The same data were also reconstructed with an isotropic reconstruction technique. The MRE/DTI results were correlated with histology results (HES staining). Areas of necrotic regions were selected manually and calculated using ImageJ.

Results:

Typical anatomical image and wave image from a wild type mouse is shown in Figure 1a&b. Figure 1c&d show the shear modulus maps parallel and perpendicular to the local fiber direction. Figure 1e shows the ratio of the shear modulus parallel and perpendicular to the fibers, and demonstrates that this technique can detect changes in tissue anisotropy in this muscle degeneration model (student t test, $p<0.05$), while no significant difference was observed in terms of the isotropic shear modulus (Figure 1f). Figure 2a shows the HES staining of a 3µm cross section of the plantaris muscle of a healthy wild type mouse. Significant more areas (student t test, $p<0.05$) of active muscle necrosis can be seen from a matching Mdx mouse (Figure 2b).

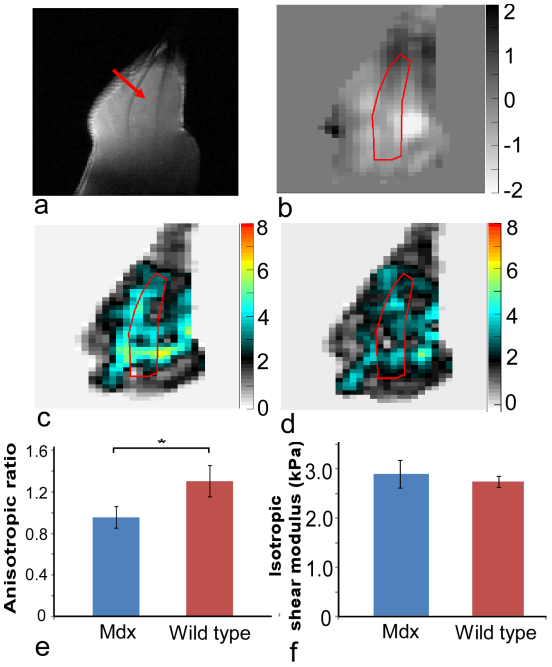

Figure 1. a) Anatomical image b) Wave image [µm]. c&d) Shear modulus parallel and perpendicular to fiber direction [kPa]. e) Anisotropic ratio $\mu_{\parallel}/\mu_{\perp}$ f) Isotropic shear modulus [kPa]

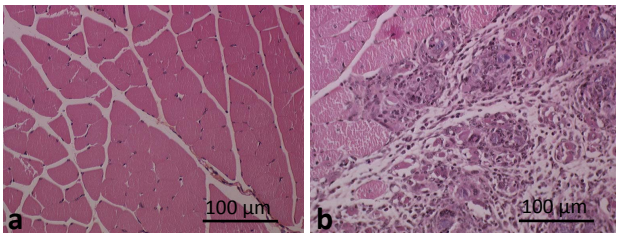

Figure 2. a) HES staining of the plantaris muscle of a wild type mouse. b) Matching Mdx mouse, showing regions of active muscle necrosis

Discussion:

The combined MRE/DTI technique successfully quantified and visualised the anisotropic shear moduli. A significant difference in anisotropic ratio was detected between the Mdx and wild type mice, which agree favourably with histology findings. The decreased anisotropic ratio in Mdx mice could be due to the active muscle necrosis which resulted in the disintegration of the muscle fibers. In contrast, the isotropic MRE reconstruction could not detect significant changes in terms of the isotropic shear modulus (Figure 1f). Results of this study suggest that it is important to apply an anisotropic model (as opposed to an isotropic assumption) when conducting MRE experiments on anisotropic tissues. Also, this combined MRE/DTI technique has demonstrated the ability to detect changes in tissue properties of muscular diseases in vivo. Potentially, it can be developed into an imaging modality to monitor disease progression in patients with muscular disorders, as well as assessing the efficacy of drug therapies in vivo.

References:

1. Muthupillai, R, et al, *Magnetic resonance elastography by direct visualization of propagating acoustic strain waves.* Science, 1995. **269**(5232): p. 1854.
2. Sinkus R, et al. *High-resolution tensor MR elastography for breast tumour detection.* Phys Med Biol, 2000. **45**(6): p1649.
3. *Centers for Disease Control and Prevention,* National Center on Birth Defects and Developmental Disabilities, July 27, 2005