Masters/PhD project in skeletal muscle physiology 2014

CONTRACTILE PROPERTIES OF SINGLE SKELETAL MUSCLE FIBRES IN MCARDLE DISEASE (GLYCOGEN STORAGE DISEASE V)

INTRODUCTION

Patients suffering from McArdle disease (glycogen storage disease V) have a general inability to perform moderate to high intensity exercise. Although they store almost twice as much glycogen in their muscle, they lack the enzyme myophosphorylase that is responsible for the breakdown of glycogen to glucose-1-phosphate, which consequently enters the glycolytic pathway. It is well known that once these patients start exercising, they typically experience muscle cramps, accompanied by muscle breakdown (rhabdomyolysis) that leads to high creatine kinase and myoglobin concentrations in the blood. Myoglobinuria frequently occurs and if untreated may in turn lead to renal failure. As a result, exercise is generally contra-indicated for patients with McArdle disease. The result is that many McArdle patients lead sedentary life-styles, and this in itself appears to further exacerbate their condition. Interestingly, low intensity exercise has been shown to improve the overall quality of life for these patients. Therefore, finding the correct balance between avoiding the unhelpful consequences of a sedentary lifestyle and minimising the risks associated with high intensity exercise is of clinical relevance in terms of improving the quality of life of these patients. Building on from existing research, it seems that a better understanding of the mechanisms behind their exercise intolerance is necessary.

The primary setback for these patients is their inability to generate sufficient force from their muscles to accomplish certain tasks during exercise and during daily activities. Indeed, it was shown that these patients have twice the surface electrical activity in their *Rectus femoris* and *Vastus lateralis* muscles (measured using electromyography (EMG)) while exercising at the same relative power output compared to their healthy counterparts. Although only an indirect measure of muscle activation or recruitment, these EMG results indicate that the McArdle patients recruit twice the number of fibres to match the power output of their healthy counterparts, which suggests gross inefficiency and/or weakness of their muscles.

These findings from a previous study have sparked new interest in the apparently weakened muscles of McArdle patients. Particularly, the results suggest that their muscle fibres may have altered mechanical properties, i.e. reduced force generating capacity, compared to their healthy counterparts. Importantly, when both groups of participants started exercising, baseline EMG was already higher in the McArdle group than the healthy controls, implying that even in a non-fatigued state, the muscles (and muscle fibres) require a greater number of fibres to be activated to produce the same amount of force as their healthy counterparts. This implies that in addition to not being able to utilize glycogen as a source of ATP, the disease may also affect the contractile apparatus of each fibre. Whether a metabolic disease has the capacity to affect the contractile apparatus of skeletal muscle is currently unknown.

AIM OF THE STUDY

The aim of this study is to assess the contractile properties of single muscle fibres from a McArdle patients and compare the findings to properties from healthy individuals. Specifically, maximum force generation, unloaded shortening velocity, power and calcium sensitivity of individually typed single fibres will be determined. Skinned single fibre technology bypasses the metabolic components of the muscle fibre and only reveals the properties of the cross-bridge cycle. In this technique, chemical agents disrupt the sarcolemma and sarcoplasmic reticulum. By supplying the required metabolic substrates (ATP and calcium), the fibre can be maximally activated independent of the effect the myopathy has on the metabolic pathways.

HYPOTHESIS

The hypothesis is that the mutation not only affects the energy-supplying pathway, but also affects the contractility (including absolute force, shortening velocity, power and calcium sensitivity) of the skeletal muscle. The data obtained from this study will help understand the mechanisms responsible for the poor muscle mechanics and hence, exercise intolerance observed in patients with McArdle disease. This information will be clinically relevant, as it could help to develop and prescribe appropriate exercise programmes for these patients to improve overall quality of life.

This study is funded by the National Research Foundation of South Africa.

For more information, please contact the principle investigator **no later than 28th of February 2014**:

Principle Investigator:
Dr. Tertius Kohn
UCT/MRC Research Unit for Exercise Science and Sports Medicine, Sport Science Institute of South Africa, Boundary Road, Newlands

Email: ta.kohn@uct.ac.za