DENERVATED MUSCLE UNDERGOING ELECTRICAL STIMULATION: DEVELOPMENT OF MONITORING TECHNIQUES BASED ON MEDICAL IMAGE MODELLING

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ABSTRACT

Muscle tissue composition accounting for the relative content of muscle fibres and intramuscular adipose and loose fibrous tissues can be efficiently analyzed and quantified using images from spiral computed tomography (S-CT) technology and the associated distribution of Hounsfield unit (HU) values. Muscle density distribution, especially when including the whole muscle volume, provides remarkable information on the muscle condition.

We analyse the content of fat, connective tissue, normal muscle and dense fibrous connective tissue in spinal cord injured patients undergoing electrical stimulation treatment using 3-D modelling and segmentation tools.

The results show in a novel way and quantitatively the muscle restoration and growth induced by electrical stimulation; the amount of normal muscle fibres increases from 45% to 60% of the whole volume while connective tissue and fat reduce respectively of 30% and 50%.

Moreover the effectiveness of the FES treatment using surface electrodes is evaluated calculating the density distribution along rectus femoris cross sectional areas. The results show that muscles undergoing FES restore in certain areas and decline in others depending on patient anatomy and surface electrodes positioning.

Keywords: Functional electrical stimulation, Segmentation, Numerical methods, spinal cord injury.

1. INTRODUCTION

Loss of muscle mass occurs with many pathological conditions and is linked to increased patient disability, morbidity and mortality (Janssen, 2002; Fisher 2004) thus, it is important to discover how to deter muscle degeneration. Empirical clinical observations (Kern 1999) revealed that lower motor neuron (LMN) denervated degenerated muscle can recover by a specific variation of home based daily functional electrical stimulation (FES) therapy. This is in contradiction to earlier data which suggested that FES was effective only when started immediately after LMN lesion. These observations led to the founding of the European funded project RISE in November 2001. The project's aim was to establish the biological basis for a clinical rehabilitation treatment for patients who have permanent muscle LMN denervation in the lower extremities. To this end, it funded research designed to reverse muscle degeneration induced by the permanent lack of innervation in spinal cord injured (SCI) patients using muscle FES. Some of the funding has been used to fund research in rehabilitative centres in Vienna (Austria), Heidelberg (Germany), Hamburg (Germany), Tübingen (Germany), Reykjavik (Iceland) and Vicenza (Italy). The RISE project has achieved its goal (Kern, 2010) using a multidisciplinary approach to optimize technology to stimulate LMN denervated muscle with custom-designed electrodes and stimulators (see figure 1) developed in Vienna, Austria (Mayr, 2001).

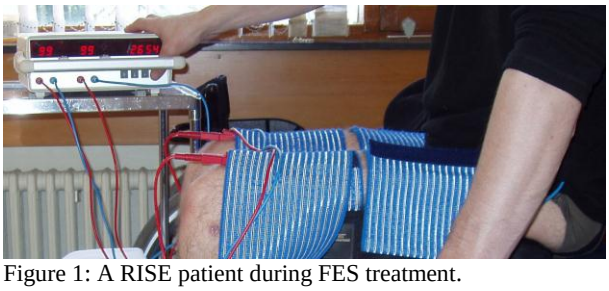

Figure 1: A RISE patient during FES treatment.

The project encompassed a clinical trial with over 25 voluntary patients and additional animal experiments to research the muscle restoration process by combining physiological, histological, immunohistochemical, and biochemical analyses with anthropometric techniques (Kern, 2009; Mödlin 2005).

The results of the EU RISE Project, and of the related animal research, provide different perspectives. Twenty out of 25 patients completed a 2 years h-b FES program (Kern 2010a; Kern 2010b), which resulted in: 1. Significant increase of thigh muscle size and of the muscle fibers, with striking improvements of the ultra-structural organization of contractile material; 2. Significant increase in muscle force output during electrical stimulation (knee extension torque); 3. The recovery of quadriceps m. force was sufficient to allow compliant subjects to perform FES-assisted stand-up and stepping-in-place exercises; 4. Ultra structural analyses demonstrated that the shorter was the time elapsed from SCI to the beginning of h-b FES, the larger were the number and the size of recovered fibers. The study demonstrates that h-b FES of permanent LMN denervated muscle is an effective home therapy that results in rescue of muscle mass and tetanic contractility. Important benefits for the patients are the improved cosmetic appearance of lower extremities, the enhanced cushioning effect for seating (Kern 2004; Kern 2010a; Kern 2010b; Boncompagni 2007) and the early result of impressive reduction of the leg edema (Bizzarrini 2007). The last observation is supported by changes of the capillary networks observed in the muscle biopsies harvested from subjects suffering with long-lasting LMN denervation before and after h-b FES (Scelsi, 2006) and thoracic level SCI (Lotta 1991; Lotta 2001; Scelsi 1991; Scelsi 1995; Scelsi 2001; Scelsi 2005).

Many of the tissue analyses employed to study structural changes occurring in LMN denervated muscle (both after long term LMN denervation and during electrical stimulation) were performed with biopsies which meant that only a few milligrams of muscle could be analyzed (Kern 2010b). Complementary imaging techniques, such as X-ray computed tomography (CT), were also employed in order to assess and validate histological information. The value of the imaging methods demonstrates that the development and use of non-invasive anthropometric techniques is critical to this area of research.

2. MATERIAL AND METHODS

As a consequence of long term denervation the muscle degenerates dramatically. The muscles become very thin and the single bellies are no longer recognizable in their shape. Only rectus femoris (RF) remains recognizable among the quadriceps muscles though it is severely degenerated compared to the normal situation. Therefore 3-D modelling and segmentation techniques are used to isolate RF from other bellies and to monitor changes occurring during the degeneration and restoration process.

Besides, accurately measuring changes in RF during electrical stimulation treatment is important to evaluate treatment effectiveness. Surface electrodes are placed on top of the quadriceps and since RF occupies the middle of the thigh it is especially exposed to the current distribution (Mandl 2008). RF is thus the optimal target for monitoring therapeutical effects and morphological changes with a 3D approach (Gargiulo 2008; Gargiulo 2010).

2.1 Data set source

X-ray computed tomography is an imaging method that uses X-rays to produce images of structures 'inside' the body. Patients are scanned slice-per-slice and each slice is scanned several times from different angles. Each imaged volume element (voxel) is traversed, during the scan, by numerous X-ray photons and the intensity of the transmitted radiation is measured by detectors. The measured intensity profile contains information on the densities the beam encountered on its path through the body (i.e. the denser the regions the weaker the signal). With suitable mathematical methods the measured profiles of each slice are transformed into an image of the structures inside – the image is reconstructed, the grey value corresponding to the linear attenuation coefficient.

This way, 3-Dimensional data are gathered scanning the patient's lower limbs with spiral CT. The scan starts above the head of the femur and continues down to the knee joint, both legs being covered in one scan. Slice increment is set to 0.625 mm resulting in a total of about 750–900 CT slices, depending on the patient's size.

Every acquired CT slice is subdivided into a matrix of different size, from a minimum of 128×128 up to 1024×1024 volume elements. The average linear attenuation coefficient μ of the tissue contained in each voxel is represented by floating numbers in the computer which range from 0.0 up to values equal to 1.0.

Once the image is calculated from the 3D data set it is converted into a matrix of picture elements (pixels) with each pixel assigned the attenuation value of the corresponding voxel. Linear attenuation coefficients are rescaled to an integer range that encompasses 4096 values, between -1000 and 3095. From these intensity readings, the density or attenuation value of the tissue at each point in the slice can be calculated. This scale is called CT number or Hounsfield unit (HU) and it is expressed by the following formula:

$$\text{CT Number} = 1000\times \frac{\mu\text{pixel}-\mu\text{water}}{\mu water} \quad (1)$$

With this scaling, if the linear attenuation coefficient of a given pixel (μpixel) is equal to that of water, the CT number will be 0. If μpixel is less than μwater the CT number will be negative which is typical for air spaces, lung tissues and fatty tissues. Values of μpixel greater than μwater will result in positive CT numbers. Very dense tissue such as bone has large

positive numbers. Table 1 displays main organic tissues and respective HU intervals.

Table 1: The table displays the main human tissues and their empirical HU intervals. (Gargiulo 2011)

Anatomical Tissues	Hounsfield intervals	
	Min	Max
Bone	250	3071
Compact bone	601	1988
Spongy bone	250	600
Normal Muscle	41	80
Dense fibrous connective (Tendons-dense muscle)	81	200
Loose connective (low dense muscle)	-5	40
Fat	-200	-6
Skin	-30	60
Tooth	1200	3071

2.2 Segmentation of RF

The threshold interval chosen to segment RF is: [-5, 200] HU. A wide interval is chosen because it must display muscle tissue and allow monitoring of changes, particularly the restoration-degeneration process. Within the selected interval the displayed pixels are representing both normal and degenerated muscles, additionally connective tissue and water but subcutaneous fat is excluded. In this way the surrounding fat in RF is automatically excluded from the segmentation mask (Fig.2 A). After thresholding, the next step for the segmentation is to isolate RF form the other muscles. For this purpose the following procedure is used. The process starts from a cross section where the muscle boundaries are well visible (usually in the middle, along the length of the muscle). A contour is manually drawn around the muscle and projected to the next cross sections in both directions. If the contour fits the new cross sectional area well then it is projected unchanged forward to the next slice, otherwise it is adapted and then projected ahead. We assume that shapes change little from one slice to the next the adaptation necessary is small. It is done with active contours that 'snap' to boundaries.

The process continues until all cross sections containing RF cross sections are edited (Fig.2 B). The contour areas are then erased creating a gap between segmentation target and surrounding. Finally, a new segmentation mask representing RF is created by applying a region growing procedure which creates a new mask separating the edited structure that is no longer connected to the surrounding (Fig.2 C). The result of the segmentation process and a 3D rendering thereof is shown in Fig.2 D.

All Segmentation was performed with MIMICS 10.1. (www.materialise.com)

2.3 Muscle tissue analysis

In order to discriminate the biological tissues in the data set, different thresholds are established using the HU scale. Specific attenuation values are assigned to each individual voxel. The degree of attenuation depends on the energy spectrum of the x-rays as well as on the average atomic number of the mass density of the patient tissue. Most computer display hardware requires integer numbers and therefore the linear attenuation coefficients are rescaled to an integer range that encompasses 4096 values, between -1000 and 3095. Dense tissue such as bone has large positive CT number while negative CT numbers are typical for air spaces, lung tissues and fatty tissues. Muscle tissues are normally displayed with HU values between 50 and 100 HU though within a normal muscle belly there are also other tissue elements such as connective and fat which are coded with much lower HU values. Anyway the specific HU value depends also on the pixel size. Indeed every element can express its absolute HU value if it occupies completely the specific pixel volume otherwise this value will be an average between the different parts contained in it. This fact explains the wide range of values present inside a data set and suggests the definition of various intervals to study muscle structural changes. Therefore to monitor and quantify tissue composition in the stimulated muscle volume the HU values present within the segmented volume are divided in four HU intervals [-200, -6], [-5,–40], [41, 80] and [81, 200] representing respectively fat, loose connective (low dense muscle), normal muscle and Dense fibrous connective (Tendons-dense muscle).

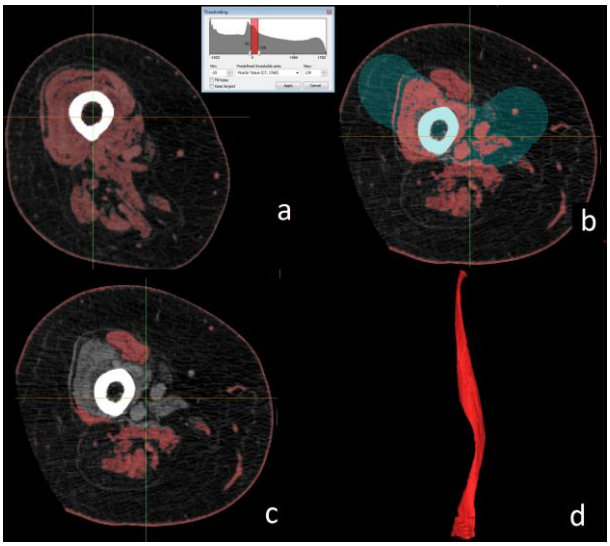

Figure 2: Main steps for the Segmentation of rectus femurs (A) Thresholding (B) A contour is manually drawn around the muscle and projected to the next cross sections in both directions (C) The contour is erased and rectus femoris is isolated from the surrounding muscles (D) 3D rendering of rectus femoris.

2.4 Cross sectional density analysis

In order to evaluate the effectiveness of the FES treatment using surface electrodes we develop a Matlab (Matworks Inc) subroutine to analyse the density distribution along rectus femoris cross sectional areas. Each cross section provides a mean HU value. The

measured rectus femoris lengths are between 400 and 500 mm depending from patient anatomy (starting from the pelvis attachment and ending at patellar tendons) the slice increment is 0.625 mm therefore the number of mean values is between 640 and 800.

Figure 3 shows the computation results on a healthy subject. It can be noticed how the mean values on the cross sectional areas are rather uniform and displayed in the interval [50-70] HU. Density values are higher at the muscle extremities where the muscle attaches to the tendons.

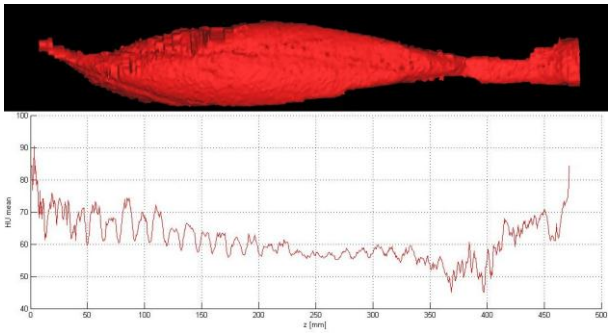

Figure 3: Density distribution along the cross sections in healthy subject.

3. RESULTS

Muscle restoration due to electrical stimulation can be seen quantitatively using the muscle tissue analysis. Figure 4 shows muscle tissue changes after 4 years of electrical stimulation treatment. Due to stimulation treatment the fraction of normal muscle fibres increases from 45% to 60% of the whole volume while connective tissue and fat reduce to 30% and 50% respectively.

Figure 6 shows the results from cross sectional density analysis from two RISE patients:

- Patient 1 started the FES treatment 1 year after the paralysis (fig.5a). He was compliant to the stimulation protocol for approximately 1.5 years and successively interrupting the treatment.
- Patient 2 started the FES treatment 4 year after the paralysis (fig.5b). He was compliant over all the monitored period.

Muscle density increase: Patient 1 and 2 are stimulated in the same way but the stimulation is more effective on patient 1 because muscles at beginning are in better conditions and adipose tissue is thinner. The area indicated with *a* in figure 6 (Patient 1) displays a localised increase of density - from 45 to 50 HU - starting at 120 mm and ending approximately at 400 mm from the pelvis attachment

The areas indicated with *d* and *f* (patient 2) displays a localised increase of density - from 40 to 55 HU - starting at 170 mm and ending approximately at 350 mm from the pelvis attachment.

Muscle density decline in non-compliant patient: comparing the areas indicated with *a* and *b* (patient 1) can be seen a general muscle density decrease of 10 HU over the all length after 2 years of interruption from FES treatment.

Muscle density decline in compliant patient: the areas *c*, *e*, and *g* (patient 2) display zones on rectus femoris between 50 mm and 150 mm from the pelvis attachment where muscle density continues to decrease – from 30 down to 5 HU- during the FES treatment. Here the electrical stimulus does not reach efficiently the muscle fibers because the adipose tissue between skin and muscle is too thick (fig. 5A).

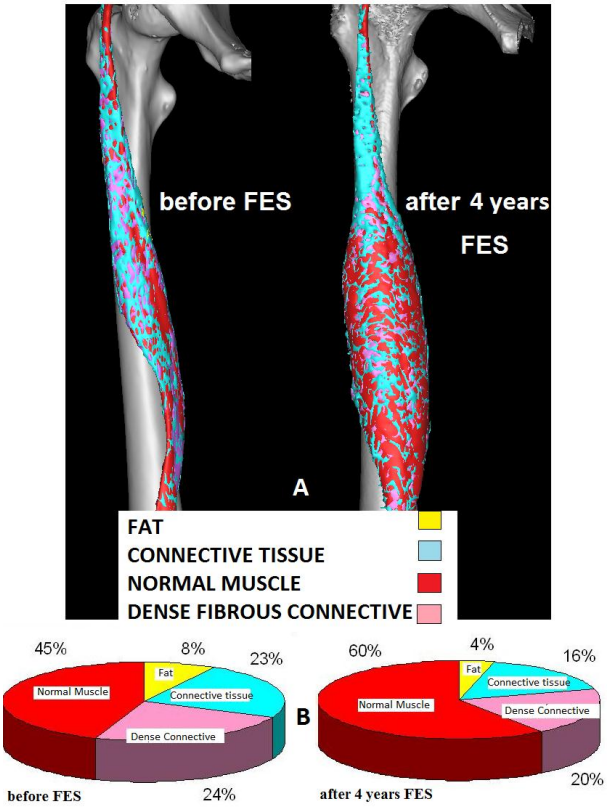

Figure 4: 3D models of rectus femoris before and after 4 years of electrical stimulation treatment (A). Chart pies showing the muscle composition at beginning and after 4 years FES according to the Hounsfield intervals referred in table 1 (B).

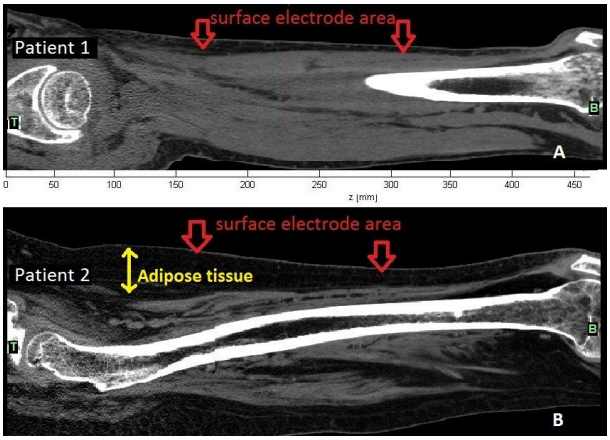

Figure 5: Spiral CT pictures sagittal view at beginning of the FES treatment: patient 1 (A), patient 2 (B).

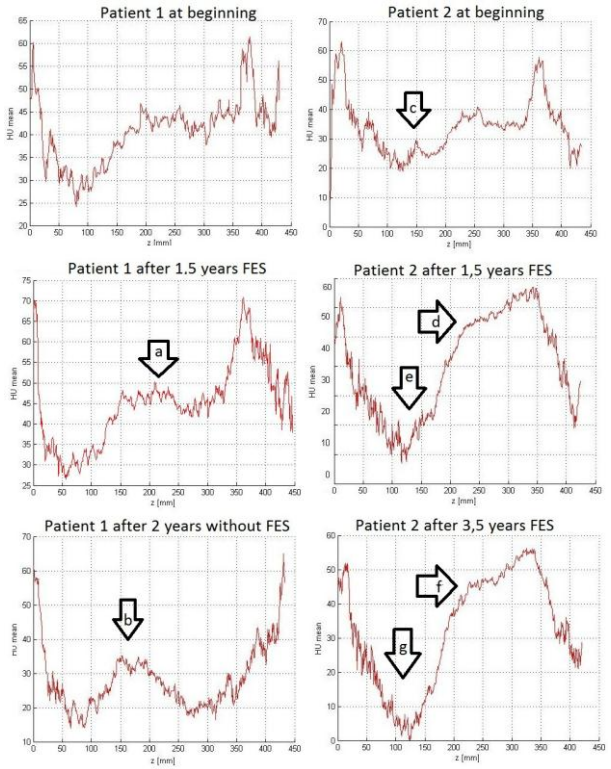

Figure 6: Cross sectional density analysis performed on two patients at beginning of the FES treatment, after 1,5 years and after 3,5 years. Patient 1 interrupt the FES treatment after 1,5 years.

4. CONCLUSION

The 3D approach combined with muscle tissue analysis, gradient distributions and cross sectional density analysis provides information on the whole muscle and on its structural changes during electrical stimulation treatment otherwise not accessible with other monitoring techniques. Muscle growth and tissue restoration can be efficiently monitored; beside the density analysis along the segmented muscle can also drive to an improved surface electrode design and positioning.

The computational method developed in this work is associated to thresholding criteria and HU values which are used to define the different tissues within the muscle. Various physical factors can influence the CT number representation during a scan session. The parameter that mostly affects the accuracy and the spatial distribution of HU values is the applied voltage across an X-ray tube; this amplitude is measured in kilo volt (kV) and determines the highest X-ray quantum energy and therefore the attenuation coefficient. CT number distribution is also influenced by phantom (or patient) orientation and position in scan aperture. Therefore it is necessary to know and account these variability's when CT numbers are used for tissue characterization and comparison.

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