Computational methods to analyze tissue composition and structural changes in denervated muscle undergoing therapeutic electrical stimulation

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Abstract

This work develops a new method to study and analyze structural muscle changes resulting form electrical stimulation treatment. The muscular changes in denervated degenerate muscle undergoing Therapeutic Electrical Stimulation (TES) treatment are seen and quantified using a novel approach based on image processing tools and medical images. Spiral CT images and special computational tools are used to isolate the quadriceps muscles. During 4 years of electrical stimulation, 3-dimensional reconstructions of the muscles from patients with long-term flaccid paraplegia were made at different points of time. The growth of the muscle and its changes through the time period are seen in the 3D and are measured quantitatively. Furthermore, changes in tissue composition within the muscle belly are classified according to their HU value and using false colors. The content of fat, connective tissue, atrophic/low dense and normal muscle within the monitored belly is visualized directly on the muscle 3D reconstruction. The results show in a novel way and quantitatively the muscle restoration and growth induced by electrical stimulation; the normal muscle fibers increases from 45% to 60% of the whole volume while connective tissue and fat reduce respectively of 30% and 50%. Likewise in non compliant patient muscles lose volume and change shape while fat and connective tissue grow and occupies larger portion of the remaining volume.
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Key Words: Three dimensional reconstruction, Modeling, Electrical stimulation, Tissue composition.

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Based on the idea and the empirical experience that denervated degenerated muscle can be recovered, in November 2001 the European funded project RISE started with the aim of establishing a scientific grounds of the clinical rehabilitation method for patients who have irreversible muscle denervation in the legs. The technique based on Therapeutical Electrical Stimulation (TES) aim to restore muscle tissue and some muscle function up to the ability to rise and perform physical exercise in standing position in these severely disabled patients. Indeed the clinical trial demonstrate that electrical stimulation can not only slow down atrophy of the denervated human muscles, but also that a new training strategy using custom-designed electrodes and stimulators developed in Vienna, Austria for the EU Project RISE (delivering currents of larger intensity than those of commercially available devices) induced surprising recovery of muscle structure, mass and force even in patients whose muscles had been denervated for prolonged periods before the beginning of TES training [4,5].

Though gluteus and all leg muscles are trained, the main target muscle for the electrical stimulation is the quadriceps femoris that includes four muscles on the front of the thigh: rectus femoris, vastus lateralis, vastus medialis and vastus intermedius (Fig. 1A). The muscle volume in the quadriceps is very large and the muscles are not uniformly activated by the electrical stimulation. In fact surface electrodes are by definition not selective and enormous energy is used to deliver electrical stimulus which can reach and cause contraction in the denervated muscles. Rectus femoris occupies the middle of the thigh and covers most of the other three quadriceps; it is closer to the surface electrodes and therefore more exposed to the stimulation as also demonstrated qualitatively in recent studies using T2 mapping [6]. Hence, it is of special interest to monitor and study the behavior of rectus femoris, model certain characteristics and measure stimulation effects accurately. In previous work medical image, segmentation techniques and special computational tools have been developed and used to isolate rectus femoris from other muscle bellies and analyze in novel way growth and muscle restoration [1,3]. The segmentation and 3-D modeling are particularly convenient techniques to study rectus femoris because of the definite shape kept even after a long term degeneration. Indeed in other muscles the degeneration process lead to a severe deterioration of the shape.

In Figure 1 are compared the 3-Dimensional models of right thighs in innervated (Fig. 1A) with a 3-years denervated thigh (Fig. 1B). The 3-D rendering show clearly how effects of degeneration in denervated muscles are dramatic: muscles in the lower limbs become very thin and not longer recognizable in their shape, rectus femoris instead remains recognizable among the muscles though is severely degenerated.

In this paper the segmentation technique are used to study rectus femoris tissue composition, measuring it quantitatively and display in a novel way growth or reduction in muscle fat and connective tissue during electrical stimulation treatment.

Materials and Methods

Data acquisition and region of interest.

3-Dimensional data are gathered scanning the patient's lower limbs with spiral CT every 4–6 months. The scan starts above the head of the femur and continues down to the knee joint, both legs being covered by one scan. Slide increment is set on 0.625 mm resulting in a total of about 750–900 CT slices, depending on the patient's size. Each slice has 512 × 512 pixels, and each pixel has a gray value in the Hounsfield (HU) scale of 4096 gray-scale values, meaning that it is represented with a 12-bit value. A total data set from a single scan is therefore 512 ×512 ×750 ×12 = 2.36 GB. This data set gives a complete 3D description of the tissue, including the muscles and bones in both upper legs.

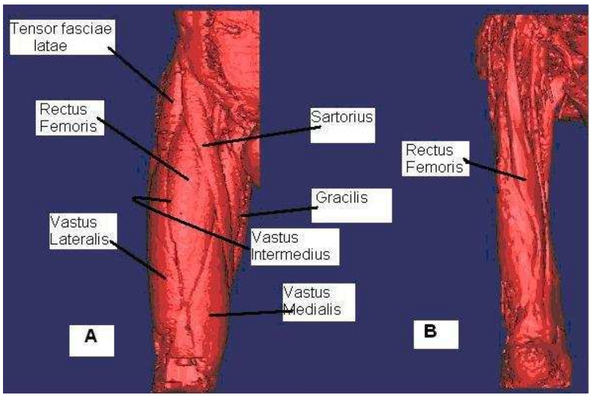

Fig 1. *(A) Healthy thigh musculature. (B) 3 –years' denervated degenerate thigh musculature.*

Special efforts and attention was paid to isolate and monitor rectus femoris during stimulation treatment because of two main reasons: 1. Rectus femoris is the belly closer to the surface electrodes and therefore it is the most stimulated muscle. 2. Isolation and 3D reconstruction is possible in rectus femoris even when it is severely degenerated. Indeed, over time, denervated degenerate musculature loses mass, volume and shape, becoming unrecognizable with respect to healthy muscles. Rectus femoris instead remains roughly recognizable during degeneration.

In previous work rectus femoris evolutions in 3D and morphological changes during stimulation treatment have been demonstrated accurately [2].

Muscle tissue analysis: false color

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. This scale is called CT number or Hounsfield unit (HU). Dense tissue such as bone has large positive CT number while negative CT numbers are typical for air spaces, lung tissues and fatty tissues.

Results

Muscles 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 from 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.

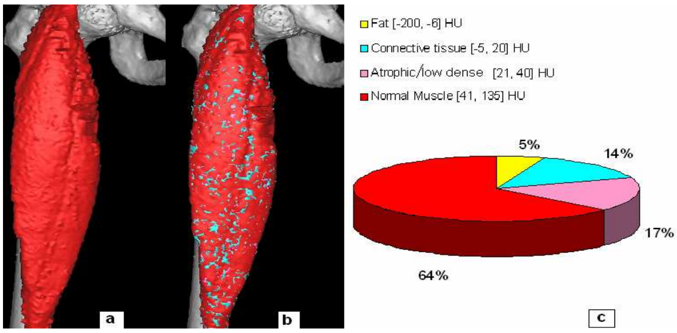

Fig. 2 *3D reconstruction of Rectus femoris from healthy 51 years old subject, (a) without and (b) with tissue distribution on the rectus femoris; (c) muscle composition in terms of fat, connective, low dense and normal muscle tissue within rectus femoris volume.*

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 estimate the tissue composition in to the stimulated muscle volume the HU values present within the segmented volume are divided in four HU intervals [-200 – -10], [-9 – 20], [21 – 40] and [41 – 139] representing respectively fat, connective tissue, low dense/atrophic and normal muscle fibers. A special image processing and editing computer program called MIMICS [7] is used to isolate rectus femoris from the other muscle bellies. The resulting volume of interest contains both the information to reconstruct rectus femoris three dimensionally and all the CT numbers accounting the specific pixel density value. Figure 2a shows a rectus femoris in a healthy 51 years old man.

The four density intervals are seen using different color: yellow for the fat, cyan for the connective tissue, pink for the atrophic/low dense muscle and red for the normal muscles. The false color scale is applied on the 3D model to show muscle tissue composition on the muscle volume (figure 2b) while the density distribution is evaluated quantitatively using chart-pie (figure 2c). Though the majority of rectus femoris volume has HU values above 40 HU, there are still a considerable amount of pixels displaying low density muscle tissues (17% of the total) and different tissues such as connective and fat (14% and 5% of the total, respectively).

Effects of long-lasting muscle denervation

Figure 3 shows the dramatic consequences occurring in muscle after long term paralysis are evaluated applying the same approach and computational setting to a rectus femoris that have been denervated for 7 years. In figure 3a the 3D reconstruction of a long term degenerated rectus femoris is displayed together with the tissue distribution in false color. The degree of degeneration in muscle is severe; indeed fat and connective tissue surrounds the muscle surface comple-

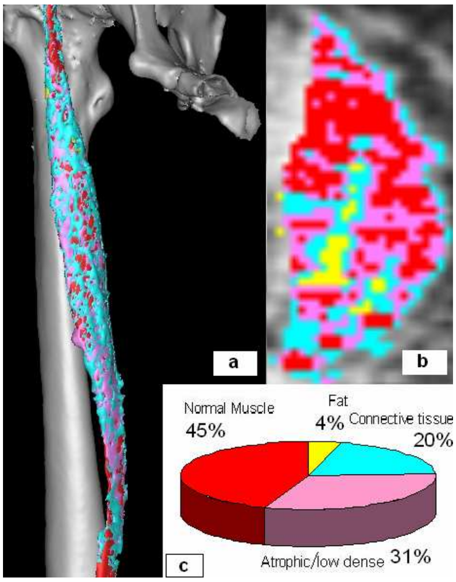

Fig. 3 *Seven years denervated rectus femoris, (a) 3D reconstruction and tissue distribution; (b) Cross section of the Rectus femoris showing the degeneration of the muscle belly; (c), Tissue composition within the muscle belly.*

tely developing even inside the belly (figure 3b). Degenerate and denervated muscle lose most of its original volume changing completely the shape as can be noticed comparing the two rectus femoris reconstruction in figures 2a and 3a. Beside in denervated muscle occurs also a dramatic reduction of muscle fiber within its volume as calculated in the chart pie in figures 3c.

Effects of TES in long-lasting muscle denervation

The effects of electrical stimulation treatment on denervated muscle are evaluated performing the false color analysis on a compliant patient which has been denervated for 4 years. The analysis is performed at beginning of the treatment (in year 2004) and after 4 years of electrical stimulation treatment (in year 2008).

In figure 4a and b are respectively displayed the 3D models and the tissue composition within rectus femoris volume in 2004 and 2008.

Finally, the structural changes occurring in denervated muscle during stimulation treatment are correlated with the patient compliance. The clinical trial demonstrates that denervated muscles are sensible to the applied regime of stimulation; indeed the muscle reduces and degenerates immediately when the patient is for any reason not fully compliant or interrupting the treatment for few weeks. In figure 5 rectus femoris from the same subject are segmented in 2006, 2007 and 2008.

The patient who wasn't very compliant in general (stimulating 1-2 times a week) stimulates every day in the three months previous the CT scan measurement taken in March 2007.

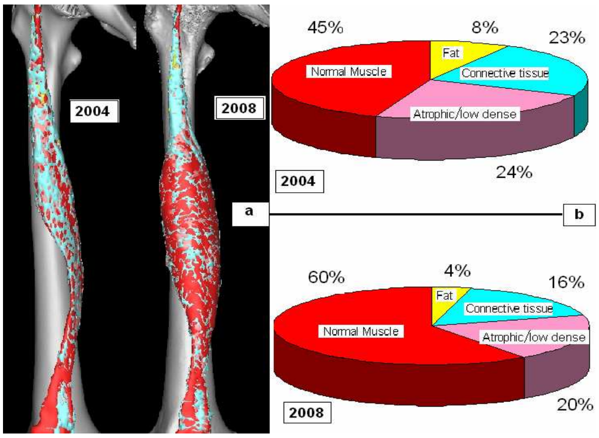

Fig. 4 *3D models of rectus femoris (a) at beginning and after 4 years of electrical stimulation treatment; (b) chart pies showing the muscle composition in 2004 and 2008.*

The 3D models and the tissue analysis from the three dataset show the changes in the muscle composition induced by an increase of stimulation treatment. These variations are seen qualitatively on the 3D models and quantitatively with chart pies. In this way the changes in the muscle are clearly demonstrated and the restoration process induced through electrical stimulation treatment unquestionable.

Discussion

The method described in this work produce the following results. 1. Composition of the innervated muscle is various: the high dense muscle fibers occupy the greater part of the muscle volume but some fat and a considerable amount of connective tissue and low dense musculature are also present (fig. 2). This last group is probably the result of average of different tissue types present through the same pixels. 2. Degeneration in denervated muscle is both morphological and structural, indeed the muscle loses volume and change shape while fat and connective tissue occupies larger portion of the remaining volume (fig. 3). 3. Electrical stimulation produces important structural changes in the muscle. The muscle grows and restores the shape and tissue composition in the activated muscle volumes. Due stimulation treatment the normal muscle fibers increases from 45% to 60% of the whole volume while connective tissue and fat reduce respectively of 30% and 50% (fig. 4). 4. The regime of stimulation strongly influences the restoration process. Once or twice a week stimulation is not enough to recover denervated muscle. When stimulation treatment is provided every day the results are seen clearly even after few months of treatment (fig. 5).

The computational method developed in this work is associated to thresholding criteria's and HU values used to define the different tissues within the muscle.

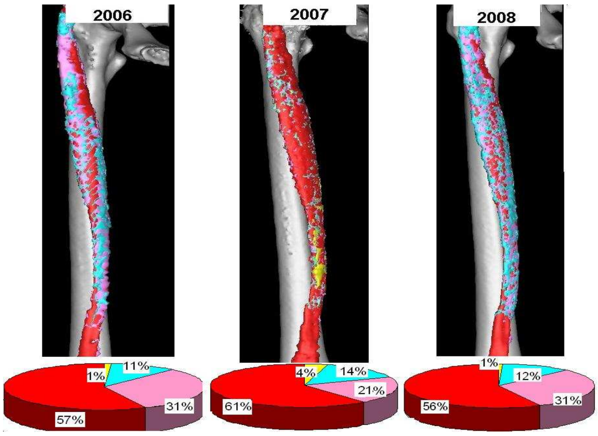

Fig. 5 *Rectus femoris 3D reconstruction and tissue distribution at different point of time with the patient differently compliance; poorly compliant in year 2006, compliant in 2007 and again poorly compliant in 2008*

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. Therefore to avoid or at least limit possible displacement between HU values representing the same element at different point of time a scanning protocol was established in the beginning of the clinical trial and some calibration tools used during every measurement since 2005.

In conclusion, the 3D approach combined with muscle tissue and false color analysis provides information on the whole muscle and on its structural changes during electrical stimulation treatment otherwise not accessible with other monitoring techniques.

Abbreviations

TES, Therapeutical Electrical Stimulation; DDM, Denervated Degenerate Muscle; RFM, Rectus Femoris Muscle; HU, Hounsfield units; ROI, Region of Interest

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