THE MUSCLEHEALTH COMPANY

MUSCLESOUND®

"POSITION STAND"
Science and Application

OUR VISION
"MuscleHealth will be universally recognized as an essential vital sign"

OUR MISSION
"To establish MuscleHealth as the foundation of optimal health, fitness and wellness, through innovative use of musculoskeletal ultrasound, and dependable, ethical customer support"

"MUSCLEHEALTH" DEFINITION
"The capacity of a muscle to store, generate and replenish energy"

1. **WHAT DO WE DO?**
    - "MUSCLESOUND® provides immediate and actionable information on MuscleHealth
2. **HOW DO WE DO IT?**
    - By enabling practitioners to "look inside the muscles" of their clients/patients using musculoskeletal ultrasound
3. **WHAT INFORMATION DO WE ACQUIRE?**
    - Our patented algorithms analyze the scanned images and provide practitioners with information on a muscle's energy producing and structural elements. These important contributors to MuscleHealth currently comprise:
        - Muscle Size
        - Muscle Quality
        - Muscle Fuel
        - Body Composition

INTRODUCTION
Skeletal muscle is a unique and extensive body tissue that on average makes up approximately 40% of total body mass. While it is typically only thought of as having a physical, movement-oriented role, the skeletal muscle system also makes important contributions to a range of crucial health related functions (Wolfe, 2006), including breathing, protein metabolism, digestion, blood circulation, immune system status, blood glucose regulation, and overall quality of life. The health of our muscles (our "MuscleHealth") therefore, makes an essential contribution to wellbeing at any age and any level of fitness or mobility. This reality is the basis of our vision for MuscleHealth to become a recognized as an essential Vital Sign in the same way that Body Temperature, Blood pressure, Pulse and Respiratory Rate are used in current medical practice.
We are currently developing an algorithm that will begin to quantify a MuscleHealth "Index", initially using a combination of Muscle Quality and Muscle Size. Another important aspect of MuscleHealth is the muscle's capacity to produce energy, what we refer to as its "Muscle Energy Status" (MES). The major contributor to MES is Muscle Fuel. All three of these muscle-related components (Size, Quality and Fuel) can be assessed from the same scanned image using MuscleSound's patented algorithms. Other contributors to MuscleHealth, such as Pennation Angle and Fascicle Length, will be added as our research continues to expand.

In addition, using the same image processing procedures, our software is able to assess Body Composition: percent body fat and lean muscle mass in pounds or kilograms. While not strictly a 'muscle measure', Body Composition can provide important supplementary information related to an individual's health, fitness and wellness.

Assessing the 4 components described above allows healthcare practitioners, coaches, or trainers to monitor and track an individual's MuscleHealth status whether patient, athlete or somewhere in between. This personalized information can help to guide individuals along the path of increased fitness, readiness for exercise/training, wellbeing and optimal MuscleHealth.

CONTRIBUTORS TO MUSCLEHEALTH

Muscle Size

The thickness of a muscle as measured by ultrasound at predetermined locations, is representative of "Muscle Size." Research has shown that Muscle Thickness can be considered a surrogate for Muscle Mass/Volume, particularly in the lower limbs (Abe et al., 2015). Muscle Size has been reported as an important contributor to health and wellbeing (Wolfe, 2006), and age-related loss of muscle mass/size (Sarcopenia) has been described as the single most frequent cause of late-life disability (Cruz-Jentoft et al., 2010). In sports-related situations Muscle Size has been linked to greater endurance, delayed fatigue and increased bone integrity in female collegiate runners (Roelofs et al., 2015), increased muscle strength (Hirsch et al., 2016) , and enhanced speed and power (Delecluse, 1997). The ability to easily assess and monitor changes in Muscle Size can provide practitioners with valuable information on the impact of any exercise or dietary-related intervention/training protocol. The following linked articles provide more comprehensive information on the importance and application of Muscle Size for Physical Therapy and Sports Medicine, Fitness and Sports Performance, Health Care and Research.

Assessment of Muscle Size

A recent review (Abe et al., 2015) confirmed the validity and reliability of ultrasound measures of muscle thickness in the lower limbs when compared with cadaver measures. Fukunaga et al., (2001) reported that differences between ultrasound and manually measured values ranged from 0.03 (SD 0.02) cm to 0.05 (SD 0.09) cm for muscles of the upper and lower leg. Ultrasound measurements of muscle thickness were also reported (Kawakami et al.,1993) as differing from manual (cadaver) measurements by 0.1 cm. The authors concluded that the *"precision and linearity of image reconstruction have been confirmed."*

Muscle Quality

Increased fat depots within skeletal muscle is a determinant of Muscle Quality and are associated with functional decline and metabolic disorders (Shaw et al., 2010). Muscle Quality is not only an important component of healthy aging (Cruz-Jentoft et al., 2010), but has been shown to have links with sports performance (Hirsch, 2016), overall health and quality of life (Fragala, 2015), and a range of metabolic, orthopedic and neurological conditions commonly seen in rehab settings (Addison et al., 2014). As with Muscle Size, the ability to easily assess and monitor changes in Muscle Quality can inform practitioners of the impact of any exercise or dietary-related intervention/training protocol.

Assessment of Muscle Quality

In an ultrasound scan, contractile tissue (Muscle fibers) are seen as darker areas on the image, while non-contractile tissue (Fat and connective tissue) are seen as brighter areas on the image. Muscle Quality can therefore be assessed as a digital representation of the relative brightness/darkness of the whole ultrasound image, referred to as "Echo intensity" or "Echogenicity". A recent review (Fragala et al., 2015) has reported the utility and reliability of ultrasound for assessing Muscle Quality in this way. Other studies have also reported the validity and reliability of ultrasound to assess Echo Intensity/Muscle Quality compared to MRI (Young et al.,2015).

Muscle Fuel

Well established research has reported that (i) glycogen stored as fuel in muscle tissue provides the main source of energy during high intensity anaerobic exercise (ii) higher levels of pre-exercise glycogen improve endurance and delay fatigue (Hermansen et al., 1967) and, (iii) depletion of muscle glycogen leads to fatigue and increased risk of muscle injury (Schlabach, 1994). Hence, assessing fuel levels in muscles can inform practitioners of their client/patient's level of readiness for exercise, as well as their capacity to delay fatigue and contribute to muscle injury prevention.

Assessment of Muscle Fuel
The use of MuscleSound in assessing muscle glycogen levels by ultrasound was validated in two clinical studies (Hill & San Millán, 2014; Nieman et al., 2015) conducted with trained cyclists during (i) a 90-minute steady state ride at moderate-high intensity and, (ii) a 75-km time trial. The glycogen "score" generated by MuscleSound was compared to the gold standard of muscle biopsy. Measures were taken from the thigh muscle pre- and post-exercise. Both studies reported very high correlations between these two measures, ranging from $r = 0.81$, $p<0.0001$ to $r = 0.94$, $p<0.0001$.

Elements of Muscle Fuel Assessment
We are able to provide 4 separate, but related, elements from analysis of our Fuel Assessment:
1. *Estimated Fuel Level*
2. *Muscle Fuel Rating*
3. *Muscle Energy Status*
4. *Muscle Fuel Symmetry*

- **Estimated Fuel Level (EFL): The level of energy (fuel) stored in a muscle at any given time.** This is made up predominantly of glycogen but also includes other constituents such as creatine, carnitine and protein. MuscleSound uses a 'fuel tank' analogy for this measure and is able to provide a continuously updated 'percentage full' EFL for each muscle.
- **Muscle Fuel Rating (MFR): The comparison (rating) of an individual's muscle fuel score with the fuel scores of tens of thousands of individuals in our MuscleSound database**. Comparing scores in this way shows what the potential of a muscle fuel score may be. It also answers an important question: "How do my muscles compare to others who have been assessed in this way?"
- **Muscle Energy Status (MES): A combined value made up of Estimated Fuel Level and Muscle Fuel Rating**. A fully fueled, well-rated muscle is at high MES status and can be the basis for monitoring optimal levels of readiness for, as well as recovery from exercise.
- **Muscle Fuel Symmetry (MFS): The symmetry (balance) of MuscleSound scores between contralateral muscles of the upper or lower body**. Such differences have been linked to increased injury risk and performance deficits. We use the scores to support a step by step return to full MuscleHealth.

The following linked article provides more comprehensive information on Muscle Fuel and Muscle Energy.

Body Composition
Excess body fat has long been linked to a range of diseases including hypertension, diabetes mellitus, cardiovascular disease as well as joint diseases such as arthritis (Booth et al.,2014). More recent research (described above) has also reported the importance of other aspects of body composition (i.e. Muscle Size and Quality) to health, fitness and quality of life. Body Composition is listed by the CDC as a "Health-Related" component of physical fitness. Understanding the importance of the relative amounts and changes in muscle and body fat, versus overall "scale" weight, is one of the most effective and meaningful ways to track personal progress in health and fitness. The ability to easily assess and monitor changes in Body Composition can inform physicians/practitioners of the impact of any exercise or dietary-related intervention/training protocol. In addition, all 5 of the MuscleHealth measures described here can be assessed in the same scanning session over a period of minutes and be stored in the cloud for later analysis. The following linked article provides more comprehensive information on Body Composition.

Assessment of Body Composition
A substantial body of research has confirmed the validity and reliability of ultrasound to measure subcutaneous adipose tissue, both in athletic (Müller et al., 2016) and non-athletic populations ranging from lean to obese (Störchle et al., 2017). Research has also confirmed that ultrasound measures of body composition, across a range of athletic and non-athletic populations, are highly correlated with other validated methods of body composition, including skinfolds (Wagner, 2013), DEXA, BodPod and BIA (Pineau et al., 2007).

4. **WHAT DO WE MEASURE AND WHY IS IT IMPORTANT?**
We provide a range of unique ultrasound-derived measures (described below) that are tailored according to the industry involved and made possible by MuscleSound's ability to "Look inside the muscle."

Physical Therapy

- Start and Monitor Rehab
  - Provides previously inaccessible data to enhance recovery process
- Conduct Comprehensive Physical
  - Monitors and tracks recovery through changes in size, quality or fuel storage capacity
- Assess Body Composition
  - Monitors and tracks changes in body fat and lean body mass
  - Monitors and tracks changes in site specific measures
- Assess Event Preparation
  - Monitors "Readiness" for exercise
  - Assesses how full is the Muscle's "Fuel Tank"

Sports Teams

- Assess Game Readiness
  - Monitors "Readiness" for Game
  - Assesses whether a muscle's "Fuel Tank"? is fully charged
  - Provides previously inaccessible input on whether athlete is "Ready to Go"
- Start and Monitor Rehab
  - Provides previously inaccessible data to enhance recovery process
- Conduct Comprehensive Physical
  - Monitors and tracks recovery through changes in size, quality or fuel storage capacity
- Check Recovery
  - Monitors Recovery from Game
- Determines whether muscle fuel has returned to pre- game levels
  - Provides previously inaccessible input on whether athlete is fully recovered
- Monitor Muscle Size
  - Provides a pre-season/pre-injury baseline measures of muscle size
  - Monitors the impact of training interventions on muscle gain
  - Assesses symmetry of muscle size in contralateral limbs
- Assess Body Composition
  - Monitors and tracks changes in body fat and lean body mass
  - Monitors and tracks changes in site specific measures

Gyms/Fitness Centers

- Conduct Initial and Final Evaluation
  - Monitors and tracks recovery through changes in size, quality or fuel storage capacity

- Assess Body Composition
  - Monitors and tracks changes in body fat and lean body mass
  - Monitors and tracks changes in site-specific subcutaneous fat measures
- Assess Event Preparation
  - Monitors "Readiness" for exercise
  - Assesses how full is the Muscles' "Fuel Tank".
- Monitor Muscle Size
  - Provides a pre-season/pre-injury baseline measures of muscle size
  - Monitors the impact of training interventions on muscle gain
  - Assesses symmetry of muscle size in contralateral limbs

Sports Medicine/Chiropractors

- Start and Monitor Treatment/Rehab
  - Provides previously inaccessible input to enhance recovery process
- Conduct Comprehensive Physical
  - Monitors and tracks recovery through changes in size, quality or fuel storage capacity
- Assess Body Composition
  - Monitors and tracks changes in body fat and lean body mass
  - Monitors and tracks changes in site specific measures
- Assess Event Preparation
  - Monitors "Readiness" for exercise
  - Assesses how full is the Muscles' "Fuel Tank"

Research

- Data Collection
  - Collect valid and reliable data with innovative, non-invasive techniques
  - Provide new insight into muscle research by assessing and analyzing previously inaccessible aspects of muscle & body composition
- Assess Body Composition
  - Monitors and tracks changes in body fat and lean body mass
  - Monitors and tracks changes in site-specific subcutaneous fat measures

NOTE: Go to our Support Page http://support.musclesound.com for more information on these and other measures of MuscleHealth.

5. OPTIMAL AND SUBOPTIMAL TIMES FOR USING MUSCLESOUND

For certain of our Assessments, the timing of a scan is essential to provide a valid and reliable measure. The following sections identify these Assessments and provide a rationale for optimal and suboptimal scan times.

MUSCLE SIZE

OVERVIEW

MuscleSound determines the size of a muscle by measuring its thickness at predetermined locations. However, the fluid content of a muscle is increased both during and following exercise. This will transiently increase the muscle volume and resulting in an erroneous assessment of its actual size.

Optimal and Sub Optimal Times to Assess Muscle Size

The timing of scans for this measure needs to be considered for two separate, but linked situations:
1. A time frame for individual scan sessions
2. A time frame for follow up scan sessions

BACKGROUND

1. Time frame for individual scan sessions

During exercise, blood and associated fluids shift into the muscle to meet the increased metabolic demand (Andersen & Saltin, 1985), a condition known as "Exercise-induced hyperemia" (Wray et al., 2005). This process, also referred to as "Transient Hypertrophy", increases the size of the muscle, both during, and for a variable period of time after exercise. While the magnitude and extent of this well-established phenomenon are generally dependent on the mode, duration and intensity of the exercise session, there are wide individual variations in responses (Garton et al, 2014).

Optimal times to measure Muscle Size

Muscle Size should be measured when the subject is rested and/or fully recovered from exercise for the following reasons:

- Measures are unlikely to be influenced by fluid shifts
- Resting measures are the best reflection of a 'normal' status for muscle size
- Similar conditions are required for other physiological measures such as blood pressure and pulse rate

Sub-Optimal times to measure Muscle Size

Muscle Size should not be measured within 2-3 hours after exercise for the following reasons:

- If scans are conducted too soon after an exercise session, the subject will not be fully recovered
- Muscle Size is likely to be transiently increased as a result of exercise-induced hyperemia
- Depending on the mode, duration and intensity this transient increase in size can last up to 3 hours after exercise, assuming no further exercise is performed

2. Time frame for follow up scan sessions

Over the last several decades, strength Increases occurring early in a training program were thought to be caused by neural adaptations in the muscle over a period of between 6-12 weeks. An increase in muscle size (Hypertrophy) was considered to be a relatively slow process, beginning only after these neural adaptations were completed (Moritani & Devries, 1979; Sale, 1988). However, recent studies using ultrasound have shown that hypertrophy can occur within the first 2-3 weeks of training. (Loenneke et al., 2017; Seynnes et al., 2007; Ogasawara et al., 2012; Krentz & Farthing, 2012). The magnitude of such changes and the capacity of ultrasound to detect them will vary according to the mode, intensity, and duration of exercise.

Optimal Times for follow up measurement of Muscle Size

Changes in Muscle Size should be monitored/measured after a minimum of 2-3 weeks ***** of training for the following reasons:

- Research has shown that ultrasound is capable of detecting changes over this time frame, depending on the mode of exercise, and assuming it is of sufficient duration and intensity
- Follow up scans can be repeated at similar intervals
- Increases in Muscle Size will vary depending on the mode, intensity and duration of training

Sub-Optimal times for follow up measurement of Muscle Size

Changes in Muscle Size should not be monitored/measured within 2 weeks of training for the following reasons:

- Research has shown that ultrasound is unlikely to detect changes in Muscle Size within the first 2 weeks of a training program, regardless of mode, duration and intensity of exercise
- Any changes detected within this period are likely to be produced by scanning errors or other artifact

MUSCLE FUEL

OVERVIEW

MuscleSound determines the fuel levels of a muscle by assessing the brightness of its scanned image. The brightness of this image is determined by the muscle's water content (Hill & San Millán, 2014; Nieman et al., 2015) which fluctuates both during and post exercise (Sjogaard & Saltin, 1982; Hackney et al., 2012). This can potentially introduce artifact into the scan producing erroneous assessments of actual Fuel levels.

Optimal and Sub-Optimal times to assess Muscle Fuel

Muscle Fuel is composed mainly of glycogen but may also include other water-bound constituents such as protein, carnitine and creatine. Research has shown that, because of the fluctuations of muscle fluid during and following exercise, identifying optimal time frames for scan sessions is essential for producing valid and reliable results.

BACKGROUND

MuscleSound scans display the 'echogenicity' (Brightness) of a muscle image which is based on the speed at which sound waves reflect back from different tissues within the muscle. Connective tissue is very dense, and the sound waves quickly reflect back to the transducer. Images of this tissue appear brighter (hyperechoic) on the scan. Water, on the other hand, allows the sound waves to pass through without resistance and so they are not reflected back to the transducer. Images of scan areas containing water appear darker (hypoechoic): the higher the water content of the muscle, the darker (hypoechoic) the image will be (Hill & San Millán, 2014).

Each gram of glycogen is tightly bound to three grams of water (Olsson and Saltin, 1970; Fernández-Elías et al., 2015). When the muscle contains more glycogen, it also contains more water, producing a darker (more hypoechoic) image. During exercise, as glycogen is used up, the water associated with it leaves the muscle.

This exposes the muscle fibers, which are denser than water. This enables the sound waves to be more easily reflected back producing a brighter (more hyperechoic) image. In predictable situations, therefore – as explained in the following paragraphs - the darker areas of the image can be assumed to contain more glycogen.

Note: other energy-producing constituents of muscle such as protein, creatine and carnitine are also tightly bound to water, and may well contribute to the darkness of the image.

"Fluid Dynamics"

Considerable shifts in muscle fluid occur during and after exercise as part of the metabolic process of energy production. During this process, water shifts into and out of different compartments of the muscle (Sjogaard & Saltin, 1982; Hackney et al., 2012). This includes both "free water" as well as the "bound water" released when muscle glycogen is broken down for energy.

The type of exercise performed can also impact the amount of fluid inside muscle. For example, eccentric contractions (an essential component of many types of sports and exercise) can produce micro-damage resulting in post-exercise swelling (Proske & Morgan, 2001). This may also increase intramuscular fluid content. At certain times, such fluid shifts can introduce artifacts in MuscleSound scans that mask the water actually bound to glycogen. This will produce dark images that could be interpreted (erroneously) as showing greater levels of muscle fuel/glycogen than is actually the case. Identifying these situations will differentiate between optimal and suboptimal times to use MuscleSound. See below.

Despite the fluid shifts accompanying exercise of different types, research has confirmed that hydration levels, per se, do not impact the accuracy of MuscleSound scans. The glycogen/water bond is very strong and, even when the body is dehydrated, the water molecules will remain attached to glycogen until it is broken down for energy. Only when this happens is the bound water released and made available to the rest of the body, In effect, contributing to hydration status. While dehydration does not impact normal muscle glycogen breakdown for energy, it does increase the rate of glycogen breakdown. Because of this, in dehydrated conditions glycogen stores are used up much faster and the muscle becomes fatigued a lot sooner (Logan-Sprenger, 2015).

Under certain circumstances some research has indicated that there is a supra-physiological amount of fluid being retained by the muscles. For example, research has shown that in the 1-4 hours post exercise, glycogen synthesis (refueling) is at its highest rate. However, in some conditions research shows that the water taken into the muscle is very high. An apparent ratio of 1:17 has been reported, compared to the commonly reported ratio of 1:3 (Fernández-Elías et al., 2015). Not all this water may be bound to glycogen, however, some may be 'unbound' water freely distributed inside the muscle (Peters & Lavietes, 1933). More research is needed in this area. Regardless, as referenced above, this may well create artifact in MuscleSound scans, since the transient increases in muscle water volume will produce an over assessment of Fuel/glycogen.

Both internal and external research has shown that these periods of extra-normal muscle fluid movements and volumes primarily occur soon after and/or several days after exercise, depending on the intensity, duration, and eccentric nature of the exercise.

<u>Optimal Times to Assess Muscle Fuel</u>

1. MuscleSound can be used pre- and immediately post-exercise for the following reasons:

a. As indicated by the validation studies, MuscleSound provides a good, indirect assessment of glycogen utilization pre-post exercise. However, the MuscleSound value <u>is unique to the individual</u>. Person-to-person and muscle-to-muscle values may differ considerably within the same sport/exercise session. This is due to the fact that, while fluid is distributed relatively evenly throughout the whole muscle, Glycogen is distributed unevenly both in its location and depth. It is also used at different rates depending on its fiber type, location in the muscle, intensity of the exercise and the fitness level of the individual.

2. MuscleSound can be used several hours after the end of moderate to high intensity/long duration steady state exercise (such as cycling) that does not involve extensive eccentric contractions for the following reasons:

a. After this time muscle fluid levels are likely to have equilibrated and fuel/glycogen can be more accurately assessed. If the session involves extensive eccentric contractions, MuscleSound should be postponed as indicated below.

3. MuscleSound can be used one to two days or more after high intensity/long duration sports such as soccer, football, rugby, and basketball for the following reasons:

a. The 1-2 days minimum period allows time for muscle damage to be repaired, edema to subside, fluid levels to equilibrate and fuel/glycogen to be more accurately assessed.

4. MuscleSound can be used one to two days before a competition (as described in the 'Readiness and Recovery' paragraph above) to make sure fuel is adequate. If fuel levels are low, there is adequate time to replenish and recover using appropriate nutritional and workload strategies.

<u>Sub-Optimal Times to Assess Muscle Fuel</u>

1. MuscleSound should not be used within several hours of the end of moderate to high intensity/long duration steady state exercise for the following reasons:

a. During this post-exercise period, muscle fluids that shift during exercise are still in flux and have not equilibrated to pre-exercise levels. As mentioned above, the glycogen to water ratio in the recovery phase could be as high as 1:17 and could also include fluid not bound to glycogen. This additional fluid will appear as more hypoechoic on any MuscleSound scans taken at that time and will give an exaggerated assessment of Fuel/glycogen content.

b. If exercise also includes prolonged or repeated eccentric contractions (e.g. downhill running, multiple set heavy weightlifting), it will cause increased micro-damage inside the muscle. This produces additional fluid in in the muscle in the form of intramuscular swelling (edema). This process typically begins soon after exercise ceases but under certain circumstances (Marathon/ultra-distance running, high intensity weightlifting) can occur during activity. If this occurs, it will give an exaggerated assessment of Fuel/glycogen usage or replenishment that may take several days to normalize.

2. MuscleSound should not be used the day after high intensity/long duration competition in sports such as soccer, football, rugby, and basketball for the following reasons:

a. Rapid changes of direction are an integral part of many sports and are a major source of eccentric contractions. This can result in extensive micro damage accompanied by intramuscular swelling (edema) and can transiently increase the volume of fluid inside the muscle. The image will be more hypoechoic and MuscleSound scans taken at that time will have an exaggerated assessment of fuel/glycogen replenishment.

b. Allowing at least one day post-game provides time for edema to subside, fluid levels to equilibrate and glycogen to be more accurately assessed.

FLUID DYNAMICS

Summary

The foundation of our fuel scoring system is that elements of muscle fuel (glycogen, creatine, carnitine, protein etc.) are tightly bound to relatively large proportions of water. This water is displayed as darker areas on the ultrasound muscle scan, and our current algorithm assesses a “Fuel Score” based on the relative darkness (echogenicity) of the pixelated image. On occasion however, as explained above, some individual scores in these data sets actually appear to increase post exercise. In other words, the post exercise image is shown as darker than the pre-exercise image. We have seen examples of such results in running, cycling and, more recently, in high-volume strength training.

Next Steps

Absent scanning issues, we know, as explained above, that such paradoxical occurrences are the result of artifact related to exercise related fluid shifts within the muscle. While the excess fluid erroneously produces an apparently elevated fuel score, it also impacts architectural components of the muscle. For example, as muscle fluid increases, so too do scores for muscle pennation angle, muscle thickness and muscle fascicle length. We can now measure and track these fluid-influenced changes in muscle architecture, and this may allow us to quantify the extent of the fluid change and, ultimately, to control for its impact on fuel scores. Utilizing this approach using pennation angle has already produced some promising preliminary results. We will be reporting more on this phenomenon as our investigations progress.

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