Ultrasound

American Association of Neuromuscular & Electrodiagnostic Medicine
Ultrasound

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Ultrasound

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Course Description
The AANEM 2010 course on Neuromuscular Ultrasound reviews the basic principles of ultrasound relevant to neuromuscular disease. Building on these principles, the course addresses role of ultrasound in evaluating pediatric neuromuscular disorders including a discussion of key technical points. Similarly, the use of ultrasound in interventional procedures, particularly, musculoskeletal procedures is reviewed. Finally, the course covers the concept of biomarkers in clinical trials and the potential for ultrasound to serve in this capacity for a variety of, as yet, untreatable neuromuscular disorders.

Intended Audience
This course is intended for Neurologists, Physiatrists, and others who practice neuromuscular, musculoskeletal, and electrodiagnostic medicine with the intent to improve the quality of medical care to patients with muscle and nerve disorders.

Learning Objectives
Upon conclusion of this program, participants should be able to:
(1) list five indications for performing neuromuscular ultrasound in children.
(2) describe how ultrasound can be used to guide interventional therapy.
(3) discuss the use of ultrasound in tracking changes in nerve and muscle disease over time.
(4) define four basic concepts in ultrasound physics: attenuation, anisotropy, time gain compensation, and brightness mode imaging.

Activity Profile
This enduring material activity is a reproduction of the printed materials from a course at the AANEM Annual Meeting (October 6-9, 2010). Physician participation in this activity consists of reading the manuscript(s) in the book and completing the clinical and CME questions.

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Ultrasound

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No one involved in the planning of this CME activity had any relevant financial relationships to disclose. Authors/faculty have nothing to disclose.

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The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
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Dr. Walker is currently professor of neurology and director of the Electromyography (EMG) Laboratory at Wake Forest University. He is a long-time member of the American Association of Neuromuscular & Electrodagnostic Medicine (AANEM) and has served on eight different committees and task forces. He has also been the chair of the Training Program Committee. He has presented numerous hands-on workshops, conducted courses, and organized symposia for the AANEM. He has trained 30 EMG fellows, received the Class of 1997 Teaching Award at Wake Forest University School of Medicine, and authored or co-authored more than 100 papers in peer reviewed journals. Currently, he is on the Examination Committee for neuromuscular medicine of the American Board of Psychiatry and Neurology and serves on the steering committees of major multicenter clinical trials. Dr. Walker is certified by the American Board of Electrodiagnostic Medicine. His interest in neuromuscular ultrasound dates back to the mid-1980s when he began exploring the technique for its use in characterizing myopathies and evaluating fasciculations.

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INTRODUCTION

This presentation will steer the reader through the physics of ultrasound. There are more elegant sources that summarize the material in mathematical format. However, for the typical electrodiagnostic (EDX) physician, it helps to put the concepts into descriptive terms. The following ultrasound topics will be reviewed: modes of display, transducers, instrument controls of the transducer, spatial control of the transducer, the behavior of sound in tissue, measuring echogenicity, and future directions.

MODES OF DISPLAY

A-mode Ultrasound

The simplest and earliest forms of ultrasound involved A-mode displays.1-4 The A in A-mode stands for amplitude; and in A-mode displays the vertical axis represents the amplitude of the echo signal (echogenicity) and the horizontal axis represents time. Needle electromyography (EMG) and nerve conduction studies (NCSs) are always displayed in A-mode as well. Both ultrasound and EDX studies were first carried out with simple oscilloscopes, which were designed for A-mode displays.5

It is easy to understand ultrasound in terms of A-mode. A sound pulse is emitted from the transducer, and, as the sound energy enters tissue, it creates echoes from structures within. The echoes return to the transducer at slightly different latencies, with nearer structures creating earlier echoes and more distant structures creating later ones. Figure 1 shows the results of a theoretical A-mode ultrasound of either side of a fetal skull. Knowing the speed of sound in tissue (about 1430 m/s) the distance between opposite sides of the skull could be calculated from the image. This approach formed the basis for the earliest uses of ultrasound to study fetal measurements.

The amplitude of an ultrasound echo is determined by the tissue interface that creates it. If the abutting tissues are of similar acoustic impedance, a measure of stiffness or hardness, then the echoes created are relatively small in amplitude (e.g., two adjacent muscles). If the tissues that interface are of distinctive acoustic impedance, however, the echo created is of high intensity (e.g., bone and muscle). Another potentially much greater factor, however, determines the amplitude of the recorded echo: the distance through tissue that sound must travel before it creates the echo, and the echo travels back through tissue to the recording device, the transducer. This is because sound is attenuated as it travels through any medium, through backscattering or absorption (see Fig. 2).

To address the effects of attenuation and distance, ultrasound instruments typically use an internal correction factor to magnify echoes from distant structures more than from near structures, so that echogenicity consistently reflects the nature of the tissue interface in a way that is independent of tissue depth.3 However, this automatic correction process is based on average calculations of the typical speed of ultrasound in human tissue and the average attenuation of sound in human tissue. In fact, ultrasound travels slightly faster in some tissues than in others, but attenuation varies even more from tissue to tissue. As such, the process is not perfect. In addition, the automatic correction factors for time gain compensation vary from instrument to instrument, and the algorithm used is commonly proprietary, so it can be difficult to precisely interpret the significance of echogenicity findings by ultrasound. Almost all ultrasound instruments have a
time-gain compensation panel (see Fig. 3) which allows the user to override the correction factor to enhance the visualization of ultrasound findings (see Fig. 4).

B-mode Ultrasound: Creating an Image

Although A-mode ultrasound provides those comfortable with needle EMG an intuitively familiar display of information, it is rarely found on instruments other than those used to study the eye. This is because it is now routinely possible to obtain a linear array of adjacent A-mode images from a single probe containing multiple, equally-spaced transducer ultrasound elements. If each element were to display serial A-mode images, the screen would be cluttered and uninterpretable. B-mode imaging is similar to A-mode imaging except that it collapses the A-mode information into a single linear trace by displaying amplitude, not by vertical displacement, but by brightness (brightness mode). Using B-mode imaging, therefore, allows serial linear displays to be stitched together to create a single tapestry of tissue anatomy. Tissue interfaces are earmarked by areas of brightness captured by sequential transducer elements generating an easily recognizable image of tissue interfaces beneath the probe.

Figure 1 This is a schematic (cartoon) that represents the theoretical appearance of an A-mode ultrasound of a fetal head. The large spikes represent the echoes from near and far side of the fetal skull. The amplitude of each echo is equivalent due to the intrinsic time-gain compensation hard-wired into the processing of echo signal amplitudes.

Figure 2 This is an axial image of the tibialis anterior taken at the upper third of the muscle. Note the prominent central aponeurosis (top arrow), which is composed of thick fibrous tissue and which reflects a disproportionate amount of sound compared to the rest of the muscle. Just below the aponeurosis, note how the muscle looks hypo-echoic (right lower arrow), particularly when compared to muscle tissue imaged medial to the aponeurosis, where sound waves, not having to pass through this sound energy attenuator, create stronger echoes from the underlying muscle tissue. The aponeurosis creates artificial shadowing of the muscle deep to it.

One of the unanticipated consequences of brightness mode imaging is the relative insensitivity of the human eye to brightness changes compared to size changes. The relative size of two objects, one twice the size of another, is automatically apparent, but the relative brightness of two objects is not. If you light one match in a cave, it significantly
elevates the brightness factor, but lighting a second match far from
doubles one’s sense of relative enlightenment. This is because per-
ceived brightness does not have a linear relationship to light intensity;
rather it correlates with the square of light intensity (e.g., lumens). As
such, ultrasound tends to convey much better the spatial relationships
of tissue than the relative acoustic impedance of distinct tissue layers.

(Note: Needle EMG cannot be displayed in B-mode in a mean-
ful anatomic fashion, because electrical activity 1) is ephemeral and
2) propagates through excitable tissues. It does not reflect structure
but function, and as such, cannot be used to create a spatial map.
However, presentations by Dr. Erik Stålberg include a fascinating
B-mode needle EMG image reconstructed from a macro-EMG
needle that he moves through tissue.)

M-mode Ultrasound

Available on almost every instrument is M-mode ultrasound. This
is a cross between A-mode and B-mode and uses the vertical axis as
time. Only one linear B-mode image, however, is displayed, but it is
swept over time so that any sequential changes in tissue morphology
are captured. The technique is useful for measuring events of temporal
interest, such as the duration of a muscle twitch, or fasciculation7,8

(see Fig. 5). It is important to become familiar with M-mode images
as it provides insight into the nature of A-mode and B-mode and how
ultrasound images are created.

ULTRASOUND TRANSDUCERS

The part of the ultrasound instrument that comes into contact with
the patient is the probe, sometimes called the transducer. The terms
are not quite interchangeable since most ultrasound probes consist of
a series of ultrasound transducer elements, and, for neuromuscular
and musculoskeletal ultrasound, the probe is almost always a linear
array of transducer elements. Regardless if discussing single or multiple transducers, their function is to convert one type of energy to another, which, in the case of ultrasound, is the conversion of electrical energy into sound and sound energy back into electrical energy.

A transducer element is a small chip of piezoelectric material. This is a material that has asymmetrically-charged molecules in a lattice array. When an electric current is applied there is a slight shift in the molecular structure, causing a mechanical change in the chip. This emits a sound pulse. Ideally, only a single cycle of sound is emitted, so the pulse is extremely brief. As it travels through tissues, it creates echoes. Transducers are in the emit mode less than one percent of the time (except in certain Doppler studies, when they may have more on time). Transducer elements are designed to receive returning echoes. These strike the transducer element, which then generates a small electrical signal in response to the sound energy that is relayed back to the instrument for display.

The linear array of transducer elements allows for the creation of multiple simultaneous B-mode linear images, which, when combined, create the real time ultrasound image. To do this, each of the hundred or more transducer chips in the probe has to be wired separately and the wiring to each is contained in the probe and the cord that connects the probe to the body of the ultrasound instrument. For anyone who has performed multi-channel needle EMG recordings, this prefabricated wiring is a highly desirable engineering achievement. The casing and shape of the transducer element help determine some of the characteristics of the sound beam and its directionality, as well as how well it matches with a gel-coated skin surface. Ultrasound probes are therefore expensive and need to be handled with care.

**ELECTRICAL CONTROL OF THE ULTRASOUND TRANSDUCER**

The instrument panel on most ultrasound machines appears to most beginners (and even many experts) as a complex arrangement of control switches, dials, and levers. In practice, some of the controls are more useful than others. Two controls are already familiar to those who perform NCSs: the power dial and gain dials. The power control determines how much sound energy is pulsed into tissue and the gain dial determines how much the signal is amplified. Since the predominant image is B-mode, increases in either gain or power will result in brighter images (see Fig. 6). As in the case of electrodiagnosis, excessive power or gain does not necessarily enhance signal display; in general, the lowest power needed to generate a good image is desirable.

The time gain compensation panel, which usually consists of a series of small levers, adjusts signal amplification based on depth. Sometimes sound passes through tissue (e.g., a cyst) that does not attenuate sound as much as average tissue; other times, it passes through tissue that attenuates sound (e.g., scar tissue) more than average tissue. The time gain compensation panel provides a way for the examiner to independently correct for image distortion as a result of local findings.

Ultrasound beams are focused to some extent. This is in part due to the shape of the transducer elements and its surrounding material, but also in part can be due to sequencing of pulses across different transducer elements. Ultrasound focus is depth dependent, and instruments can have different focal zones. Focusing in ultrasound takes place out of plane with the transducer. If a nerve is viewed in cross section, the volume averaging of the nerve just distal or proximal to the transducer is reduced when the nerve is in the focal zone of the instrument. The practical result is improved resolution. The depth of the focal zone is usually denoted by a small arrow(s) to the side of the screen. When imaging nerves, it is important to continually adjust the

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Figure 5 B- and M-mode imaging. These are axial images of the abductor hallucis muscle at high magnification. The top figure in each frame is the B-mode image of this muscle. The vertical line in the center represents the single line of data recorded in the image below that is displayed over time. The small perturbations in this image (arrows in top frame), are fasciculations in the muscle, that occur under this line. Note that they occur at different depths within the muscle, and have different durations (these measure 124ms) or longer as shown in the bottom frame. The value of M-mode imaging within the muscle and have different durations (these measure 124 ms or longer) as shown in addition to clarifying how A-mode images are created, is that it provides precise temporal information regarding tissue movement. The long duration of fasciculations measured by ultrasound compared to needle EMG results from the fact that the mechanical contraction of a motor unit, as captured by ultrasound, far outlasts the transient membrane potential that actually precedes motor unit contraction.
focal zone to accommodate the depth of the nerve from the surface as the probe is moved up or down an extremity.

Transducer frequency can be controlled by the instrument to some extent as well. Higher frequencies provide better resolution but less depth of penetration. Different transducer elements can provide different ranges of frequencies. For most nerve evaluation, high frequencies are required. Modern instruments have a variety of novel features that can further enhance resolution. As with many adjustments that simplify ultrasound, there can be a tradeoff. Often the frame rate of the instrument is reduced when multiple focal zones, increased persistence, or other image enhancement features are employed. Although such changes help with the creation of static images, they tend to impair the ability of the instrument to reliably capture quick movements, such as fasciculations or fibrillations.

SPATIAL CONTROL OF THE ULTRASOUND TRANSDUCER

Ultrasound imaging depends on manual dexterity, but unlike needle EMG, which involves ear-hand coordination, ultrasound requires eye-hand coordination. Ultrasound examines tissue in planes whereas needle EMG records from a spherical area with a monopolar needle and a hemispheric area if using a concentric needle. Furthermore, EMG needle recordings are dependent solely on the location of the needle tip and not the angle of needle insertion, whereas, with ultrasound, the image varies considerably with angle of insonation, even if the probe maintains contact at the same surface location.

The reason why an image varies so much with the angle of insonation is due to a property of tissue known as anisotropy. Some tissues backscatter insonated sound diffusely, others tend to reflect insonated sound directionally, the way light is reflected from a mirror. Tissues with prominent anisotropy appear brightest when the incident sound is perpendicular, and as the probe is tilted and the sound strikes at an acute angle and is reflected away from the transducer. If you shine a flashlight on a wall, it tends to backscatter and provide diffuse lighting to a room; however, if it is shined on a mirror, the beam reflects off the mirror to strike another wall in a narrow beam. If you look at where the light hits the mirror, you will not see reflected light. Tendons have high anisotropy, so they appear brightest when the ultrasound probe is held perpendicular; as the probe veers off from this angle the tendons quickly become dark (echolucent) (see Fig. 7). A needle viewed with ultrasound may not reflect much sound back to the ultrasound probe, and this can make needle guidance with ultrasound complicated.

Getting used to controlling for angle of insonation, as well as keeping the probe in a strict axial or sagittal section of a structure of interest, involves a learning period of weeks to months. Learning how to image an injecting needle takes a similar time commitment.

Figure 6 These axial images of the anterior tibialis are shown at different power levels in A (top image), and different gain levels in B (bottom image), to demonstrate the effects of increasing power or gain on overall image brightness(left images). Careful attention to multiple parameters during imaging will provide the most consistent results when attempting to interpret changes in brightness observed in different tissue structures.

Figure 7 These are side-by-side images of the median nerve at the wrist taken with slightly different angles of insonation. The left image, in which the probe is held strictly perpendicular to the wrist, the tendons appear bright (lower arrows). The right image, which is only one or two degrees off vertical, shows the tendons as dark. The nerve (top arrows) shows much less variation in signal brightness, because it has significantly less anisotropy than tendon. This is one way to distinguish nerve from tendon.
SOUND BEHAVIOR IN TISSUE

As mentioned above, sound travels at slightly different rates through different types of tissue, and sound is attenuated in varying degrees by different types of tissue. Furthermore, different types of tissue possess differing degrees of anisotropy. Whereas computed tomography (CT) and magnetic resonance (MR) can distinguish tissues based on X-ray or proton spin differences, ultrasound relies on anisotropy and echo patterns. Although at first, ultrasound shadows are quite confusing, with experience, tissue and structural analysis become second nature to the examiner. What ultrasound lacks in the ability to distinguish different tissues, it compensates for in resolution, which is significantly superior to that of currently used MR and CT instruments.

Ultrasound is one of the safest imaging modalities currently in use. It does, however, introduce sound energy into tissue, which can elevate its temperature somewhat. In fact, therapeutic ultrasound is ideal for warming tissues from the bones and ligaments up, since ultrasound energy is best absorbed by these deeper structures. Unlike surface warming, which is limited in how much energy it can deliver to deep structures, ultrasound can deliver therapeutic warming preferentially to musculoskeletal problem areas. The Food and Drug Administration (FDA) is particularly restrictive on the use of ultrasound in the eye, as there is a theoretical potential for injury to the lens with excessive ultrasound power.

MEASURING ECHOCENICITY

In evaluating nerve and muscle disorders, changes in echogenicity are frequently observed but difficult to quantify. In part this reflects the numerous factors which combine to determine the brightness of an ultrasound image: angle of insonation, gain, power, time-gain compensation, proprietary instrumentation software that converts amplitude into brightness, skin thickness, thickness of subcutaneous fat, attenuation of sound by intervening tissues, focal depth, transducer frequency and depth of penetration, filtering, etc. However, despite these variable drivers, echogenicity conveys useful information about tissue. If a tissue is edematous or engorged with venous blood, it will tend to be more hypoechoic, and if it becomes lipid laden or has more marbling (with fat), has inflammatory changes, or increased fibrous tissue, it will become hyperechoic. In a sense, ultrasound, like MR and CT, can convey key information about histopathologic changes in tissue, in addition to identifying morphological distortions.

However, unlike spatial parameters such as depth, width, and cross-sectional area, which is quickly and easily measured, current ultrasound instruments are not designed to provide simple quantifiable readouts of overall brightness or echogenicity. Some examiners have compensated for this by using standard instrument settings and probe placements, exporting images to standard software (e.g., Adobe Photoshop), and then measuring brightness using this free standing equipment. This approach is valid, but does not necessarily allow investigators to compare findings across different instruments. There are other more sophisticated approaches, which can be used across instruments, but the technology is not readily available on most instruments. However, perhaps the real reason for the absence of such capability on most instruments has simply been lack of demand. The engineering involved in providing color Doppler (not reviewed here) is far more complex than that needed to generate reliable estimates of tissue brightness, and as such, it may be that niche manufacturers will design instruments with intuitive software to measure brightness. Alternatively, it may be that instruments will be designed to compare the echogenicity of a given structure with a phantom, or with easily imaged and fairly representative human tissue, such as subcutaneous adipose tissue in adults or children. In either case, there is reason to be optimistic that more quantifiable measures of tissue echogenicity will be made routinely available on future instruments.

FUTURE DIRECTIONS

Like needle EMG, a great deal of neuromuscular ultrasound can be performed without in depth knowledge of the underlying physics of the technique. However, to do the procedure well, once enough experience is gathered, this knowledge can enhance the ability to use and interpret ultrasound. All ultrasound technicians and radiologists are expected to know basic physics of ultrasound, and all are tested on it before being certified. Knowledge of ultrasound physics, of course, is particularly important for those who are the first generation of neuromuscular sonographers, as it is necessary to understand how current instruments work in order to be able to communicate needs to instrument manufacturers and to be able to envision the kinds of modifications that will make ultrasound more useful for patient care. It is also helpful in determining what types of technology ought to be invested in as new instruments with new capabilities evolve. As neuromuscular ultrasound becomes mainstream, it can be expected that new advances will become available, and the sooner EDX physicians can provide input into the process, the sooner useful modifications will be developed.

Although color Doppler ultrasound is not discussed here, there is reason to believe that better understanding of this technology, and the use of contrast agents, might eventually have a positive impact on diagnosis. However, at this time, we have a fairly rudimentary understanding of how to use it routinely, but this may change as additional experience is gained (see Fig. 8).

Elastography is a new technique, that is useful for measuring tissue stiffness. Very little standardized work in nerve or muscle has been performed with this technique, but it seems likely that it would be informative in certain types of disorders. Currently, some studies have evaluated its ability to distinguish carcinoma from fibrocystic disease in the breast, and, as such, it may be useful for diagnosing subtle histologic changes in nerve or muscle tissue.

Higher resolution instruments are currently on the market under different guises. Most ocular ultrasound is performed with very high resolution probes, but these are not routinely helpful for studying routine tissue in the extrimitity. However, it is possible the technology may evolve or be modified to help identify changes in very superficial structures such as digital nerves. Animal ultrasound instruments, of sufficient resolution to image the blood flow in the heart of fetal mice, are also available. It makes sense that image resolution will continue to improve over time and become more available to routine users.
At this time, 3D and 4D images, such as of fetal faces, are quite popular. There are certain kinds of pathological disorders in obstetrics in which this capability is of particular value, but, for now, most of this type of imaging is more for demonstration purposes than for enhancing patient care. It has not proven yet to be of particular value for nerve or muscle.

New technology has been developed to enhance needle imaging for interventional procedures. This technique involves steering the ultrasound beam to find the needle, which enhances visualization. It is not clear how useful this technology will be for routine procedures, but further hands-on experience for those active in this area will likely be informative.

**CONCLUSIONS**

Ultrasound physics can be understood in an intuitive/descriptive fashion which can enhance understanding of the technology and improve interpretation skills:

- Proper understanding of ultrasound physics may enhance the ability of the examiner to help engineers find better ways to design future ultrasound instruments.
- The sophistication of ultrasound engineering surpasses that of standard needle EMG/NCS instruments, and this sophistication continues to evolve.
- Image display in ultrasound depends on signals from multiple serial transducer elements in the imaging probe.
- Brightness, or B-mode imaging, enhances spatial resolution at the cost of quantifying echogenicity.
- Anisotropy is a useful distinguishing characteristic of certain tissues that requires dynamic alterations of the angle of insonation in order to be appreciated.
- The role of color Doppler and ultrasound contrast agents in the evaluation of neuromuscular disorders has not been well studied and likely will be of diagnostic significance in certain conditions.
- EDX physicians, because of their appreciation of peripheral neuroanatomy, hands-on patient evaluations, and electrophysiology, are in an excellent position to understand and appreciate the potential applications of ultrasound in patient care.

**REFERENCES**

INTRODUCTION

Ultrasound is a painless, noninvasive technique to identify skeletal muscle and nerve pathology. Its use was pioneered by Heckmatt and Dubowitz in the early 1980s, in the evaluation of Duchenne muscular dystrophy (DMD). Since this time, studies of ultrasound imaging of skeletal muscle and nerve has expanded to include neuromuscular disorders of various etiologies. Ultrasound provides a practical and effective supplement to the physical examination in the evaluation of neuromuscular pathology in children. It can be performed at the bedside and allows for examination of multiple muscles quickly and without reliance on patient participation. This allows for a directed electrophysiologic examination and can be of assistance when selecting sites for biopsy. These qualities make ultrasound a practical and informative tool in the evaluation of the infant or child with a suspected neuromuscular disorder.

NORMAL MUSCLE

Normal muscle shows low echogenicity (mostly dark) on ultrasound. Interspersed within this low signal are multiple, homogeneously distributed, well-defined brighter punctate or curvilinear bright areas. These represent the fibroadipose septa and tendinous fibrils interspersed among the muscle fibers. The myofascial fibrils coalesce near the myotendinous junction. At these areas, the echo intensity is increased and there is higher anisotropy. For diagnostic purposes, it is best to avoid these areas and focus on the bulk of the muscle belly. The fascia around the muscle belly is brighter and thicker than the fibrous tissue in the muscle belly. At high magnification, multiple low-signal, dark honeycombed structures surrounded by a thin, medium intensity ribbon can be seen. These structures appear like individual muscle fibers; however, ultrasound does not have sufficient resolution to visualize individual muscle fibers. Rather, these areas are likely bundles of muscle fibers surrounded by brighter fibroadipose tissue. Bone is very bright (highly echogenic) with a well-defined, crisp edge and casts a shadow on ultrasound deep in this boney reflection. Subcutaneous fat has similar echo intensity to muscle and is interspersed with poorly organized threads of brighter connection tissue.

The appearance of skeletal muscle on ultrasound changes with age. In infants, muscle is more echo–dark than in older children. At this age, there are few myofascial planes in the muscle parenchyma. By age 2-3 years, there are more myofascial planes than in an infant. By age 5, myofascial planes are seen in a homogenous pattern typical of the adult. After age 5, muscle echogenicity increases more gradually, if at all, through most of early adulthood. In later life, at about age 60 years, muscle echogenicity increases more rapidly with advancing age. These changes vary with muscle group and are most pronounced in the biceps brachii and quadriceps muscles, particularly in males. There is no difference in echogenicity...
between males and females until the teenage years. From this age forward, muscle in males is slightly darker on ultrasound than in females.31

Muscle bulk also changes throughout the lifespan and varies with age, gender, and muscle group.2,3,13 In the first 20 years of life, muscle thickness increases. As with muscle signal intensity, differences in gender begin in the early teenage years, with males having larger muscles than females.16 Until age 40 years, muscle thickness remains relatively stable in both genders. In older adults, muscle thickness in some muscles declines considerably. Muscle thickness decreases in the quadriceps by 30% in women and 50% in men between ages 40 to 90. In the biceps brachii, similar but less severe declines (20-30%) are seen. In contrast, muscle thickness in adults in the sternocleidomastoid, tibialis anterior, and, in women, the forearm flexors remains more stable through the lifespan.

Muscle atrophy can also be assessed qualitatively by comparison of the thickness of muscle to subcutaneous fat. The typical ratio of muscle to subcutaneous fat is approximately 2:1.14,4 While this method is helpful as a quick screening tool, the muscle to subcutaneous fat ratio can be misleading in obese patients and in infants as the thickness of the subcutaneous fat changes rapidly through the first year of life.13,30 Thus, assessment of muscle thickness must be interpreted using norms adjusted for patient characteristics, including age and body habitus.

NEUROMUSCULAR ULTRASOUND AS A DIAGNOSTIC TOOL

In children, myogenic weakness typically appears as an homogeneous increase in echo signal intensity with relatively preserved muscle bulk. In contrast, ultrasound in an infant/child with neurogenic weakness shows reduced muscle size with an increase in the subcutaneous fat to muscle ratio, and a pattern of streaky, increased echoes scattered heterogeneously within the muscle. Central hypotonia does not cause substantial alterations in the muscle signal intensity on ultrasound, although in the author’s experience disuse can reduce muscle size. Using these criteria, ultrasound can play a role as a well-tolerated screening test in hypotonic children and can be performed at the bedside without need for sedation or patient discomfort.

The sensitivity and specificity of diagnostic ultrasound in children with neuromuscular disorders depends on the type and severity of disorder (reviewed by Pillen and colleagues27). In the evaluation of infants, in whom electrophysiologic evaluation can be technically challenging, ultrasound has similar sensitivities and specificities for identifying and characterizing neuromuscular pathologies to electromyography (EMG). In a study of 41 hypotonic infants aged 2-24 months, qualitative ultrasound was highly concordant with needle EMG 4. Ultrasound and needle EMG both showed abnormalities consistent with myopathy in 6 of 6 infants with myogenic hypotonia and both showed neuropathic abnormalities in 16 of 16 infants with neurogenic hypotonia. In 17 infants with central hypotonia, both ultrasound and needle EMG were normal. Needle EMG and ultrasound results conflicted in only two infants.

In these two two infants, the muscle and nerve biopsy ultimately did not reveal a diagnosis.

In older children, qualitative ultrasound is also sensitive and specific for detecting neuromuscular disease. In a study of 134 patients with suspected neuromuscular disorders, qualitative ultrasound showed sensitivities of 81% and specificities of 96% in the assessment of any neuromuscular disorder.6 Ultrasound was less sensitive (71%) in identifying abnormalities in children with neuromuscular disorders under age 3.

In a study of 100 children with suspected neuromuscular disease, ultrasound was 78% sensitive and 91% specific for identifying any neuromuscular disease, was more reliable in children over age 3 years, and was least reliable in those under 1 year of age.35 Sensitivity and specificity varied with the degree of ultrasound abnormality. A mildly abnormal ultrasound is neither sensitive nor specific for a neuromuscular disorder. Only 7 of 13 children with a mildly abnormal ultrasound scan had a neuromuscular disorder. In contrast, all of the children with moderate or severely abnormal ultrasounds (Heckmatt Grade III or IV) had a neuromuscular disorder. Similarly, nearly all (62 of 69) children with a normal ultrasound (Heckmatt Grade I) did not have a neuromuscular disorder. Quantitative ultrasound results in similar sensitivities for detecting neuromuscular disorders. A prospective study of quantitative grey-scale ultrasound analysis of 150 children referred for evaluation for neuromuscular disorders was 71% sensitive and 91% specific for identifying neuromuscular disorder.26 Again, the sensitivity of ultrasound in children younger than 3 years old was lower than in older children; however, specificity was 100%, with no false positives in the younger age group.

Ultrasound has higher specificity than sensitivity in differentiating myopathic and neuropathic changes.6,26,18 Thus, abnormalities that distinguish the two pathologies such as muscle size and patterns of homogeneity are helpful when present but are less useful as a screening tool. Ultrasound was more specific than sensitive for detecting myogenic (92% versus 67%) and neurogenic (98% versus 77%) changes in 134 children studied by Brockmann and colleagues. The pattern of muscle involvement can also be helpful in identifying neuropathies, which affect the distal more than proximal muscles of the legs. In a quantitative ultrasound study of 31 children with myopathic and 27 with neuropathic disorders, brighter echoes and more atrophy in the legs than arms was 67% sensitive and 94% specific for identifying neurogenic disease.26 This type of analysis did not distinguish myopathic disease from nonneuromuscular conditions.26 In adults, a study comparing 145 healthy control subjects, 17 myopathic patients, and 15 neuropathic patients, brighter signal in the biceps brachii (increased greyscale values) was 94% sensitive and 93% specific for myopathy while increased signal in homogeneity was 100% sensitive and 93% specific for neuropathy.18 However, in children, this same quantitative approach did not distinguish between myopathic and neuropathic disease.19

The relationship between strength, function, and the degree of image abnormality may vary with differences in the underlying pathologies. In patients with muscular dystrophies, subclinical abnormalities and changes with disease progression have been
detected on magnetic resonance imaging (MRI) and ultrasound, suggesting that imaging can be used to evaluate disease severity and progression.9,15,17,24,32,33 In contrast, the severity of imaging findings in children with mitochondrial myopathies25 or congenital muscular dystrophies11 may not correlate with disease severity of function. Additional studies of the neuromuscular pathologies are needed to compare patient strength, function, and prognosis with the degree of image abnormality.

ULTRASOUND ABNORMALITIES IN INHERITED MYOPATHIES

Hereditary myopathic disorders are a diverse group of pathologies that include the muscular dystrophies and the metabolic, mitochondrial, and congenital myopathies. They generally present with progressive, symmetric weakness more than atrophy of the proximal arms and legs and are classified by the pattern of inheritance, clinical findings, histopathology, and genetic abnormality. Muscle dystrophies are the most common type of myopathy and are characterized by findings on muscle biopsy of early and extensive muscle fiber degeneration and regeneration. Later in the disease, prominent increased connective tissue and fatty replacement of muscle fibers are seen. The muscular dystrophies include DMD and Becker muscular dystrophy (BMD), as well as fascioscapulohumeral, Emery-Dreifuss, limb girdle, and congenital muscular dystrophies.

ULTRASOUND OF MUSCULAR DYSTROPHIES

Abnormal ultrasonography in neuromuscular disease was first described in males with DMD,14 an X-linked muscular dystrophy caused by mutations of the dystrophin gene. Much of the ongoing work in ultrasonography of myopathies continues to be performed in patients with DMD and BMD, a less severe form of the disease. Ultrasound in DMD/BMD, as well as other muscular dystrophies characterized by increased connective tissue and fatty replacement of muscle, shows a diffuse and often marked increase in muscle echogenicity. The muscle shows a grainy, ground-glass like appearance, typically with preserved muscle bulk. In more advanced pathology, the muscle echoes are very bright and the attenuation greatly increased, resulting in a relatively darker appearance in the deep rather than superficial portion of the muscle and reduced or absent bone echoes.

The sensitivity of ultrasound to pathology associated with dystrophinopathies increases with age and disease severity. In DMD, ultrasound is often abnormal in children by the time they are toddlers. In one study, qualitative ultrasound was abnormal in nearly all (21 of 22) boys with DMD aged 3-7 years but in none of the seven boys aged 2-30 months.14 In a study of quantitative ultrasound, abnormalities were detected in 32 of 38 boys aged 1 to 11 years;9 all six normal ultrasounds were in children under age 6 years. In another quantitative ultrasound study, greyscale levels were abnormally high in 10 of 11 boys with DMD ages 3-9 years but in only one of two boys aged 3 weeks and 7 months.26

In DMD and BMD, ultrasound measurement of muscle pathology varies with the severity of muscle pathology. Both ultrasound and strength abnormalities are more severe in the quadriceps than the biceps brachii.7,14 Ultrasound backscatter is higher and increases twice as much with age in patients with DMD than those less severely affected with BMD.34 Ultrasound signal abnormalities also increase with worsening strength and function in DMD.9,34 Additional studies in the dystrophinopathies are needed to determine the sensitivity of ultrasound to detect effects of treatment.

Calf enlargement is a common clinical finding in patients with dystrophinopathies and other neuromuscular disorders. Calf enlargement can be either associated with normal or increased echogenicity and is a common and nonspecific finding in neuromuscular disorders.28 Interestingly, when there is severe fatty infiltration in the calf muscle, the ultrasound actually appears dark, similar to subcutaneous fat. As muscle pathology from increased fat typically results in brighter ultrasound echoes, the ultrasound appearance of severe pathology in the calf may be misleading.

ULTRASOUND OF MITOCHONDRIAL MYOPATHIES

Mitochondrial myopathies are a heterogeneous group of neuromuscular disorders that can affect multiple organ systems. Symptoms are related to dysfunction of energy metabolism and include weakness and exercise intolerance. Skeletal muscle ultrasound in mitochondrial myopathies can be abnormal but is less sensitive than in other myopathies. In 14 children with mitochondrial myopathies, ultrasound assessment was concordant with histologic findings in only eight patients, including one myogenic, two neurogenic, four nonspecific, and one normal pattern on both ultrasound and histology.6 In a prospective study of quantitative ultrasound in 53 children with suspected mitochondrial disorders prospectively, only seven of 28 children with definite or probable mitochondrial disorders had abnormal ultrasound echogenicity.25 An additional six children had only borderline ultrasound abnormalities. Echo intensity in the 28 subjects with mitochondrial disorders did not correlate with strength or the percentage of intramuscular fat or connective tissue, but did increase with age. Six of the eight children with abnormal ultrasounds were over 5 years old. Ultrasound is thus not sufficiently sensitive to use as a screening test for mitochondrial disorders but does detect pathology that is independent, and complimentary, to functional and histologic results.

OTHER CONGENITAL AND HEREDITARY MYOPATHIES

The congenital and hereditary myopathies are comprised of a large group of heterogeneous disorders and phenotypes. Radiologic studies of specific congenital or hereditary myopathies are often limited to small case series. Although relatively few radiologic studies of specific congenital or hereditary myopathies have been reported, ultrasound and MRI can detect the presence and pattern of skeletal muscle pathology in patients with these disorders (Reviewed by Pillen and colleagues27 and Mercuri and colleagues32). Certain patterns of muscle involvement can direct focused genetic testing or guide selection of a muscle for biopsy. However, as with many
neuromuscular disorders, the patterns and degree of muscle involvement on ultrasound varies within a genotype and with disease severity. The heterogeneity in phenotype and the small numbers of reported cases makes it difficult to determine the specificity of a pattern of muscle involvement on ultrasound or MRI.

Nonetheless, a few case reports in hereditary myopathy report unique, specific radiologic patterns. Imaging of Bethlem and the more severe Ullrich congenital muscular dystrophies, both collagen type VI disorders characterized by proximal weakness and contractures, shows a unique “outside-in” pattern of muscle involvement.5,20,23 These studies show relative sparing of the central portion of the muscle belly with involvement of the outer rim of muscle in a concentric pattern. This pattern is best described in the rectus femoris of patients with Bethlem myopathy and is termed the “central shadow” sign. This shadow seen on ultrasound refers not to darkening but rather increased echogenicity and thickening along the central fascia—a normally thin, bright, band that vertically divides the rectus femoris from the superficial fascia to the middle of the muscle belly. Similar but more severe findings to are seen in Ullrich myopathy. In a study of nine patients with Ullrich myopathy,23 the involved concentric rim with central sparing was best seen in the vastus lateralis and was present but less distinct in the rectus femoris. Increased signal is also seen in the connective tissues between the soleus and gastrocnemius in both Bethlem and Ullrich myopathies. This finding was more distinct in Bethlem myopathy. In contrast, Emery-Dreifuss muscular dystrophy, which shares some clinical features with collagen VI disorders, shows more diffuse thigh and selective medial gastrocnemius involvement21 and does not show the outside-in pattern or central shadow sign.

Another unique pattern of pathology on ultrasound has been reported in six patients with hereditary inclusion body myositis with homozygous UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase (GNE) mutations.5 These patients showed selective involvement of the rectus femoris with relatively spared vastus medialis, lateralis, and intermedius muscles. Additionally, these patients showed areas of increased echogenicity within the central portion of the hamstring muscles, producing a “target” like brightness inside a rim of relatively spared, hypoechoic muscle. This study also showed more severe atrophy of the anterior foreleg compared to the calf and more severe involvement of the hamstring muscles compared to the anterior thigh. These studies of hereditary inclusion body myositis and collagen VI disorders demonstrate how imaging of neuromuscular disorders can assist in diagnosis. Additional radiologic imaging studies are needed to describe more myopathies with specific patterns of muscle involvement.

REFERENCES

22. Mercier E, Jungbluth H, Muntoni F. Muscle imaging in clinical practice: diagnostic value of muscle magnetic resonance imaging in...


Ultrasound as a Biomarker in Neuromuscular Disease

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INTRODUCTION: WHAT ARE BIOMARKERS AND WHY THEY ARE USEFUL

A biomarker is an index of disease diagnosis and status. As defined by the United Kingdom Medical Research Council, a biomarker as "an objective measurement that acts as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to therapeutic intervention." Although initially generally defined as a molecule (usually a protein) that could serve this purpose, over the past decade the term generally has been expanded to include virtually any measure. In the field of neuromuscular disease, this includes clinical measures (such as muscle strength testing), electrophysiologic measures (such as motor unit number estimation [MUNE]), or radiologic studies (such as detecting alterations in muscle size on magnetic resonance imaging [MRI]).

The main purpose of a biomarker is to evaluate disease status and to assist in determining the effects of treatment. In the broadest sense, we all use biomarkers in the care of individual patients daily in our practice without giving it much thought. For example, in a patient with myositis, we may choose to follow the serum creatine kinase (CK) level and muscle strength to determine whether or not the corticosteroids can be tapered or whether a second-line therapy needs to be added. Or we may use a measure such as the acetylcholine receptor antibody test to assist in initial disease diagnosis.

Recently, however, there has been increased interest in using biomarkers in clinical trials since they offer the possibility of providing an early readout as to whether a new therapy is going to be successful. While such biomarkers may not be able to provide definitive evidence of efficacy in a disease, they can offer information on a surrogate disease marker. For example, in the case of treating amyotrophic lateral sclerosis (ALS), the ultimate goal is to prolong survival. However, performing a clinical trial using survival as an outcome measure is unwieldy at best, as each patient needs to be treated for a lengthy period of time until they die or are ventilated. This was the standard approach taken back in the mid-1990s when riluzole received Food and Drug Administration (FDA) approval. A simpler approach is to use a surrogate biomarker of decline, such as muscle strength testing or the ALS Functional Rating Scale-Revised (ALSFRS-R). These measures may show substantial declines over periods much shorter than 1 year and are thus considerably more convenient and cost effective. These biomarkers can be considered surrogate markers since the presumption is that the more rapidly the disease progresses the more rapid the marker changes. A good surrogate biomarker should correlate strongly with whatever ultimate outcome is chosen. In the case of ALS, it is survival. Biomarkers are generally relied upon most in Phase II clinical trials, those that are meant to establish potential efficacy, and not Phase III clinical trials in which FDA-approval is sought. However with time and familiarity, if the validity of a biomarker has been shown repeatedly to be closely associated with the ultimate clinically relevant outcome measure, it may start to substitute for it and could eventually be used to obtain FDA approval. The ALSFRS-R in ALS is now reaching this level of trust and is being used in several ongoing clinical trials in the disease.

Considered simply, in neuromuscular disease, the major biomarkers used aim to assess motor or sensory nerve health. For sensory assessments, sensory nerve conduction studies, autonomic testing, intraepidermal skin biopsy, and quantitative sensory testing are all used. For motor assessment, muscle strength, timed functional tests (such as the 6-minute walk test), CK levels, and electromyographic parameters (like the MUNE) have been used.

In both groups of testing, there are considerable limitations to these markers. For example, initially the Medical Research Council scale was used to quantify strength. But it became clear over many years
that this measure was not that accurate, and bulky quantitative motor testing systems in which force transducers attached to a fixed frame were used to more accurately assess isometric strength. This approach was found to be cumbersome and costly and thus over the past 5-10 years, handheld dynamometry has become the standard approach for assessing muscle strength. Still, handheld dynamometry has substantial limitations, including, most importantly, being very insensitive to varying degrees of mild and severe weakness (so called floor and ceiling effects), as well as requiring considerable evaluator training, being tiring on patients, and requiring multiple muscles to be examined. Moreover, handheld dynamometry cannot be performed accurately in children less than 4-5 years of age, thus substantially limiting its value in studies of pediatric neuromuscular disease.

Accordingly, there is a need for improved indices of motor dysfunction in neuromuscular disease. MUNE\textsuperscript{13} is potentially valuable in the assessment of motor neuron disorders, but cannot be used easily in the assessment of primary muscular conditions, including muscular dystrophy. Another electrophysiological approach, electrical impedance myography, offers the prospect of being valuable in this regard as it could be applied widely to both primary neurogenic and myopathic conditions and is currently being studied in several illness including spinal muscular atrophy (SMA), ALS, and myopathy.\textsuperscript{11} Evaluating changes in muscle signal and muscle size on MRI can also serve in this role; although potentially a very useful tool, it is also costly and inconvenient.\textsuperscript{7}

One radiological test that only recently has become of interest that could provide novel biomarkers of neuromuscular disease status is that of diagnostic ultrasound (US). The remainder of this section of the syllabus explores the advantages and limitations of employing US for this purpose.

ULTRASOUND AS A BIOMARKER: THE PROMISES

Quantifying US data for use as a biomarker to assess neuromuscular disease severity is appealing in several respects. First, US can be applied rapidly, with data being gathered in seconds. In addition, a variety of muscles can be tested; in fact, there really is no limit to the potential muscles which could be studied, thus allowing truncal, proximal, distal, or even focal disorders to be followed effectively. Third, and perhaps most importantly, US is painless, requiring minimal patient cooperation. Even infants can undergo US imaging without requiring sedation, a feat not possible with many other techniques. Thus, regardless of age, data can be gathered quickly from multiple muscles and analyzed to provide a “whole body” index of disease status.

THE CHALLENGE: HOW TO QUANTIFY THE ULTRASOUND DATA

US has been developed primarily as an imaging technique. Its aim is to provide a noninvasive means of providing detailed structural assessments of human organs and tissues, including the heart, kidneys, and liver. Thus, for the most part, the major effort in the US industry has been focused on improving image quality. The more expensive systems commonly used in hospital radiology departments are excellent at obtaining detailed imaging data; however, there has been little to no effort at actually refining the technique as an index of disease status. In order to use US as a biomarker, it is necessary to quantify some aspect of the acquired data. One obvious choice, discussed later, is that of muscle size. Another and potentially more compelling option is to quantify muscle echo intensity.

As previously discussed, both neurogenic injury and progressive primary muscle disease result in increased echo intensity of the tissue, likely due to increased connective tissue within the muscle.\textsuperscript{8} Thus, diseased muscle will appear more echogenic than healthy muscle. These changes are sufficiently dramatic that they are usually apparent to even the less-experienced observer; indeed, 2 decades ago a simple ordinal scale of disease severity was proposed based on one’s visual impression of the US image.\textsuperscript{9} But the goal of US quantification is to capture and quantify the degree of change with much greater precision.\textsuperscript{10} There are two potential methods for achieving this: grayscale image analysis and direct analysis of the acoustic signals.

Approach One: Grayscale Image Analysis of Muscle

One simple approach is to take the static US image and determine the echo intensity, or luminosity, of the muscle.\textsuperscript{5,9} As noted, healthy muscle will have a lower luminosity and less echo intensity than neuropathic or myopathic muscle. The goal in grayscale analysis simply is to use digital image processing methods to quantify that degree of whiteness. This basic approach has been spearheaded by the Drs. Sigrid Pillen, Ilse Arts, and Machiel Zwarts and colleagues at Radboud University, Nijmegen Medical Centre, the Netherlands.

In order to do this, a 2D US image of the muscle is obtained, saved typically as a JPEG file, and then imported into an image-processing program. Adobe Photoshop has been used pretty much exclusively but a dedicated program could also be developed to do this. After the image is imported, an area of interest in the muscle is selected with the selection tool (see Fig. 1). As much as is possible, one should attempt to select the largest region of the muscle obtainable. One then uses the “image analysis” tab in the menu to select luminosity analysis. A histogram of the relative luminosity of the selected area of muscle will then be displayed. In this histogram, the x-axis bins are grayscale values, with lower values corresponding to lighter pixels and higher values corresponding to darker ones. There are 16 bins corresponding to the 16-bit grayscale used here. The y-axis simply provides a count of the number of pixels in each category. In addition to the histogram of values, a median and mean value for the histogram are provided.

Zwarts and colleagues primarily have taken this approach and have evaluated data from a variety of normal subjects of varying age to determine the relative ranges of normality as well as those of groups of adults and children with varying diseases.\textsuperscript{7,12} Their data suggest that using such values is sufficient for distinguishing diseased from healthy muscle and also, potentially, for following disease status over time.
One difficulty of simply evaluating the raw muscle luminosity values and using that as a biomarker itself is that the values are dependent on a variety of factors, including the US system used, whether the transducer is placed truly perpendicular to the muscle or at a slight angle, and the brightness and contrast settings of the US system itself (these issues are discussed further below). Thus, a simple approach we have adopted is to use the subcutaneous fat as an internal reference because it is unlikely to change echo intensity in neuromuscular disease. In this modification of the basic approach, in addition to collecting muscle luminosity data, we also collect subcutaneous fat luminosity data. As with the muscle, we attempt to select as large a region as possible. We try to be as consistent as possible in evaluating all subjects and include everything below the skin up until the superficial layer of fascia overlying the muscle. This is usually easy to determine, simply by having the subject contract the muscle slightly. These two values can then be combined into a single index by either taking their ratio or difference. Regardless of the approach used, this “luminosity ratio” or “luminosity difference” may serve as an US-based biomarker and appears to be quite sensitive to disease change in at least one disease: SMA. Figure 2 shows an example of those luminosity ratios in two children with SMA and a normal subject. Although promising, the technique still requires further study and validation.

**Approach Two: Raw Backscatter Analysis**

In this approach, rather than relying upon the postprocess images, we attempt to analyze the raw acoustic data to determine, literally, how echo intense the muscle is. Recall that in US we evaluate the alterations of the transmitted sound waves. The more reflective the tissue is of the sound, the greater the echo intensity, and ultimately the more echogenically “whiter” a given image will appear. Tissues or interfaces that are minimally reflective generally appear brighter than those that allow the sound waves to pass through and appear darker. Thus, rather than evaluating the postprocessed image, here we simply quantify the characteristics of the reflected sound itself. Zwarts and colleagues have divided this up somewhat into two

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**Figure 1** Screen capture image from Adobe Photoshop showing an ultrasound image of the biceps brachii muscle of a normal subject. The histogram to the left shows the corresponding grayscale luminosity values (mean 31, median 23).

**Figure 2** Transverse ultrasound images of the biceps brachii from a normal subject (A), an SMA type 3 patient (B), and an SMA type 2 patient (C). Note the increasing echo density of the muscle from normal to severe (type 2 SMA being more severe than type 3). The luminosity ratios for these images were 0.92, 1.81 and 4.04, respectively.

SC = subcutaneous, SMA = spinal muscle atrophy
categories: “radiofrequency analysis” and “backscatter” analysis, the latter utilizing a phantom to help normalize the amount of reflected echoes. However, these approaches are merely different approaches of analyzing the raw data.

Unfortunately, no US systems are specifically designed for this kind of data analysis. Because US was designed as an imaging technique, the raw data is immediately transformed into images without the user being privy to it. To obtain this raw acoustic data usually requires the assistance of the US manufacturer. The units of this raw data are not in lumens, as is the case in the luminosity, but rather in decibels, the standard unit for measuring sound waves. Put simply, the louder the muscle, the sicker it is.

Figure 3 shows an acoustic histogram generated from the tibialis anterior of a normal subject and a subject with Duchenne muscular dystrophy.

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Figure 3 Acoustic histogram of ultrasound data from the tibialis anterior muscle of a 14-year-old male DMD patient and a 13-year-old male normal subject.
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DMD = Duchenne muscular dystrophy

One immediate problem confounding this analysis is that we still need to determine which part of the acoustic data is coming from the muscle rather than other components, which requires some incorporation of the image analysis itself. Although not intuitively satisfying, using all the acoustic data from an image (including those components generated by skin, fat, and bone) potentially could work as a biomarker since the expectation is that neither the skin-subcutaneous fat or other structures are going to change substantially due to the disease process itself. Thus, differences over time in the acoustic signature of the image presumably would be due to muscle deterioration only. Another option would be to attempt to visually identify the area of the image relevant to the muscle and use the backscattered data from that region only; this was attempted by Zaidman, and colleagues.

LIMITATIONS AND CHOICES IN QUANTIFYING THE ULTRASOUND SIGNAL

In the two approaches for collecting data, there are a variety of potential problems and limitations:

1. Much of the image acquisition software is proprietary in nature. For most, an US system is very much a black box. We turn on the device, apply conductive jelly on the transducer head, and place it on the patient. The image seen on the screen is all we get and it is very difficult to attempt to extract or analyze the raw acoustic data. Only with the direct help of the engineering team at a device manufacturer is it possible to attempt such an analysis. We have had the good fortune of working with interested engineers at Teratech, Inc., Burlington, Massachusetts, in some of our most recent work in this area and thus have been able to begin to assess the raw acoustic signals.

2. It is difficult to compare image data directly between two devices. This issue is an extension of the fact that the systems are proprietary and there is little effort to standardize either the hardware or the software. In addition, even with a single system, all data collection needs to be performed with an identical approach, using the same US modes (e.g., “muscle-skeletal mode”), the same depth of focus, gain, and image size. Similarly, the contrast and brightness of the image must be kept the same. To solve this problem, Zwarts and colleagues have suggested using a phantom and a conversion equation.

3. There are uncertainties as to whether the muscle data collected should be transverse (cross-sectional) or longitudinal. For the most part, authors have used the transverse plane rather than the longitudinal since slight alterations in the angle of the probe can greatly alter the appearance of tissues if longitudinal measurements are made. However, we recently compared both approaches and saw very little difference between the two when using the luminosity ratio (unpublished results). Still, this remains an area that requires further study and standardization.

4. Choosing the region of muscle to quantify is not always easy. While identifying the interface between the subcutaneous fat and muscle is generally obvious, identifying where the muscle ends and bone begins may not be straightforward. In normal subjects, with muscle of relatively low echo intensity, a clear reflection from the bone can be observed and the examiner simply chooses tissues superficial to that point. However, in patients with more advanced disease, the increased echo intensity of the muscle may completely obscure that interface. It can be very challenging to decide how deep to extend your field. Asking the patient to contract the muscle, assuming the individual has sufficient function to do so, can help, but may not solve the problem.

In addition, it can be difficult to know which other structures to include or exclude. For example, if there is a large fascial plane, it may be difficult to completely separate it from the muscle itself. Similarly, blood vessels or tendon can also contribute inconsistencies.
5. The analysis needs to be blinded. As with any form of data analysis in which there is a subjective component, blinding is especially important here. The person reviewing the data and selecting the muscle should have no prior knowledge of the clinical status of the individual whose data they are evaluating.

6. The pressure and placement of the transducer can affect the results. The amount of pressure applied to the transducer can alter the image to some extent. This is most obvious if the transducer is placed too gently on the muscle. The edges of the transducer may not make good contact and the resulting image may appear excessively dark. Excessive pressure can also alter the image. Also, the angle of the transducer, if not placed perfectly perpendicular to the muscle can also alter the image quality and grayscale analysis.

MUSCLE SIZE AS A BIOMARKER

The focus of this discussion is on quantifying the muscle US signal; however, another choice of biomarker is that of muscle cross-sectional size. There is no question that in most neuromuscular diseases, muscle size decreases with disease progression. Indeed, studies in ALS suggest that this approach may work, although issues regarding more advanced disease obscuring the deep border of the muscle could make definitive measurement uncertain. Similarly, it may be possible to evaluate changes in muscle contractility in a quantitative fashion as well (e.g., quantify the percent change in muscle size with a sustained, constant-force contraction). However, to our knowledge, this line of investigation has not been pursued.

CONCLUSIONS

The use of US as biomarker in neuromuscular disease is a new and relatively unexplored area. Even though a considerable number of studies have been performed, all have been cross-sectional in nature, merely confirming that more severe disease correlates with a more abnormal US image. The only way to truly evaluate whether US can serve as a valuable biomarker and ultimately a surrogate marker of disease status in neuromuscular disease is to obtain longitudinal US data in individual diseases, evaluating US’s ability to detect subtle change and assessing its relationship to standard markers of disease progression. Finally, US manufacturers could assist researchers in this effort by developing software that can help perform automated analyses of muscle echo intensity.

REFERENCES

INTRODUCTION

High frequency ultrasound is an emergent imaging musculoskeletal modality. It facilitates the performance of diagnostic evaluations as well as interventional procedures as reported in the literature from multiple specialties. This is a growing field that allows physicians to deliver patient care with demonstrated benefits, including safety, availability and cost, among others.¹,²

High frequency ultrasound’s ability to depict neuromuscular structures and provide guidance for interventional procedures with high resolution and accuracy enables physicians to perform procedures that previously were performed blindly or in some cases utilizing imaging modalities such as computed tomography (CT) with its inherent limitations. The recent advances in high frequency ultrasound technology allow physicians to diagnose and treat patients with a greater degree of confidence.³

The literature shows that specialties such as radiology, rheumatology, physical medicine, neurology, anesthesiology, sports medicine, podiatry, and others utilize high frequency ultrasound as a diagnostic and interventional tool.⁴a,⁴b The number of articles, websites, and other public internet based media about this technology continues to grow.

One of the most common procedures performed is peri- and intra-articular aspiration and injection. Table 1 shows the success rate when ultrasound is used to guide the aspiration of different joints. This shows a 68% failure rate with blinded aspirations.

In patients with painful shoulder in a short-term (6 weeks) evaluation, significant functional and pain (using the visual analog scale [VAS]) improvement was shown when shoulder ultrasound-guided steroid injection was performed.⁵ Only 37% of glenohumeral and subacromial injections are considered to be accurately placed utilizing standard nonguided techniques.⁶

Small structures such as peripheral nerves in most cases are more difficult to identify by palpation or localization of mus-

<table>
<thead>
<tr>
<th>Aspiration site</th>
<th>Conventional</th>
<th>US guided</th>
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<tbody>
<tr>
<td>Shoulder</td>
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<tr>
<td>Wrist</td>
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<td>Hip</td>
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CMC = carpometacarpal, MTP = metatarsophalangeal, PIP = proximal interphalangeal, US = ultrasound

From Balint and colleagues.¹⁹
closkeletal landmarks such as bone, tendon, or muscle. The use of high frequency ultrasound is becoming a more frequently used tool for evaluation, temporary anesthetic regional blocks, and in some cases the injection of steroids as in the treatment of painful neuromas.9

Current literature includes studies that have evaluated the accuracy and compared the effectiveness when interventional perineural-guided ultrasound is used, as in the case of the lateral femoral cutaneous nerve.10 These studies support ultrasound guidance as an effective modality, although the literature is more difficult to evaluate given the multiple variables including anatomical areas, dose and type of anesthetic, electrical stimulation versus palpation, lasting effect, and motor versus sensory response, among others.

One particular study concluded that ultrasound improves efficacy of peripheral nerve block compared with techniques that utilize a peripheral nerve stimulator (PNS) for nerve localization. Larger studies are needed to determine whether or not the use of ultrasound can decrease the number of complications such as nerve injury or systemic local anesthetic toxicity.11 The trend seems to indicate that high frequency ultrasound has the potential to become the standard of care for peripheral nerve block procedures.

Ultrasound guided muscle biopsy has been reported in the literature as a useful procedure, facilitating diagnosis in acute muscular disease. It provides results comparable with those of open surgical biopsy in acute muscular disease and it also may be of help in chronic disease.12 This particular study makes a cost comparison of open biopsy, being approximately three times more expensive than percutaneous ultrasound guided. It also considered the time of the procedure being reduced from 2-3 hours in the case of an open biopsy to 15-20 minutes when ultrasound guided was performed. The use of ultrasound guidance for botulin injections has also found to be of significant value in clinical practice.13 Dry needling of trigger points in the cervicothoracic musculature may reduce the potential of complications such as a pneumothorax.14

SOME INDICATIONS IN NEUROMUSCULAR MEDICINE

Peripheral Nerve

• Regional temporary blocks

• Steroid injections

• Biopsy

Muscle

• Biopsy

• Aspiration

• Dry needling

• Botulim injections

GENERAL PRINCIPLES

These are some of most important factors to consider when guided ultrasound guided procedures are performed.

Knowledge of the basic ultrasound physics, equipment, settings, and techniques are required to obtain the best possible image of the target structure and needle.

Documentation by static images and video clips is essential for patient followup (medicolegal as well as billing). Digital formats such as JPEG or DICOM are options that can facilitate archiving these images. Printed static images can also be used but their size and lifetime may present some limitations.

It is imperative to have a detailed knowledge of anatomy and sonoanatomy of the area to be treated. Of no less importance is to perform a complete diagnostic study so that a clear indication for the procedure to be performed is established. Other occult pathologies need to be considered and ruled out so that the diagnosis is as accurate as possible, decreasing the potential of unexpected findings. Awareness of normal anatomical variants is also important.

Neurovascular structures and tendons should be identified to prevent iatrogenic lesions. The use of Doppler can be helpful not only for the identification of vascular structures but also in some cases to visualize the needle.

It necessary to evaluate the potential contraindications such as anticoagulation, bleeding disorder, skin infection, etc. Informed consent should be obtained and the benefits and potential risks discussed.15 Practitioners should recognize their skills and limitations in performing these procedures as well as those that the equipment could present. For instance, it would not be advisable to perform procedures on targets such as small peripheral nerves with less than equipment of 12 MHz or use a large footprint probe for an anatomical area in which its positioning would limit the field of view.

It is recommended to plan the procedure including the all the steps already mentioned. In addition to the previously listed recommendations, the material to be utilized—the needle length and gauge, anesthetic and steroid to be used, etc.—should be determined in advance. If a biopsy is planned, it is important to become familiar with the type of needle to be used and how the TRU-CUT is operated. Whether this material comes in a tray or as individual items, they should be ready and within easy reach, particularly if these procedures are performed without the help of an assistant.

Following principles of aseptic technique including the use of a sterile envelope or sleeve is advised by most of the experts in this field. This includes the use of sterile gel at the area of needle insertion. Compliance with the standards of practice of the institution or office policy manual where the procedure is being performed is recommended. See Figure 1.
The patient should be preferably in a supine and comfortable position in case a vasovagal reaction occurs. It is also important for the physician performing the procedure to adopt an ergonomic position which includes optimal location of the ultrasound machine and direct view of the monitor.

With all the above in mind and after the diagnosis is confirmed, the path approach to the already-identified target becomes of great importance. The frequency of the transducer and its footprint size needs to be selected as well as the frequency that would better fit the anatomical area where the procedure is to be performed, so that adjustments to the transducer position will provide optimal visualization of the needle at all times during the intervention within an optimal field of view.

**TECHNIQUE**

The visualization of the needle and target structure is the basic goal of ultrasound-guided procedures so that the needle can be advanced following the shortest possible and safest path to the target. The intervention can be achieved by indirect and direct techniques.

**Indirect**

Indirect ultrasound is utilized to identify the target structure and approach considering the surrounding structures and depth. The procedure in itself is not real-time guided but based on measure-
ments and markings on the skin of the optimal site for needle insertion. See Figure 2. For confirmatory and documentation purposes an image can be obtained after the needle is in the expected position. See Figure 3.

**Direct**

This technique uses real-time ultrasound that allows the physician to visualize the needle as it moves towards the target. The ability to depict the needle will depend on the angle of the needle in relation to the ultrasound beam. The long axis or longitudinal approach is in general recommended over the short axis or transverse approach. Ideally, the needle should be parallel to the transducer so the ultrasound view will be depicted as a straight hyperechoic line with the characteristic artifact called a comet tail. The bevel can be identified and should be maintained in the field of view at all times during the advancement of the needle. See Figure 4, top.

The short axis or transverse approach will place the needle perpendicular to the transducer and it will appear as a hyperechoic dot. This is not a recommended approach, although it may be the only option in some areas, such as superficial joints. When using this approach moving the tip in and out may be needed to find the angle that will allow reaching the target. As in the long axis approach the bevel should be in the field of view at all times. See Figure 4, bottom.

There are available needle guides that adapt to the transducer to facilitate the procedure but there appears to be no literature available to evaluate the benefit of their use with the exception of breast biopsy.

The described “free-hand” technique basically is the procedure in which the transducer is held with the nondominant hand to allow the handling of the needle with the dominant hand, maintaining a sterile technique.

The target must be identified and then the skin marked at both ends of the transducer so that after the skin is disinfected one can easily find the target. See Figure 5. The insertion point of the needle will depend on the depth of the target. Deeper targets will require an entry site located farther away from the transducer to prevent a steeper angle in relation to the ultrasound beam that would cause limitations visualizing the needle.

After using local anesthesia penetrate the skin approximately 1 cm and localize the needle, advance under real time guidance. Injecting an anesthetic or normal saline can help by performing

**Figure 4** The needle position in direct ultrasound. **Top:** Long axis (or longitudinal approach): the needle should be parallel to the transducer so the ultrasound view will be depicted as a straight hyperechoic line with the characteristic artifact called a comet tail. **Bottom:** Short axis (or transverse approach): the needle should be perpendicular to the transducer and it will appear as a hyperechoic dot.

**Figure 5** In the “free-hand” technique the target must be identified and then the skin marked at both ends of the transducer so that after the skin is disinfected one can easily find the target.
hydrodissection as the needle is advanced always under real time visualization. If the tip of the needle cannot be seen, DO NOT advance the needle. Sometimes it will be necessary to withdraw and redirect the needle or adjust the position of the transducer.

The so-called “heel-toe” maneuver can be used to position the transducer parallel to the needle. Also, the oblique stand-off technique can be used by applying a thicker layer of gel under the transducer at the needle entrance, filling the gap between the skin and the end of the transducer. New software is also available that allows depiction a needle at 45 degree angle in relation to the ultrasound beam. See Figure 6.

Adjustment in the positioning of the transducer or needle may be needed for the visualization of the needle. It MUST be remembered that the tip of the needle should be visualized at all times and that one should move or adjust the positioning of either the transducer or needle but NEVER move both at the same time.

Using beam steering or Doppler also can help localize the needle without moving it. The larger needles are more reflective and better visualized.16 Jiggle, rotating the bevel, and a stylet can improve the visualization of the needle. There are echogenic needles available but for the most part a regular needle should be visualized following proper technique.

Figure 6 New software allows depiction a needle at 45 degree angle in relation to the ultrasound beam. Top: Needle parallel. Bottom: Needle at 45 degrees.

Figure 7 Top and middle: an injection of the median nerve at the carpal tunnel under ultrasound guidance. Bottom: 15 days post-injection with 30 mg of triamcinolone.

Figure 7, top and middle, shows an injection of the median nerve at the carpal tunnel. The bottom of Figure 7 shows 15 days post-injection with 30 mg of triamcinolone. Most of these injections are performed blindly. The advantage of performing this procedure under ultrasound guidance is in case of normal variants, such a bifid median nerve or after carpal tunnel release, because the location of the nerve cannot be anticipated. The ulnar side approach and its advantage has been described.17
COMPLICATIONS

The most frequent complications to consider are bleeding, hematomas, and infection. Observing general precautions should minimize the potential risks.

BILLING AND CODING

Documentation is a must when performing these procedures. A report should be generated that includes the diagnosis and the indication for ultrasound guidance. Description of the procedure itself should be included. Permanent pictures and video, if possible, also is necessary. The procedure code to be utilized is 76942-ultrasound guidance.

SUMMARY

Ultrasound allows physicians to perform guided neuromuscular interventions in a safe and efficient way. A diagnostic evaluation MUST be performed prior to a guided procedure. Planning the approach and anticipating the material to be utilized will increase the success of the procedure. Experience in neuromuscular ultrasound is essential and cannot be emphasized enough prior to adopting this new tool for interventional purposes.

If the target structure and the instrument is available for a particular percutaneous procedure can be depicted by ultrasound in real time, does not increase significantly or even reduces the cost of the procedure,\textsuperscript{18} has demonstrated different benefits, and is likely to improve overall patient care, why not use it? Perhaps the time for physicians to develop or improve their skills utilizing this new imaging tool has arrived. Albeit, further studies are needed to evaluate long-term outcomes.

REFERENCES