

# NIH HEAL Initiative Workshop on MYOFASCIAL PAIN

Quantitative Evaluation of Myofascial Tissues: Potential Impact for Musculoskeletal Pain Research

# September 16-17, 2020

Co-organizers NCCIH NIBIB NIH Partners NIAMS NICHD/NCMRR NIDCR NINDS

# Workshop Summary

#nihHEALinitiative



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# Welcome Remarks: NIH HEAL Initiative

#### Rebecca Baker, NIH HEAL Director

The National Institutes of Health (NIH) Helping to End Addiction Long-term<sup>SM</sup> (HEAL) Initiative is working to address two related crises affecting the United States: addiction/overdose and chronic pain. In 2018, more than 67,300 Americans died from drug-related overdose, including many affected by opioid addiction. The COVID-19 pandemic appears to be reversing the progress made in this area. Among American adults, 50 million are affected by chronic pain, 25 million report daily severe pain, and 20 million experience high-impact pain that interferes with work and daily life.

HEAL receives \$500 million/year in sustained research investment. To date, more than 25 HEAL research programs have been funded. HEAL has a trans-NIH governance structure, and research is collaboratively supported by 20 NIH institutes/centers. The two overarching goals of HEAL are to enhance pain management and improve treatment for opioid misuse and addiction. Research is being done in the following areas to meet these goals: preclinical/translational research in pain management, clinical research in pain management, novel medication options, enhanced outcomes for affected newborns, new prevention and treatment strategies, and translation of research into practice. Information on ongoing HEAL projects, workshops, and funding opportunities can be found on the <u>HEAL website</u>. HEAL fiscal year (FY) 2020 investments will address gaps in the areas of understanding the relationship between pain and opioid use disorder (OUD), addressing OUD and co-occurring mental health conditions, understanding diversity of care received across settings, and increasing diversity among HEAL investigators. NIH also is working to increase patient engagement in HEAL. HEAL is continuing to look for innovative approaches to understand the problems of pain and addiction in new ways and develop durable solutions.

# **Opening Remarks: Historical Overview of Myofascial Pain Syndrome and Hypotheses**

#### Helene Langevin, Director, National Center for Complementary and Integrative Health

Dr. Langevin thanked the HEAL Initiative and the institutes and centers that contributed to the workshop: the National Center for Complementary and Integrative Health (NCCIH), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Neurological Disorders and Stroke (NINDS), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The workshop focus is on myofascial pain syndrome (MPS), which is currently a clinical diagnosis based on history and physical exam, including the palpation of localized tender nodules in muscles and/or associated connective tissues. So far, these abnormalities that are detected by palpation have not been documented using objective measurement methods. The primary goal of the workshop is to review what methods are currently available, or could be developed, to quantitatively evaluate myofascial tissues and support better basic and clinical research on the pathophysiology and treatment of MPS.

The term "myofascial pain syndrome" was coined by Travel in the 1960s and described in books coauthored by Travel and Simons. The syndrome is characterized by the presence of focal, tender, and indurated nodules or "trigger points" that feel firm to palpation compared with surrounding tissues. It includes both active and latent phases with respect to spontaneous and palpation-induced pain. There is likely substantial overlap between MPS and fibromyalgia. Developing better methods to evaluate myofascial tissues may enhance understanding of fibromyalgia as well as MPS. Understanding of MPS is currently very limited. MPS prevalence estimates of 30 to 80 percent of the population are based entirely on subjective clinical evaluations. There are no objective biomarkers and little understanding of pathophysiology, making it difficult to evaluate treatment efficacy. None of the currently available treatments have been adequately tested in clinical trials.

The palpable, tender, indurated nodules in MPS may involve muscles and/or perimuscular fascia. MPS is distinct from acute soft tissue injury, but some patients with acute injury develop chronic pain. The nociplastic and behavioral mechanisms of this transition are a topic of research and are relevant to myofascial pain; however, this workshop will focus on other mechanisms of pain chronification. Four hypotheses have been proposed for how physical exertion could produce symptoms of myofascial pain. The myogenic amplification/chronification hypothesis suggests that malfunction of the muscle at the level of the muscle endplate or spindle leads to "leakage of acetylcholine resulting in a hypercontractile band within the muscle." The fasciogenic amplification/chronification hypothesis suggests that chronically abnormal load distributions over time lead to microinjuries, chronic inflammation, scarring, and adhesion within connective tissue, which contribute to muscle weakness and malfunction. The neurogenic amplification/chronification hypothesis proposes that abnormal tissue loads cause chronic inflammation, fibrosis, and scarring around peripheral nerves, causing both sensory and motor dysfunction. Another variant of this hypothesis is that chronic abnormal tissue loads and repetitive faulty movement can lead to degeneration at the level of the spine, with nerve root compression and segmental symptoms. This type of mechanism also could lead to sympathetic dysfunction, with segmental vasoconstriction, reduced perfusion, ischemia, and metabolic dysfunction, a mechanism referred to as the vasculogenic amplification/chronification hypothesis. The behavioral amplification/chronification hypothesis suggests that myofascial pain might be behavioral, with pain, distress, and fear avoidance causing further deterioration of movement, posture, and motor control. There are limited data to support any of these hypotheses, in large part because of the lack of good methods to study myofascial pain.

Dr. Langevin provided an overview of the workshop agenda. Session 1 will focus on the current state of the science with respect to the previously described hypotheses. Clinicians who diagnose and treat MPS will provide different points of view on its clinical presentation. Sessions 2, 3, 4, and 5 will focus on methods for quantitative evaluation of myofascial pain. Structural, mechanical,

vascular/immune/metabolic, and neurophysiological measurements will be discussed. There will be a focus on noninvasive and minimally invasive techniques, which likely will be most useful for longitudinal studies and evaluation of treatment responses in both humans and animal models. Session 6 will put these measurements in context of musculoskeletal pain pathophysiology. The field of musculoskeletal pain is organized around different types of constructs—body regions, types of musculoskeletal tissue, structures, pain mechanistic domains, and diagnoses—that often do not translate well into one another and have significant conceptual gaps between them. This workshop focuses on the clinical diagnosis of MPS and will touch on elements from each of the other constructs. There will be a focus on muscle and fascia because the clinical presentation suggests palpable abnormalities that there may not yet be tools to quantify. The myofascial unit as a structure also will be considered, particularly in the context of imaging. Measurements will apply to multiple pain mechanism domains and body regions. Speakers and discussants are encouraged to think about the potential generalizability of a given type of measurement to different body regions, as well as limitations and challenges that could be region specific.

Session 1: State of Science of Myofascial Pain Syndrome: Clinical Presentation, Pathophysiological Hypotheses, and Challenges

# Session Chair: Michael L. Oshinsky, NINDS Session Cochair: Leslie Derr, NIAMS

### Fascial Anatomy, From Macro to Micro

### Carla Stecco, University of Padova

The superficial and deep fascia are highly innervated and can be a source of pain. The fascia is highly integrated with muscle and interacts closely with joints, tendons, blood vessels, and nerves. Changes in one tissue type can impact the others, so it makes sense to consider them collectively as the myofascial unit. Muscle insertions into the fascia and distortions in muscle contraction affect the fascia, in which muscle spindles and Golgi corpuscles are embedded. Structural disorders of the fascia could distort information sent by spindles to the central nervous system (CNS) and contribute to pain. The fascia can detect tension in the tendons. It protects blood vessels during movement, helps them maintain an open state, and is involved in thermoregulatory responses.

The fascia is a dynamic tissue. An increase in type I collagen, which is more rigid than type III collagen, is observed with advancing age. Sex hormones cause an increase in production of collagen type III and elastic fibers, leading to more elasticity in pregnant women than in postmenopausal women. Fascial cells express CB1 and CB2 receptors and release hyaluronan in response to endocannabinoid agonists. More research is needed to understand the dynamic nature of the fascia and its interactions with other tissues in the myofascial unit.

# Chronic Myofascial Pain: Myogenic Considerations in Its Pathogenesis and Clinical Manifestations

# Jay Shah, NIH Clinical Center

The definition and etiology of myofascial pain are not fully understood. Disagreement persists about the nature of myofascial trigger points (MTrPs) and how they contribute to myofascial pain. An MTrP is defined as a discrete, palpable, hyperirritable locus formed by a cluster of contraction knots in a taut band of skeletal muscle. These can be active or latent. MTrPs are central to diagnosis of MPS; however, latent MTrPs often are found in asymptomatic individuals and in pain patients with other active MTrPs. Palpation of MTrPs is key to clinical diagnosis of MPS. In search of objective measures, Dr. Shah's team uses pain pressure threshold (PPT) as a way of clinically measuring discrete local tenderness and as an outcome measure in treatment trials.

The current prevailing theory on the pathogenesis of MTrPs is Simons's Integrated Hypothesis, which considers the pathophysiology, histopathology, and histochemistry of the site. Electromyography (EMG) has demonstrated increased electrical activity at MTrPs that occurs spontaneously, suggesting MTrPs could be the result of a neuromuscular disorder. Biochemical data validate the diagnostic distinction clinicians make among active MTrPs, latent MTrPs, and uninvolved muscles. Active MTrPs have a unique biochemical milieu associated with inflammation, muscle tenderness, sensitization, persistent pain states, and intercellular signaling. There is a release of excessive acetylcholine from the motor nerve terminal, which results in depolarization of the muscle membrane, influx of sodium, and release of calcium from the sarcoplasmic reticulum. The calcium induces persistent muscle contraction and vasoconstriction, which leads to ischemia and hypoxia. The subsequent energy crisis leads to an increase in sensitizing substances that activate nociceptors and lead to pain and muscle tenderness. The biochemical milieu results in further upregulation of acetylcholine signaling and autonomic activation, both of which contribute to further cycles of muscle contraction and pain.

# The Role of Neurogenic Mechanisms in the Pathophysiology and Clinical Manifestation of Chronic Myofascial Pain

# John Srbely, University of Guelph

Disagreement persists about whether MTrPs are the primary pathology in MPS or a secondary physical sign. About two-thirds of clinicians surveyed indicated that MTrPs are not essential to diagnosis of MPS. Elucidation of the mechanisms underlying myofascial pain is needed to allow for development of reliable, objective biomarkers. The integrated hypothesis suggests that the onset of chronic myofascial pain is brought on by an acute or chronic muscle overload; however, clinical observations do not align with this model. MTrPs are associated with a number of somatic and/or visceral conditions in the absence of muscle injury (e.g., osteoarthritis, psychosocial stress). Trigger points do not respond like an injured locus in that pressure on the MTrP does not induce a withdrawal reflex. The neurogenic hypothesis suggests that chronic myofascial pain and MTrPs are clinical manifestations of neurogenic inflammation in the muscle evoked by distinct primary pathologies that are outside of but neurosegmentally linked to the affected muscle. Activation of motor neurons by interneuronal pathways also can contribute to the MTrP. The neurogenic hypothesis is consistent with the muscle spindle hypothesis proposed by Partanen; a neurogenic inflammatory response could result in release of proinflammatory neuropeptides by the muscle spindle, thereby activating a cycle of gamma and alpha motor neuron activation. A study in animal models has demonstrated a causal relationship between experimentally induced osteoarthritis and neurosegmentally released neuroinflammatory biomarkers. In humans, increases in motor unit pool activity have been observed with experimentally induced sensitization.

Clinically feasible biomarkers to measure these phenomena are being explored. Central sensitization is characterized by an enhanced input:response profile at the synapse. In anesthetized rats, this is observed as an accelerating input-response profile and pain persistence after removal of the input stimulus. In humans, this manifests as a greater temporal summation of pain. Weighted pinpricks provide quantitative data for mechanical detection and pain thresholds (temporal summation). A series of pinpricks is being used to generate a "windup ratio" that correlates with temporal pain summation. This may help address sensory/motor nerve dysfunction.

# A Clinician's Perspective on Treating Myofascial Pain: Overview and Challenges

# David Lesondak, University of Pittsburgh

Many patients with myofascial pain are treated with myofascial release, a subjective, inner sensation on the part of the patient of something "letting go." This is accompanied by greater physical ease, reduced tension, and/or improved range of motion, as well as a palpatory difference in the affected tissue. Myofascial release is a manual technique using the hands and arms that involves compression, shear, and stretch/traction. Experiments in cultured cells have shown that compression, sheer, and stretch reverse some of the effects of repetitive motion strain on a cellular level (e.g., reduced cell-cell contact, apoptosis, cytoplasmic condensation). A lack of motion leads to deterioration of collagen to a state that does not support movement. Fibroblasts, which produce collagen, are responsive to both pressure and vibration. Release may stimulate the fibroblast network to produce collagen in different ways. The fascia is rich in hyaluronan, a lubricating fluid, which densifies without proper stimulation, which then interferes with motion and the output of sensory and proprioceptive nerves.

Pathoanatomical analysis and postural evaluation also are done to see how posture may be contributing to mechanical difficulties and pain. Clinical treatment of patients is benefiting from efforts to map the myofascial "global supply chains" (i.e., myofascial connections beyond individual segments). One such myofascial chain identified is the superficial back line, a contiguous chain from the epicranial fascia to the plantar fascia. The 2021 International Congress on Manual Therapies will provide an opportunity for practitioners and researchers to coordinate efforts with respect to manual therapies.

# Basic Research/Animal Models Relevant to Myofascial Pain

# Mary Barbe, Temple University

Four animal models relevant to myofascial pain were presented. In the repeated contusion and eccentric exercise rat model by Huang and Zhang, there was repeated contusion of the vastus medialis and treadmill running at a downward grade (-16°) followed by recovery for 4, 8, or 12 weeks. Palpable taut bands associated with increased spontaneous electrical activity were observed. At 4 weeks recovery, there was dense EMG activity suggestive of acute injury and inflammation. At 8 and 12 weeks of recovery, there was intermediate EMG activity suggesting there may be resolution of inflammation and formation of chronic MTrPs. Closer analysis of EMG signals found doublet fasciculation/fibrillation potentials that may represent central hypersensitivity or chronic inflammation in the neuromuscular system. Histologic analysis of the muscle tissue identified myofiber knots, thinning, rounding, inflammatory cell infiltration, and disrupted sarcomeres.

In Sluka's mouse model of muscle acidosis, mice were given repeated acid injections into muscle (5 days apart). This induced secondary cutaneous allodynia as measured by forepaw cutaneous mechanical threshold but no significant muscle damage. Mild lymphocytic response and inflammation were observed following the injections. Knockout mouse experiments revealed that the allodynia is due to acid-sensing ion channels in the muscles, specifically *ASIC3*. Macrophage activation also plays a critical role. Depletion of resident muscle macrophages with clodronate liposomes prior to acid injections attenuated the muscle hyperalgesia; however, blocking macrophage activation with a TLR4 antagonist before the second acid injection had no effect on acid-induced hyperalgesia. Activation of macrophages was accompanied by increases in several proinflammatory cytokines.

In a chronic repetitive unusual movement model by Fujiwara, rats performed repetitive reaching and foot pellet retrieval for 6 weeks. This resulted in progressive decline in grip strength and withdrawal thresholds. No increase in inflammation was observed, but there was an increase in muscle atrophy and autophagy proteins.

In the chronic repetitive strain injury model by Barbe, rats performed a high-repetition, high-force lever bar pulling task 2 hours daily for up to 18 weeks. After 3 weeks, the animals began to demonstrate increased behavioral indices of muscle discomfort (e.g., limb switching, forelimb guarding), nerve inflammation, and degraded myelin. Increased abnormal activity in the median nerve also was observed, similar to what was seen in the repeated contusion and eccentric exercise model. At 6-12 weeks, nerve and musculoskeletal inflammation and central sensitization were observed and were not alleviated through treatment with ibuprofen or rest unless these treatments were given preventatively. Fascial changes were observed at 18 weeks, including fibrosis in muscle and nerve fascia and degraded myelin; rest resolved the nerve damage but not the fibrosis. The fibrosis could be reversed using a monoclonal antibody against CCN2 (anti-cell communication network factor 2, FG-3019), resulting in reduced muscle fibrosis and grip strength normalization. FG-3019 also was able to reverse muscle and median nerve fibrosis and neuronal stress, the latter evidenced by a reduction of ATF-3 expression in the spinal cord ventral horn neuronal nuclei.

These models suggest myofascial pain is associated with structural (degraded myelin, scarring/fibrosis, and disorganized architecture) and vascular/immune/metabolic (reduced pH, acute/chronic inflammation, and autophagy) changes, which can be measured through electrophysiological techniques and assays of tissue dysfunction.

# **Panelist Comments**

# Lynn Gerber, George Mason University

Speakers consistently noted inconsistencies in the literature about myofascial pain diagnostic criteria and the kinds of measurements that can be used to evaluate treatments. An objective MPS biosignature that integrates sensory, motor, and autonomic findings must be developed. There has been progress in identification of microanalytes associated with inflammation, characterization of collagen changes associated with posture and aging, and development of quantified sensory testing. However, it has been difficult to link these objective measures to patients' perception of their experiences. One of the main challenges is to quantify and better understand the relationships that enable conversations about pain. Together with a biosignature of the internal and external stressors that contribute to pain, this will help increase understanding of the mechanisms underlying myofascial pain.

# Kendi Hensel, Texas College of Osteopathic Medicine

Fascia can be thought of as a sheet with continuity that can be felt and assessed all over the body. The fascia should feel slick and slide easily over tissues, like a silk sheet. However, inflammation can result in a stickier texture, more like flannel. Somatic or visceral dysfunction can cause binding or restriction in the fascia, making it feel "tacked down." This binding gives a palpatory directionality to the fascia; application of tension in one area can localize the area of restriction, helping the clinician know what area needs to be treated. After treatment, the fascial motion should be unencumbered and the texture slick.

#### Eric Jacobson, Harvard Medical School

Two clinical phenomena typical of structural integration and myofascial pain were presented, along with related clinical experiences and hypotheses. First, Rolf postulated that densification and fibrosis of the myofascia impedes perfusion and fluid migration. Work by Shah and colleagues suggests that reduced fluid migration may contribute to high concentrations of nociceptive amplifiers and proinflammatory cytokines in interstitial fluid at sites of chronic pain. Manual pressure with simultaneous fascial movement appears to reduce density and increase pliability and fluid content, and reductions in chronic pain have been reported. It is hypothesized that increased fluid migration may enhance clearance of nociceptive amplifiers and proinflammatory factors. Second, Rolf postulated that densification and fibrosis of the myofascia reduce elasticity, which limits voluntary stretching of the soft tissues. Manual pressure and simultaneous fascial movement appear to increase elasticity and extent of stretch, and reductions in chronic pain have been reported. It is hypothesized that an increased magnitude of stretch activates anti-inflammatory, antinociceptive, and proresolvin effects found in animal studies.

#### Jan Mundo, Mundo Lifework

Migraine is a neurobiological disorder with throbbing trigeminal pain and associated symptoms, including nausea, vomiting, and sensitivity to light, sound, or odors. Myofascial pain is experienced during and between episodes. Ms. Mundo has been using and teaching a targeted, gentle, precise-pressure transcranial touch and focused concentration therapy to treat migraine patients for 50 years. There are several outstanding questions about how this therapy works. How do touch and focused concentration modulate and resolve acute migraine and associated symptoms? What are the connections and neurocognitive pathways between touch, attention, and migraine pain? Is fascia the mechanosensory transducer between touch, migraine pain perception, somatosensory cortex activation, and neural circuitry? Do interstitial or Ruffini receptors or Piezo channels play a role? How can a manual protocol on the head be measured without artifact? Does therapy produce biomarkers (neuropeptides, cytokines, calcium channel ions) as in pharmaceutical treatment? Are there changes of state from migraine to pain and symptom resolution? Research on mind-body therapy for migraine is needed to advance this type of therapy, which is holistic, has few side effects, and has potential for self-application.

### Niki Munk, Indiana University

Therapeutic massage has potential to address the systematic expressions and mechanistic causes of chronic myofascial pain. The therapeutic massage paradigm is informed by the MTrP concept and involves addressing the tissue through mechanistic means using the hands or tools that apply compression, shear, or glide. Dr. Munk has transitioned into academic research; she noted there often is a gap between practice, research, and education. One question being considered is how the ideal MTrP therapy dose aligns with how massage therapy is accessed in the real world. The ideal dose is likely short and repetitive therapy, but this is not how massage therapy is accessed in the real world. Consideration should be given to how to engage patients in their healing process, possibly through teaching them self-massage tools that they could apply between sessions. This raises additional questions of how to teach patients these tools and how to measure the fidelity of these techniques.

#### Kathleen Sluka, University of Iowa

Speakers have described an important role for the fascia in myofascial pain. Dr. Sluka urged discussants to consider whether the right animal models are available and what components are needed in animal models to address the questions that have been identified. Some existing animal models may be appropriate, while others may not. Potential research topics raised by presenters are whether immune cells are involved, what fibroblasts are doing, and changes in collagen and hyaluronan. What role do these phenomena have in driving pain behavior, and can they be modified to reduce the pain behavior observed in animal models?

#### Heather Tick, University of Washington

Cannon's 1949 book, *The Supersensitivity of Denervated Structures*, outlines research on how denervation leads to sensitization of organs, including the myofascial system. Sharpless expanded on this work, showing that sensitization also occurs with partial denervation and disuse. In the 1970s, Gunn recognized MPS as a neuropathic disorder and began using intramuscular stimulation (dry needling) to systematically treat muscles innervated by the anterior and posterior primary rami in the affected myotomes/sclerotomes. Systematic review by Lee showed that Gunn's protocols resulted in more robust improvement compared with approaches that did not use a neurosegmental model. Barbe's group's repetitive strain injury model has tremendous clinical implication, particularly for those who fail conventional treatments. Current demonstrations of the dynamic nature of connective tissue and the role of the fascia as a connector explain patterns of dysfunction and healing and lead to a more integrative and integrated understanding. Future meetings should discuss recent findings on mitochondrial dysfunction and how this confounds recovery.

#### **Panel Discussion**

Dr. Srebly noted that one key determinant of central sensitization is persistent nociceptive input. Osteoarthritis is one of the few clinical conditions that results in persistent nociceptive input. Age is a strong risk factor for both osteoarthritis and musculoskeletal pain, but no one has drawn connections between the two. The Srebly lab is using animal models to explore this. Other sources of persistent nociceptive input could be a tumor or chronic metabolic disease. Drs. Srebly and Shah noted that pain due to a neurological injury would be neuropathic pain, which has a different clinical presentation than neurogenic pain (neuropathic is more defined and neurogenic, more diffuse). Their work focuses on functional changes in the nervous system in the absence of pathology. Work is ongoing to distinguish neurogenic pain with the Gunn model for neuropathic pain. Research has shown subthreshold potentials occur in chronic muscle lesions and can cause sensitization without pain. Injection of nerve growth factor (NGF) also has induced sensitization without pain. Tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β), both of which

are elevated in active MTrPs, can stimulate release of NGF. The Srebly lab is interested in changes at the membrane level in the absence of overt pathology (e.g., amplification due to activation of the *N*-methyl-D-aspartate [NMDA] receptor). For example, patients' transition from acute to chronic pain is demarcated by a transition from  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) to NMDA receptor activation, which leads to activation of various signaling cascades and sensitization.

- Dr. Gerber added that linkage of structural and functional changes would help distinguish the mechanical versus neuropathic models; for example, if structural changes (e.g., MTrPs or changes measured through imaging) could be correlated with biochemical changes and related to mechanical abnormalities.
- Participants discussed aspects of patient self-care. Dr. Munk has conducted multiple studies on educating patients to administer self-care, either by themselves or with a partner. In her experience, patients are initially enthusiastic, but their enthusiasm wanes over time. Future work will explore incorporation of behavioral and behavioral motivation pieces into patient education to help patients engage over the long term. Ms. Mundo stated she uses a step-by-step approach to teach her clients to administer self-care. She fosters a mind-body connection and aims to make them feel empowered to help motivate them. Dr. Lesondak related recent studies on use of foam rolling and other techniques for self-delivered myofascial release. Many patients do too much too aggressively, subscribing to the "no pain, no gain" philosophy; however, it is often better to use softer tools that allow patients to ease into the therapy.
- There sometimes is a disconnect between the time allotted for appointments and optimal delivery of therapy. Dr. Lesondak reported that he uses a 30-minute appointment model for convenience and monetary reasons, but this often is an inadequate amount of time, especially for newer patients. It can take 20 minutes for a patient to "downregulate" in order to receive the therapy in the manner intended. This observation is supported by recent functional magnetic resonance imaging (fMRI) work on tactile-based therapies. Mr. Lealem Mulugeta stated he has found that 90 minutes is the minimum appointment time needed, particularly if time will be spent on education of patients who are not familiar with the techniques being used. Dr. Munk noted that the therapeutic encounter is important for cultivating a partnership with clients and helping them learn to use shorter repetitive mechanistic approaches to address trigger points between sessions.
- The incidence of myofascial pain in the United States is similar to that in other countries. Panelists noted that research on myofascial pain (sometimes called myalgia) is ongoing in Australia, Japan, and other countries. Dr. Tick raised the possibility that although incidence of myofascial pain is not higher in the United States, prevalence may be because the U.S. healthcare system and culture are not conducive to healing. The United States leads the developed world in ill health. Unlike other developed countries, the United States does not have universal health care, which affects access to care. Many Americans also do not have access to healthy food and live proinflammatory lifestyles.
- The importance of functional measures to evaluate clinical outcomes was emphasized. Dr. Gerber described a soft tissue myofascial trigger point twitch response study that used an extensive battery of examinations, including patient self-report and physical examinations. Metrics of function included range of motion, symmetry of movement in the upper trapezius, quality of life, and sleep. Inclusion of standard metrics like sleep and quality of life acknowledges that MPS is not a regional problem; it is a general problem that affects daily function. In the study, improvement of these functional measures was observed with treatment. These same measures may not necessarily be useful in the context of clinical practice. Dr. Jacobson added that, from a

structural integration point of view, quantitative measures of whole-body biomechanical fitness are lacking.

- Validated assessments of myofascial release are needed to allow better measurement and validation of the techniques used. This validation would help make these interventions available to a broader socioeconomic audience.
- Fibromyalgia previously was referred to as fibrositis, but this nomenclature changed because it was determined that fibromyalgia is not an inflammatory disease. However, fibromyalgia cooccurs with myofascial pain, which does have an inflammatory component. Dr. Sluka clarified that fibromyalgia and MPS, while commonly co-occurring, are separate entities. She noted that fibromyalgia is associated with changes in the immune system systemically and locally within the muscle. While there are proinflammatory changes, it is not the same type of widespread inflammation response that is observed in other settings (e.g., injury).
- Dr. Jacobson noted that his patients often present with inability to stretch and very tight, fibrotic, and underhydrated fascia. This condition predisposes people to injury. Structural integration aims to treat fascia through the whole body to improve overall biomechanics and reduce the liability to repeated injury.
- Myofibers heal quite well after injury, but there can be lingering changes in the surrounding fibrotic tissue, neural tissue, and vasculature that do not resolve with rest. Though the pain is often referred to as "muscle pain," it is caused by the surrounding tissues. This is why people with repetitive strain injury require therapy, not just rest, to recover.
- There was discussion about common mechanisms and differences between musculoskeletal pain and myofascial pain. Dr. Srbely noted that musculoskeletal pain is due to structural injury of the myotendinous unit and is a well-defined localized pain that induces a withdrawal reflex when touched. Myofascial pain presents differently; it is generally ill defined and not associated with a withdrawal reflex. Dr. Jacobson stated that, from a structural integration point of view, musculoskeletal injury cannot occur without serious disruption of the tension and fibrosis in the fascia. Dr. Oshinsky suggested different types of C fibers may be involved in musculoskeletal versus myofascial pain. New biomarkers may help evaluate this question in animal models. Dr. Stecco noted that different types of fascia are different with respect to connective fibers, innervation, etc. This must be taken into account in order to understand the role of fascia in pain. There may be different densities and types of C fibers in different types of fascia.

# **Questions and Answers From the Zoom and Videocast Audiences**

• What progress has been made toward establishing clinical criteria for diagnosis of MPS? Dr. Lesondak responded that clinical criteria and a legitimate diagnostic code are needed to integrate into the medical world at large and better serve patients. Dialogues such as those at this workshop will help move the field in that direction. Dr. Gerber reported that Dr. Shah recently published a paper describing their group's efforts to find consensus regarding MPS in the literature. In their view, consensus in the field has not been reached. They found that the Treval and Simons criteria were used in about 80 percent of publications. Common constructs included trigger points, pain, and abnormal muscle function. It was not possible to identify features to differentiate MPS from regional pain syndrome or musculoskeletal pain. Dr. Gerber noted that there has been a shift in the types of journals in which MPS studies are published. Initial reports were in clinical journals. More recently, discussion of MPS has increased in pain and physical therapy journals, with a focus on treatment and evaluation of outcomes.

- *Has there been research into the reasons why some medication users develop addiction while others do not? Has any effort been made to measure resilience before prescribing drugs?* Research suggests only a small percentage of people prescribed opioids develop misuse disorder, but many people are affected because opioid use is so common. There is ongoing work to identify genetic markers associated with risk of opioid misuse, but there currently is no test available. There is information about categories of people who are at higher risk of misuse, including types of pain and presence of other health conditions. Dr. Baker noted that the HEAL Initiative aims to ensure that there is a sufficient number of options beyond opioids to treat pain. The goal is to develop multimodal and complementary approaches to reduce overall reliance on opioids.
- *Have any correlations been made between active versus latent MTrPs and levels of inflammatory mediators and cytokines?* A study done by Drs. Shah and Gerber found elevated levels of inflammatory mediators in distal unaffected muscle of patients with an active trigger point in the upper trapezius. These patients may have systemic issues predisposing them to myofascial pain, or the presence of MPS may predispose them to systemic changes. Studies of plasma markers may be useful to learn more about this.
- *Can MPS lead to cell necrosis? What signaling pathways are responsible for apoptosis induced by shear stress?* Dr. Barbe stated that necrosis has been observed with MPS. In osteocytes, shear-induced apoptosis is driven by the Wnt pathway and sclerostin. The mechanism presumably is the same in other tissues.
- *Has work in rats showing that sustained stretching slows the spread of breast cancer cells been replicated?* This study was done by Dr. Langevin's lab using a p53/PTEN mouse model. The lab currently is doing a follow-up experiment to determine whether stretching can prevent spontaneous mammary tumor formation in a different mouse model. They also are looking at underlying mechanisms. Dr. Hensel added that this observation makes sense from an osteopathic point of view—opening the fascia through stretching or massage will improve lymphatic drainage and optimize the immune system.

# Session 2: Current Structural Imaging Approaches With Potential Application to Myofascial Pain Syndrome

# Session Chair: Guoying Liu, NIBIB Session Cochair: Merav Sabri, NCCIH

# Current Magnetic Resonance Imaging Approaches With Potential Application to Myofascial Pain Syndrome

Garry E. Gold, Stanford Schools of Engineering and Medicine

Several routine and advanced magnetic resonance imaging methods can be used to assess structural changes associated with MPS. MRI can capture rapid volumetric images of joints and tissues, including bilateral images. Quantitative measurements can be acquired with scan times as low as 5 minutes. Deep learning techniques (e.g., DeepResolve) can help reduce the noise and increase the inherent resolution of MR images. Availability of these techniques enables use of faster acquisition times. Deep learning and machine learning (ML) also can be used for automated segmentation, allowing a high level of accuracy for volumetric measurements.

MRI can be used to image muscle, connective tissue, and nerves. MRI can distinguish between water and fat content in muscle. Proton density fat fraction in muscle has been used for many years to generate highly repeatable measurements of fatty infiltration of the muscle. Diffusion tensor imaging allows assessment of muscle status in injury and disease. Muscle fiber length can be measured by capturing

images when a muscle is both flexed and extended (e.g., image of soleus in both dorsiflexion and plantarflexion). Radial diffusivity can be used to measure diffusion of water through the muscle, which can be altered in conditions like MPS. T2 and T1p relaxation times can be measured in muscle to provide insight into microstructural features and changes (e.g., with exercise/recovery or stroke). T2 scans allow visualization of MTrPs in muscle. Principal strain directions in muscle can be measured to provide a functional measure of muscle strain under load. Creatinine chemical exchange saturation transfer (CrCEST) and related techniques can be used to evaluate muscle energetics. Ultrashort echo time (uTE) MRI enables visualization of tissues that normally appear black on MR images, such as tendons and connective tissue. These images can be quantitatively measured using automated segmentation. The macromolecular proton fraction of tendons can be measured to visualize inflammation.

# Quantitative MRI Methods With Potential Application to Myofascial Pain

# Bruce Damon, Vanderbilt University

MRI methods are capable of quantifying unique aspects of MPS pathology, including blood flow and tissue oxygenation. MR angiography characterizes arterial structure and blood flow through the arteries and veins. Dynamic contrast-enhanced MRI and arterial spin labeling can be used to measure tissue perfusion. The former uses a contrast agent, while the latter uses the blood as an endogenous source of perfusion-related contrast. Arterial spin labeling can be done more quickly, facilitating repeated measurements during a dynamic event. Quantitative blood oxygenation level dependent (BOLD) MRI can be used to look at tissue oxygenation (ischemia) since MR signals decay more quickly in the presence of deoxygenated hemoglobin. Perfusion, oxygen extraction, and oxygen metabolic rate are dynamic measures, and multiparametric methods are being developed to allow simultaneous measurement of these features in close proximity within the tissue. Lymphangiography MRI can be used to characterize the distribution and size of the lymphatic system. Standard approaches use diffusion-weighted imaging with background signal suppression; long echo time (long-TE) imaging also can be used to directly image the lymphatics. MR also can be used to quantify tissue sodium content, which is expected to be altered with lymphatic dysfunction. This requires specialized hardware and pulse sequences, and images tend to be noisier and have lower spatial resolution. To date, the application of these types of approaches to MPS has been limited.

# Use of Molecular Imaging and Magnetic Resonance Neurography in the Identification of Peripheral Pain Generators

#### Sandip Biswal, Stanford University

Positron emission tomography (PET)/MRI is a whole-body, quantitative, multiparametric tool that can be used to look at functional tissue abnormalities associated with MPS (e.g., tissue hydration, perfusion/ischemia, inflammation, metabolic changes, immune activation, nerve dysfunction). Nociception is associated with significant biochemical, molecular, and physiological changes that potentially can be exploited for molecular imaging. PET can detect changes that often are not visible via MRI. Simultaneous MRI and PET can provide excellent spatial and contrast resolution along with functional information. For example, <sup>18</sup>F-fluorodeoxyglucose (FDG) PET/MRI of a patient with sciatica identified an impinged nerve and herniated disc associated with hypermetabolic pathology. <sup>18</sup>F-sodium fluoride PET/MRI was used to investigate the patient's leg pain; no abnormalities were detected by MR, but PET images showed early muscle atrophy and denervation changes. PET also can detect metabolic activity in osteoarthritis before structural changes are detectable by MRI. Hypermetabolic lymph nodes were found in a patient with complex regional pain syndrome, suggesting a potential immune component. Small foci of enhanced <sup>18</sup>F-FDG uptake were observed near the thoracic sympathetic chain in another complex regional pain syndrome patient, leading the treating physician to consider use of a sympatholytic drug to complement the analgesic currently taken. <sup>18</sup>F-FTC-146 is a highly specific sigma-1 receptor PET

tracer that is currently in clinical trials. In one example, a patient with knee pain had no abnormalities detected via MRI; however, <sup>18</sup>F-FTC-146 PET identified an inflamed intercondylar notch. Exploratory surgery found and removed a highly inflamed synovial lipoma, which resulted in dramatic improvement in the patient's symptoms. <sup>18</sup>F-FTC-146 PET also labeled symptomatic regions in a fibromyalgia patient. Another PET tracer, <sup>11</sup>C-peripheral benzodiazepine receptor (PBR) 28, can detect activated macrophages.

MR neurography can be used to look at structural changes in nerves associated with MPS, as well as scarring, fibrosis, and fatty infiltration of the muscle. MR neurography can be done on a 1.5T or 3T machine.

# From Qualitative to Quantitative: Musculoskeletal Ultrasound Imaging for the Evaluation of Myofascial Tissues: Opportunities and Limitations

Siddhartha Sikdar, George Mason University

Ultrasound is a widely available, high-resolution modality that can provide structural information at the macroscopic and, potentially, microscopic levels. Some vascular information also can be obtained. Two features of ultrasound images are echogenicity (brightness) and echotexture ("speckle"). These features depend on the size and distribution of fibers/fascicles, tissue composition, fiber orientation, and the microstructure and organization of the tissue. Musculoskeletal ultrasound can provide information on tissue thickness, presence of fluid, muscle tears, and scarring/healing. Ultrasound images can be qualitatively assessed to provide insight on fibrosis, fatty infiltration, and muscle quality. Envelope statistics can be used to try to quantify differences in heterogeneous muscle architecture. For example, muscles affected by cerebral palsy can be clearly distinguished from normal controls. In ultrasound images of MPS, MTrPs appear as hypoechoic regions, fascia appear to be thickened, and hyperechoic bands are observed in the muscle belly. However, quantification of MPS is challenging because of the complex milieu of the myofascia. Another challenge is that ultrasound imaging is operator dependent, which limits reproducibility. The appearance of MTrPs is strongly affected by probe orientation, which suggests MTrPs are subtle architectural changes rather than solid lesions.

Color Doppler ultrasound allows visualization of blood flow. Large blood vessels have been observed near active MTrPs, suggesting neovascularization in these regions. Blood flow waveform measurements indicate high peak systolic velocity and retrograde diastolic velocity, suggesting altered vasculature and sensitivity to small changes in pressure.

Emerging ultrasound modalities for MPS include contrast-enhanced ultrasound for perfusion; photoacoustic imaging that allows quantification of oxygen saturation and blood flow; microvascular flow imaging, which is more sensitive than color Doppler; ultra-high-frequency ultrasound, which can better quantify architecture; and elastography, which will be discussed during a later session.

# **Panelist Comments**

# Panelist: Christine Chung, University of California, San Diego

Musculoskeletal pain and myofascial pain have different clinical presentations. There is a sophisticated set of tools available to clinically evaluate myofascial pain, but there are challenges. Standard MR imaging findings can be very subtle. Robust noninvasive imaging evaluation will require development and deployment of new tools that enable structural, biochemical, and even mechanical assessment. Reference standards for imaging biomarkers must include pain, physical examination, and/or function in additional to structure.

# Panelist: Bharti Khurana, Harvard Medical School

Myofascial architecture as observed via various imaging techniques (MRI, computed tomography [CT], ultrasound) does not necessarily correlate with pain. Some patients with architectural distortion have no

pain, and some with normal tissue architecture have pain. Structural imaging would be enhanced through the addition of functional and mechanical biomarkers. Dr. Khurana asked participants their view on the need to suture fascia following surgery and the potential value of thermal imaging for MPS.

#### Panelist: Levon Nazarian, Thomas Jefferson University

Ultrasound contrast agents are microbubbles encapsulated in saccharide or a lipid shell. They are injected into a peripheral vein and can enhance blood flow signals in tissue. Changes in signal intensity over time can be used to quantify muscle perfusion. Changes in Doppler signal also can be assessed. Preliminary work in fibromyalgia using ultrasound contrast agents has shown decreased muscle perfusion, particularly following exercise. Reproducible and accurate pressure estimates, including of muscle compartments, can be obtained by combining ultrasound contrast agents and subharmonic imaging. Ultrasound contrast agents are very safe and could be an important tool for both research and clinical care.

# Panelist: Antonio Stecco, New York University Langone Health

Fascia comprises dense and loose layers. Dense layers transmit force, while the interspersed loose layers allow the dense layers to glide independently from one another. T1p imaging of a patient with spastic muscle stiffness in the arm revealed high levels of unbound water, indicating hyaluronan aggregation. Injection with hyaluronidase resulted in a decrease in unbound water (hyaluronan disaggregation), which correlated with an increase in range of motion. Similar improvements in unbound water and symptoms were observed with fascial manipulation of a patient with right epicondylitis. These are the first data showing that manual therapy can change the biology of deep fascia.

#### **Panel Discussion**

- Dr. Bruce Damon noted that the MRI of a muscle herniation looked like a signal void. He asked Dr. Chung how the fascia can be distinguished from a void caused by a chemical shift artifact in MR images. Dr. Chung acknowledged that changes detectable by MRI are very subtle, and it can be difficult to determine the etiology of the changes. Fascia has low signal intensity with standard MR sequences, making it difficult to assess. One approach that is sometimes used is to collect an image while the patient is contracting the muscle to check for contour changes.
- The literature does not include reports of systematic study of fatty infiltration of the muscle in MPS. Dr. Gold suggested this may be one approach for studying the long-term sequelae of MPS since fatty infiltration often is observed in later stages of muscle diseases.
- Dr. Gold explained that fat and water resonate at different frequencies, which makes it possible to distinguish between the two in MR scans. This has been validated in many systems. In conventional MR scans (e.g., T1-weighted sequence or uTE without fat suppression), fat and connective tissue can be difficult to distinguish. However, most modern scanners can distinguish between the two if the operator adjusts the echo time and pays attention to the chemical shift caused by fat.
- PET tracer targets that may be of use in the study of MPS include calcitonin gene-related peptide receptor, substance P receptor or translocator protein (TSPO) or other macrophage-related targets, and sigma 1 receptor. It was noted that substance P did not turn out to be a good target for analgesia, but it may play an important role in collagen production. Sigma 1 receptor has been shown to be upregulated in the neuroma in a rat model of spared nerve injury. A sigma 1 receptor antagonist was able to decrease the pain response in the model. A sigma 1 receptor antagonist currently is being evaluated in a clinical trial for treatment of paclitaxel-induced neuropathy. Dr. Biswal expressed hesitation about a tracer targeted to hyaluronan given how ubiquitous it is in the tissue; this likely would create problems with background signal.

• In animal models, macrophage-related changes associated with MPS are subtle. Dr. Biswal noted that PET would be able to pick up macrophage increases of 50 to 100 percent if a good tracer were available. To be most effective, it must be possible to remove background tracer signal. It would be possible to distinguish between different types of macrophages if biomarkers for the cell population of interest were known and tracers were developed to target those biomarkers. Dr. Barbe added that researchers at the University of Pennsylvania are developing a macrophage-targeting antibody linked to a lead particle. She is unsure of the status of the project.

### **Questions and Answers From the Zoom and Videocast Audiences**

- *How commonly is exercise used in conjunction with imaging as part of the clinical workup for MPS*? Exercise provocation is used in conjunction with imaging in research, but it is exceedingly rare in the clinical setting. Dr. Gold noted that it would be difficult to fit an exercise challenge into a standard clinical workflow given scheduling constraints. Exercise challenge and imaging are used in other settings (e.g., cardiology). Applying this for treatment of MPS would require demonstration of clinical value (e.g., would the results alter the course of treatment?). Dr. Chung noted that some of the sites most commonly affected by MPS (e.g., trapezius) may not be amenable to exercise provocation. Dr. Sluka commented that the exercise challenge would not necessarily need to be long or extensive; for example, sitting and standing five times can increase pain. Of all the imaging modalities discussed, it would be most feasible to integrate ultrasound into the clinical workflow.
- *How does the cost of these imaging modalities impact their clinical applicability for MPS?* Of the technologies discussed, in general, PET/MRI is most expensive, followed by MRI and ultrasound. The cost of MRI could be reduced if scans could be collected more rapidly. Imaging would not be clinically useful unless it changes the patient's course of treatment. Dr. Biswal noted that PET/MRI has led to resolution for patients who have suffered with pain for years despite being seen by medical providers. In these cases, it would be cost-effective to use PET/MRI to expedite diagnosis and cure. The clinical benefit of ultrasound for MPS will improve if approaches for measuring function are developed and validated. Dr. Nazarian pointed out that one benefit of ultrasound is that it allows correlation of imaging with physical examination. Diagnostic and/or therapeutic intervention also can be delivered during the scan.
- *Do imaging observations correlate with pain in MPS?* There is not a clear correlation between structural features detected via imaging and pain. Dr. Stecco suggested the correlation may be clearer once imaging is better able to measure tissue function.
- *Why do many patients have MTrPs at the same site?* Dr. Tick noted that research done in the 1970s found that there was a correlation between motor points and MTrPs. This may account for why there are common MTrP sites; however, it does not account for all MTrPs.
- It has been hypothesized that the only unbound water in the body is in urine. What is the composition of the unbound water detected in Dr. Stecco's studies? Dr. Stecco acknowledged that it is unclear to what the water might be bound. The change observed upon treatment with hyaluronidase makes it clear that there is a change in water binding to hyaluronan.

# Session 3: Elastography Imaging Approaches With Potential Application to Myofascial Pain Syndrome

# Chair: Helene Langevin, NCCIH Cochair: Merav Sabri, NCCIH

### Ultrasound Elastography for Evaluation of Tissue Mechanical Properties

Kevin Parker, University of Rochester

Elastography emerged about 30 years ago with the use of radiology-including ultrasound-to image the biomechanics of tissue. External sources are used to propagate shear waves or static compression through tissue during imaging. The speed of shear waves depends on tissue stiffness. Three types of stimulus can be applied: slow compression, harmonic shear waves, or transient push pulses. Many elastography techniques have been developed, but only a few are widely available in commercial machines. A few examples of ultrasound elastography were presented. Shear wave elastography is widespread in ultrasound systems and is used for imaging of liver, breast, thyroid, and other soft tissues. Sharp, short pulses of ultrasound are focused on a specific point, which imparts a radiation force that launches a measurable shear wave disturbance away from the focal point. Musculoskeletal elastography has been rapidly developing for the last 20 years. Elastography yields quantitative and relatively reproducible data and can be repeated under different conditions. A transient elastography technique allows anisotropic measurement of the muscle by providing shear wave displacement information along and across muscle fibers at different angles. MTrPs disrupt the propagation of shear waves and can be visualized via vibration elastography and shear wave elastography. Elastography can be used to look at changes in a resting versus contracting muscle and during passive stretching. A group from Hong Kong has developed a hand-held device that takes local measures of the skin around a muscle; they claim results correlate with ultrasound.

Elastography-capable ultrasound scanners are commercially available and can be purchased for as little as \$100,000. Less expensive research scanners are available, but users often must do their own programming. To date, most models view soft tissue as homogeneous, passive, and simple whereas muscles are known to be more complex, with active innervation, different layers, and anisotropy. Elastography models and technologies will be addressing these issues to achieve higher special resolution to untangle the fine structure of the myofascia, allowing better analysis of chronic and acute pain.

# Measurement of Shear Plane Tissue Mobility Using Ultrasound Elastography Techniques

Helene Langevin, NCCIH

Shearing forces are unaligned forces pushing one part of an object in one direction and another part in the opposite direction. Application of shearing forces during palpation allows clinicians to evaluate shear strain. Strain is the deformation in a material that occurs as a result of stress. With a given applied force, the stiffer the material, the smaller the strain. Shear strain is inversely proportional to the distance between the layers: the closer and thinner the layers, the greater the strain. Shear strains play a very important physiological role in the body, especially in myofascial tissues because they are organized in layers. Shear strain naturally occurs when the tissues are passively moved due to an external force or actively moved by muscle contractions. Pathological processes like inflammation, fibrosis, scarring, and adhesions can potentially reduce shear strain within the thoracolumbar fascia in human subjects with and without chronic low-back pain using a technique derived from ultrasound elastography. This is done by plotting the lateral displacement of the tissue in two small adjacent windows, computing the differential displacement, and dividing it by the distance between their centers. By incrementally moving the windows, it is possible to determine the point where the maximum shear strain occurs. This method

showed lower average shear strain within the thoracolumbar fascia in human subjects who had chronic low-back pain compared with those who did not. Work in a porcine model suggested that the decreased strain is at least in part due to fascial adhesions. It is possible that muscle abnormalities could also contribute. The technique also can be used to measure shear strain at the interface between nerves and adjacent tissues in humans, but this has only been done in large nerves such as the sciatic nerve. To date, this technique has not been used to study MPS. Strengths of using ultrasound elastography to study MPS include that it is a relatively simple technique that can be done using standard ultrasound equipment. It is reliable for measurement of musculoskeletal tissue shear strain if the target is a simple structure and the ultrasound probe position is carefully controlled. Limitations of this approach include the need for post processing and the strong dependence on ultrasound probe positioning. This makes it challenging to do repeated measurements and to image complex tissue structures or tissues in hard-to-reach locations or planes. In addition, ultrasound data are two dimensional.

# MR Elastography: Quantitatively Characterizing the Mechanical Properties of Skeletal Muscle and Myofascial Interfaces

#### Richard Ehman, Mayo Clinic College of Medicine and Science

Magnetic resonance elastography (MRE) is an MRI-based technology that was developed to quantitatively image tissue properties such as stiffness, viscosity, attenuation, and strain. Currently, the main clinical application of MRE has been for detection of hepatic fibrosis. More than 1,500 MRI systems globally have been equipped to use MRE. There is a standard Medicare charge for MRE and an established billing code. MRE is not used for clinical musculoskeletal imaging, but it is used in research. Over 50 publications have reported on use of MRE to assess the mechanical properties of normal and myopathic subjects, explore identification of taut bands, and assess loading behavior and tension distribution for biomechanics studies. MRE has been used to characterize muscle stiffness under load. An example of an MR-compatible load cell that applies known loads of plantarflexion and dorsiflexion during imaging was provided. It is possible to evaluate and quantify features of multiple muscles during one examination. MRE has been used to detect differences in muscle shear stiffness before and after treatment, measure the impact of exercise-induced injury, and map the elastic and viscous components of muscle. MRE has detected increased stiffness in myofascial taut bands; however, there has been modest concordance between the location identified via MRE and physical examination, which likely could be improved with further technological development. MRE has potential for use in evaluation of myofascial interfaces through shear strain mapping, which currently is being used to measure adhesion of tumors to surrounding brain tissue. Movement of muscles in the forearm can be measured following application of vibration to individual fingers, providing insight into movement at myofascial interfaces. The loss of MR signal due to motion (intervoxel phase dispersion) also can be harnessed to measure shear. With further clinical development, MRE could make it feasible to quantitatively assess the viscoelastic properties of myofascial structures and the degree of adhesion at functional myofascial interfaces. MRE can be used to look at the mechanical properties of increased stiffness and altered viscous properties, reduced strain with applied force, and reduced shear plane mobility, as well as the structural features of scarring, fibrosis, and disorganized architecture. Further technological development likely would allow assessment of several vascular, immune, and metabolic features.

#### **Panelist Comments**

#### Panelist: Shigao Chen, Mayo Clinic Rochester

Recent advancements in ultrasound microvascular imaging may be useful for MTrP imaging. Superresolution imaging with contrast allows visualization and measurement of flow velocity in vessels down to 20–50 microns. This technology has deep tissue penetration. Kidney cortex microvessels can be seen and flow speed can be measured. Differences in normal and diseased tissue can be detected.

# Panelist: Dieter Klatt, University of Illinois, Chicago

Pathological processes have an impact on the mechanical properties of tissues; however, it also is true that abnormal tissue loads can cause pathology. Muscle is not a homogeneous structure. *Ex vivo* deformation test results represent an average over all tissue components. Similarly, *in vivo* mechanical properties determined in elastography represent averages over the tissue components within image volumes defined by the resolution limit. Multifrequency elastography may give subresolution information of the mechanical properties of tissue components. Elastic properties can be measured over multiple frequencies and fit to models that take the different tissue components into account. Tissue prestress must be considered when relating shear wave velocity to mechanical properties of skeletal muscle; in skeletal muscle the type of imposed prestress (active contraction or passive stretching) also plays a role.

# Panelist: Neil Roberts, University of Edinburgh

Excellent work has been done on MRE, including simultaneous assessment of the nine muscles of the thigh (Bensamoun) and statistical mapping of the effects of movement and aging on muscle (Burnhill, Kennedy). Research funding is needed to support development of MRE methods that integrate wave propagation and statistical mapping. Also, research has shown that guided exercise can be an effective supplement to treatment (e.g., with the Alexander technique). Books by Dart and by Murray and Murray highlight these do-it-yourself techniques. Awareness of these techniques should be raised.

# Panelist: Sergio Sanabria, Stanford University School of Medicine

MRI is the gold standard for measuring the fat fraction of muscle, but it would be beneficial to develop objective ultrasound elastography methods to accomplish this. Speed of sound has emerged as an elastography biomarker for tissue composition since pressure waves propagate more slowly in fatty tissue than in muscular tissue. This could be an affordable bedside tool for muscle density monitoring. Emerging clinical applications of speed of sound as an elastography biomarker include breast cancer, liver steatosis, and fatty muscular degeneration. Speed of sound has been found to quantitatively correlate with muscle fat fraction as measured by MRI. Preliminary data indicate speed of sound is not affected by muscle tension or muscle fiber orientation.

# Panelist: Siddhartha Sikdar, George Mason University

Muscle in the area of MTrPs has areas of color void on Doppler images, indicating that shear waves are not propagating through a portion of the tissue. The mechanical heterogeneity index measures the proportion of muscle with color void and is reduced in response to dry needling treatment. Shear speed is a function of the orientation of the ultrasound transducer; it is faster along fibers and slower across fibers. In normal tissue, changes in shear speed distribution with angle of the transducer are symmetrical; however, asymmetrical changes are observed in muscle with active MTrPs.

# Panelist: Robert Vining, Palmer College of Chiropractic

All manual therapies interact with the fascia regardless of therapeutic intent. Manual therapists work on a theoretical and/or experiential basis; there are no objective tests to confirm MPS diagnosis or assess treatment response. There also is no way to quantitatively determine myofascial contributions to pain. Mechanical imaging and other modalities offer potential for improved diagnosis and assessment of MPS. They also will enable research that will allow clinicians to better determine when manual therapies should be used.

# **Panel Discussion**

- Ultrasound measurements of shear pain must be done in one part of the body at a time. There are challenges associated with imaging certain areas of the body using ultrasound. MRI offers opportunity for whole-body measurements.
- It is not clear whether alterations in mechanical functioning observed via imaging are the cause of pathology or the result of another problem elsewhere in the body. It was agreed that this is a difficult question. Additional research from a whole-body biomechanics standpoint and new methods are needed to provide insight into disease drivers and secondary pathologies. Although imaging may not be able to identify with certainty the root cause of the pathology, it is clear that abnormal mechanobiology can cause disease (e.g., polycystic ovarian syndrome).
- New technologies provide researchers with new tools to answer existing questions and enable them to address new types of questions. This is why methods development is such an important part of research. Researchers should think outside the box about ways to use the technologies at their disposal to generate a better understanding of MPS. The ability to do longitudinal studies and measure responses to interventions is particularly exciting.
- Fatty infiltration of muscle occurs with aging, but it is not clear that MPS is more prevalent among older adults. The role of fatty infiltration in MPS is unclear. Fatty infiltration results in loss of muscle density and strength, which could result in changes in posture and/or movement that could lead to disease mechanisms. Good methods for bedside monitoring of muscle loss are needed to better look into these relationships. Dr. Klatt noted that fitting rheological models to multifrequency elastography data can help provide insight into mechanical differences associated with differences in fat content within a tissue.
- MRI is a well-developed technique for measuring the volume of fat (i.e., tissue composition), but other types of methods are needed to look at mechanical properties. The ultimate goal is a noninvasive measurement that correlates with treatment response.
- It is important to do elastography measurements when a subject is in a relaxed position.
- Dr. Ehman explained that his group's observations of movement using MRI were done using a phase contrast technique. This approach leverages the fact that the phase of an MR signal is affected by motion. Vibrations as small as the wavelength of light can be observed with MRE. This approach has not been fully explored, but it has tremendous potential for studying myofascial interfaces. Dr. Ehman confirmed this approach could be used to look at the spine using either mechanical waves or cyclic motion.
- Dr. Myers noted that, as a surgeon, he has observed clear differences in the density and characteristics of fat in different patients. Dr. Sikdar noted that differences in muscle are observed via ultrasound. It would be interesting to determine whether these differences correlate with MPS. Techniques that evaluate the mechanical properties of fat could help with this. One challenge of studying tissue biomechanics is the need to distinguish disease-related changes from normal age-related changes.
- It may be informative to compare changes in tissue structure, function, and physiology observed in MPS with those observed in other muscle pathologies. It is likely that MPS is not a homogeneous disorder. There may be multiple underlying drivers of the set of symptoms and observations that lead to an MPS diagnosis.

# **Questions and Answers From the Zoom and Videocast Audiences**

- *Could elastography be used to image intra-abdominal or intrathoracic adhesions*? Dr. Ehman noted that this could be a potential application for MRE, but it has not yet been developed. Imaging of abdominal adhesions is difficult. It would be theoretically possible to fill the abdomen with vibrations and look for the loss of shear interfaces to identify suspected adhesions, but this has not been done. Dr. Parker added that ultrasound elastography has been applied to the bowel; however, MRI has an advantage when it comes to three-dimensional assessment of large volumes, particularly when there may be gas present.
- In phase contrast MRI, how is myofascial interface movement differentiated from blood flow movement? Dr. Ehman explained that the blood flow is unidirectional during measurement. For MRE, motion caused by the exact frequency of the applied motion is measured; other movement is ignored for measurement purposes.
- *Are there protocols for MPS treatment at NIH?* Panelists were not aware of trials being conducted at the NIH Clinical Center.
- *How is MPS treated? Are anti-inflammatory agents effective?* The primary treatments for MPS are injections (either with lidocaine or dry needling) into MTrPs, followed by massage or exercise. Dr. Tick noted she prefers dry needling to injections, in part because more areas of the body can be treated. Exercise is essential to maintain the treatment effect. It also is important to address factors like sleep and stress. There are no pharmaceutical treatments with clinical evidence of effectiveness against MPS. The benefits of nonsteroidal anti-inflammatory drugs (NSAIDs) for treatment of MPS have not been tested. There does not appear to be a strong inflammation component to MPS, though there could be changes in the localized milieu of inflammatory substances. Dr. Barbe noted that it is not beneficial to dampen all inflammation, and NSAIDs can have a negative effect on muscle repair. In her animal models, ibuprofen initially was beneficial but ultimately resulted in more damage because it masked the pain, which removed the incentive for the animals to avoid damaging behaviors. Dr. Tick added that NSAIDs are associated with a rebound effect and negative side effects. An anti-inflammatory diet can be effective if patients adhere to it. Turmeric is an example of an anti-inflammatory without adverse effects.

# Session 4: Emerging Promising Technologies for Myofascial Pain Syndrome: Electrophysiology, MRI, and PET

# Session Chair: Alex Tuttle, NINDS Session Cochair: Chuck Washabaugh, NIAMS

# Innovations in PET for Future Applications in Myofascial Pain Syndrome

Abhijit J. Chaudhari, University of California, Davis

PET has lower spatial resolution than other imaging modalities, but it has high sensitivity and provides quantitative, nondestructive assessment of molecular and cellular targets. PET imaging involves injection of a radiotracer, detection of annihilation photons using a PET scanner, and application of image-processing methods to create images of radiotracer distribution. PET has played a limited role to date in characterization of myofascial tissue and MPS; however, recent advances in PET radiotracers and instrumentation are providing new opportunities. Modern PET scanners are capable of total body coverage and can generate higher resolution images more quickly and with lower radiotracer doses. Whole-body scanning also is available for animal models, which facilitates translational research. Modern radiotracers have improved specificity, and radiotracers are now available for many molecules and cells.

Radiotracers are available to target different molecules and processes involved in inflammation (e.g., <sup>18</sup>F-FDG for glucose metabolism, TSPO for macrophage activation and infiltration). <sup>18</sup>F-FDG also can be used to observe fatty infiltration and perfusion. Improvements in imaging approaches may facilitate use of <sup>15</sup>O-water or <sup>11</sup>C-butanol for study of blood flow. PET also can be used to study drug biodistribution in animal models and humans.

# Application of Techniques That Assess Physiological and Metabolic Parameters of Skeletal Muscle To Advance Our Understanding of Myofascial Pain Syndrome

Espen Spangenburg, East Carolina University

Different muscles have different composition, which can significantly impact muscle function. Differences in mRNA and protein expression have been documented across different muscles. There likely are differences among fascial tissues from different parts of the body as well. Ideally, imaging will take differences into account and collect information on both structure and function.

Laser Doppler imaging allows assessment of limb perfusion, and near-infrared spectroscopy can be used to assess muscle oxygen content in both animals and humans. There are both invasive and noninvasive techniques for assessment of mitochondrial respiration. Imaging techniques such as MRI can be used to measure muscle volume. Muscle strength is a strong predictor of myofascial pain and can be measured invasively and noninvasively. In animal models, the animal can be anesthetized, a stimulus can be applied to the motor neuron, and muscle activation can be measured. Measurements also can be made in humans, albeit with more sophisticated equipment. Muscle quality (force/size) also is an important measure that correlates with mortality in humans. Invasive and noninvasive assays are available to measure various regulators of muscle strength, including nuclei (invasive only), capillaries, sarcoplasmic reticulum, sarcolemma, mitochondria, tendons, and sarcomeres (invasive only).

# **Electrophysiology Techniques and Potential Applications for Myofascial Tissues**

Seward Rutkove, Beth Israel Deaconess Medical Center, Harvard University

Electrophysiological approaches may offer insight into motor and sensory dysfunction in the muscle and nerve; however, to date, peripheral electrophysiological techniques have been applied only in limited ways to the assessment of myofascial pain. Electrical excitability testing (also called threshold tracking) is a series of "stress tests" to the peripheral nerve and muscle to measure motor and sensory neurons. The tests include conditioning stimuli (hyperpolarizing or depolarizing pulse) followed by a test stimulus. The response under different conditions provides insight into the nerve and muscle function; different types of outputs provide insight into different channels and mechanisms. No work has been published to date on myofascial pain.

Electrical impedance myography (EIM) can provide information on muscle morphology and composition using surface electrodes. EIM is a bioimpedance-based technique that involves application of a weak, high-frequency, alternating current to an area of muscle and assessment of resulting surface voltage, which provides insight into tissue resistance and reactance. EIM is similar to ultrasound in that it applies energy to a tissue (electrical vs acoustic) and looks at transmission rather than reflection. EIM does not generate an image but provides information on tissue composition (e.g., fat, connective tissue, edema), myofiber size, fiber organization, muscle shape and size, and muscle fatigue. EIM can be done using different approaches in animals and humans. Stimuli can be applied at the surface or via a needle. An EIM needle able to collect standard myography and muscle impedance data is being developed. EIM also can detect changes associated with disease (e.g., amyotrophic lateral sclerosis, Duchenne's muscular dystrophy), aging, and changes in load bearing (e.g., partial gravity, during/after bone fracture healing). Impedance data also can be used to predict muscle fiber size. EIM in lumbar paraspinal muscles of patients with chronic low-back pain revealed decreased phase compared with healthy patients and left-toright asymmetry. The reason underlying the asymmetry is unknown. Some people may be less excited about adopting electrophysiological methods since there is no image, but they may be of value because they are easily quantifiable and can be generated relatively quickly and easily.

# In Vivo Imaging of Tissue and Muscle Microstructure

Els Fieremans, New York University Langone Health

MRI has millimeter-scale resolution. Diffusion MRI extends this resolution to the micron scale through measurement of the random movement of water molecules in tissues. Muscle diffusion MRI provides a range of biomarkers that are sensitive to microstructure and microcirculation that could be used to study muscle pathology in MPS. Diffusion tensor imaging (DTI), the most commonly used form of diffusion MRI, can provide quantitative biomarkers on skeletal muscle microstructural integrity. Diffusion MRI and DTI are sensitive to changes in fiber size, tissue permeability, inflammation, edema, fat infiltration, fibrosis, and perfusion. Higher cellular specificity can be achieved using simulations and modeling. Time-dependent DTI can be used to determine myofiber size. The random permeable barrier model (RPBM), which has been validated in multiple models, predicts muscle fiber size, surface-to-volume ratios, and permeability. RPBM detected an increase in muscle fiber size over time during muscle recovery following immobilization due to a bone break. The RPBM method also detected the expected myofiber dilation with exercise, while this dilation is notably absent in patients with chronic exertional compartment syndrome. Intra-voxel incoherent motion (IVIM) can be used to measure perfusion of the muscle. The perfusion fraction is different in different muscles at rest and after exercise. Larger changes in IVIM than DTI were observed following exercise in one study.

# **Panelist Comments**

# Vania Apkarian, Northwestern University

It is unfortunate how few of these technologies have been used for pain research to date. Dr. Apkarian urged further discussion about how these technologies could be used specifically to look at peripheral factors involved in pain. For example, can stimulus response curves be generated for muscles in the back? Can DTI be done to look at the fascia and connective tissue in the back?

# Mark D. Does, Vanderbilt University

Dr. Does has worked on sub-voxel tissue characterization with MRI. Research in this area is a cyclic process that involves modeling the tissue, developing methods to probe that model, and developing computational methods. Validation of findings is challenging.

# Jordi Serra, King's College Hospital, London

Researchers at King's College have developed microneurography for clinical use. Microneurography is routinely used to evaluate patients with pain, including patients with small fiber neuropathies and chronic myofascial pain. These analyses have shown that pain in these patients is caused by spontaneous discharge of C-nociceptors in the periphery. Microneurography also has shown that the majority of fibromyalgia patients have abnormalities in the peripheral nervous system.

# Samuel R. Ward, University of California, San Diego

The Ward laboratory uses animal and human tissue to study the biology and physiology of chronic diseases of the shoulder and spine. Biological changes sometimes create competing demands on imaging signals, creating challenges for interpreting images. To address this, tissue samples are being used to generate both *in silico* and *in vitro* models of muscle disease that allow analysis of imaging signal changes with perturbation of one or more biological variables. This enables better understanding of clinical images. Direct analysis of tissue is a good idea until imaging signals can be better understood.

# **Panel Discussion**

- Muscles can release a variety of substances, including lactate, anti-inflammatory cytokines, and other metabolites. These substances could activate processes associated with pain (e.g., through activation of fibroblasts or macrophages). It is important to determine if and how these substances interact with the fascia. Animal models with genetic mutations in genes of interest can help address these questions. Translation to humans will be a larger challenge.
- The potential role of muscle fiber types in myofascial pain was discussed. Different muscles have different proportions of fiber types. It is unclear based on current evidence whether one fiber type is more susceptible to pain and/or whether the different fiber types release different substances. Dr. Ward noted that there are large animal data suggesting that there are differences in the susceptibility of type I fibers and type II fibers to degeneration. This may be something to explore in the context of myofascial pain. Dr. Rutkove added that many astronauts develop chronic back pain while in space, which may be related to the shift from type I to type II fibers. It will be challenging to determine whether one fiber type plays a dominant role in pain using noninvasive approaches.
- It would be interesting to determine whether and how muscles and muscle fibers change in the presence of painful stimuli. Are there changes in excitability or other muscle properties? There could be changes common among all pain conditions. It is known that muscle immobilization causes instability of the muscle membrane, which, to some extent, causes excitability of the myofibers. It is unclear how this relates to neuronal or small fiber changes and/or to pain.
- EIM data presented by Dr. Rutkove showed high variability in impedance among healthy children as they entered puberty. The variability was lower among children with muscular dystrophy. Dr. Rutkove acknowledged that the variability observed in healthy children could be due to changes in the muscle or connective tissue or increased fat deposition. All of these factors could contribute to impedance, and it is difficult to distinguish between them using surface measurements. The source of the impedance is clearer when needles are used.
- Dr. Does asked Drs. Rutkove and Fieremans to comment on the sensitivity of their respective models on confounding factors (e.g., fat infiltration). Dr. Rutkove acknowledged that the presence of several confounding factors in complex pathologies makes it more difficult to interpret results. Dr. Fieremans noted that some confounding factors can be addressed to some extent. For example, fat suppression can be done in diffusion MRI to minimize the role of fat, but fatty infiltration may still affect the signal. She emphasized that validation of models is critical. The Ward laboratory is doing sophisticated realistic geometries based on numerical simulations and phantoms to validate methods. Histology studies in animals and imaging of well-characterized changes in humans can be used for validation. Cross-validation with other methods (e.g., arterial spin labeling MRI) also can be done.
- Dr. Apkarian stated that it would be informative to collect images of the brain and back (or other muscles) during the same scan to allow assessment of correlations between brain and muscle properties. Dr. Fieremans noted that the technologies and methods needed for this type of study are available. Many techniques developed for brain imaging can be applied in other areas of the body. Diffusion MRI is ready for clinical research applications. A grant application could be developed to look at this type of question.
- Whole-body PET imaging is not widely available in the United States at this time. Historically, commercial vendors have not been interested in making these machines because of the high cost. The first machines have become available only in the past few years. The PET EXPLORER

machines at the University of California, Davis and the University of Pennsylvania are currently the only ones in the country. About 20 similar systems are being used clinically in China. The manufacturer, United Imaging, has a long-term plan for marketing in the United States. It is unlikely that whole-body PET will be standard at all hospitals, but it may be available as a core resource. Companies also are increasing the field of view for other machines. Some scanners now image up to a 1-meter field of view. This does not allow whole-body scanning but does allow simultaneous imaging of multiple parts of the body.

- None of the speakers or panelists were aware of data on the effect of peripherally active analgesics (e.g., NSAIDs, steroids) on the parameters measured by various imaging techniques in muscle. Dr. Chaudhari noted that PET has been used to measure changes in glucose metabolism in rheumatoid arthritis patients treated with NSAIDs and in the brain in the presence of opioid analgesics. There also have been PET studies of radiolabeled cyclooxygenase-2 (COX-2) in the context of swelling. Other participants noted that the reduction in inflammation with NSAID treatment could affect signals (e.g., T2 signals in MRI, water content as measured by MRI or impedance), although the effects may be too small to measure. Dr. Spangenburg stated that the impact may vary across NSAIDs depending on the local mechanism of action. NSAIDs can negatively impact muscle recovery from acute injury, so there is an impact on the biology of the muscle. Dr. Ward clarified that NSAIDs impede biological recovery of the muscle, but it is not clear whether they impede overall performance recovery in humans because performance is determined both by muscle biology/physiology and pain/motor control. Dr. Langevin added that NSAIDs may affect natural inflammatory response recovery processes.
- Dr. Majumdar noted that phosphorus spectroscopy has been used in the past to look at muscle fiber types, fiber type conversion, and pain. However, its potential role in studying myofascial pain was not raised by speakers and panelists. Dr. Spangenburg suggested this is likely because experts in this area are not present at the meeting. He noted that Marcinek at the University of Washington likely would champion a role for phosphorus spectroscopy in providing unique insights into myofascial pain.
- Potential tools for measurement of tissue pH were discussed. Using microdialysis, Dr. Shah found that the pH of active MTrPs is as low as 4 or 5, which could affect acetylcholinesterase and other factors. Dr. Sluka noted that acid-sensing ion channels could be activated at slightly acidic pH levels (e.g., 6.8). These channels may even be activated at pH 7 if other factors sensitize the response (e.g., inflammatory substances). MR spectroscopic imaging-including phosphorus or proton spectroscopy—could be used to detect pH. Dr. Damon noted that MR spectroscopy could measure pH down to centimeter-level resolution, particularly if a 7 Tesla field were used. Palpable MTrP lesions are a few centimeters in size, although the lesion may be smaller (millimeter scale). Dr. Damon suggested phosphorus spectroscopy could be used to measure phosphocreatine:inorganic phosphate ratio or postcontraction phosphocreatine resynthesis. Phosphocreatine:inorganic phosphate ratio is somewhat nonspecific but may be useful as a predictive biomarker. Postcontraction phosphocreatine resynthesis, which would require an exercise challenge, is an indicator of oxidative metabolic rate. Saturation transfer experiments once were thought to be a proxy for oxidative metabolic rate at rest, but this now is known to be an oversimplification. For proton spectroscopy, the carnosine peak is pH sensitive. Both phosphorus and carnosine are intracellular metabolites, so these signals would reflect intracellular pH. Dr. Damon noted that Gillies has used a pH-sensitive contrast agent to image cancer. There also may be semivalidated chemical exchange saturation transfer (CEST) or PARAmagnetic CEST methods that could be of use. Dr. Chaudhari added that the PET radiotracer <sup>11</sup>C bicarbonate, which has been used in cancer, may also allow measurement of pH.

• The ability to measure extracellular pH or other extracellular markers is still a gap. Invasive microdialysis can be done to analyze the extracellular milieu, but there are no imaging tools to do this. More options are available for animal studies (e.g., intravital imaging).

# **Questions and Answers From the Zoom and Videocast Audiences**

- In Dr. Rutkove's data, was the EIM left-to-right asymmetry observed in lumbar paraspinal muscles of patients with low-back pain measured three dimensionally? Was it measured relative to the whole torso? Alexander technique interventions focus on whole-body schema and proprioception that can address asymmetries through proprioceptive awareness. EIM may be a useful outcome measurement research tool. Dr. Rutkove reported that the data for this experiment were collected sagittally along the length of the lumbar paraspinal muscle. No comparisons were made relative to the rest of the torso.
- Do you think the small fiber neuropathy observed in fibromyalgia is a causal factor or an epiphenomenon? Dr. Serra stated he thinks it is pathogenic. He noted that abnormalities observed in fibromyalgia patients are in cutaneous nociceptors, not in nociceptors coming from the muscles. There are many "mystery diseases" (e.g., chronic dry eye, burning mouth) that are now collectively thought to be due to underlying abnormalities in peripheral nociceptors. Dr. Apkarian asked Dr. Serra to comment on the correlation of C fiber activity and localized pain perception. Dr. Serra responded that not every C fiber action potential will be experienced. He has investigated both temporal and spatial summation constraints on perceived pain. Temporal factors were not correlated with pain; however, there was a strong correlation between pain and the number of fibers simultaneously discharging. Thus, the spatial summation of factors appears to be more important than temporal summation with respect to pain. This may explain why existing antineuropathic drugs acting in the periphery have not been very effective. Dr. Serra added that while a single action potential in large myelinated Pacinian corpuscles will be perceived, more than one action potential is required for perception in the C fiber nociceptor system.
- Segmental sarcomere contraction is thought to be associated with MTrPs and/or taut bands. Can imaging help identify segmental sarcomere structural changes or ion channel changes (e.g., K<sub>ATP</sub> channels) associated with muscle function? Drs. Spangenburg and Ward agreed that it would be difficult to directly measure sarcomere structure or ion channels using noninvasive imaging approaches. Dr. Spangenburg suggested it may be more feasible to measure downstream physiological changes. Dr. Ward noted that it may be possible to cannulate the muscle and perform two-photon microscopy; however, given that needling is used to alter physiology, there are concerns that cannulation also could affect physiology.
- Studies have suggested there is a 17-year lag between evidence and practice. This is likely due to many clinician barriers (e.g., lack of time, lack of training to appraise research). Being knowledgeable about research is substantially different than making use of it. How do the speakers and panelists envision their research being applied by allied health practitioners (e.g., occupational therapy, physical therapy, speech therapy)? Dr. Ward noted it is important to include health practitioners on research teams. There is a field of research devoted to dissemination and implementation. This is a complicated issue. Dr. Sluka added that understanding the pathophysiology of a disease will lead to development of better treatments. The pathophysiology of myofascial pain is not yet understood. More needs to be done in this area. She expressed optimism that the internet would facilitate faster implementation of clinical trial findings.

# Session Five: Emerging Promising Technologies for Myofascial Pain Syndrome: Tissue Engineering, Artificial Intelligence, and Computational Modeling

# Session Chair: Yolanda F. Vallejo, NIDCR

Session Cochair: Theresa Hayes Cruz, National Center for Medical Rehabilitation Research (NCMRR)

# Quantifying Associations Between Paraspinal Muscle Quality, Spinal Pathologies, and Skeletal Biomechanics

Jeffrey Lotz, University of California, San Francisco

Low-back pain is the leading cause of disability worldwide. The target for back pain diagnosis and therapy is typically the intervertebral disc; however, disc degeneration does not always correlate with pain. The challenge is to disentangle the multiple factors that contribute to the complex condition of lower back pain. Paraspinal muscles (PSM) work synergistically with vertebral discs, vertebrae, and ligaments to stabilize posture and movement. A longitudinal study found that changes in the fat fraction of the PSM—specifically, the multifidus—as measured by IDEAL (iterative decomposition of water and fat with echo asymmetry and least squares estimation) MRI were consistently observed in astronauts with back pain after return from zero gravity. The loss of stabilization significantly altered posture and motion. These observations may be relevant to clinical presentations of chronic lower back pain. Cartilage endplate damage as measured by uTE MRI also is associated with lower back pain; however, the presence of high-quality multifidus can compensate for this pathology and reduce the risk of pain.

Global biomechanics can be assessed using noninvasive motion capture with depth mapping, and these data can be used to generate biomechanical models scaled to the individual. This approach allows longitudinal measurement of postural stability following surgery. ML can be used to define and classify distinct patterns that reflect different compensatory strategies to mitigate load on the spine, thus informing rehabilitation strategies.

The NIH Back Pain Research Consortium (BACPAC) aims to identify validated biomarkers and define clinically relevant phenotypes that allow alignment of pain mechanisms with treatments, thus informing clinical decision making. Initial results from BACPAC will be generated within the next few years.

# The Role of Machine Learning for Muscle Segmentation and Characterization of Muscle Properties

# Sharmila Majumdar, University of California, San Francisco

Myofascial pain is multifaceted, though research and measurement often focus on one aspect. Artificial intelligence (AI) and ML have not yet been applied in imaging for myofascial pain, but there are opportunities to do so. AI could be used for objective segmentation of tissues, quantitation of alignment, determination of muscle cross-sectional area and composition, evaluation of disc composition and morphology, assessment of nerves, and measurement of endplate changes. AI has been used to assess spinal alignment (coronal imbalance and sagittal imbalance) using x-rays at least as well as a team of two radiologists. Trained models were able to automatically segment MRI data of the thigh and paraspinal muscles in a vendor-independent way. Results correlate with manual segmentation but are highly dependent on the training dataset. Images of disc degeneration, endplate changes, Modic changes, and canal stenosis also have been evaluated successfully using AI. Biochemical data from images also could be integrated into AI models. By analyzing and integrating data from multiple modalities, AI/ML could help create subject-specific musculoskeletal models that include information on alignment, tissue morphology, tissue composition, tissue pathology, and possibly, function. Models also could include results of other tests (e.g., electromyography, functional brain MRI) and patient-reported outcomes, and could be built using derived or raw data. The ability to use raw data opens up the possibility of evaluating

large cohorts. More validation, testing, and deployment are needed to apply AI/ML for myofascial pain, and large, well-curated datasets will help with analyses. Multidisciplinary teams and adequate funding for computational resources also are needed.

# Multiscale Computational Modeling Integrates Biology and Mechanics To Prove New Insights into Muscle Dysfunction

# Silvia Blemker, University of Virginia

The overarching goal of the Blemker lab is to create, validate, and apply computer simulations at multiple scales to provide a new "model system" for understanding and treating muscle tissue. Computer models can integrate the wealth of data from experiments with knowledge about cell behavior and the laws of physics. This can reveal causal relationships, allow investigation of "what if" scenarios, and estimate unmeasurable features to explore questions and generate new hypotheses that inform new experiments and/or treatments. Computer models have been used to explore why some muscles degenerate more quickly than others in Duchenne muscular dystrophy. Numerous mechanisms are known to contribute to muscle degeneration over time, including increased susceptibility to contraction-induced injury as a result of movement and loading, profibrotic state, chronic inflammation, and altered satellite stem cell dynamics. Macro-scale movement biomechanical, micro-scale mechanical, and cellular models have been used to explore these mechanisms.

Mouse models of muscular dystrophy have shown that dystrophic muscles are highly susceptible to damage from eccentric contraction. Models were created to predict eccentric contraction of various muscles during walking, and there was a correlation between predicted eccentric contraction and known patterns of muscle degeneration. The models also predicted how changes in walking patterns could change eccentric contraction, which could inform management. Micro-scale mechanical models were used to look at relationships between muscle fibers, extracellular matrix (ECM), and associated membranes, and fiber membrane strain was determined as a measure of fiber damage. Simulations of different conditions (reduction in transmembrane proteins, fibrosis, fat infiltration) predicted how changes in microstructure influence membrane strain. Results suggest that ECM stiffness significantly influences membrane strain during early disease stages. Cellular dynamic models were used to simulate muscle injury recovery based on the experimentally derived information on the behavior of key players in regeneration. The model was validated in experimental models and modified to simulate different stages of disease. Results suggest that satellite stem cell recruitment predicted regenerative capacity and that collagen density predicted satellite stem cell recruitment.

Multiscale imaging may be useful for providing insight into myofascial pain. The Interagency Modeling and Analysis Group (IMAG), a group of NIH-funded investigators doing multiscale modeling, has an annual meeting that may provide opportunities for interaction between myofascial pain researchers and the multiscale modeling research community.

# Integrating Multimodality Measurement and Multiscale Modeling To Assess Temporomandibular Disorders

# Hai Yao, Clemson University and Medical University of South Carolina

The temporomandibular system is complicated, with multiple joints and muscles involved in movement. Patients with temporomandibular disorders (TMDs) most frequently present with pain, limited or asymmetric mandibular motion, and temporomandibular joint (TMJ) sounds. Multiscale modeling that integrates behavior, anatomy, biomechanics, and cell biology could lead to better understanding of TMD pathophysiology and patient-specific predictions. Body/joint-level measurements, including motion and imaging data, can be combined to predict muscle and joint forces. Oral behavior assessments should be done in natural environments; this is facilitated by smart sensors, such as one to detect the magnitude and

duration of clench during sleep of patients with TMJ pain. Differences in anatomy/morphology drive differences in TMJ biomechanics, including sexual dimorphic patterns. Tissue/cellular-level measurements include second harmonic generation microscopy, 3D diffusion tensor, and 3D fluorescence recovery after photobleaching (FRAP). Body/joint- and tissue/cellular-level data can be combined with subject-specific joint loads to create a multiphysical finite element model capable of making predictions about mechanical, electrical, chemical, and biological features of the system. Behavioral and genetic data also could be integrated into models. These types of multiscale, multimodal models can help with patient-specific diagnosis, risk and progression, and treatment planning.

# **Panelist Comments**

# Lucia Cevidanes, University of Michigan

Dr. Cevidanes has used data science approaches to model and predict TMJ osteoarthritis. Many of the same approaches can be used for myofascial pain. Biological, imaging, and clinical data are captured, combined, and processed, and various analytics tools and ML approaches are used to identify markers and interactions between markers to generate models for TMJ osteoarthritis diagnosis. The goal is to help clinicians with decision making. Long-term analysis is needed to determine whether models improve diagnosis and predict progression.

# Adam Hantman, Janelia Research Campus

Dr. Hantman is focused on systems neuroscience; specifically, how the nervous system produces patterns of activity that guide movement and how feedback regulates motor control. There is possible overlap between motor control and the nociceptive system.

A wealth of multimodal data on myofascial pain are being collected. Are there efforts to create large databases that could be used by the AI community? There seems to be a relative lack of behavioral data. The systems neuroscience field has undergone a revolution over the past few years in annotation of behavioral data, and properly annotated behavioral data could be mined by AI techniques.

# Lealem Mulugeta, InSilico Labs, LLC, and Medalist Performance

Mr. Mulugeta worked on integrative computational methods at the National Aeronautics and Space Administration. His two companies—*InSilico* Labs and Medalist Performance—are based on similar methods and incorporate myofascial techniques. Most of Mr. Mulugeta's work is with healthy populations, such as tactical operators. One client was paralyzed and grew frustrated with the lack of progress during rehabilitation. Mr. Mulugeta was able to use his approaches to help the client regain the ability to pick up a ball and pass it from hand to hand.

# Thomas Myers, University of Rochester

There are three types of data inputs for AI models: demographic data, clinical data (labs, radiographic findings, biopsy results), and real-time data captured by remote patient-monitoring devices (e.g., electrocardiogram, oxygen saturation). AI attempts to make sense of data patterns, while traditional statistics determine the likelihood that a finding would occur by chance. For MPS, data inputs could include chronicity, triggers, patterns of flare, EMG input, biopsy findings, pH, MRI data (e.g., fatty infiltration), elastography, etc. Outputs could include diagnostic subtypes, treatment options, clinical trials, prognostic/predictive factors, and, possibly, a patient activation measure. MPS will need to be clearly defined for AI algorithms.

# **Panel Discussion**

• Dr. Lotz reiterated that his study of astronauts included pre- and postflight imaging to look for evidence of vertebral damage, including endplate irregularities. There was an association between

presence of preflight irregularities and changes during flight and subsequent muscle changes. Bone density measurements were not part of this study. Osteopenia or osteoarthritis were not explored as possible drivers of pain.

- There was strong agreement from several participants that AI and computational modeling are complementary approaches. AI brings a data-driven approach, while computational modeling allows prediction of events that have not or cannot easily be measured. AI can be used to extract data from imaging and other modalities that can be put into computational models. AI and ML often can help extract data more quickly and efficiently than can be done manually (e.g., image segmentation). AI also can be used to distill large datasets and identify important parameters, which can inform and optimize computational models. This helps address uncertainties, which are a downside of computational models. Models perform better when properties are established through data-driven processes. AI approaches could bring the computational physics field closer to person-specific models, which would not have been thought possible only 10 years ago. Participants expressed hope that AI could help computational models incorporate behavioral data.
- In addition to informing computational models, AI also could be used to create purely data-driven models.
- Validation of computational models is critical and challenging. Dr. Blemker noted there has been progress in this area; however, continued work is needed. Models also need to be more representative than they historically have been (e.g., include features of women, multiple racial/ethnic groups).
- Several panelists and presenters emphasized the importance of high-quality data for AI and ML. Data availability is a fundamental issue that should be addressed for pain research. A few initiatives—including BACPAC and HEAL—are working to bring together data generated within their groups. Dr. Majumdar noted that the Osteoarthritis Initiative (OAI) facilitates sharing among four centers. Dr. Apkarian noted that his lab shares its brain imaging data without restriction; however, despite NIH data-sharing policies, many labs do not share their data. There currently are no large-scale efforts to centralize myofascial pain data. This is an area of opportunity. Dr. Blemker noted that other fields have created AI/ML "challenges" to encourage researchers to mine the data and see how they could be used.
- Participants described several related efforts in other fields to harmonize and facilitate sharing of data. Dr. Hantman described work to harmonize single-cell sequencing data generated on multiple platforms. Dr. Majumdar stated that there also are efforts to harmonize imaging data across platforms and vendors, although it has been challenging to keep up with technological updates and to develop and promote use of standards. Dr. Apkarian noted there is a centralized database for Alzheimer's disease data that has been enormously helpful. There are discussions about data and model sharing within IMAG and the Multiscale Modeling Consortium. The Committee on Credible Practice of Modeling and Simulation in Healthcare has been developing rules and guidelines to ensure that models are credible and appropriately disseminated. It may be worthwhile to collaborate with these groups to help determine the best way to address the challenges facing myofascial pain research. Dr. Blemker noted that there will be a session on this topic at the next IMAG meeting.
- Dr. Myers described challenges in obtaining high-quality clinical data for AI/ML. These include substantial variations in quality across systems, lack of interoperability among different electronic health record vendors, regional differences in clinical care, insufficient detail for AI, and databases that better reflect billing than clinical care.

- There was discussion about the appropriate time to engage computational modeling and AI experts. Data on myofascial pain are accumulating. Should modeling and AI experts get involved now, or should they wait until the body of data is more developed? Multiple panelists agreed it would be better to do this sooner rather than later. Dr. Majumdar stated that it would be helpful to get input from AI and modeling experts on study design and data collection so that the data available can be efficiently used.
- If a large, curated database is created, steps need to be taken to ensure data are adequately protected. Standardization also will be important. A balance must be struck between establishing rules about data and fostering innovation.

# **Questions and Answers From the Zoom and Videocast Audiences**

- How promising are myometric devices that look at soft biological tissues for early diagnosis of the causes of myofascial pain? None of the panelists and speakers were able to address this question.
- In addition to looking at the anatomy of multifidi, information is needed on neuromotor control. Injured multifidi are associated with loss of proprioception and sequencing of motor neuron firing, including cocontraction of the transversus abdominis. Could motion models and EMG data be combined to help better understand axial myofascial breakdown? Dr. Lotz noted that in physics-based models, muscle forces need to balance out to create moment in the spine consistent with movement. Asymmetry in muscle activation that arises from the dysfunction of a particular muscle should be measurable. This should be an intrinsic prediction in combined finite element movement models. Dr. Hantman added that his group is looking at how peripheral disturbances affect motor plans in central brain regions (e.g., cortex). In animal models, and possibly in some human models, an electroencephalogram can provide a good assessment of the neural activity that is driving behaviors and how this is influenced by proprioceptive stimuli, including pain. However, well-controlled *in vivo* work in this area remains to be done.
- People with benign hypermobility syndrome have a higher incidence of pain. Based on the questioner's clinical experience, a high percentage of myofascial pain patients also have generalized hypermobility. Has anyone compared noninjured muscles from hypermobile and normal patients? Mr. Mulugeta agreed with the observation that hypermobility often is present in myofascial pain patients. Myofascial release techniques are effective in addressing this type of pain, most effectively when combined with exercise and a noninflammatory diet.
- There has not been discussion at the workshop about referred pain, which is a primary component of MPS. Referred myofascial pain is distinct from referred pain due to nerve compression, although there may be overlap. Are there any thoughts on referred myofascial pain? Dr. Cruz noted that a decision was made not to include referred pain within the scope of the workshop. Dr. Allan Basbaum commented that the myofascia is ideally situated to cause referred pain due to its extensive innervation. This creates challenges for identifying the original source of a patient's pain. He noted that pain is a product of nerves, not muscles.
- Muscles are part of a myofascial unit that is embedded in and integrated with a larger web of tissues that extends from head to toe. Fascial restrictions in one area of the body can influence pain in other areas (e.g., fascial restrictions outside the cranium can result in TMJ pain). Should this influence how researchers are measuring outcomes and determining the sources of pathologies? Dr. Yao acknowledged that this is a challenge. Research on TMJ often has been done in silos, with some researchers focused on the joint and others looking at pain. His group is trying to bring these factors together, but research in this area is not yet fully integrated. Dr.

Myers confirmed the role of distant tissues in TMJ pain, noting that physical therapy for TMJ pain includes postural exercises to strengthen the rhomboids and trapezius. Forward sloping posture extends the cervical spine, which causes tightening in cervical extensors, which can contribute to pain.

# **Session 6: General Discussion**

# Panelist Comments Chair: Wen Chen, NCCIH Cochair: Dena Fischer, NIDCR

#### Allan Basbaum, University of California, San Francisco

Biomarkers that predict patients' pain are needed. Most biomarkers discussed at the meeting are markers of myofascial architecture or other features. More must be learned about what factors actually are driving pain. Pain is perceived in the brain based on signals from nerves in the periphery, and more research is needed to determine how muscles and the myofascia are communicating with the nerves.

There is a strong need to integrate the pain and myofascial measurement research communities; joint meetings are needed. The Dahlem meetings in Berlin—at which 40 scholars from different fields were brought together for in-depth discussions—could be a good model.

#### Christine Chung, University of California, San Diego

Workshop presenters discussed many sophisticated noninvasive techniques to measure tissue structure and function. It is important that the field remember that the most important thing is the presentation of myofascial pain. Researchers should ensure that the sophisticated tools at their disposal are measuring clinically meaningful things that will help address pain in patients. Imagers may need to reset the ways in which they evaluate musculoskeletal tissues. The change observed in chronic pain can be very subtle. The OAI database includes clinical and structural data that should help link structural and functional changes to pain. AI and other tools may be able to help put all the pieces together. This workshop should help the field move forward.

# Kathleen Sluka, University of Iowa

There are multiple players involved in pain, and the roles of each of these factors in activating nociceptors must be elucidated. Most likely, multiple underlying pathological processes result in the clinical manifestation of myofascial pain. Interdisciplinary research is needed to move the field forward. Clinicians, pain scientists, muscle biologists, connective tissue biologists, imaging experts, clinical researchers, basic science researchers, and computer modeling experts should be involved. Standard diagnostic procedures are needed so common language can be used across the field. Criteria were developed for fibromyalgia in the early 1990s and have evolved based on evidence since that time; a group should be convened to develop criteria for myofascial pain.

Clinical studies are needed to understand the pathobiology of myofascial pain. The relationship of various imaging outputs to pain must be established, including on a longitudinal basis. Better phenotyping is needed across pain domains (e.g., pain, function, fatigue, psychological, social, cognitive, sleep). Differences between acute and chronic pain and the transition between the two should be explored. Animal models are needed to study neuronal-nonneuronal cell interactions and the contributions of various key players to pain (e.g., muscle, fascia, immune cells, fat, collagen, ECM). Multiple models and approaches likely will be needed. Research should be done on the molecular mechanisms and the role of central processing in myofascial pain.

# Julie Fritz, The University of Utah

Formation of transdisciplinary teams will be essential to advance research on myofascial pain. These teams should reflect the urgency of the HEAL Initiative and maintain a focus on the translation of findings to accelerate the science to the extent possible. Efforts must be made to determine what imaging results and phenotypic characteristics are unique to MPS. It is important to be able to distinguish MPS patients from those with other musculoskeletal or pain disorders. Imaging and other results also must be integrated with behavioral models. Research on myofascial pain should be synced with the interagency pain strategy, which will include distinguishing high-impact chronic pain from other types of chronic pain.

# Daniel K. Sodickson, New York University Langone Health

Workshop presenters and panelists discussed many exciting modalities that have promise for addressing myofascial pain, including multimodal tools (e.g., PET-MR), multiparametric MR, microstructural and functional imaging approaches, and multiscale modeling. Of note, PET-MR adoption has been relatively low to date despite its potential. Experts in that area are looking for research problems that can leverage the strengths of PET-MR; myofascial pain may be that research area. There are a few modalities that could be useful for myofascial pain but were not discussed much at the workshop, including spectroscopy (e.g., MR or optical spectroscopy), optical imaging, and at-home or point-of-care devices. It may be worth exploring these areas.

Opportunities for exchange between myofascial pain researchers and tool developers—like this workshop—should be created. It is important to leave room for "aha" moments and find ways to create excitement among experts in other fields. Tool developers should realize that myofascial pain is an important problem and that their tools can help. Myofascial pain experts should not dwell on their perceived limitations of imaging; instead, they should tell imagers what metrics they need and see what can be done. To engage the broader community of tool developers, myofascial pain researchers should consider attending and presenting at conferences (e.g., International Society for Magnetic Resonance in Medicine). Conference program planning committees are always looking for opportunities to highlight unsolved problems. Creating public datasets is another way to engage researchers from other fields, including ML experts. Concerns about security and other factors should not get in the way of doing this. Public challenges are a great way to stimulate interest, including the interest of big tech.

# **Panel Discussion**

- Dr. Tick pointed out that pain is subjective. Clinicians and researchers depend on patients' reports of pain, which makes it difficult to identify a biomarker for pain. Myofascial pain also often co-occurs with other conditions. It may be more useful to identify biomarkers for nociception or other events. Dr. Apkarian agreed about the lack of biomarkers for pain, which is similar to the lack of biomarkers for other perceptions like touch and vision. He noted that there are biomarkers that predict future pain, which may be even more clinically relevant than those that correlate with current pain. Dr. Sluka clarified that what is really needed is a biomarker that distinguishes myofascial pain from other types of pain (e.g., neuropathic pain, fibromyalgia). Dr. Basbaum added that biomarkers are needed to inform treatment selection for individual patients in the clinic; to fill this role, biomarker assays must be inexpensive and easy.
- Mr. Mulugeta stated that pain is not always the most relevant outcome to measure. He related that many of his clients who are involved in tactical operations do not experience or report pain in the same way that other people do. Clinicians should focus more broadly on quality of life and functional outcomes, which may be more closely related to mobility, sleep, etc. An integrated approach is needed to address these issues. Computational models may help with this. Dr. Sluka

reiterated that phenotypes beyond pain are needed, as well as comprehensive phenotyping of patients. She noted that some clinical manifestations, such as motion, resolve if pain is effectively addressed, but others do not.

- Dr. Apkarian encouraged the pain research community to embrace the types of technologies discussed at the workshop.
- Dr. Apkarian acknowledged that ML approaches can be powerful but expressed concern that the enthusiasm about them often outpaces the results. ML approaches often lack controlled experiments and fail to validate their outcomes. In his experience, ML tends to overfit data. Dr. Sodickson agreed that ML/AI has limitations, but there are now physics-driven ML approaches that may address some of these concerns. Drs. Apkarian and Sodickson agreed that the pain research community should engage ML researchers.
- Ms. Mundo emphasized that pain can be addressed through touch. The importance of touch often is not acknowledged, and there should be increased awareness and education about this issue.
- Diagnosis of myofascial pain is based primarily on physical examination. Dr. Sikdar stated that ultrasound could help link physical examination results to imaging. Ultrasound could be used as a starting point, with more specific imaging modalities used to dig deeper into findings.
- Dr. Liu explained that the workshop planning committee discussed the potential relevance of MR spectroscopy and optical imaging to myofascial pain; however, they were unable to identify investigators who actively are developing these techniques or using them to study muscle and connective tissue. She agreed with Dr. Sodickson's suggestion that these modalities be further explored. She noted that while optical imaging has many advantages, its low depth penetration may limit its application to more superficial tissues.
- Dr. Liu asked discussants to comment on which technologies are ready or close to ready for use in evaluating myofascial tissue and pain. Dr. Chung stated that many modalities are ready for use. She suggested starting with modalities that are available across multiple institutions to allow for multi-institutional studies. This could include uTE, elastography, and, possibly, MR spectroscopy. Dr. Sodickson agreed with the suggestion of elastography and added multiparametric MR as another option. It is available on thousands of scanners worldwide and can be added to others. Diffusion imaging sequencing also is widely available, although postprocessing may need to be done on a shared basis. PET-MR is well established but is available at relatively few centers.
- There was discussion about whether the near-term focus of myofascial pain research should be smaller, single-institution studies or large, multicenter studies. Dr. Apkarian argued that smaller studies are needed to establish causal relationships between pain and specific measurements. Some baseline mechanistic data are needed before investing in larger studies. Dr. Sodickson countered that imaging can be hypothesis generating and that large datasets could be valuable for discovery. Dr. Majumdar added that myofascial pain is caused by a heterogeneous cascade of events. Establishing correlations likely will require multivariate analyses by interdisciplinary teams. This likely would be most feasible with at least a few key centers. All centers would not necessarily need to have all of the technologies being explored. There could be a core set of technologies and a few ancillary technologies used at only a subset of centers.
- Dr. Ehman noted that the workshop identified many opportunities to follow up on various changes observed in patients with myofascial pain. There is a toolbox of powerful imaging tools and markers that can be used to explore this area. He echoed the sentiment that the imaging field

moves quickly and likely could develop tools to address myofascial pain research questions within a short timeframe. He suggested that small longitudinal studies could be valuable for studying specific targets over time, including changes with intervention.

# **Summary and Concluding Remarks**

### Helene Langevin, NCCIH Director

Dr. Langevin thanked the presenters, panelists, and other participants for an excellent meeting. Common themes emerged, including the importance of the myofascial unit. The presentations collectively identified new ways to think about the causes and various aspects of myofascial pain, including the "active" and "latent" phases. Dr. Langevin suggested the possibility that the myofascial unit may be vulnerable to damage from chronic nociceptive bombardment (e.g., from local as well as segmental sources such as osteoarthritis, disc degeneration). Speakers suggested that low-grade chronic inflammatory processes are present in the myofascial unit of patients with myofascial pain (distinct from acute inflammatory process that occur with injury). Other speakers described muscle contractile dysfunction, hyperexcitability, and taut bands, along with the possibility of an "energy crisis" or excess lactate production due to constant contraction. Potential roles of connective tissue inside and outside the muscle were discussed. The muscle spindle is connected to the perimysium, suggesting that inflammatory and/or fibrotic processes involving fascia could affect the muscle spindle. The muscle spindle also could affect neighboring fibers and possibly could be involved in taut bands. Continuous contraction could create additional nociceptive input that leads to characteristic myofascial pain (i.e., dull ache that is relieved by pressure). The possibility that this pain could be caused by a different kind of C fiber was discussed. Dr. Langevin hypothesized that the combined nociceptive input-from continuous contraction and/or inflammation —could contribute to chronic nociceptive bombardment, creating a loop of nociception that leads to muscle malfunction. Such a mechanism might help relate MPS to other categories of musculoskeletal pain such as low-back pain.

Dr. Langevin articulated several goals. Longitudinal studies with tissue-level measurement must be conducted. These measurements should be correlated with symptoms and collected before and after interventions. Increased understanding of the pathophysiology and innervation of myofascial tissues is needed, as is comprehensive phenotyping.

MPS is complex; it involves multiple systems/domains (nervous, musculoskeletal, vascular) and must be studied on multiple scales (biomechanics, tissue, cell, molecular). It has heterogeneous presentation and dynamic components. Dr. Langevin emphasized the need for a widely accepted starting definition of a clinical syndrome. This should be based on history and physical exam and should identify what is unique about the clinical presentation of myofascial pain. Standard diagnostic procedures and multidisciplinary collaboration networks also are needed. The most promising animal models and tools must be identified, and tool developers must be engaged.

The current workshop brought together clinicians who treat pain with those who use and/or develop tools to begin conversations about possible approaches to research on myofascial pain. Future meetings may focus more on integration with the pain research community.

# **Final Comments**

• Dr. Shah highlighted the potential segmental component of myofascial pain and the importance of the osteopathic model of understanding sensitization and facilitation. He echoed the call for standard criteria and urged the community to think about nonpharmacologic (e.g., dry needling, electrical stimulation, manual) as well as pharmacologic interventions.

- Dr. Sanabria expressed his interest in continuing to engage in this effort. Dr. Langevin encouraged him and others to stay tuned to learn about next steps. She noted that international partnerships may be beneficial since Europe has generated a large body of work on myofascial pain. It is hoped that interest in research on myofascial pain will increase in the United States.
- Drs. Tick and Langevin noted that there is a gap in medical education with respect to myofascial pain. Medical students and residents often learn very little about myofascial pain despite its prevalence. This gap should be addressed.
- Dr. Basbaum stated that the vast majority of pain research is done on the skin, despite the fact that musculoskeletal pain is a larger problem. Additional animal models should be developed to facilitate research on musculoskeletal pain.