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Researchers Engineer Artificial Intervertebral Discs

Contributing faculty for this article: **Roger Härtl, MD**

Spine surgeons at NewYork-Presbyterian Hospital/Weill Cornell Medical Center are using tissue engineering techniques to create and repair intervertebral discs with promising results in animal experiments. If the discs could be engineered and validated for use in patients, they would represent an alternative treatment for the hundreds of thousands of people in the U.S. each year who experience debilitating pain and neurological dysfunction from degenerative disc disease in the neck and back.

Removal of herniated intervertebral discs is the most common surgical spine procedure: 300,000 lumbar discectomies are performed each year in the United States. Eighty to 90 percent of patients report excellent or good outcomes, though 6 to 13 percent experience recurrent disc herniation that requires more complex surgery than the first and is associated with a higher rate of complications and poorer outcome.

"Intervertebral discs are a tricky part of the anatomy. They take on a lot of stress, but have no blood vessels to feed them oxygen and nutrients," said Roger Härtl, MD, Chief of Spinal Surgery at NewYork-Presbyterian/Weill Cornell and Associate Professor of Neurological Surgery at Weill Cornell Medical College, who is leading the artificial disc research.

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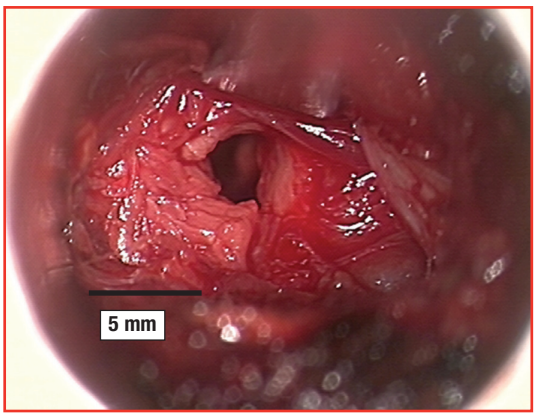

Intraoperative picture demonstrating large annular defect after microsurgical removal of a lumbar disc herniation. A successful repair strategy would aim at filling the defect and sealing it permanently.

Findings Encourage Continuous EEG Monitoring in ICU Patients

Contributing faculty for this article: **Lawrence J. Hirsch, MD, and Stephan A. Mayer, MD**

Nonconvulsive seizures are not uncommon among patients in intensive care units: seizures occur in about a third of patients attached to electroencephalography (EEG) in neurological ICUs and about 10 percent of patients in medical ICUs. That number climbs even higher for patients with sepsis, with 31 percent experiencing seizures or periodic discharges. The longer they go unrecognized and untreated, the greater the risk of brain damage, disability, and death.

Because the seizures are not visible to an observer, they would not be detectable without continuous EEG monitoring. "The only way to know patients are seizing is to hook them up to an EEG. You can't tell just by looking at them," said Lawrence J. Hirsch, MD, Professor of Clinical Neurology at NewYork-Presbyterian Hospital/Columbia University Medical Center and Director of the Continuous EEG Monitoring Program – one of the largest and most academically productive programs in the world.

Dr. Hirsch and his colleagues have reported data supporting the use of continuous EEG monitoring among ICU patients and the value of an invasive form of EEG monitoring, which is even more sensitive for seizure detection, allowing for earlier therapeutic intervention. In addition, the researchers are assessing the correlation between seizure activity in the ICU and long-term outcome, and evaluating biomarkers that may be used to determine the effectiveness of treatments and predict patient outcome.

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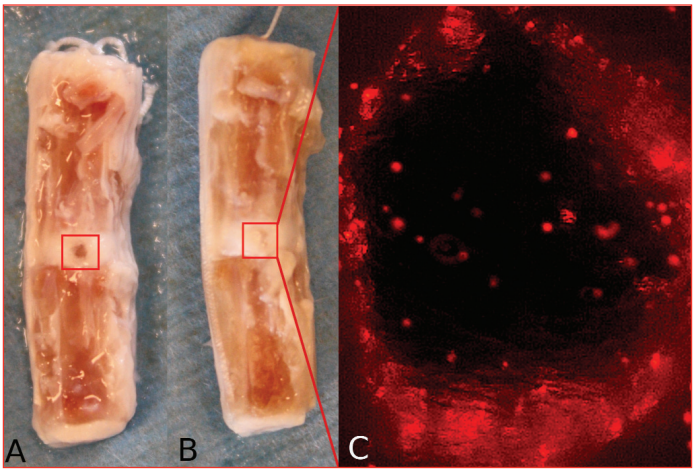


AF defect in motion segment (A.) before and (B.) after collagen gel defect repair. (C) Fluorescent image. The bright spots are the labeled cells that were injected. The background material is collagen matrix.

"A properly tissue-engineered implant would ideally restore function and have the ability to continuously remodel its own structure, in a way similar to a natural intervertebral disc."

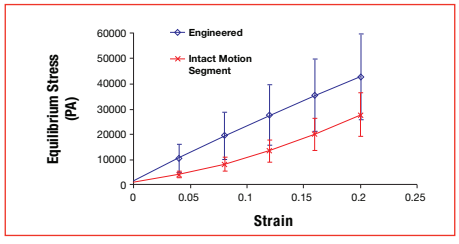
— Roger Härtl, MD

Moreover, recurrent disc herniation results in prolonged debilitating symptoms and higher healthcare costs, not to mention indirect costs such as reduced productivity due to time away from work. "If we can find a treatment to prevent recurrent disc herniation, it would have a profound impact on healthcare costs," added Dr. Härtl. Indeed, a recent review of 141 lumbar discectomies and their follow-up care found that the costs associated with the management of recurrent herniated discs totaled $300,000 per 100 surgeries.

Spinal fusion and insertion of synthetic (metal or plastic) artificial discs are current treatment options for degenerative disc disease. For annular defect repair there is currenlty no effective surgical treatment available. Fusion can result in loss of range of motion, and places the patient at risk of adjacent segment disease above and below the fusion. And in some patients who receive artificial disc implants, the disc becomes dislodged and may need to be removed in another surgical procedure.

Dr. Härtl is collaborating with biomedical engineers at Cornell University in Ithaca to create the artificial discs. Lawrence Bonassar, PhD, Associate Professor of Biomedical Engineering in the Sibley School of Mechanical and Aerospace Engineering at Cornell University, extracted and then recombined cells from the annulus and nucleus of sheep discs. He created an artificial disc in the laboratory with a tissue-engineered annulus fibrosus matrix.

The annulus was made of circumferentially aligned collagen fibrils seeded with sheep annulus cells, and the nucleus was constructed with an alginate scaffold seeded with sheep nucleus cells. Each disc took about two weeks to grow in the laboratory. "A properly tissue-engineered implant would ideally restore function and have the ability to continuously remodel its own structure, in a way similar to a natural intervertebral disc," explained Dr. Härtl.



Top: Mean equilibrium stress strain curves for engineered motion segments (n=5) and intact native motion segment (n=5)

Left: Engineered motion segment mounted on Enduratec testing frame

The researchers implanted the artificial discs between vertebrae in rats' tails and left them in place for six months. MRI scans were obtained to determine the presence of normal annular and nuclear anatomy. They then removed the discs – as well as the bones above and below – and compared them with normal discs that had been removed and reinserted in the same rats (to simulate surgical trauma). They examined them using biochemical and histological techniques: histology to detect the presence of implanted cells; polarized light microscopy to reveal the presence of a continuous collagen network across different tissue boundaries; and biomechanical testing to assess compressive properties and stability.

"These tests showed that the artificial discs were very much the same as the normal discs, and sometimes even better," said Dr. Härtl. The next steps will include evaluating the discs in larger animals, and if those studies show promise, eventually in patients. Dr. Bonassar has been able to grow a disc the same size as a sheep lumbar disc, which approximates the size of a human cervical disc.

These studies would be critical for determining the value of this technology in people – a clinical setting where the discs would be subject to the mechanical loads of standing upright and moving. The discs would have to be strong and stable enough to withstand the types of tensile forces seen in humans. For patients, it might be possible for artificial discs to be created from cells extracted from discs donated by deceased individuals.

The same tissue engineering technology could also be useful for repairing a hole in the annulus that allows nuclear contents to slowly leak out, causing spinal cord compression or sciatica. "Right now there is little we can offer these patients," Dr. Härtl explained. "An effective strategy to repair an annular hole would be a tremendous contribution to medicine."

Even if the technology does not hold up under these stresses, the research will still be of value to the field. "The whole idea of tissue engineering is fascinating," concluded Dr. Härtl. "We're still learning so many new things along the way that could have other applications for improving healthcare."

Virtual Reality Exposure Therapy for Real Consequences of Combat

Contributing faculty for this article: **JoAnn Difede, PhD**

JoAnn Difede, PhD

For more than 15 years, JoAnn Difede, PhD, Director of the Program for Anxiety and Traumatic Stress Studies and an Associate Professor of Psychology in Psychiatry in the Department of Psychiatry at Weill Cornell Medical College, has worked with individuals suffering the consequences of burns, motor vehicle accidents, industrial accidents, air disasters, life-threatening illness, and terrorism as well as with New York City firefighters, rescue and recovery workers, emergency services personnel, and other disaster relief workers. Most recently, Dr. Difede's program received a Welcome Back Veterans Award from the McCormick Foundation enabling the program to offer free psychological services for veteran and active duty U.S. military personnel and their loved ones as part of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF).

An internationally recognized expert in the assessment of post-traumatic stress disorder (PTSD) and a pioneer in the application of virtual reality technology to its treatment, Dr. Difede and her colleagues first became involved in working with the military through their relationship with the New York City Fire Department. "We took care of firefighters following 9/11 so our research was known to them," says Dr. Difede. "The then chief of personnel asked if we could see someone who was in the reserves. This was in 2004, the first year of conflict, and the reservist had mild traumatic brain injury and post-traumatic stress disorder. The Fire Department didn't feel that it was in their medical department's area of expertise."

PTSD became an officially recognized medical condition in 1980 when it was entered into the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders. The disorder is now recognized as one of the most common conditions facing those who have served in combat, often co-occurring with depression and, now, traumatic brain injury as well.

"PTSD encompasses a core constellation of symptoms involving intrusive imagery, re-experiencing symptoms, avoidance of things reminiscent of the event or injury, irritability, anger, and sleep difficulties," notes Dr. Difede. "OEF/OIF veterans, in particular, have been found to exhibit high rates of PTSD. Unlike victims of other traumatic events, returning military often have traumatic brain injury as a confounding condition."

Weill Cornell's Program for Anxiety and Stress Studies was the first clinical program in the Northeast to use virtual reality exposure therapy to treat post-traumatic stress disorder and one of the few VR treatment facilities in the nation when it was introduced in early 2002 following the terrorist attacks on the World Trade Center.

The PTSD system, which depicts the World Trade Center on September 11, was co-developed by Dr. Difede and Hunter Hoffman, PhD, a researcher at the University of Washington. Until this time, cognitive behavioral therapy with imaginal exposure was the first-line therapy for PTSD. "In order to get better, patients must confront what they fear," says Dr. Difede. "A therapist encourages patients to imagine what frightens them and to talk about it. But for many patients, especially those with PTSD or phobias, this can be a problem. Inherent in the ailments is the tendency to avoid fear, and this leaves many patients unwilling or unable to open up."

According to Dr. Difede, this is where virtual reality offers a major advantage. By putting on a virtual reality (VR) helmet, the patient is immediately immersed into a three-dimensional scene. When they look down or sideways, the scenery shifts with their gaze. "It's a sensory rich virtual world that creates an evocative therapeutic environment," explains Dr. Difede. "It encourages the patient to emotionally engage. This is significant because avoiding cues and reminders of the trauma is one of the principal symptoms of the DSM diagnosis of PTSD."

One of the project's initial PTSD patients, a young female executive who survived the World Trade Center attacks, suffered from flashbacks, avoidance (i.e., refusal to watch news reports or stay in tall buildings), sleep problems, hypervigilance to avoid disaster, and irritability. Traditional imaginal exposure therapy was ineffective, and during her initial evaluation for VR, the patient's engagement was limited. With little emotion, she described her experience on September 11.

"It may sound counterintuitive, but we know that the most effective way of overcoming the emotional fragility that marks PTSD is to safely re-expose oneself to the event itself." — JoAnn Difede, PhD

However, upon putting on goggles and entering into the virtual world of lower Manhattan, she saw the twin towers and began to cry for the first time. After six VR sessions, an independent evaluator determined that the patient no longer met the criteria for PTSD, major depression, or any other psychiatric disorder. Her verbal self-report was also consistent with the evaluator's findings.

"It may sound counterintuitive, but we know that the most effective way of overcoming the

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emotional fragility that marks PTSD is to safely re-expose oneself to the event itself. "Virtual reality offers the therapist and patient total control over their environment and the ability to proceed at an individualized pace and desensitize people to their fears in a graded fashion," says Dr. Difede, who served as principal investigator of a National Institute of Mental Health-funded study for the treatment of PTSD following the World Trade Center attacks of September 11, 2001. "We have the person gradually and systematically recount their memory just as if it were happening again but in the context of virtual reality. They're telling their story while watching the story unfold in 3D through the head-mounted display. The goal is to facilitate their emotional processing of the event and extinguish the fear associated with the memory."

Results of the study, published in the November 2007 issue of the *Journal of Clinical Psychiatry*, provided preliminary evidence of the efficacy of VR simulation to enhance treatment for PTSD, with nine of 10 patients with severe PTSD showing clinically meaningful and statistically significant improvement compared with a waitlist control group.

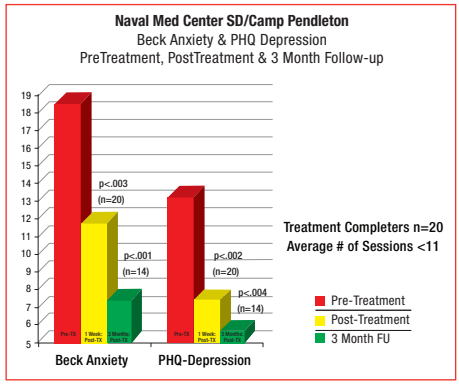
The work pioneered by Dr. Difede in virtual reality exposure therapy for victims of 9/11 now plays an important role in therapy for the nation's armed forces returning from Iraq and Afghanistan. These military conflicts are taking an immense psychological toll on returning soldiers. According to a report in the March 12, 2007 issue of *Archives of Internal Medicine*, of 103,788 OEF/OIF veterans seen at VA health care facilities between September 30, 2001 (U.S. invasion of Afghanistan), and September 30, 2005, more than 30 percent received mental health and/or psychosocial diagnoses. The youngest group of OEF/OIF veterans, 18-24 years old, was at greatest risk for receiving mental health or post-traumatic stress disorder diagnoses compared with veterans 40 years or older. Other reports indicate that at least one out of six Iraqi War veterans are exhibiting symptoms of depression, anxiety, and PTSD.

The "Virtual Iraq" application of virtual reality exposure therapy was developed by Albert A. Rizzo, PhD, of the University of Southern California Creative Technologies Laboratory and Ken Graap of Virtually Better, Inc., with funding from the U.S. Naval Research Office. "The software was beta-tested on soldiers in Iraq," says Dr. Difede. "The two scenarios that came up over and over again involved traumatic memories of convoys driving in the desert and on patrol in a city."

The creators tapped into *Full Spectrum Warrior*, a commercially successful X-Box game and tactical training simulation scenario, for development of the Virtual Iraq application and a new Virtual Afghanistan tool. Scenarios include middle-eastern themed city and desert road environments. Visual stimuli are complemented by directional 3D audio, and vibrotactile and olfactory stimuli when relevant – all of which can be controlled by the therapist, who is in full audio contact with the patient. "Therapy experiences are customized, and the clinician can gradually introduce and control real-time trigger stimuli as required to foster the anxiety modulation needed for therapeutic habituation," explains Dr. Difede, who co-developed the treatment protocol along with Dr. Rizzo and Barbara O. Rothbaum, PhD, at Emory University.

During the initial study conducted at the Naval Medical Center San Diego, the treatment protocol generally consisted of twice weekly, 90-120 minute sessions over five weeks depending on the needs of the patient.

- **Session 1:** During the first session, patients underwent a clinical interview that identified the index trauma and were provided with psychoeducation on trauma and PTSD, as well as instruction on a deep breathing technique for general stress management purposes.
- **Session 2:** In the second session, participants learned how to use Subjective Units of Distress, which is the rationale for prolonged exposure. They also engaged in their first experience of imaginal exposure.
- **Session 3:** Session three introduced the participants to the rationale for virtual reality exposure therapy (VRET) and their first experience with the VR environment absent the trauma narrative or any provocative trigger stimuli.



The first 20 participants in the clinical trial using Virtual Iraq showed improvements in both anxiety and depression scores that were sustained three months post-treatment.

During virtual reality exposure therapy for PTSD, veterans are exposed to several war zone scenes, including driving through the desert and patrolling an Iraqi city.

- **Sessions 4-10:** The participants engaged in VRET while recounting the trauma narrative in the first person, as if it were happening again, with as much attention to sensory detail as they could provide.

Participants were given homework, which included listening to the audiotape of their exposure narrative. This was to reinforce the continual exposure for processing the index trauma to further enhance the probability for habituation to occur. Self-report measures were obtained at baseline; prior to sessions 3,5,7,9,10; and one week and three months post treatment to assess in-treatment and follow-up symptom status. The measures used were the PTSD Checklist-Military Version, Beck Anxiety Inventory and Patient Health Questionnaire-Depression. Initial clinical outcome data from the first 20 patients to complete treatment as of October 2009 indicated that 16 no longer met diagnostic criteria for PTSD at post treatment.

Research is also underway to test the treatment's effectiveness when combined with a low dose of D-Cycloserine (DCS; a broad-spectrum antibiotic), theorized to decrease fear symptoms faster when combined with this therapy. At NewYork-Presbyterian/Weill Cornell, traditional techniques shown to be effective in treating PTSD are incorporated with cutting edge virtual technology and pharmacology in hopes of improving patient care and decreasing the cost that PTSD has on the individual, their family, and society at large.

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Value of EEG Monitoring

Last year, Dr. Hirsch and Stephan A. Mayer, MD, Professor of Clinical Neurology and Neurological Surgery and Head of the Critical Care Neurology Division, published two studies demonstrating the value of continuous scalp EEG and intracranial EEG monitoring in the ICU.

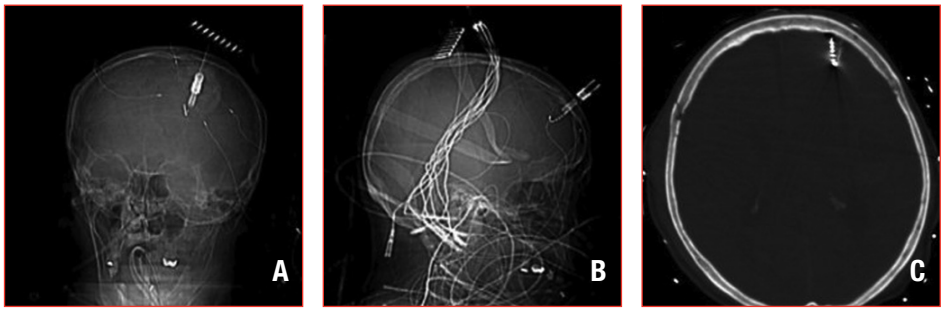
In *Critical Care Medicine*, they reported that most seizures occurring in patients in medical ICUs are nonconvulsive, especially among patients with sepsis. "Sepsis has effects on the functions of all organs in the body, and the brain is not spared," said Dr. Hirsch. "The findings may help explain the enigmatic condition known as "sepsis-associated encephalopathy," in which patients with sepsis become delirious or stuporous.

To determine the long-term effects of ICU seizures in patients with sepsis, Emily Gilmore, MD, a Critical Care Neurology fellow, is conducting a pilot study to prospectively follow patients who were admitted to the medical ICU with severe sepsis or septic shock to evaluate the relationship between septic encephalopathy and EEG findings, and to determine the effects of seizures on patients' cognition at 3 and 6 months after hospital discharge.

"We want to tease out whether seizures are a contributing factor to mental status changes, or if they just serve as a marker for the effects of sepsis on the body," she explained. "We're monitoring cognition because patients' ability to interact with their environment determines how well they return to their normal level of function."

The second study by the investigators, published in the *Annals of Neurology*, compared the use of standard scalp EEG and intracranial EEG in patients in neurological ICUs. The type of intracranial EEG utilized is termed intracortical EEG (ICE), an invasive technology in which a depth probe is placed into the cortex of the brain, and is used mainly in patients with serious acute brain injuries already undergoing invasive neuromonitoring with other devices. More than half of patients undergoing ICE had seizures that were not detectable using scalp EEG. "This was quite a surprise," noted Dr. Hirsch. ICE is now a standard approach used in the neurological ICU at NewYork-Presbyterian/Columbia for select patients.

Dr. Stephan Mayer (center), Dr. Jan Claassen, and Dr. Lawrence Hirsch evaluated continuous scalp EEG and intracranial EEG monitoring in the ICU, showing that most seizures occurring in patients in medical ICUs are nonconvulsive.



Intracranial electroencephalography is an invasive technology in which a probe is placed on the cortex of the brain, and is used mainly in patients with serious acute brain injuries.

As data supporting continuous EEG monitoring for nonconvulsive seizures accumulate, the scalp EEG approach is becoming the standard of care in ICUs.

Individualizing Treatment Approaches

ICE is one of several invasive devices that neurologists use to monitor the brains of seriously brain-injured patients in the neurological ICU. "We need better outcome measures and better ways to assess whether the brain is being injured, so we can more accurately tailor treatment," explained Dr. Hirsch.

Toward that goal, some patients in neurological ICUs have a microdialysis catheter put in place as part of an invasive monitoring "bundle" to evaluate tissue oxygenation, cerebral blood flow, intracranial pressure, and fluid levels of lactate, pyruvate, glucose, and neurotransmitters that may serve as markers of neuronal injury. Patients who experience a rise in the lactate: pyruvate ratio are more likely to have neuronal damage and require more aggressive therapy. "This invasive approach enables us to individualize treatment based on what is happening inside each patient's brain and how their brain cells are responding," Dr. Hirsch noted.

According to Dr. Hirsch, "the NewYork-Presbyterian/Columbia Neuro ICU team, headed by Stephan A. Mayer, MD, is leading the nation in this type of neuromonitoring. For example, Jan Claassen, MD, one of the Neuro ICU attendings who also has specialized EEG training, is studying the physiological effects of nonconvulsive seizures and other EEG patterns in these patients. Dr. Claassen is using a variety of state-of-the-art techniques to do so, including neuroimaging and cerebral microdialysis." What still remains to be determined is how aggressively to treat patients who are having seizures in the ICU. Intravenous antiseizure medications such as fosphenytoin, valproate, levetiracetam, and lacosamide are commonly used, and sometimes propofol and midazolam in patients who are refractory to other agents.

To better determine how well treatments are working, the team is assessing neuron-specific enolase (NSE) as a biomarker of seizure-related neuronal injury and seeking to determine if levels of this enzyme correlate with EEG findings and long-term patient outcome. Moreover, NSE levels can be assessed with a simple blood test.

As data supporting continuous EEG monitoring accumulate, the scalp EEG approach is becoming the standard of care in ICUs throughout the country. Neurologists are witnessing the very early days of neurotelemetry, where patients' brain function is continuously monitored by technologists and signaled by alarms, with data automatically entered onto patients' electronic records.

"In the not-too-distant future, we'll see real-time continuous quantitative brain monitoring with EEGs and alarms in more places," Dr. Hirsch concluded. "It's time we started paying more attention to the brain in the ICU, and not just the heart and lungs."

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