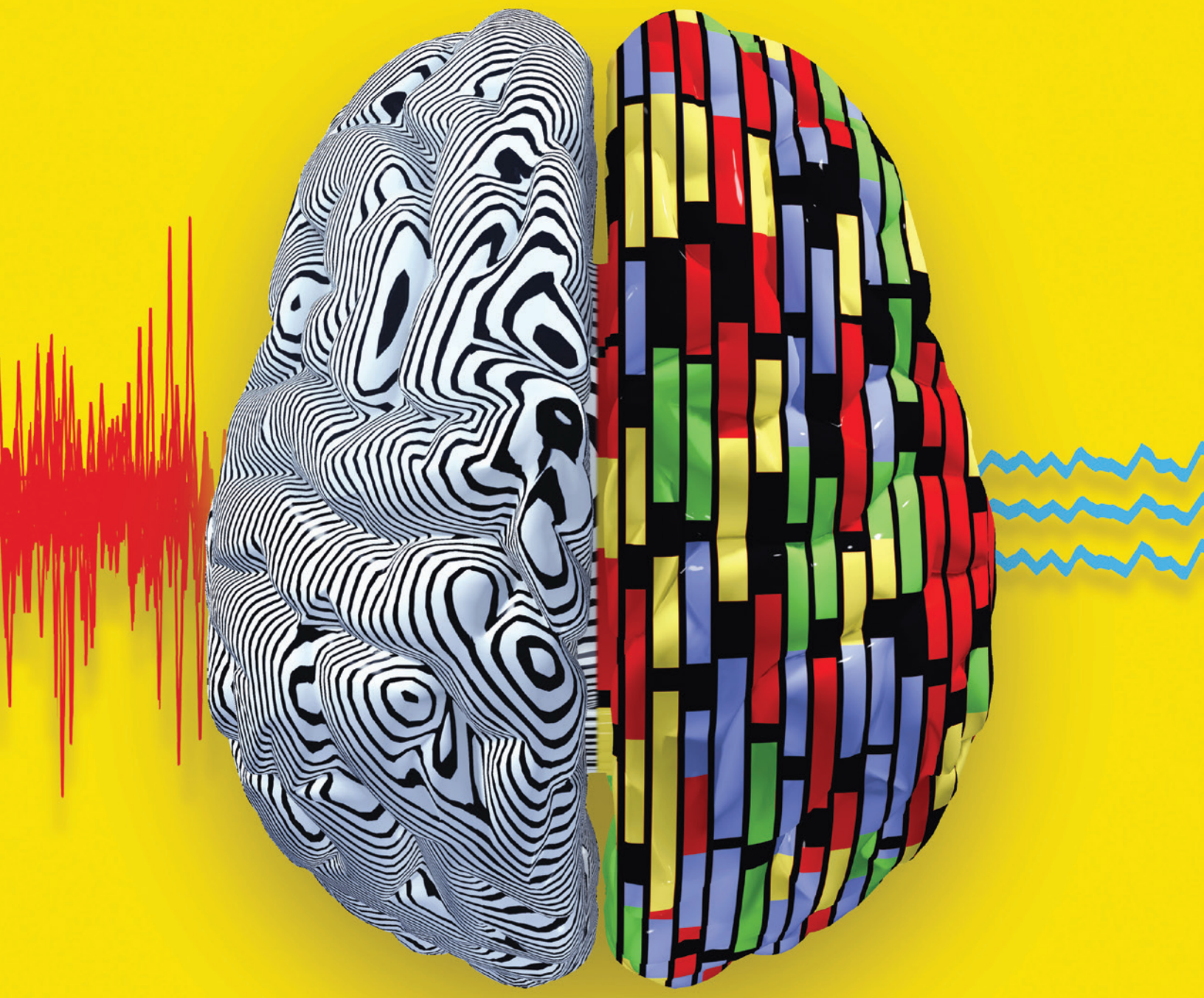
PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // SPRING 2020



MUSC Featured in Microsoft's NextGen Health Podcast

MUSC's innovative approach to artificial intelligence and machine learning was recently highlighted in Microsoft's NextGen Health podcast, which showcases health care's ongoing digital transformation and the ways that technology can streamline operations and care while keeping data secure.

Matt Turner, MUSC's Chief Data Officer, joined the podcast for the recent episode 7 — Saving Patients: Using AI To Fight Sepsis — to discuss a pilot project at MUSC that uses artificial intelligence and machine learning to decrease incidences of sepsis. Turner describes the design process behind his team's projects and explains how the sepsis project could allow patients with rising risk to be flagged sooner than they would have been without machine learning tools. This has the potential to lead to proactive interventions to fend off sepsis.

While many commercial predictive models are available, Turner and his team often create new models or tailor existing models to meet the specific needs of the MUSC organization, its specific electronic health record and the South Carolina populations that MUSC serves. And while the data science team at MUSC works the technical magic, they do it by engaging with a range of clinical experts to understand the state of the art of prediction for the targeted disease state.

Turner says, "We're really proud of our sepsis work and our entire suite of efforts around clinical deterioration, which could be everything from early warning systems to pediatric sepsis, adult sepsis, and other reasons why you would deteriorate while you're in the hospital."

His team continues to work on a range of similar projects to move health care forward.

Listen to the episode by searching for NextGen Health wherever you access podcasts, or link to discover.microsoft.com/next-gen-health-podcast/using-ai-to-fight-sepsis/.

Have feedback on Progressnotes? We'd love to hear from you!

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MUSC Health Medical Video Center

MUSChealth.org/medical-video

A sampling of current videos:

Brexanolone Infusion Provides Fast Symptom Relief for Women with Postpartum Depression

Constance Guille, M.D., a reproductive psychiatrist and the director of the MUSC Women's Reproductive Behavioral Health Program, details the first FDA-approved treatment for moderate to severe postpartum depression.

Duodenal Switch Procedure Technique and Variations

Rana Pullatt, M.D., director of robotic and bariatric surgery at MUSC, demonstrates a duodenal switch procedure and illustrates several technical variations. This procedure is highly effective for patients with significant excess weight (BMI > 50 kg/m^2) and/or diabetes.

Precision Cranial Reconstruction Using Custom 3D-Printed Skull Prosthesis

Nathan Rowland, M.D., Ph.D., shares technical details and sample footage of a unique cranial reconstruction case where the frontal portion of the skull was removed and later replaced using a precisely mapped 3D-printed skull prosthesis.

Bolstering Damaged Rotator Cuff Through Bioinductive Tissue Grafting

Shane Woolf, M.D., discusses a new twist on a procedure to treat rotator cuff disease with partial-thickness tearing and degenerative tendinopathy.

Hyperthermic Intraperitoneal Chemotherapy for Abdominal Cancers

MUSC surgeon **Ramsay Camp, M.D.**, discusses HIPEC for patients with cancer within the peritoneum, which is hard to treat with intravenous chemotherapy.

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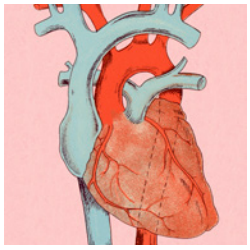
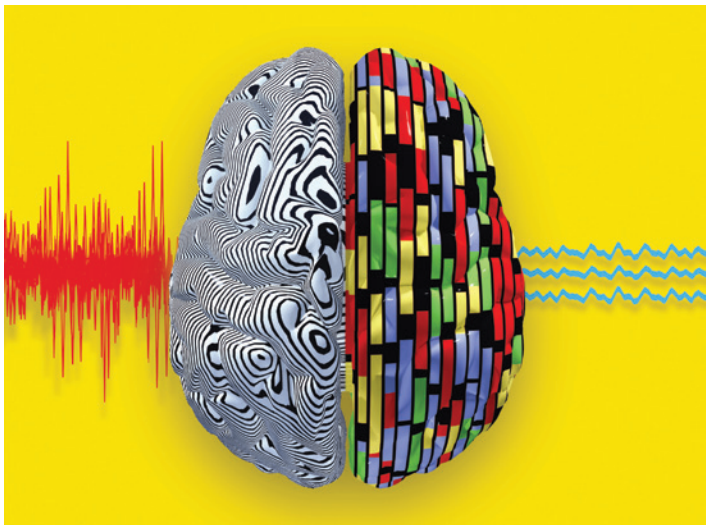




On the cover: Progressnotes looks at the ways that MUSC is using technology to reimagine health care. Illustration by Jean-François Podevin.

MUSC
Medical University of South Carolina

Evert Eriksson, M.D., performs SSRF procedures on patients with fractured and dislocated ribs to decrease complications and improve comfort during recovery.

CLINICAL RESEARCH

Bend and Snap: New Interventions for Rib Fractures

By stabilizing fractured and partially dislocated ribs, physicians can improve patient quality of life

BY CELIA SPELL

When an arm snaps, a leg cracks or a wrist twists, physicians set the bone to ensure it heals properly and with as little discomfort to the patient as possible. But the same cannot be said for most rib fractures.

Past practice and teaching call for little to no treatment, even if it takes months for the patient to breathe normally or just get back to work. The prevailing wisdom has been succinct. "Offer medicine for the pain and a ventilator if breathing is an issue," said **Evert Eriksson, M.D.**, a trauma surgeon at MUSC. "But otherwise, the bone will form a callus over time that allows it to function."

And while that idea has morphed over the last decade to make multiple-fracture repair more common, patients with less severe fractures often still go untreated despite pain.

This extended discomfort is what led Eriksson to join eleven other national centers in evaluating the success of surgical stabilization of rib fractures (SSRF), which involves installing a plate to line up the two ends of the fracture and hold them in place throughout the healing process.

As recently published in the Journal of Trauma and Acute Care Surgery, patients who underwent SSRF for three or more rib fractures with partial dislocation reported less pain on the numeric pain scale and a better quality of life after their stabilization surgery.

"This research shows that patients who have partially displaced fractures as well as some pulmonary compromise also

benefit from a procedure that is generally reserved for a more severely injured cohort," said Eriksson.

Technological limitations have played a role in keeping surgeons from performing this procedure in the past. It wasn't until recently that surgeons acquired the right equipment to keep surgical incisions small and the risk of complications in the pleural space low. By pulling the muscles aside, instead of cutting through them, surgeons are able to access the chest wall and ribs less invasively. Even the material of the stabilization plates has improved, becoming less rigid and moving more naturally with the patient as the chest expands and contracts with each breath, according to Eriksson.

While the level of narcotic use did not change significantly in patients who received SSRF, these patients consistently reported more comfort and less pain at each interview interval than those who had not undergone the operation. The fractured ribs took just as long to completely heal, but the patients' experiences during this process were far superior, and they reported feeling less pain and easier breathing throughout.

Patients also experienced fewer complications from their rib fractures. By opening the chest, addressing any additional injuries, guiding the bones back into position and removing any excess blood from the area, surgeons decreased the chances that study participants would have any additional bleeding or fluid accumulation in that space.

Next, Eriksson wants to look at other bones that are not treated surgically. "I had a patient from this study come to me and say, 'My chest no longer hurts. You fixed that. But now it's my shoulder that's the problem.'"

PHOTO: LAUREN HOOKER

TRANSLATIONAL RESEARCH

Nanoparticle To Deliver Transplant Drug

BY LESLIE CANTU

Organ transplants have allowed hundreds of thousands of people in the United States to add years to their lives. But the procedure is far from perfect. Recipients must take antirejection drugs for the rest of their lives, and these drugs leave them vulnerable to serious side effects.

"In the current state of affairs, people are taking antirejection medications which are going through their whole body," said **Satish Nadig, M.D., D.Phil.**, who holds the P.K. Baliga, M.D. Endowed Chair in Solid Organ Transplantation. "It's preventing early rejection, which is great, but patients are also succumbing to heart disease, diabetes, infections, and failure of the organs that the drugs are supposed to be protecting, because they're toxic to those organs as well."

But the team of Nadig; bioengineer **Ann-Marie Broome, Ph.D., M.B.A.**; immunologist **Carl Atkinson, Ph.D.**; nanochemist **Suraj Dixit, Ph.D.**; and the MUSC Foundation for Research Development has just been granted a patent for a method of delivering antirejection drugs directly to the transplanted organ. The scientists believe that targeting the drugs to the transplanted organ will allow the rest of the immune system to continue to guard against infection and disease.

Nadig was particularly affected by the death of a college-aged patient who succumbed to the antirejection medication. He started thinking there must be a way to target transplanted organs in the same way oncologists target tumors. Broome was excited about the idea.

"The satisfaction and effectiveness of team science is that you come up with a lofty idea and then you delve down and think, where is the low-hanging fruit that you can do quickly?" Broome said.

As they tossed around ideas, they realized that organs often spend hours in transport after being removed from the donor. And what's being done to the organs during that time? Not much.

"That's a prime opportunity where not much is happening other than storage and delivery," Broome said. "It gives us a chance to treat for events that we know are going to happen after the transplant."

So the group began working on an idea to bathe the donor organ in the antirejection drug rapamycin as it was en route to the destination hospital.

Constructing the nanoparticle took quite a bit of work, Broome said. As the nanochemist, Dixit took the lead in figuring out the best elements to use to encapsulate the drug. The group then went a step further by developing a targeting system so the nanoparticle would head to the organ and then rupture upon contact with the endothelium, releasing the drug.

The group tested three ideas: letting the drug float freely in the perfusion solution, encapsulating the drug in a nanoparticle and encapsulating the drug while also adding the targeting effect.

"We were very excited to see that packaging and targeting worked. In fact, we repeated many of the experiments multiple times because we could not believe our eyes," Broome said.

While this research is still in preclinical trials, Nadig said that it could be paradigm shifting. "It's really the next era of transplant," he said.

PHOTO: SARAH PACK

MUSC researcher Kevin Gray, M.D., examined the effectiveness of a common smoking cessation drug on adolescents in a recent study.

NEWS

Smoking Cessation Treatment Targets Adolescents

Researchers seek smoking cessation treatments designed for adolescents rather than adapted from adults

BY CELIA SPELL

Preventable deaths are those that can be stymied by public health intervention, and deaths related to tobacco use are at the top of that list in the U.S. as well as globally.

And while rates of adolescent smoking have declined over the years, 4.9 million middle and high school students reported using tobacco in 2018, according to the U.S. Department of Health and Human Services.

The primary focus of smoking cessation research in the past has always been adults, but a new study in JAMA Pediatrics zeroed in on adolescents. "Too often, we make the assumption that adolescents are just little adults," said **Kevin Gray, M.D.**, a psychiatry and behavioral sciences professor and physician at MUSC. "And so we treat them the same way as we do our adult patients. But it's much more complicated than that."

One of the key differences in treating adolescents is the pressure surrounding their smoking habit. Adolescents are more likely than adults to start using addictive substances, especially if they're being influenced by peers. They are also more likely to do something risky without considering the long-term consequences. "Most people who decide it's time to quit are well into adulthood," said Gray. "Oftentimes, their health consequences are becoming quite real for them."

Varenicline tartrate, more commonly recognized under the brand name Chantix, is a popular pharmacotherapy for smokers looking to quit. It has proven effective in adults but has not been examined as a smoking cessation tool for adolescents.

Gray and his team found that at the end of a 12-week treatment, there was no significant difference between the placebo group and the treatment group in terms of end-of-treatment smoking abstinence. But when Gray looked at posttreatment abstinence — that is, the number of participants who remained smoke-free even after treatment had ended — he saw that those in the varenicline group were less likely to relapse.

"The group differences at the end of treatment, considered in isolation, may not always be the most important marker of efficacy," said Gray. "The nuanced piece of it is that quitting smoking earlier on in treatment, which in our study occurred in the varenicline group, is a better indicator of a participant's long-term success."

This study showed that varenicline affects smoking cessation in adolescents differently than in adults and may not be an effective treatment on its own. Overall rates of quitting were lower in these trials than in previous adult varenicline trials, a common finding when comparing studies between the two age groups, which may have to do with motivation and life situations. The desire to quit waxes and wanes over time, especially in adolescence. Gray compares it to a dimmer switch as opposed to an on-off switch. He embraces the idea that medication alone likely won't work as well for adolescents as pairing a medication like varenicline with therapy and behavioral treatments, and he looks forward to improving on this treatment process.

CLINICAL RESEARCH

Fragile: Handle with Care

Risk of death remains higher for interhospital transfer patients than for patients admitted via emergency departments

BY SHAWN OBERRATH

Seriously ill patients require serious, higher-level care and sometimes must be transferred from one hospital to another to gain access to procedures, tests or expertise that only an academic medical center can deliver. The benefits of interhospital transfer (IHT) are believed to outweigh the risks, but national studies indicate that transferred patients have a higher risk of dying than patients admitted to the hospital locally through the emergency department. And with about 1.6 million patients transferred between hospitals each year, this safety risk needs to be resolved as a top priority.

While national studies demonstrate worse outcomes for IHT patients, these studies are unable to control for patient-level details such as individual vital signs, laboratory values and specific disease processes. A few single-center studies controlling for patient-level characteristics were performed in the 1980s and 1990s, but health care has changed enormously since then.

Marc Heincelman, M.D., a hospitalist and assistant professor at MUSC, notes that patient safety has become a major target over the last two decades. As he explains, "With the implementation of electronic health records, expansion of hospitalists, and enhanced focus on quality improvement and safety, we need to look at patient-level characteristics associated with transfer."

He led a new study, recently published in the Journal of General Internal Medicine, to examine the safety of IHT within the modern health care system. The research team separated data for about 9,000 hospital inpatients into groups based on how the patients were admitted — via IHT, the emergency department or a clinic. The team then used data modeling to examine the relationship between IHT and the risk of death in the context of individual patient details, such as the receiving hospital service, demographic information, specific disease processes, vital signs and laboratory data.

"We found two interesting things," says Heincelman. "First, detailed patient-level variables do play a role in predicting mortality, and second, even after controlling for those variables, interhospital transfer itself is still associated with inpatient mortality."

The study revealed that while the overall mortality risk was about two times higher for IHT patients than for patients admitted via an emergency department, that risk changed to 1.7 times after the researchers controlled for patients' vital signs and laboratory values. But even allowing for the effect of vital signs and lab values, outcomes for transfer patients were still worse than those for patients admitted through emergency departments.

Heincelman and colleagues next plan to examine the transfer process in detail, looking at factors like the day and time of transfer, the busyness of the admitting service during transfer, the time between the hospital accepting the patient and the actual arrival time, and the accuracy and effectiveness of communications.

"I still think that the patients are inherently sicker; we just don't have a way to measure their illness with models that we currently have," Heincelman said. "But I also think that there are areas within the transfer process that can be improved to increase patient safety."

He hopes that this will lead to better outcomes for patients who need to be transferred from one hospital to another.

PHOTO: SARAH PACK

Bohuslav "Bob" Humplik serves as a pilot for the MEDUCARE Flight Team, which transfers patients by ambulance and helicopter 24/7.

PHOTO: BLINKTBI

EyeStat delivers five light puffs of food-grade carbon dioxide at random intervals to the corner of the eyes over a 20-second time frame to assess the blink reflex.

NEWS

Portable Device To Monitor the Blink Reflex Cleared by FDA

BY BRANDON YOUNG

EyeStat, a portable, lightweight device for measuring the natural blink reflex, received clearance by the U.S. Food and Drug Administration (FDA) in December 2019.

The blink reflex activates when sensory or mechanical stimuli come close to the eye. These stimuli trigger nerves to send a signal through the brain and back out telling us to blink. Ophthalmologists can use the blink reflex to test for a variety of diseases that can cause nerve damage, and neurologists can use it to evaluate brain function.

To elicit the blink reflex, EyeStat delivers five light puffs of food-grade carbon dioxide at random intervals to the corner of the eyes over a 20-second time frame. During those 20 seconds, the device takes over 12,000 pictures to record the natural blink reflex. It specifically measures five things: the time it takes from the moment the air touches the side of the face until the eyelid on the stimulated side begins moving; the lag time between when the stimulated eye begins to move and the nonstimulated eye starts moving; how long the eye stays closed during a blink; the number of blinks immediately after the stimulus; and the distance between the place your eyelid sits when you are simply looking forward and when it is closed.

The FDA clearance enables blinktbi to market EyeStat as a means to measure and display the mechanically induced blink reflex, but not yet as a diagnostic device for particular clinical conditions.

However, blinktbi is currently researching whether the portable device could be used to clinically assess relevant changes in the blink reflex in patients subjectively diagnosed with traumatic brain injury.

"Our clinical trials show our blink reflex changes with any trauma to the brain," said **Ryan Fiorini, Ph.D.**, blinktbi cofounder and chief operations officer.

The idea of creating a more maneuverable device for measuring the blink reflex originated from **Nancey Tsai, M.D.,** an assistant professor in the Department of Neurosurgery at MUSC. Tsai wanted to create a portable blink "reflexometer" to measure the blink reflex of athletes on the sidelines during games to monitor for concussions. She worked with the Zucker Institute for Applied Neurosciences (ZIAN), a technology incubator embedded in MUSC, to take the first steps towards producing a research device that could eventually be commercialized by a company such as blinktbi.

"We built some devices that could do preliminary testing, but they were large and had to be wheeled around on carts, and they had no use as an on-field device. They weren't very practical," said **Mark Semler**, coinventor of the device and ZIAN chief executive officer. "Blinktbi was able to shrink the device to a more usable size and obtain FDA clearance."

EyeStat is currently being sold to high

school, collegiate and professional sports teams around the country to measure the mechanically induced blink reflex. These devices "in the field" are helping blinktbi to collect the data needed to assess whether the device can effectively diagnose concussion.

However, the research being done by blinktbi does not stop there, according to Fiorini. "We are starting multiple studies looking at indications in many different fields," said Fiorini. "Including sobriety testing and early onset of neurological diseases, such as multiple sclerosis and Alzheimer's disease."

With the recent FDA approval, the device has cleared an important hurdle, meaning that an idea that began at MUSC is closer to having a national benefit.

DISCOVERY

Bad to the Bone

Specific gut bacterium impairs normal skeletal growth and maturation

BY MATTHEW GRESETH

The gut microbiome, the collection of microorganisms that colonize the healthy gut, can regulate host biological functions, including skeletal health. MUSC researchers who study osteoimmunology, the interface of the skeletal and immune systems, recently examined the impact of segmented filamentous bacteria (SFB) on postpubertal skeletal development.

Their results, published in the Journal of Bone and Mineral Research Plus, showed that SFB elevated the responses of specific immune cells in the gut and the liver, leading to increased osteoclast activity and decreased osteoblast activity. The cumulative effect was impaired bone mass accrual.

"This is the first known report to show that within the complex gut microbiome, specific microbes have the capacity to effect normal skeletal growth and maturation," said **Chad M. Novince, D.D.S., Ph.D.**, assistant professor in the MUSC colleges of Medicine and Dental Medicine.

To study the effects of SFB and the gut microbiome on skeletal health, the Novince lab utilized a mouse model with a defined microbiota. This research was facilitated by MUSC's Gnotobiotic Animal Core, which is directed by **Caroline Westwater, Ph.D.**, a professor in the College of Dental Medicine.

The Novince lab examined whether the presence of SFB within a complex gut microbiota could influence normal skeletal development. Indeed, the presence of SFB led to reduced trabecular bone volume – the type of bone that undergoes high rates of bone metabolism – and to a proinflammatory immune state in the gut.

Interestingly, the presence of SFB also profoundly stimulated hepatic immunity by upregulating proinflammatory immune factors and increasing T_H17 cells in the liver draining lymph nodes. Furthermore, SFB colonization resulted in increased circulating levels of IL-17A and the antimicrobial peptide Lipocalin-2 (LCN2), both of which support osteoclast activity and suppress osteoblast activity.

These data show that SFB plays a role in regulating the immune response in both the gut and the liver, which has significant effects on the skeleton and provides strong support that gut microbiota actions on the skeleton are mediated in part through a gut-liver-bone axis.

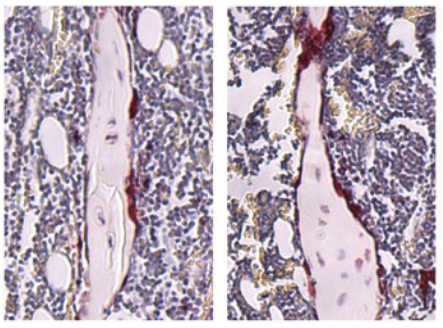


PHOTO: CHAD NOVINCE

Stained tibiae from germ-free (left) and SFB-mono-associated (right) mice. Mice colonized with SFB displayed an increase in osteoclasts (stained red), which resorb bone.

Additionally, the contribution of SFB to skeletal health may have significant clinical implications. It is known that diet, probiotics and antibiotics influence the makeup of the microbiome. A majority of a person's bone mass, approximately 40%, accrues during adolescence. As people age, they slowly begin to lose bone mass, which puts them at risk for fractures and osteoporosis. Modulation of SFB could allow for the buildup or optimization of peak bone mass accrual during adolescence, limiting the risk for aging-associated low bone mass.

"If we can prevent the colonization or deplete specific microbes such as SFB from the microbiome, there is clinical potential to optimize bone mass accrual during postpubertal skeletal development," said Novince.

A Smile Is Born

Surgeons at MUSC use multiple techniques to help children with congenital facial paralysis show their feelings

BY SHAWN OBERRATH

Victor Borge once said, "A smile is the shortest distance between two people." But what if one physically cannot smile? The gap widens.

"Facial paralysis can be a very devastating condition," says **Samuel Oyer, M.D.**, a facial plastic and reconstructive surgeon at MUSC who often works with children. For one of his young patients, he describes that many people in stores or other public places would think she was angry or upset when she was actually trying to smile. This type of misunderstanding can significantly impair positive interactions between people.

Facial paralysis in children is rare but can happen for a variety of reasons. Infections, trauma, tumors and Bell's palsy can all cause damage to the seventh cranial nerve, which is critical for facial movement,

but the cases most commonly seen at MUSC are congenital. And Oyer explains that pinpointing the cause of the paralysis is crucial to determining the correct treatment.

"If it's an ear infection you treat it with antibiotics and maybe ear tubes. If it's a trauma or Bell's palsy you usually wait a little bit and see how much recovery you get," says Oyer. "But if it's congenital it's not going to recover on its own."

Enter the expertise of Oyer and his surgical partners, **Krishna Patel, M.D., Ph.D.**, and **Judith Skoner, M.D.**, who together run the MUSC facial paralysis clinic, one of just a few such centers in the Southeast. For children with congenital facial paralysis, these physicians offer the chance to learn to smile.

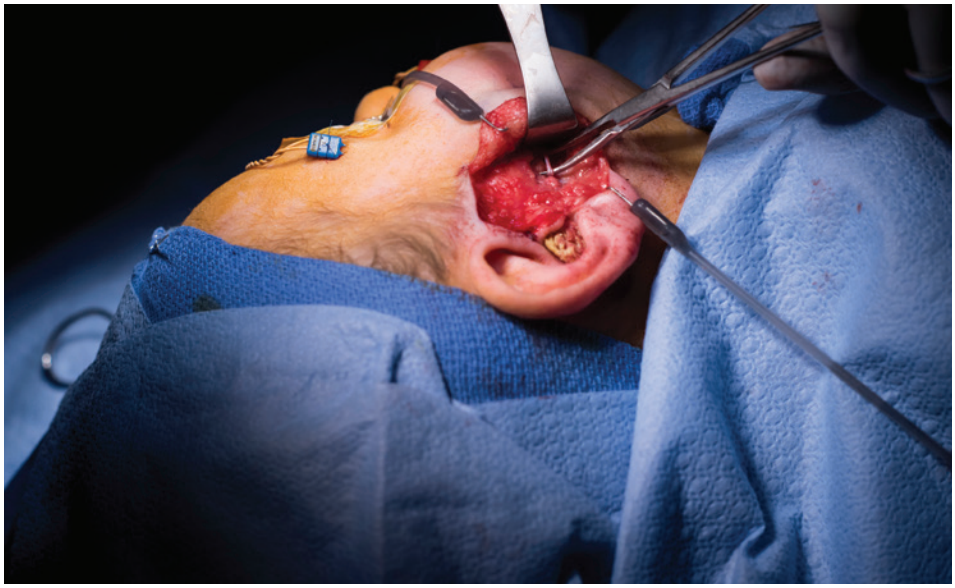


PHOTO: BRENNAN WESLEY

For a patient with a functional masseter nerve, the surgeon reroutes that nerve to a branch of the facial nerve (shown).

There are two main surgical approaches to animating a child's smile. In the first, the surgeon reroutes the child's masseter nerve to a branch of the facial nerve. Once this nerve detour is up and running, the child can learn to grin by clenching the teeth — the new nerve signal triggers the muscles to lift into a smile.

If the child's facial nerve can no longer be stimulated to function or never developed properly, the second approach requires a transplant from a leg muscle, usually once the child has reached at least 5 or 6 years of age. This approach involves facial surgery as well as a leg surgery to remove a strip of gracilis muscle along with intact blood vessels and nerves. The muscle is transplanted to the face and attached to the facial blood vessels and a functioning nerve, which may be the masseter nerve or a facial nerve graft from the opposite side. This is performed painstakingly under a microscope to ensure good blood flow and eventual efficient nerve input to the muscle.

Oyer also notes that the art and technique of the muscle placement determine how natural the smile will look. He says, "If one corner of the mouth has a three-millimeter difference in height compared to the other, the eye will pick it up on a glance."

After several months of tissue healing and waiting for the new nerve to begin firing, patients can start physical therapy to learn to flash their new smile at will.

Sarah Murphy, PT, DPT, works with young facial paralysis patients and their families and is awed by the resilience of these children. "One thing that I think is really wonderful about kids is that they are still so confident," Murphy says, "No matter what is going on."

Murphy spends much of her time on parent education, teaching playful techniques so the family can practice together every day.

The pediatric facial paralysis team at MUSC sees patients from across South Carolina and the Southeast, and they are incorporating telemedicine into their follow-up visits to help patients avoid long commutes to the doctor.

Finally, Oyer stresses that for patients with facial paralysis, the sooner the intervention the better. Intervening within less than two years of paralysis onset gives the highest chance of success, but even with an extended timeline or a congenital condition there are options. "We can't totally recreate what was lost or never formed," Oyer states. "But we can usually take steps to make it better."

PHOTO: SAM OYER

A gracilis transplant patient flashes her smile before (left) and after (right) surgery.

Surge Detection

Physicians use artificial intelligence and new wearable technology to locate, predict and prevent seizures in epilepsy patients

BY CELIA SPELL

Chatter in the brain consists of rapid zaps of electrical impulses.

These impulses travel along a network of synapses and culminate in a brain wave. It's these brain waves that then direct a particular action, thought or emotion. A healthy brain processes each of these brain waves and translates the signal into a response, but when too many neurons send the wrong signals, electrical activity is discharged. Enough misfiring leads to blood pressure spikes, a pounding heart and muscle convulsions — in other words, a seizure.

According to the Centers for Disease Control and Prevention, three million adults and almost 500,000 children in the U.S. had epilepsy in 2015. In 2014, there were 2.5 million traumatic brain injury-related visits to emergency departments in the U.S., and in 2018, almost 600,000 people came to the emergency department for stroke. Any kind of scarring in the brain can lead to an isolated seizure — whether congenital or from an injury — but when someone is diagnosed with epilepsy, they are experiencing recurrent seizures that impact their lives regularly. And it's important to know right away if a patient's seizure is isolated or part of a disease like epilepsy.

Researchers and physicians in the neurology and neurosurgery departments at MUSC are working together to incorporate the latest technology into patient treatment plans to detect seizures and attempt to predict a patient's chances of having another seizure.

"Often, when a patient has severe seizures, their family is scared to leave them at home alone," said **Jonathan Halford, M.D.**, a professor of neurology and director of the translational research unit for the two departments. "Many family members don't feel like they can leave their loved one at home to go to the grocery store in case they have a horrible seizure when no one is there to help them."

Halford looks at seizures as a symptom of a greater disease, illness or injury. "And while treating the symptom doesn't cure the patient, it can help them resume their daily lives." This symptom in particular varies from patient to patient. One patient may have a seizure every week while another has only one a year. But even at such varied intervals, people with epilepsy can't drive, and not knowing when a seizure might occur can produce constant anxiety. "Even though the disease isn't necessarily constant, it's still a significant one to tackle — for both patients and physicians," he said.

The ways epilepsy and intermittent seizures strip away someone's independence as well as their cognitive function and mental health have led physicians at MUSC to work with collaborators at biotechnology companies and other universities to develop new devices, tools and treatment options.

Formulated for speed

Since seizures can affect memory, it is possible for patients to have seizures, potentially daily, and have no recollection of them. Physicians use an electroencephalogram, or EEG, to measure and record healthy brain activity as well as seizure activity.

IMAGE: JEAN-FRANÇOIS PODEVIN

PHOTO: SON NGUYEN

Jonathan Halford, M.D., worked with device company Brain Sentinel, Inc., to develop the first FDA-approved system to detect generalized tonic-clonic seizures using a wearable device that continuously records EMG activity in the bicep.

An EEG is performed by placing electrodes in strategic places all over the skull, almost like a cap. These electrodes read the patient's brain activity for a period ranging from minutes to sometimes even days. Once the EEG recording is complete, a neurologist must pore over the output data: dizzying page after page of horizontal lines and vertical spikes. Physicians spend hours looking for any anomalies and attempt to determine whether a person had a seizure during that period or if they are at risk for another one in the future.

Sarah Schmitt, M.D., an associate professor of neurology at MUSC, is working with multiple centers across the country to create and test a prediction algorithm that uses AI to help physicians learn more from their patients' readings. By tapping into data collected by the Critical Care and EEG Research Monitoring Consortium, the team assessed the validity of this algorithm and rating scale, which is referred to as 2HELPS2B, and found it to be a promising tool for hospitalized patients, especially when a reading was performed over the course of 24 hours, by helping physicians predict which patients were at risk for a seizure in the future. Results were published in a recent paper in JAMA Neurology.

Schmitt said it is important to stratify seizure patients into urgent and non-urgent care groups but also to make sure she is seeing everything in each of her patient's EEG readings. By alerting her to which patients are most at risk for a future seizure, 2HELPS2B saves her time. "Our goal is always to make sure that we find the seizures as quickly as possible," she said. "And that we identify those who are at the highest risk as quickly as we can."

While neurologists at MUSC have used AI in the past, Halford has been looking for ways to improve upon it. As recently published in JAMA Neurology, there are not enough experts qualified to read and interpret EEG results, so in conjunction with Massachusetts General Hospital, Halford helped create an algorithm that looks specifically for interictal epileptiform discharges (IEDs), which represent a critical biomarker for epilepsy and seizure risk. By recognizing these spikes in the readings, the algorithm can quickly assess a person's brain activity, and after testing its validity, the team found the algorithm to be as good as, if not better than, expert analysis.

"With automation and AI, we can spend less time in front of a screen and more time engaging with patients," said Halford.

Devised to ease

In addition to algorithms and automation, physicians, researchers and engineers are working together to develop new and wearable neurophysiology-based recording devices.

Wearable devices for seizure detection have been in development by multiple companies over the past five years. Immediate treatment and intervention during a seizure can be critical, so both physicians and caregivers are looking for new ways to recognize and respond to these episodes.

In the last few years, Halford and a team at MUSC have been working with the company Brain Sentinel, Inc., to develop and test a device that is worn on the upper arm and is designed to recognize when someone is having a tonic-clonic seizure and then notify either physicians in an inpatient setting or caregivers and family members for patients no longer at the hospital.

A generalized tonic-clonic seizure, also known as a grand mal seizure, takes place across the entire brain rather than in a localized area. The electrical signaling disturbance takes place on both sides of the brain and can cause a patient to lose consciousness and have severe muscle convulsions. Using the Brain Sentinel monitoring and alerting system with patients, Halford and his team found that the device detected these seizures and notified hospital staff in under eight seconds, according to their study in Epilepsia in 2017.

Seizure notifications can be sent via text message, email and signaling from the device, and patients can wear the rectangular device on their upper arm every day.

As the first FDA-approved wearable device for patients with epilepsy, this system continuously measures surface electromyographic (sEMG) activity in the arm. The multicenter study mentioned above showed that a device like this is effective and can provide peace of mind to caregivers while also aiding in immediate intervention for people with epilepsy.

Utilizing the growing trend in wearable devices is becoming

increasingly popular as physicians like Schmitt and Halford want easier ways to monitor patients without additional clinical or hospital visits. In addition to immediate intervention, these devices can help detect seizures in people who aren't aware they're having them.

"I have young patients, 17 or 18 years old, and they want to go off to college, but their parents are so afraid they will have a seizure when no one is around," said Schmitt. "The security and comfort that comes with devices like these is so helpful to their quality of life."

Coming into focus

Another way physicians are enhancing their treatments and techniques is with neuroimaging. **Ekrem Kutluay, M.D.**, professor of neurology and medical director for the MUSC clinical neurophysiology labs, says that enhanced neuroimagery has been one of the most impactful technologies in his practice.

"Ten years ago, almost 50% of patients who came to see me would have a normal MRI scan," he said. "Sometimes, we wouldn't know why they were having seizures." But with today's enhanced MRI technology and dedicated MRI protocols he can see structures at a higher resolution and determine where any minor changes or abnormalities might be.

"It's like when we had tube TV's," Kutluay said. "We liked them. But now that HD TV has emerged, we can never go back."

Some treatment options for patients with epilepsy include medication, deep brain stimulation and epilepsy surgery. The medications are designed to alter either the electrical activity in neurons by targeting ion channels or the chemical transmission between neurons by targeting neurotransmitters. The challenge with anti-seizure medications, according to Schmitt, is that there are side effects to consider, such as weight gain, sleepiness and slowed thinking. There are also patients for whom medications don't decrease the number of seizures, and so some of them look to surgery.

Surgery targets the area of the brain where the seizure activity takes place, but it only works in, at most, two thirds of patients. **Ezequiel Gleichgerrcht, M.D. Ph.D.**, who is currently completing an epilepsy fellowship at MUSC, combines enhanced imagery techniques like diffusion MRI with deep learning and computer algorithms to learn more about his patients' brains before surgery and to predict who is likely to be seizure-free after surgery.

In a study published in Epilepsia, Gleichgerrcht and other members of the team used this imagery to reconstruct the whole-brain neural architecture in his patients.

The abnormalities associated with epilepsy are unique to each patient. "When looking at someone's neural network, you can decide

PHOTO: SON NGUYEN

The latest model of this device is smaller and less bulky for patients and should be approved by the FDA this spring.

which nodes have a greater influence and are more critical to their information flow and what is affected by their epilepsy," Gleichgerrcht said. This information is then given to a computer to build an algorithm that looks for patterns between patients and helps predict which ones are more likely to become seizure free after surgery.

Leonardo Bonilha, M.D., Ph.D, epilepsy division director and endowed chair at MUSC, is currently leading a five-year, multisite study to expand on this algorithm as well as combining diffusion MRI, functional MRI and resting state MRI to create an even more detailed picture of the brain and predict epilepsy's effect on a patient's brain.

All these improvements in wearable technology, brain imaging and seizure prediction help physicians at MUSC and around the world treat people with epilepsy more successfully. Schmitt says it helps give some of her patients back their independence. "It can give them their life back."

EXPANDING HORIZONS VIRTUALLY

Researchers and physicians study the brain using virtual reality

BY CELIA SPELL

Sliding on a pair of large black goggles can transport you to another plane. It can virtually change your reality, taking you from the mountains of Nepal to the beaches of Hawaii. Or it can help you experience something entirely new, like the adrenaline rush from jumping out of an airplane. And now that same technology is being applied to patients at MUSC.

While some can argue that 360-degree murals from hundreds of years ago were our first attempt at virtual reality (VR), the Sensorama, invented in 1957 and patented in 1962, is widely considered the original VR technology. Created by Morton Heilig, the Sensorama was essentially a viewing screen surrounded by a booth. To immerse its viewer in a fully 3D world, the machine used a combination of sound, smell, vibration and wind.

Today that viewing screen is smaller. A modern VR headset consists of a large, clunky pair of black goggles whose lenses face a screen directly in front of the eyes. In addition to goggles, people can use a handheld remote similar to a video game controller to help them react to and manipulate this virtual world.

It wasn't until the 1990s that physicians started to incorporate virtual reality into the ways they treat their patients. What began as something novel in the medical field is now being used as a common way to practice procedures. Using VR goggles, practitioners can fully immerse themselves in a new surgery and practice in a risk-free environment before ever performing it on a patient. They can even tailor it to an upcoming patient using that patient's imagery to practice and prepare for any obstacles ahead of the actual procedure.

PHOTO: BRENNAN WESLEY

PHOTO: SON NGUYEN

Physicians can use virtual reality to simulate the reach movement in the brain, which can be highly affected after a stroke or with Parkinson's disease.

And now physicians are taking the leap into the operating room. At one of the first hospitals in the country to take VR from a training tool to a clinical and surgical tool, MUSC physicians are using VR to treat the tremors of patients with Parkinson's disease as well as learn more about those who have experienced a stroke and help them one day regain mobility.

Operating with virtual reality

The National Institute on Aging defines Parkinson's disease as a brain disorder that occurs when neurons in the area of the brain involved in movement begin to die. Without these neurons to produce the neurotransmitter dopamine, people affected by Parkinson's disease can experience tremors, stiffness, balance and coordination issues as well as difficulty walking.

While there are medications and therapies to relieve the symptoms of Parkinson's disease, they are not always effective. Some patients for whom medication does not work undergo deep brain stimulation (DBS), where a physician surgically implants electrodes far inside the brain. These electrodes then connect to a device that is surgically implanted in the chest and stimulates that area of the brain with electrical impulses that help decrease tremors.

DBS is both an expensive surgery and an invasive one, and although it is available to patients with Parkinson's disease, its effects are not fully understood. Even so, if physicians could find different ways to harness the power of DBS for other disorders, they could potentially help even more patients.

Nathan Rowland, M.D., Ph.D., a neurosurgeon at MUSC, has been using VR as a method of studying how planning for an upcoming movement affects the brain while it's being stimulated. Rowland places VR goggles on his patients in the operating room and has them perform reaching exercises while recording the area of the brain that controls their arm and hand motion.

The VR goggles work by showing the patient a red ball against a blue backdrop. The patient is asked to grab the ball, which simulates the reaching movement used to perform many everyday tasks and activates the same area of the brain needed to pick up a pencil on a desk at home or to open a door.

"What we hope to learn," said Rowland, "is how and when to assist the brain."

Rowland hopes that through these experiments, physicians can tailor electrical stimulation to specific regions of the brain and only activate it when needed. He pictures a procedure where DBS electrodes are placed on the surface of the brain rather than deep within. VR may even one day help make this procedure more precise by showing physicians how patients interact with their environment and, in turn, how the brain responds.

"If we can understand how to control the symptoms of Parkinson's disease by using VR to pinpoint the placement of electrodes," he said. "We can extend that technique to patients with other chronic, neurological disorders like stroke."

And stroke is exactly where he's taking this research next.

Rehabilitating with virtual reality

Christian Finetto, Ph.D., a research associate in the Department of Health Sciences and Research at MUSC, is working with Rowland to assess patients who have trouble moving after experiencing a stroke.

A stroke occurs when a person's artery is blocked or when a blood vessel bursts — and either way, the blood supply to the brain is affected. A disruption like this can have a permanent effect on someone's ability to move, and it can limit what they can do on their own.

The same program that works for patients who have Parkinson's disease also works for those who've had a stroke because both affect someone's reaching movement. By assessing areas of the brain involved in reaching for a red ball or a blue dot, Rowland and Finetto can learn more about how to help their patients.

Rowland has seen improvement in one of his Parkinson's disease patient's upper extremity movement with VR. "If we simulate throwing a ball inside the VR goggles, the patient has to catch it," said Rowland. "If we do that faster and faster, it improves their mobility."

At MUSC's Stroke Recovery Research Center, which is directed by **Steve Kautz, Ph.D.**, Finetto performs many similar biomedical assessments to see how people move. By analyzing that data and

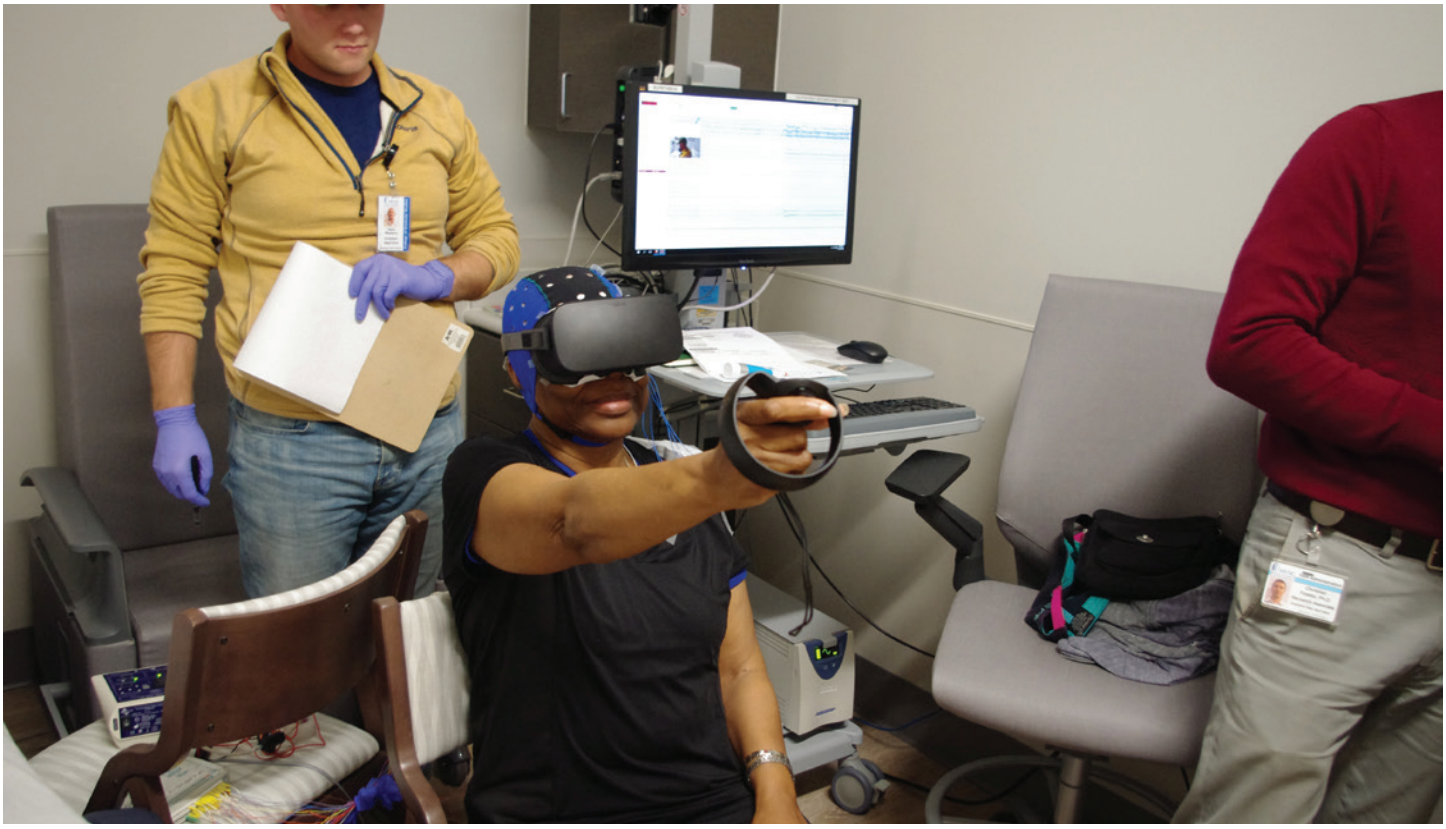


PHOTO: BRENNA BAKER-VOGEL

Physicians at MUSC use VR goggles to treat and measure brain activity in both patients suffering from a stroke and those with Parkinson's disease.

testing certain interventions, Finetto can find and identify abnormal movement patterns in patients and then quantify their impairment. He compares the technology in the center's four motion capture labs to the black motion capture suits and markers often associated with film animation.

Analyzing neuromechanics in this way, however, involves a labor-intensive setup each time. "Every time you generate a new experiment, you have to generate a new physical environment to test it," said Finetto. Changing these environments involves physical equipment and the time and ability to move them around multiple times a day for each different patient. "That's what got me thinking about VR. We could use that to streamline our process and make it possible to generate any environment and test any stimulus."

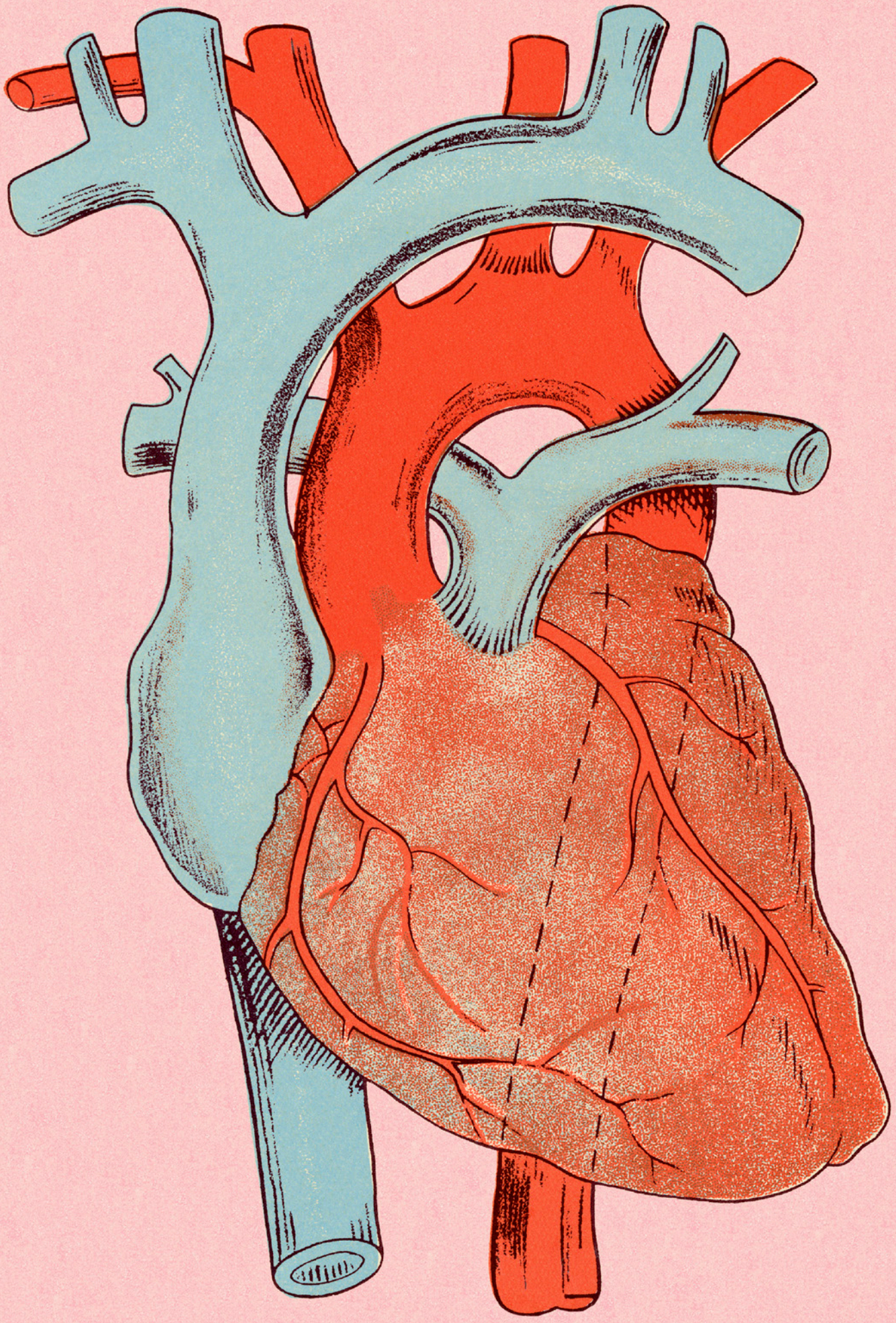
Finetto has since done multiple studies to show that movement patterns in virtual reality are essentially equivalent to movement in real life. "VR is a tool for us to study the brain, manipulate a patient's environment and watch how the brain responds," he said.

While Finetto and Rowland haven't used this program as an interventional tool yet, VR has been used before as a form of physical therapy for stroke patients. This is a subcategory of exergaming, which is when people have to be physically active in order to play a video game. By exposing patients to different scenarios through VR goggles, researchers can observe their different movements in a controlled environment, for example, a lab at MUSC.

Rowland hopes to expand the university's program to address this area of research as well as investigate whether VR can help patients suffering from post-traumatic stress disorder.

"We want to expand this work to cognitive mood disorders as well," said Rowland. "Like depression and obsessive-compulsive disorder. There is just so much exposure therapy that can be done to help patients, so much that can be done in general." He wants to study exposure therapy through virtual reality as a method of treatment next.

The world changes constantly, but by harnessing that change and controlling it virtually, physicians and engineers like Rowland and Finetto can help their patients retrieve some of their much-needed cognitive function and motor control.



Mending a Broken Heart

MUSC has several innovative strategies to help patients quickly address and manage their heart conditions

BY MATTHEW GRESETH

"Man has made many machines, complex and cunning, but which of them indeed rivals the workings of his heart?" — Pablo Casals

The heart is an amazing and coordinated machine. As a muscle the size of your fist, it will beat ~100,000 times each day and pump 1.5 gallons of blood through 60,000 miles of blood vessels every minute. As incredible as that is, sometimes the heart breaks.

Broken heart syndrome, or death from a broken heart, is an extremely rare heart condition. In contrast, heart disease — issues and deformities of the heart — is a group of common and serious heart conditions causing one in four deaths in the United States. Some of the more familiar types of heart disease include coronary artery disease, myocardial infarction, arrythmia and heart failure. Oftentimes these conditions are treated with medication or surgery; however, doctors are constantly seeking to improve the lives of these patients.

MUSC is pioneering several strategies to help patients manage their heart disease. One strategy uses artificial intelligence to help physicians make detailed maps of the heart more quickly in patients with atrial fibrillation. The second strategy utilizes a novel medical device to rebalance the different arms of the nervous system in patients with chronic heart failure.

Machines learn to fix a broken heart

The four chambers of the heart beat in a controlled, steady, rhythmic pattern. This pattern is controlled by an electrical system called the pacemaker. Normally, the electric pulse is initiated in the upper chambers, the atria, and travels to the lower chambers, the ventricles. Arrhythmias, which can become fatal, occur when the rhythmic pattern is disrupted, causing the heart to beat too fast (tachycardia), too slow (bradycardia) or irregularly (fibrillation).

Atrial fibrillation is one of the most common arrhythmias and causes the atria to twitch quickly. This added strain on the heart often leads to the formation of clots. In fact, one out of seven strokes in the United States is caused by atrial fibrillation. To manage it, patients are prescribed a daily medication regimen. If the medications fail to address the problem, patients can undergo a surgical intervention,

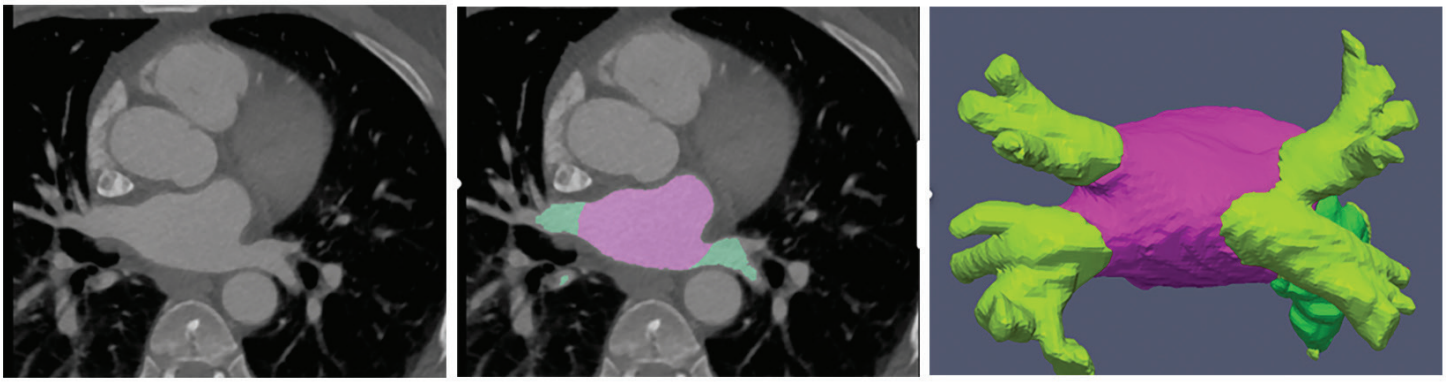


PHOTO: JEREMY BURT

Pretreatment mapping of the left atrium is much quicker with the help of AI. The images show a standard heart CT scan (left), a scan with AI mapping (middle), and a detailed AI map of the left atrium (right).

called catheter ablation, in which a wire is inserted into the dysfunctional area and heated to disrupt the damaged area.

To ensure the safety and efficacy of this procedure, physicians need an accurate map of the heart, and artificial intelligence is providing a new, better map-making tool.

"That's where we come in," said **Jeremy R. Burt, M.D.**, associate professor of radiology and radiological science and director of cardiovascular CT, who is using artificial intelligence to map the heart.

Normally, patients about to undergo catheter ablation are sent to the radiologist for a computed tomography (CT) scan or a magnetic resonance image (MRI). The radiologist then processes the image to give a detailed map of the left atrium and the pulmonary veins back to the electrophysiologist. This process can normally be completed in 10 to 15 minutes. However, Burt and his team have developed an artificial intelligence algorithm that can provide a detailed map of the left atrium with 95% accuracy in just 10 seconds.

"Artificial intelligence has such great potential," explained Burt. "There's a high threshold before you can reach that potential, but once you get past that, there are amazing things that we are going to be able to do. It is really going to change medicine, and radiology is a great example of where we can apply some of these artificial intelligence algorithms."

This new technology will be highly beneficial for physicians, who generate these detailed maps several times a day, because it will save a significant amount of time. Although the technology is not quite available to physicians, Burt and his team are currently working to test the algorithm in a specific patient group with atrial fibrillation.

These new algorithms will also allow physicians to study the left atrium and learn important details about how it contributes to normal heart function.

"We don't know very much about the left atrium," described Burt. "For a long time, we thought it was just there to hold the blood, that it doesn't really do a whole lot. Now we know it has an important function, and this algorithm is going to let us research that on a large scale."

Burt and his team are currently planning studies to look at the emptying fraction, the amount of blood pushed out of the left atrium into the left ventricle. To start, the team will examine healthy patients to monitor their blood volumes, emptying fractions and strain patterns. After defining these normal parameters, they can begin looking at different disease states, starting in patients with atrial fibrillation. Future work could focus on other heart conditions, including mitral regurgitation (the abnormal flow of blood from the left ventricle to the left atrium), mitral stenosis (an abnormal narrowing of the mitral valve that restricts blood flow out of the left atrium), and amyloidosis (an abnormal build-up of amyloid in the heart).

Overall, this new technology will allow physicians to more quickly map the left atrium of patients with atrial fibrillation and could provide the basis for a whole new understanding of how the left atrium functions.

The head, the heart and the machine

Heart failure occurs when the heart fails to efficiently pump blood around the body. It is estimated that heart failure affects 6.5 million people, with half of patients dying within five years of a diagnosis. Over the past 30 years, several medications and devices have improved patients' morbidity and mortality; however, significant challenges remain.

"Despite the many advances we've made in heart failure, patients still have an unacceptable symptom status, an unacceptable burden

of disease, and an unacceptable mortality rate," said **Michael R. Zile, M.D.**, the Charles Ezra Daniel Professor of Medicine, an MUSC distinguished professor, and chief of cardiology at the Ralph H. Johnson VA Medical Center. "We know we need to make continued efforts to improve therapy."

Heart function is regulated by two opposing branches of the autonomic nervous system — the sympathetic nervous system (SNS), which increases the heart rate and contractility among other heart functions, and the parasympathetic system (PNS), which reduces the heart rate. In heart failure, the SNS is in overdrive while the PNS is suppressed, leading to decreased myocardial efficiency, arrhythmia and inflammation.

A clinical trial, Baroreflex Activation Therapy (BAT) for Heart Failure (BeAT-HF), sponsored by CVRx and chaired by Zile, sought to rectify the dysregulation of the autonomic nervous system in heart failure patients by using a novel medical device called Barostim Neo. This device uses an electrical signal to modulate the nervous system.

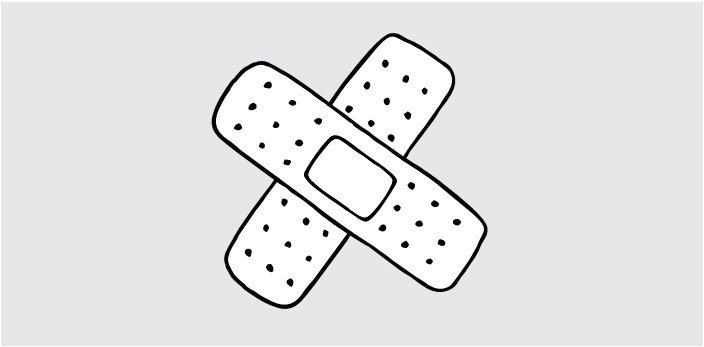
"In patients with chronic heart failure, there's an imbalance in the sympathetic and parasympathetic systems, such that the sympathetic tone is increased and the parasympathetic tone is decreased," explained Zile. "When you stimulate the carotid baroreceptor with an electrical stimulus, you rebalance that by stimulating the brain. The brain acts to move the sympathetic down and the parasympathetic up."

The device consists of a two-millimiter electrode that is attached to a pulse generator. The electrode is placed on the carotid sinus baroreceptor (on the carotid artery), while the pulse generator is implanted subcutaneously. Once implanted, a continuous afferent signal is sent to the brain. Importantly, this stimulus is titratable. Physicians can increase the signal stepwise over the course of a few weeks to reach a maximally tolerated strength.

The BeAT-HF trial began in a defined target population of greatest unmet need. The U.S. Food and Drug Administration (FDA) approved the trial for patients "who remain symptomatic despite treatment with guideline-directed medical therapy, are NYHA Class III or Class II (who had a recent history of Class III), have a left ventricular ejection fraction ≤ 35%, an NT-proBNP < 1,600 pg/ml and excluding patients indicated for Cardiac Resynchronization Therapy (CRT) according to AHA/ACC/ESC guidelines."

By all measures, the study was a huge success and proved to be safe. Patients who underwent BAT showed improvements in their six-minute walk and their quality of life score, and they raised their New York Heart Association score. They also showed a reduction in a critical biomarker that is resistant to the placebo effect.

The FDA saw significant improvement of patients and



prioritized the BeAT-HF trial for review. The trial was one of the first protocols and devices approved under the 2016 21st Century Cures Act, a congressional act that strives to rapidly bring new therapies to patients. The FDA approved the Barostim Neo system on August 16, 2019, for patients who meet the FDA guidelines. Currently, most insurance companies don't cover Barostim Neo, but it is under review with the Center for Medicare Services and they are enthusiastic about the device.

"This is the first neuromodulation device, to our knowledge, that has been demonstrated to be effective and has been approved by the FDA," said Zile.

One of the greatest benefits of the Barostim Neo system over conventional treatment modalities is that patient compliance should be greatly improved. Rather than requiring several daily medications, the device continually modulates the autonomic nervous system and reduces the risk of patients failing to take their medicine.

In the future, it is possible that the Barostim Neo system could treat a broader range of heart failure patients. There is reason to believe that across the heart failure spectrum, the imbalance between the SNS and PNS is the underlying cause of disease. Zile believes that rebalancing the system to a homeostatic level should improve heart failure symptoms and outcomes in all patients with heart failure.

On the mend

Patients with heart disease continue to have significant morbidity and mortality despite decades of drug development. Physicians at MUSC are persistently striving to reduce patient suffering. One group of physicians is using artificial intelligence to aid in quickly mapping the atrium in patients with atrial fibrillation and may now have a platform to study the atrium in both health and disease. Another group has designed a novel medical device that rebalances the nervous system to significantly improve the quality of life for patients with chronic heart failure. Both of these advances will help patients experience a higher quality of life despite heart disease.

The Big Reveal

New technologies at MUSC are poised to detect and diagnose lung cancer earlier and less invasively

BY SHAWN OBERRATH

We navigate in a world of endless information streams, but we can function by screening and judging the incoming stimuli. Our eyes casually ignore the hangings on our walls, the signposts on the way to work and the cracks in the sidewalk, but we constantly scan our environment for new or important input, which we then label and sort. A dog darts into the road? Look out — slow down! A friend gets a new haircut? It looks great — I should let her know. The phone screen lights up? I took care of that reminder — I can ignore it.

For cancer detection and diagnosis, a similar process occurs. Physicians first look for anomalies that stand out from the background and then categorize them — benign or malignant — so they can choose the next appropriate action. Until recently, these steps were performed by humans and our limited computing capacity. But in the era of artificial intelligence (AI) we are beginning to teach computers how to both detect and discern, which can help physicians save precious time and deliver the best care possible to their patients.

At MUSC, **Jeremy Burt, M.D.**, an associate professor of radiology, and **Nicholas Pastis, M.D.**, a pulmonologist and lung cancer specialist, are working with complementary technologies to drive the detection and diagnosis of lung cancer forward by using advanced robotics and AI.

Lung cancer tops list of most-wanted cancer killers

Early in 2020, the American Cancer Society (ACS) reported a 2.2% decrease in the overall U.S. cancer death rate. This is the largest recorded single-year drop and caps off a resounding 29% reduction in cancer deaths from 1991 to 2017. The latest decline was driven by decreases in lung cancer deaths among both men and women, which the ACS attributes to reductions in smoking and better detection and treatment options for lung cancer.

Yet even with this positive news, the American Lung Association (ALA) reports that lung cancer remains the leading cause of cancer death in the U.S. and globally, causing more deaths than breast, colorectal and prostate cancers combined. And importantly, the chance of survival depends on the cancer stage at diagnosis: if a tumor is detected early, when it is still contained within the lung, the 5-year survival rate is about 56%, but if the cancer has spread to other areas of the body, that rate drops to 5%.

To help increase early detection, both the ACS and the ALA endorse the low-dose computed tomography (CT) screening program for high-risk individuals: those who are 55 to 80 years old, have a history of heavy smoking, and are still smokers or quit within the last 15 years.

As a result, Pastis says that lung cancer screening has really taken off across the U.S. And studies have shown that it is working: low-dose CT screening decreases mortality by 14 to 20%, and with 8 million Americans who qualify for screening, the life-saving potential of this program is vast.

High-res detection: Finding the oddities that deserve a second look

Although the low-dose CT screening program has been in place since 2011, many high-risk patients either don't know about the

IMAGE COURTESY OF AURIS HEALTH, INC.

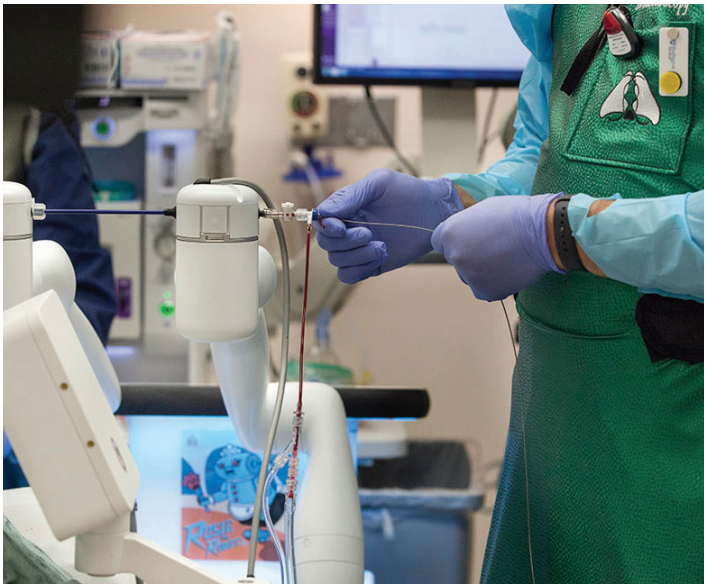


PHOTO: SARAH PACK

Nick Pastis, M.D., threads a bronchoscope into a patient's lung. He will use a joystick to maneuver the bronchoscope to the exact position of a lung nodule.

program or don't participate because of obstacles such as fear of medical testing.

Burt says, "We're not doing a great job at diagnosing lung cancer early. If we were able to diagnose that cancer earlier, we would have much better outcomes in terms of both costs and morbidity."

The barriers to participation may be lowered by patient education and physician engagement, but if all eligible patients were to show up for the test, another obstacle would rear up. Burt explains that with a low-dose CT, the scan is read slice by slice by a radiologist, and pulmonary nodules can be extraordinarily difficult to find and assess. For each patient, there can be 60 to 80 slices to read, and in some cases up to 100 slices. Multiply that by 8 million, and the workload would be unmanageable.

But with a new software tool that Burt is working on, called LungWeb, he plans to use AI to lighten the load. "Why not help the radiologist by using AI to find and identify nodules?"

The LungWeb system visualizes CT scan data on a pixel-by-pixel basis and can register differences at a high-resolution level that the human brain simply cannot match. The concept is that the software detects any nodules in the scan and clearly marks them so they are easy to identify. The radiologist can then quickly recheck the area to confirm the finding.

"The great thing about software and AI is it doesn't get tired, and it's very reproducible," Burt says. "Humans have a lot of distractions, so it makes sense to let the computer do the detection work."

This is well supported by a study published in the journal Radiology that found a 49% mean sensitivity for lung nodule detection among radiologists reading chest CT scans; whereas LungWeb's accuracy is projected to exceed 90%.

Another benefit of putting the software to work is an increase in speed and throughput. It takes radiologists an average of 3 minutes to identify lung nodules on a chest CT scan, but the computer can do it in a matter of seconds.

The downside to LungWeb at present is that it occasionally gives false-positive results by making mistakes that a human expert would not — for example, it may rarely detect a normal blood vessel and call it a nodule — so it will still be important for a radiologist to confirm the software's findings. But Burt is continuously refining the software to eliminate these false positives, and he hopes to have LungWeb ready for a clinical trial by fall.

Patient-friendly diagnosis: Judging what's dangerous without doing further harm

Locating nodules is just the first step of the detection and diagnosis pathway. Physicians must next determine which nodules are malignant tumors and which can safely be ignored.

The current standard of care is to screen patients by low-dose CT scanning and then monitor or biopsy nodules with an indeterminate or suspicious appearance. But Pastis regularly performs biopsies to diagnose lung cancer and explains that the traditional method, CT-guided needle biopsy, carries its own risks.

"The problem with screening is that the majority of nodules found are not cancer," he says. "And CT-guided needle biopsy can have a complication rate as high as 15 to 20% where people get collapsed lungs, bleeding or infection."

This danger is being minimized at MUSC with a newly purchased robotic bronchoscopy machine that is the only one of its kind in South Carolina. This machine provides greater control to the physician and a less invasive procedure for the patient. It also allows the physician to navigate to far peripheral nodules that were previously unreachable and obtain adequate sample tissue.

"The robotic scope gets you there and lets you have very fine motor control of the tip of the scope way out in the lung," Pastis says. "It has a mother-daughter scope configuration. The larger scope locks you in position, then you put out a very thin scope that allows you to steer through multiple branches of the lung and angle the needle directly into the nodule."

The machine holds a lot of promise in other ways as well. For example, Pastis explains that a staging bronchoscopy can be performed in the same setting as the robotic bronchoscopy to look for

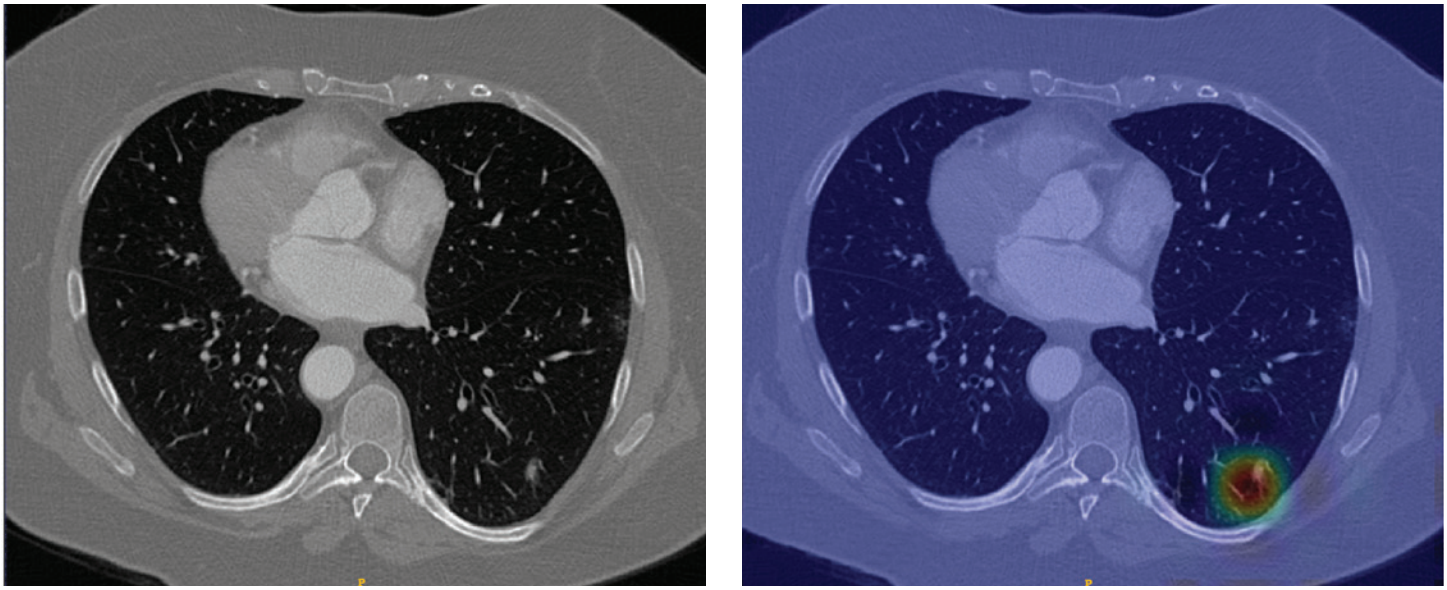


PHOTO: JEREMY BURT

Lung nodules in an unaltered CT scan require sharp eyes for detection (left), but LungWeb highlights suspicious areas to make detection much less labor intensive (right).

spread to other lymph nodes and to stage the cancer during the same procedure. There is also the potential that one day the machine can be used to deliver treatment, and preliminary experiments are under way.

The only caveat with the robotic machine is that a negative result for biopsied tissue does not automatically rule out cancer. If there is no separate diagnosis to explain the nodule — for example, infection — some patients will need further follow-up.

While robotic bronchoscopy is making lung cancer biopsy increasingly safer, another feature of LungWeb is that it can take the data collected by CT scans and use AI to determine the likelihood of cancer in specific nodules, making it easier to determine which nodules should undergo biopsy.

"The output can be something like, 'There's about a 90% chance this is benign or a 30% chance this is malignant,'" Burt says. "The great benefit would be getting rid of all those negative nodules so that the patient doesn't have to worry for months."

LungWeb is being trained on over 80,000 chest CTs from numerous publicly available databases, which translates to millions of images for training and validation. And once LungWeb enters the clinical trial phase, physicians will be able to test it in real time. Burt envisions that eventually the software can be used to examine any chest CT that comes in to catch pulmonary nodules early.

Finally, after a lung cancer diagnosis, physicians must still determine if the cancer is localized or has spread. The current method of staging is to perform a positron emission tomography (PET) scan, but this technology has a resolution limit of 8 mm, which means it can miss smaller but still critical lymph nodes as well as tumors that don't show up well on PET scans. Therefore, Burt is developing a second algorithm that uses AI to examine lymph nodes in the chest CT and predict the chance of metastasis. For example, the software will be able to say that a lymph node shows an 80% chance of metastasis, or perhaps a 10% or 0% chance, which will help with staging and with guiding the surgeon to the most suspicious areas.

This new algorithm is still in early development, but Burt hopes that it along with LungWeb will one day provide the equivalent of one-stop shopping, with detection, diagnosis and staging all performed with the chest CT — one procedure, no biopsy.

Meanwhile, the advanced robotic infrastructure at MUSC is already providing less invasive diagnosis and staging of lung cancer as early and safely as possible for patients across the state.

"A lot of times people have nodules detected but smaller hospitals don't have the technology to deal with them," says Pastis. "We have the opportunity to minimally invasively diagnose them and sometimes prevent surgeries or other procedures that are unnecessary."

Both doctors agree on the ultimate goals of these efforts: to find lung cancer early and save lives.

"The thought of being able to decrease the number of deaths from lung cancer is amazing," Burt says. "We're finally able to do it, because the technology's finally up to speed, so it's an exciting time."

Interview

Get to know David Marshall, M.D., the new chair of the MUSC Department of Radiation Oncology

PHOTO: SON NGUYEN

David Marshall, M.D., has been with MUSC for 15 years but recently stepped into a new role as the chair of the Department of Radiation Oncology. As part of the MUSC Hollings Cancer Center, this department serves patients throughout the Southeast by providing evidence-based care and treatment recommendations from a multidisciplinary team.

As a board-certified radiation oncologist specializing in genitourinary and gastrointestinal cancers, Marshall has brought innovative treatment options, such as Y-90 microsphere therapy and radiosurgical treatment for liver cancers, to patients at MUSC. He has also developed new techniques for linked and stranded seeds for prostate brachytherapy, and he wants to improve the accuracy of radiotherapy by using new immobilization and image-guided techniques.

Marshall also has leadership experience both at MUSC and on several national committees. He has served as the director of the Radiation Oncology Residency Training Program at MUSC as well as the deputy associate director for clinical investigations and the medical director of the clinical trials office at the Hollings Cancer Center. He has been a member of the National Association for Directors of Radiation Oncology Programs since 2005 and previously served as both the president and vice president of the same organization.

You joined the MUSC team almost 15 years ago. What brought you here?
After I finished medical school at the University of Texas Southwestern Medical Center in Dallas, I moved to Gainesville to complete my residency at the University of Florida. My first two jobs after residency were in New Jersey and New York. At the time that I interviewed at MUSC, my wife and I were

living in metro New York City and on vacation here, visiting my sister-in-law and her husband, who were residents at MUSC. It seemed like such a nice place to live, and the opportunity at MUSC seemed like a good fit, so we moved on down to Charleston and have been here ever since.

What first interested you in radiation and oncology?

I was actually an engineer before I got into medicine, and radiation and oncology seemed like the perfect blend of those two fields to me. I was working towards my master's degree in nuclear engineering sciences-health physics at the University of Florida when I was first introduced to the field of radiation oncology. The physicists who trained in my department also trained physicists from radiation oncology departments, so I was exposed to them early. And then when I decided to go to medical school, it was just a natural fit. Where most people have very little — if any — exposure to radiation oncology before medical school and training, I had it in mind the whole time.

"Where most people have very little — if any — exposure to radiation oncology before medical school and training, I had it in mind the whole time." —David Marshall, M.D.

What is something you're looking forward to in your position?

I am excited about growing the research efforts in our department. This is such an incredible opportunity to bring more resources to our team and expand our ability to treat people and support our research endeavors. Dr. Jenrette [Joseph Jenrette, M.D., former chair of the MUSC Department of Radiation Oncology] left a highly functional, very productive department to begin with, and it's a real privilege to be able to take that over. I'm looking forward to expanding on that legacy.

What makes MUSC Hollings Cancer Center special?

As a National Cancer Institute-designated cancer center, Hollings is recognized for both its lab and clinical research and its biomedical and health care training and education, which is great. At Hollings, we want to give the best evidence-based care that we can since many of our patients are faced with difficult decisions about their treatment — be that undergoing surgery, chemotherapy or radiation therapy. I think having a multidisciplinary team like ours helps patients understand their options and helps them make a decision they are comfortable with.

What are some upcoming opportunities for this department?

As MUSC is currently going through an expansion phase, the department of radiation oncology benefits as well. We have the opportunity to grow both our practice and our influence throughout the state, which will enable us to help a greater number of patients.

How have your past experiences prepared you for your new position as chair of the Department of Radiation Oncology?

I've worked for a number of different chairs — most of them outstanding — at a few different institutions in my time, so I've seen how they work. I think watching those other leaders, including the former chair of this department, Dr. Jenrette, do their job well has provided me with a lot of insight in addition to my tenure here at MUSC.

New Physicians

William Grossman, M.D.

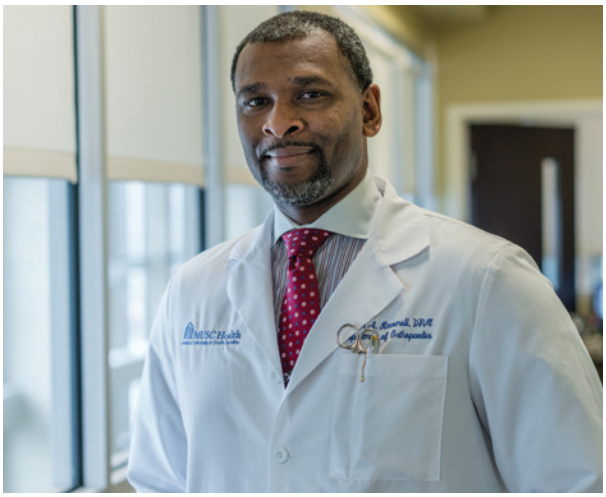
Board Certification: ABIM in Internal Medicine, Cardiovascular Disease, Interventional Cardiology // **Specialties:** Cardiology, Interventional Cardiology, Preventative Cardiology // **Clinical Interests:** pulmonary disease, pacemakers, cardiomyopathy // **Medical School:** Medical University of South Carolina // **Residency:** Medical University of South Carolina // **Fellowship:** Medical University of South Carolina

Tala Kassm, D.O.

Board Certification: Ophthalmology // **Specialties:** Glaucoma and Cataracts // **Clinical Interests:** Premium lenses for cataract surgery and laser-assisted cataract surgery, minimally invasive glaucoma procedures, the Glaucoma Support Group, patient education // **Medical School:** A.T. Still University // **Residency:** University of Louisville School of Medicine // **Fellowship:** Medical University of South Carolina

Matthew Moake, M.D., Ph.D.

Board Certification: Pediatrics // **Specialties:** Pediatric Emergency Medicine // **Clinical Interests:** Point-of-care ultrasound, procedural sedation, medical education, quality improvement // **Medical School:** Johns Hopkins University // **Residency:** Johns Hopkins University // **Fellowship:** Medical University of South Carolina



Rahn Ravenell, D.P.M.

Board Certification: American Board of Foot & Ankle Surgery (ABFAS) // **Specialties:** Orthopaedics // **Clinical Interests:** Foot and ankle injury, diabetic foot, joint infections // **Medical School:** Temple University of Podiatric Medicine // **Residency:** Dekalb Medical Center

Jared White, M.D.

Board Certification: American Board of Surgery // **Specialties:** Transplant Surgery // **Clinical Interests:** Liver transplant and hepatobiliary surgery, management of complications of end-stage liver disease // **Medical School:** University of Tennessee Health Science Center College of Medicine // **Residency:** University of Alabama at Birmingham Hospital // **Fellowship:** University of Alabama at Birmingham Hospital

Carlos F. Zayas, M.D.

Board Certification: ABIM in Nephrology // **Specialties:** Transplant Nephrology // **Clinical Interests:** Renal and pancreatic transplant recipient care, malignancies after solid organ transplantation, HIV+ and sickle cell anemia recipients, telemedicine and outreach transplant clinic access // **Medical School:** University of Puerto Rico School of Medicine // **Residency:** Emory University School of Medicine // **Fellowship:** Emory University School of Medicine

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