Thoracic Aortic Endografts

Thoracic endovascular aortic aneurysm repair, or TEVAR, has been implemented for a range of aortic pathologies, including traumatic tear, degenerative aneurysm of the aorta, and acute and chronic dissection of the thoracic aorta.1 TEVAR has been used more often than open surgery since its first introduction in the late 1990s, as it is less invasive, and several studies have demonstrated early safety and utility advantages. However, there are limited data to address concerns about the long-term durability of the technique.

Richard P. Cambria, MD, chief of Vascular and Endovascular Surgery at the Massachusetts General Hospital Fireman Vascular Center and co-director of the Thoracic Aortic Center, and his team have conducted trials on various TEVAR devices for several different aortic diseases, evaluating long-term outcomes as well as short-term mortality and other safety and efficacy outcomes.

**TEVAR FOR DESCENDING THORACIC AORTIC ANEURYSMS: A FIVE-YEAR VIEW**

In 2014, Dr. Cambria led a team that published the results of a five-year international study that compared TEVAR with open surgical repair for descending thoracic aortic aneurysms and large ulcers. The results were published in the *Journal of Vascular Surgery.*2 The five-year mortality rate was similar, at 37%, for both patients treated with TEVAR and those treated with open surgery. However, aneurysm-related mortality was significantly lower (5.9%) with TEVAR than with open surgical repair (12%). No ruptures of treated aneurysms were reported in either group. Severe morbidity was also significantly lower in the TEVAR group, at 21% compared with 39% for open surgical repair. And secondary intervention rates were similar for both groups. This study confirmed that using

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*(continued on page 2)*
TEVAR to treat anatomically suitable descending thoracic aortic aneurysms and ulcers is a safe and effective alternative to open surgical repair.

EVALUATING A CONFORMABLE TEVAR DEVICE FOR ACUTE COMPLICATED TYPE B DISSECTION

In acute complicated type B dissection, treatment with TEVAR may address rupture or malperfusion, as well as prevent the dissection from becoming a more complex aneurysm over time. Dr. Cambria and his team recently completed a multicenter trial, with the results soon to be published, of the use of a conformable TEVAR device in acute complicated type B dissection where all patients had rupture, malperfusion or both. The device was engineered specifically for some of the anatomical and clinical features referable to acute dissection. In the 50 patients treated in the trial, the study authors achieved a 30-day all-cause mortality of 8%. Historically, this category of patients has had a 30-day mortality of 30%, says Dr. Cambria, and the objective performance criteria is a 30-day mortality of 10%. The one-year survival rate from the study was 88%; the two-year survival rate was 85%. That trial was the basis for the September 2013 FDA approval of the conformable TEVAR device to treat type B dissection, the first such approval.

Dr. Cambria explains that the device has been engineered to make it more conformable at the proximal seal zone. The use of TEVAR devices for aortic dissection has typically been limited by the anatomy and aortic fragility at the proximal seal zone, where the thoracic endograft affixes to normal aortic tissue. In type B dissection, that seal zone is usually found in the mid and distal aortic arch.

GENERATING MORE LONG-TERM OUTCOME DATA FOR TYPE B DISSECTION

Currently, there is FDA approval for two TEVAR devices, soon to be three. In conjunction with the Society for Vascular Surgery, Dr. Cambria is the chair of a national study committee that, with the FDA, is conducting a five-year study of clinical results with TEVAR in the treatment of acute and chronic type B dissections. The study will enroll 200 patients with acute type B dissection and 200 patients with chronic type B dissection, all treated with TEVAR, and follow them for five years. The study will assess 30-day mortality as well as long-term efficacy, including the percentage requiring secondary procedures or additional interventions. The goal is to quantify the success of TEVAR technology in preventing the primary late complication of dissection—the formation of an aneurysm requiring complex open surgery.

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Hypertrophic scarring after burn injury presents a clinical challenge. In addition to persistent cosmetic concerns, such scarring can also cause pain, tightness, restricted motion and severe itch. Although the field has seen few advances in the treatment of such scars in the past decade, recent studies have indicated that pulsed dye laser and fractional CO$_2$ laser treatment lead to improvements in abnormal pigmentation, pruritus, pain and tightness. A fractional CO$_2$ laser that has been in use at Massachusetts General Hospital since 2011 has shown great promise as a therapy that improves appearance of burn scars and can help address other symptoms.

Burn surgeons at Mass General’s Sumner M. Redstone Burn Center, led by plastic surgeon Jeremy Goverman, MD, FACS, and colleagues, undertook a study to evaluate the effects of ablative CO$_2$ fractional photothermolysis on burn scars. The results, which have yet to be published, showed significant improvements in patient symptoms, enhanced cosmetic appearance of the burn scars and a high level of post-treatment patient satisfaction.

**MECHANISMS OF ACTION IN LASER TREATMENT OF HYPTERTROPHIC SCARS**

The fractional CO$_2$ laser used by Mass General burn surgeons creates small holes in the scar tissue using a finely focused beam of light. This technique, which can penetrate to the base of the scar, selectively ablates only thin columns of tissue, called microthermal columns of tissue, called microthermal zones, limiting damage to the surrounding tissue.

There are several mechanisms through which CO$_2$ fractional photothermolysis is hypothesized to act. First, the laser creates organized columns of microthermal injury, which break down the collagen in those columns, stimulating the process of collagen remodeling and promoting the formation of more elastic tissue. The microscopic holes could also release dermal tension, which is responsible for the tightness and raised nature of hypertrophic scars. Finally, the small columns surrounded... (continued on page 4)

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**Superficial and Deep Fractional Resurfacing**

Two laser handpieces are used for treatment: the superficial fractional handpiece and the deep Fx handpiece. The superficial handpiece helps to smooth surface abnormalities by ablating a thin layer of skin (left). The deep Fx handpiece is used to perform fractional photothermolysis (FP) by creating columns of thermal damage (referred to as microthermal zones) in the epidermis and dermis surrounded by islands of normal tissue (right). The tissue injury created with FP stimulates the process of collagen remodeling and deposition and promotes elastic tissue formation.

**SUPERFICIAL ABLATIVE FRACTIONAL RESURFACING**

(CO$_2$ & 2.94 Erb:YAG) 10-70 microns

**DEEP ABLATIVE FRACTIONAL RESURFACING**

600-1000 microns

Source: Jeremy Goverman, MD
Source: Jeremy Goverman, MD

by normal tissue might create microscopic healing zones, where the heat from the ablation induces a metabolic cascade that recruits stem cells from the bloodstream to aid in repair at the scar site.

ASSESSING EFFICACY OF LASER TREATMENT

Although preliminary data seen with ablative fractional CO₂ laser treatment of hypertrophic burn scars² has been positive, there is a need for more robust evidence to validate its use. Dr. Goverman and his team sought to quantify and assess patient-reported outcomes among those treated with fractional CO₂ laser at Mass General’s Sumner M. Redstone Burn Center. Assessing the effects of a treatment on burn scars can present methodological challenges, as it requires objective measurements of changes on scar tissue, which is highly heterogeneous. The research team instead measured success in patient-reported outcomes.

The results showed that 96.7% of the 387 patients reported overall satisfaction with laser therapy, citing a 50% reduction in neuropathic pain, tightness/contracture and pruritus.

FURTHER RESEARCH ON FRACTIONAL CO₂ LASER TREATMENT

Given the promising results of their initial analysis, Dr. Goverman and his colleagues are now pursuing studies that aim to elucidate the treatment’s underlying mechanisms of action. One chief area of investigation will be the changes in gene expression that result from laser treatment, which can be observed in samples of scar tissue removed for other purposes that are subsequently laser treated. The scar tissue data will then be compared with existing research showing the laser’s effects on gene expression in normal skin to determine any differences.

The team is also developing a study to quantify the specific parameters of treatment for the fractional CO₂ laser that confer the most beneficial effect—what doses of laser and treatment settings produce the best outcomes, what pattern of hole spacing and depth is most efficacious, how long after injury should the lasering be performed and what is the best time interval between laser treatments.

Another potential application of the fractional CO₂ laser is for more effective drug delivery into the scarred tissue. It is already common practice for topical steroids to accompany treatment, with the laser facilitating deeper delivery via holes in the tissue. But it is also possible for other medications or stem cells to be delivered to the site with the laser. Future studies are still needed to ascertain which medications may improve the healing process.

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Developments in Total Ankle Replacement

For impediments in ankle function, arthrodesis has long been favored over arthroplasty. Restoring full function through prosthetic replacement has historically been complicated by the difficulty in dislocating the ankle for surgical intervention as well as the many joints and complex biomechanics that characterize the region. Fusion has seen much wider practice, with its union rate of roughly 90%, after which significant pain relief is generally reported. Arthrodesis of the ankle, however, can disturb the gait pattern and lead to stress of nearby joints. Tertiary care orthopedic foot and ankle specialists are pursuing innovations in total ankle arthroplasty (TAA) that are likely to promote its wider adoption. Christopher DiGiovanni, MD, chief of the Foot and Ankle Service and director of the Foot and Ankle Fellowship Program at Massachusetts General Hospital, has been at the forefront of the study, design and implementation of a new generation of ankle replacement devices and protocols. While ankle replacement has not compared favorably to innovations in other load bearing and major joints, which enjoy a survivorship of 90% to 95% over 15 to 20 years, recent studies indicate that ankle replacements under more recent guidelines show a postoperative survivorship of 80% to 95% over 5 to 10 years.

Iterative Improvements in Prosthetic Design

First- and second-generation ankle prosthetic designs presented constraint issues and limited function, causing them to be either too restrictive or too unstable, leading to implant loosening, dislocation, chronic pain and occasional catastrophic failure. Many also required removal of a significant amount of bone in the distal tibia and talus before implant insertion, which often caused premature collapse in soft bone, progressive bone loss and difficult revision situations. Third- and fourth-generation models have corrected many of these shortcomings, benefiting from recent advances in implant technique and design as well as a far improved understanding of ankle biomechanics and the impact that concomitant ipsilateral foot pathology can have on ankle implant longevity. The results, says Dr. DiGiovanni, are more reproducible gait cycle, better implant function, greater postsurgical activity and, most important, fewer significant complications or need for revision surgery. Among these models is one designed and patented by Dr. DiGiovanni, the first FDA-approved third-generation design to enable insertion through either a medial or lateral approach, a strategy that has proved influential with later designs. New models are now typically put in as press-fit designs and have greater geometrical biocompatibility. They come with a greater degree of freedom that prevents undue stress transfer without being unstable, require less bony resection for insertion so that revision is easier, and offer options for significant modularity to provide for a better fit. Many are coated with tiny beads that allow for the surrounding bone to grow into the prosthesis, forming a lasting bond that allows for bony remodeling over time.

Instrumentation, Patient Expectations and Further Study

The instrumentation used during the surgery is another area upon which Dr. DiGiovanni and other surgeons have worked to improve. Precise instrumentation for making the bony cuts and ensuring anatomic alignment during surgery is critical, says Dr. DiGiovanni, as these implants are smaller than those of hip, knee and shoulder replacement, yet by virtue of location must do more work. Slight inaccuracies in this area can have large consequences on implant durability, such as subtle foot malalignment, instability or stiffness.

Ankle Replacement Imaging

This X-ray shows a total ankle replacement in the process of insertion. The prosthetic joint here is the Eclipse, designed by Christopher DiGiovanni, MD. The image also captures instrumentation for insertion, including a cutting jig designed to remove arthritic bone from either the medial or lateral side in preparation for implant insertion.

Source: Christopher DiGiovanni, MD
Sleep disturbances and circadian rhythm dysfunction are common features of Parkinson’s, Alzheimer’s and Huntington’s diseases. These symptoms adversely affect quality of life. Yet the mechanisms of sleep and circadian disruption in neurodegenerative diseases are not well understood. Aleksandar Videnovic, MD, a neurologist at Massachusetts General Hospital and director of the new Program in Sleep, Circadian Biology and Neurodegeneration, is investigating the pathophysiology of such sleep-wake disturbances.

Patients with Parkinson’s disease (PD) in particular exhibit diurnal fluctuations of motor and nonmotor symptoms, in conjunction with sleep dysfunction, which suggests a role of the circadian system in the modulation of these symptoms. Impaired circadian function in PD is suspected to underlie not only the dysregulation of the sleep-wake cycle but also autonomic, cognitive, psychiatric and motor symptoms of the disease. Investigations into the mechanisms of circadian dysfunction may help researchers understand the

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Melatonin and Parkinson’s Disease

Parkinson’s patients demonstrate significantly reduced serum melatonin secretion as compared with controls (A), with conspicuously lower amplitude of melatonin rhythmicity in PD patients expressing excessive daytime sleepiness (EDS), (B). Circadian time is measured as time since awakening.

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Circadian Dysfunction and Parkinson’s Disease

The circadian system is managed by a collection of brain cells known as the suprachiasmatic nucleus, which is influenced by exogenic factors such as light, food and physical activity. Many characteristic symptoms of Parkinson’s manifest as defects in the circadian system. Patients are often sleepy during the daytime, and characteristic motor symptoms fluctuate throughout the day.

**DISRUPTION OF CIRCADIAN RHYTHMS IN PARKINSON’S DISEASE**

In a study published in *JAMA Neurology*^1^ in April 2014, funded by a National Institute of Neurological Disorders and Stroke Mentored Patient-Oriented Research Career Development Award (K23 NS072283), Dr. Videnovic and his colleagues studied the alteration of circadian system in Parkinson’s disease.^2^ Serum melatonin secretion over a 24-hour period provides a reliable marker of endogenous circadian rhythmicity, so Dr. Videnovic and his colleagues monitored serum melatonin levels at 30-minute intervals in patients with Parkinson’s disease, taking 50 samples from each subject. Melatonin secretion proved to be severely blunted in patients with Parkinson’s disease compared with controls, with Parkinson’s patients who expressed excessive daytime sleepiness showing a markedly lower amplitude of melatonin rhythm. These findings were consistent with an assumption that circadian regulation is associated with PD and raise intriguing questions about the mechanisms underlying the blunted rhythm.

Dr. Videnovic’s work doesn’t show whether this impairment of circadian rhythmicity is a cause or consequence of Parkinson’s disease, but his team will investigate causation in future research. Instead, research is now focusing on what happens to the function of the circadian system as the disease progresses. Upcoming investigations will test interventions, such as bright light therapy and timed applications of melatonin, that target circadian function, attempting to improve the sleep-wake cycle disturbances and explore whether such interventions have any effect on the underlying neurological disease process.

**REM SLEEP BEHAVIOR DISORDER (RBD): AN EARLY INDICATOR OF NEURODEGENERATION**

REM sleep behavior disorder (RBD) is a sleep disorder, increasingly linked to an ongoing synuclein-related neurodegeneration. Symptoms of RBD include abnormal vocalizations and movement behaviors during sleep. RBD is thought to be a prodromal stage of PD, preceding the expression of cardinal motor symptoms. Patients with PD can also exhibit freezing of gait (FOG), a symptom that emerges from neuroanatomical changes in the brain stem that include the pedunculopontine nucleus and locus coeruleus. These same anatomical regions have been implicated in RBD.

Dr. Videnovic and his colleagues looked at another aspect of this connection in a study funded by the Michael J. Fox Foundation for Parkinson’s Research. The study, published in *Neurology*^3^ in September 2013, looked at several groups...
of patients: one group with PD and FOG, a group with PD that did not have FOG, and another group with RBD and no diagnosis of PD (as well as matched controls). The team saw a marked difference in tonic muscle activity during REM sleep between the PD patients with and without FOG. Patients with PD and FOG and the group with RBD, however, had similar tonic muscle activity patterns during REM sleep. These latter groups also showed similar amounts of tonic EMG activity during REM sleep.

Dr. Videnovic and his team raise the possibility that the commonalities in sleep dysfunction between the RBD and PD with FOG groups might reflect an overlap in the circuits that control muscle activity during REM sleep and FOG. Their data led them to hypothesize that the presence of excessive tonic EMG activity during REM sleep may predict development of PD with FOG, and that the pathophysiologic mechanisms that mediate FOG in PD share a common set of neurodegenerative changes that underlie the tonic muscle activity during REM sleep that is found in RBD.

While this is an initial, cross-sectional study, Dr. Videnovic and his colleagues at the Program in Sleep, Circadian Biology and Neurodegeneration hope to recruit more patients with RBD for a longitudinal study that will look more closely at the connections between RBD and FOG, in the hope of identifying additional markers in sleep patterns and via brain imaging that predict the development of FOG in Parkinson’s disease.


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