Focus on Research: VRIC Explores New Research

Vascular surgery has become an increasing clinical and technical area of expertise. The Vascular Research Initiatives Conference, to be held May 3, 2017, in Minneapolis, serves to preserve the biologic side of vascular surgery and provides a forum for vascular surgeon scientists to present and discuss new research and possibilities.

VRIC focuses on translational research and vascular biology with a heavy clinical emphasis, bringing together researchers who use biology to better understand causes of vascular disease and apply this knowledge to influence disease prevention and treatment, said Dr. Edith Tzeng, chair of the SVS Research and Education Committee, which oversees VRIC.

VRIC will be held May 3, 2017, in Minneapolis, Minn. The one-day conference, considered a key event for collaboration among vascular researchers, is held the day before the American Heart Association’s Arteriosclerosis, Thrombosis and Vascular Biology (ATVB) scientific sessions to allow for the fluid interaction between vascular surgeon scientists and scientists working in related cardiovascular fields.

The 2016 VRIC conference was extremely successful, said Dr. Tzeng. She highlighted two presentations, one on the role of exercise in treating Peripheral Artery Disease and the second focused on diabetes and wound healing.

“Our vascular surgery community deals with both of these extremely difficult problems on a daily basis,” said Dr. Tzeng. “The involvement of vascular surgeons in research brings to the forefront the important clinical problems that we struggle with in our patients. These presentations highlight the value and relevance of our research and how it eventually may have enormous impact on how we treat both conditions.”

**Studying Exercise Benefits in PAD Patients: Revascularization Benefits Greater**

Abstract title: Revascularization but Not Supervised Exercise Therapy Prevents Progression of Fibrosis in the Gastrocnemius of Patients with Peripheral Artery Disease While Improving Limb Function

This study suggests that people with muscle damage from peripheral artery disease benefit more from revascularization than supervised exercise therapy or no intervention.

The group found that increasing the blood flow to the leg in PAD patients via revascularization (bypass or angioplasty/stenting) stops the progression of damage and scarring over six months and helps patients walk longer and further. In comparison, patients having six months of supervised exercise therapy had progression of damage and
scarring in their leg muscle although they improved their treadmill walking distances. Finally, patients who had no intervention in the six month had progression of damage and scarring in their leg muscle and no changes in their walking distances.

Both exercise therapy and revascularization improved the walking performance of patients with PAD, but only revascularization operations prevented the progression of fibrosis in patients’ leg muscles, said Dr. Iraklis Pipinos. He and Dr. George Casale were lead researchers on the project.

“We found that both the exercise therapy patients and the ones with no treatment had increasing scarring in their muscles,” said Dr. Pipinos. “But the scarring stopped progressing in the patients who underwent revascularization.”

None of the therapies improved the scarring, he noted.

The results from exercise therapy were unexpected, Dr. Pipinos said. “Our group is a big proponent of exercise therapy. We expected that six months of exercise therapy would improve the histology of the calf muscle. Our findings were slightly disappointing in the sense that the way we currently prescribe exercise may not be as good for the muscles as we were hoping. Exercise, the way we currently do it, does not appear to match our expectations.”

It was a relatively small study, with 20 patients undergoing bypass, 19 with supervised exercise therapy and 17 with no intervention.

Researchers followed current SVS recommendations for exercise therapy: six months of therapy, three times a week, under supervision. “PAD patients may be one group of patients where we need to look more closely into the effect of the exercise and perhaps modify it,” Dr. Pipinos said.

He added that though surgery stopped the progression of damage and scarring, not all patients are candidates for revascularization operations, and surgical procedures carry with them risk, complications and an appreciable rate of long-term failure. His lab is now working to understand how scarring occurs and to test different medications that block the scarring pathways. “We can use these medications either alone or in combination with revascularization and exercise therapy and improve patients’ abilities to walk and leave healthy lives.”

Research continues, with more patients signing up. Read more about the study at vsweb.org/Pipinos.

Studying Delayed Wound Healing

Epigenetically Altered TLR4 Expression May Contribute to Increased Inflammation and Impaired Wound Healing in a Murine Model of Diabetes

Because delayed wound healing is a significant problem for diabetics, Dr. Andrew Kimball and senior author Dr. Katherine Gallagher led a team to look into the biomechanics and immunology driving the delays.

“While it has been previously shown in many models that diabetics have increased inflammation in their wounds, the reason for this pro-inflammatory phenotype remains elusive,” said Dr. Kimball. The team hypothesized that epigenetic changes may alter expression patterns of damage-associated molecular pattern receptors like Toll-Like Receptor 4 (TLR4) and would, in turn, result in increased inflammation via stimulation of the NF-kB signaling pathway.

Mice were fed either a normal or high-fat diet for 12 to 16 weeks to create a diet-induced obese model of physiologic type 2 diabetes. Wounds were created in mice fed both diets, wound healing was monitored daily and wound tissues were collected for protein, RNA and cell-specific analysis.

As the team expected, the mice fed the high-fat diet demonstrated significantly delayed wound healing compared to the mice fed a normal diet. As researchers had hypothesized, there were increased levels of detectable TLR4 RNA and protein in the bone marrow, blood and wounds of the high-fat diet mice. Given these findings of increased systemic expression of TLR4, the researchers deduced that there may be an epigenetic component to the increased expression patterns. Using chromatin immunoprecipitation analysis (ChIP) they found increased levels of histone methylation
marks at the TLR4 gene locus that would allow and promote gene transcription.

“This is an interesting finding for two reasons,” said Dr. Kimball. “First, it demonstrates how diabetes is a true systemic illness as it affects cells all over the body. Second, diabetes goes as far as altering the DNA software which can irreversibly affect cell function for life.” The team concluded that diabetes results in wound monocyte/macrophages that have an inflammatory predisposition and this may represent a target for translation.

Overall goals for the project were to inform researchers of novel targets for the treatment of chronic non-healing diabetic wounds. A secondary potential goal was to develop parameters and immunological tests that may help inform physicians of prognosis and to determine feasibility of limb salvage procedures.

“A logical follow-up study to the VRIC work would be to examine the expression patterns of histone-modifying enzymes in diabetic macrophages and to try to find the enzyme that is resulting in these epigenetic changes and, in turn, how that enzyme is affected by the diabetic milieu,” said Dr. Kimball.

Dr. Gallagher’s team is now working on a separate project, also in diabetes, that members hope to present at VRIC 2017. Read more about the study at vsweb.org/Kimball.

(To see all of the SVS news from the November 2016 Vascular Specialist, please click here.)

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