ASK THE EXPERTS

Predicting the Next Breakthrough in Superficial Venous Disease Care

A discussion of therapies, technologies, and research that have the potential to transform the next phase of superficial venous disease treatment.

With Eri Fukaya, MD, PhD; Robert B. McLafferty, MD, MBA; and Stephen A. Black, MD, FRCS(Ed), FEBVS

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Most therapies for superficial venous disease target treating stages of the disease where the structural abnormalities caused by venous insufficiency have already resulted in changes in the vessel wall, causing clinical symptoms. With recent advancement in technologies such as single-cell sequencing, induced pluripotent stem cells (iPSCs), and genome-wide association studies (GWASs), we may be able to gain more understanding of the many determinants of chronic venous insufficiency and the underlying molecular mechanisms, which may provide us with opportunities for early and preventive treatment strategies.

Single-cell sequencing technologies have transformed biomedical research, enabling transcriptomic and epigenomic profiling of single cells at unprecedented resolution and sample size.[1] Notably, single-cell RNA-sequencing (scRNA-seq) allows identification of novel or rare cell types, elucidates the trajectory of transitioning cells, and allows comparison of healthy and disease-related tissues at the single-cell resolution.[2] As such, scRNA-seq is a critical tool in today's research efforts and can be used to develop novel therapeutic targets. Employing this technology in venous disease may help identify the unique molecular pathways and genes regulating the dysfunction and causing structural abnormalities.

Vein wall abnormality is likely the result of overexpression of matrix metalloproteinases (MMPs), which results in degradation of the extracellular matrix proteins, further affecting the structural integrity of the vein wall. MMP immunoreactivity has been observed in the endothelial cells (ECs) and smooth muscle cells (SMCs) of varicose veins.[3] Studies suggest that MMPs directly affect venous tissue function and induce venous relaxation, leading to progressive venous dilatation and development of varicose veins.[4] Leveraging the scRNA-seq technology to decipher the key regulators affecting the different components of diseased and varicose veins may elucidate their effects on EC-SMC cross-

talk. This can be done by using bioinformatics pipelines that enable intercellular communication analysis and can potentially examine the transcriptomic changes at the single-cell level in varicose veins, which can become therapeutic targets.

iPSCs derived from somatic cells of patients possess the ability to differentiate into multiple cell types, including ECs and SMCs, which express the majority of proteins expressed by human vascular cells.[5] Multiple vascular disorders have been studied using iPSCs, showing good recapitulation of disease profiles. Thus, the use of iPSC ECs for venous disease modeling, drug screening, and drug discovery purposes hold much potential.

In recent years, with GWASs and the emergence of modern population genetics, we have started to decode the genetic factors mediating the heritable contribution to these diseases. We now have numerous candidate loci for venous diseases, including several genes regulated by the varicose vein SNPs that impact vascular development and skeletal abnormalities.[6] However, we still have significant unexplained heritability and often a rudimentary understanding of the functional role of these loci on venous disease.

Armed with recent scientific technologic breakthroughs, we hope to continue growing our understanding of the pathogenesis of venous disease. This may lead us to discover novel safe and effective therapeutic strategies for disease mitigation.

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Over 20 years have passed since the FDA approved radiofrequency ablation for the great saphenous vein. This invention led to a complete paradigm shift in how care is delivered and a further explosion of innovation in the treatment of symptomatic varicose veins. Moving from the in-hospital setting with a poised operating room team to outpatient vein clinics far and wide, physicians of any specialty can now service a population of > 20 million. Now far from a new normal, the notion of walking in and out of a clinic and having your varicose veins "taken out" can still boggle the mind. Although this fee-for-service world has been the "mother of invention," the dark side can now be viewed as too many unnecessary procedures being performed, given the ease in finding one valve that leaks a little, along with vague leg complaints.

Indeed, we have observed in a large, screened population of 2,234 nonrandomized volunteers who were undergoing an abbreviated duplex exam that the presence of reflux (deep and superficial combined) is associated with an increasing CEAP (clinical, etiology, anatomy, pathophysiology) classification.[1] However, we do not have good data on the incidence of at least finding one abnormal segment of reflux, with a more in-depth exam of the superficial system and the correlation to CEAP, Venous Clinical Severity Score, Chronic Venous Insufficiency Questionnaire, and/or symptom constellation. On the ever-increasing wave of ablation procedures being performed, we see significant variability in the type of physicians doing these procedures and in the per-patient ablation rates, which is notably higher in those with no formal vascular training.[2,3] Last year, a joint society consensus was published to further highlight appropriate use criteria in the treatment of chronic venous disease, most importantly in superficial venous disease.[4]

So, what will be the next breakthrough? Perhaps something to aid the right physician in performing the right procedure, for the right indication, for the right patient, at the right time, in the right place, and with the right follow-up. If we are really feeling lucky, we could even add for the right reimbursement, but let's not get ahead of ourselves. The Vascular Quality Initiative Varicose Vein Registry (vqi.org) should help. Launched in 2015 with > 43,000 procedures now captured, this patient safety

organization database is poised to provide valuable data from the real world, assessing quality, safety, outcomes, and hopefully, the ability to benchmark appropriateness of procedures performed. Working toward the triple aim—improving the individual experience of care, improving the health of the population, and reducing per capita costs of care—in the treatment of varicose veins should be our first and foremost mission.

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Treatment of superficial venous disease has advanced significantly since the days of high flush ligation (with or without stripping), and the technical options for treating patients are now numerous. It must be said that in the arguments over whether thermal tumescent or nonthermal nontumescent techniques are better, we are now splitting hairs over marginal differences in procedures that are almost all pretty reasonable options for patients. It is difficult to find a bad treatment unless the practitioner themselves is overreaching. My views are that the breakthroughs will not be in treatments per se—which will continue to find marginal gains—but in our understanding of the nature of superficial venous disease.

The first advance I expect is that through the opportunities presented by "big data" analysis, we will start to be able to build models that better predict disease progression. We still cannot, for example, predict exactly which patients presenting with C2 varicose veins will go on to develop leg ulcer. Which patients with superficial disease get deep vein thrombosis as a consequence? "Big data" allied with the ability to sequence genetics on a much larger and cheaper scale should enable us to really start to personalize medical care for patients with superficial venous disease and predict future disease course.

I also expect that we will start to make advances in understanding pathophysiology in greater detail. We are still very uncertain about what to treat first in the case of multilevel or complex disease—in particular, when there is both deep and superficial disease, or now more importantly, a significant nonthrombotic iliac vein lesion and superficial disease. I believe we will see a test that enables us to determine the most hemodynamically significant lesion and focus treatment on that first.

Ultimately, I think the big advances won't come from the actual treatment modality. They are going to come in a much deeper, richer understanding of disease progression and complication risks. This will enable health systems to focus treatment on patients who are at greatest risk and enable us to offer more appropriate intervention. ■